Lactate Homeostasis and Lactic Acidosis

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The roles of changes in cellular redox, interorgan lactate flux and balance, and quantitative aspects of lactate metabolism in the pathogenesis of lactic acidosis are discussed. Altered metabolism of pyruvate is central to the development of lactic acidosis and hyperlactatemia. Lactic acidosis occurs as a result of a relative or absolute imbalance in lactate production and utilization. Lactate utilization for oxidative purposes and for the resynthesis of glucose is essential for the maintenance of acid-base balance. Because of its role in lactate homeostasis the liver may play a central role in acid-base balance. Impairment of hepatic utilization of lactate may produce lactic acidosis.

Despite its relatively recent description (1), lactic acidosis is now recognized as the most commonly encountered cause of metabolic acidosis. Lactic acidosis develops when tissue perfusion and tissue oxygenation are inadequate. More perplexing and less well understood is the occurrence of lactic acidosis with diseases or conditions that are not obviously associated with impaired tissue oxygenation, such as diabetes mellitus, liver disease, and various drugs and toxins.

Regulation of lactate production and utilization, quantitative aspects of lactate metabolism, interorgan lactate flux, and lactate balance will be emphasized here. Some of the conditions associated with lactic acidosis but not with obviously poor tissue oxygenation will be discussed, and general principles of therapy will be reviewed. Less common disorders and enzymic defects associated with lactic acidosis will not be discussed; information on these topics can be obtained from several excellent comprehensive reviews of lactic acidosis (2-13).

General Background

Increased blood concentrations of lactate indicate the presence of lactic acidosis. Although the terms lactate and lactic acid are often used interchangeably, they are not the same. Lactate is the residue or "anionic slag" of previously buffered lactic acid and when present in higher than normal concentrations indicates altered production of lactic acid, utilization of lactate, or both. Lactic acidosis may not produce acidemia, depending on the severity of the process and whether there is a coexistent alkalosis, such as might occur with liver disease or sepsis. Thus, the presence of hyperlactatemia may, depending on the circumstances, be associated with acidemia, normal pH, or alkalemia.

Although the accumulation of anions of strong organic acids is associated with acidosis, it is generally understood that these acids do not exist to any significant extent in the undissociated form. Furthermore, it is doubtful that the organic acids per se are ever produced in intact form (6, 13). The conversion of glucose to lactate results in the release of one hydrogen ion, from the hydrolysis of adenosine triphosphate (ATP), for each molecule of lactate formed so that it would appear as if lactic acid were the product.

Lactic acid is a strong metabolic acid (pKₐ 3.8) that is completely dissociated at body pH. For each milliequivalent of lactic acid produced, 1 meq each of hydrogen ion and the lactate anion will be liberated. The hydrogen ion reduces the bicarbonate concentration and the body pool of buffer. Pyruvic acid, the immediate precursor of lactic acid, with which it is in equilibrium, is also a strong organic acid that is 20 times more dissociated at body pH than lactic acid. Pyruvic acid is normally present in such small concentrations, approximately 10% of the lactic acid concentration, that it does not contribute in any important way to the development of metabolic acidosis even in lactic acidosis, where its concentration is usually less than 3 mM. Furthermore, the conversion of pyruvate to lactate utilizes two hydrogen ions (as shown in equation 1, below) and can be viewed as a protective reaction whereby the acidosis is buffered or minimized.

Metabolism

Lactate is a metabolic byproduct of glycolysis and is in equilibrium with pyruvate by virtue of the reaction catalyzed by lactic dehydrogenase:

Equation 1: \[ \text{Pyruvate} + \text{NADH} + \text{H}^+ = \text{Lactate} + \text{NAD}^+ \]

In this reaction the concentration of lactate is determined by the concentrations of pyruvate, NAD (reduced nicotinamide adenine dinucleotide), NAD⁺ (oxidized nicotinamide adenine dinucleotide) and hydrogen ion:

Equation 2: \[ \text{Lactate} - k \frac{(\text{Pyruvate})(\text{NADH})(\text{H}^+)}{(\text{NAD}^+)} \]

in which \( k \) is the equilibrium constant for the reaction and NADH and NAD⁺ are the concentrations of the free (unbound) reduced and oxidized pyridine nucleotides. The NADH/NAD⁺ ratio reflects the redox state of the cytosol of the cell, and it and the pyruvate concentration are considered to be the major determinants of the lactate concentration. The lactate/pyruvate ratio (L/P) can be derived simply by transformation of equation 2:

Equation 3: \[ \text{L/P} = k \frac{(\text{NADH})(\text{H}^+)}{(\text{NAD}^+)} \]
The NADH/NAD ratio reflects the redox state of the cytosol of the cell and is primarily determined by mitochondrial function. Although the availability of oxygen is critical, it is by no means the only determinant of cellular redox and various other factors (oxidative phosphorylation, electron transport, tricarboxylic acid cycle activity and mitochondrial transfer of reducing equivalents) are also important. Consequently, alterations in NADH and NAD and in the L/P ratio do not solely reflect tissue oxygenation. The NADH is normally generated during glycolysis and is reoxidized to NAD by mitochondrial action. When mitochondrial function is impaired, NADH is not reoxidized, cellular ATP concentrations decrease, and the generation of pyruvate and its conversion to lactate are increased. As ATP concentrations decrease, the rate-limiting enzyme of glycolysis, phosphofructokinase, is activated (14) and increased flux of substrate to pyruvate occurs. The accumulation of NADH and the shift in cellular redox accelerates the conversion of pyruvate to lactate (equation 1). Reoxidation of NADH thus occurs in the cytosol by the transfer of hydrogen from NADH to pyruvate, instead of in the mitochondrion. The regenerated NAD is utilized at the glyceraldehyde phosphate dehydrogenase step of the glycolytic pathway and permits increased glycolysis.

An increase or decrease in the hydrogen ion concentration, if the NADH/NAD ratio and the pyruvate concentration remain unchanged, will alter the lactate concentration and L/P ratio. However, changes in the hydrogen ion concentration alone do not produce significant changes in the concentration of lactate but may markedly alter the L/P ratio. For example, if normal lactate and pyruvate concentrations are 1.0 and 0.1 mM and if a pH-generated shift in the L/P ratio from 10 to 21 were to occur, then the lactate concentration would increase only to 1.05 mM while the pyruvate concentration would decrease to 0.05 mM. The effects of alterations in hydrogen ion concentration on intracellular enzymic reactions and lactate transport are more important than its effects on the lactic dehydrogenase (LDH) equilibrium and they more than offset the changes in lactate concentration that occur from a shift in the equilibrium. Whereas a decrease in pH will shift the equilibrium to increase the lactate concentration, hydrogen-ion-mediated inhibition of phosphofructokinase will actually decrease lactate production and inhibit the exit of lactate from the cell. The net effect of such changes is to decrease the blood lactate concentration. Opposite effects are produced by a decrease in hydrogen ion concentration. As the pH increases there is a shift in the equilibrium that tends to reduce the concentration of lactate. Yet, phosphofructokinase is concomitantly activated, glycolysis and lactate production are increased, and lactate transport is facilitated so that the net effect is to increase the lactate concentration. In practice the changes that occur in the glycolytic rate and perhaps in lactate transport predominate and not the changes that occur in the equilibrium of the LDH-catalyzed reaction.

Hepatic extraction of lactate and lactate homeostasis may also be influenced by pH. Lactate extraction and utilization by the isolated perfused rat liver are sensitive to changes in both extracellular and intracellular pH (15). Lactate uptake by the liver decreases as pH declines due to inhibition of pyruvate carboxylase (PC), and when the pH is 7.0 or less the liver becomes an organ of lactate production (15). However, failure to observe lactic acidosis as a consequence of severe metabolic acidosis may be due to mechanisms that protect intracellular pH or, as previously discussed, to concomitant reduction in lactic acid formation by peripheral tissues due to pH inhibition of phosphofructokinase in muscle and other glycolytic tissues. In this setting, reduced peripheral lactic acid production masks reduced hepatic lactate utilization so that blood lactate concentrations are not altered. If it were possible to selectively reduce hepatic intracellular pH, such as might occur with use of phenformin, then lactic acidosis could develop as a result of impaired hepatic lactate extraction and utilization. Acidosis, when severe (pH < 7.1) also adversely affects lactate uptake by the kidney, another major site of lactate utilization. The combined reduction of lactate utilization by these organs could impose a lactate load on other tissues that could not be assimilated, and lactic acidosis would ensue. To date these are important theoretical considerations that have not yet been shown to have clinical relevance.

Pyruvate plays a pivotal role in lactate metabolism and factors that regulate its concentration will have a profound effect on lactate homeostasis (13). This critical role and the development of lactic acidosis have not been sufficiently emphasized. In fact, lactic acidosis can be basically viewed as a disorder of pyruvate metabolism wherein hyperlactatemia serves as a "marker" or indicator of the disturbance. The balance between pyruvate synthesis and utilization is particularly important. The glycolytic pathway and transamination are the major sources of pyruvate. Pyruvate may be utilized in either of two ways, both of which depend on intramitochondrial pathways, the redox state, and the availability of ATP. In adipose tissue, brain, muscle, and other tissues, pyruvate is metabolized to acetyl coenzyme A (acetyl CoA) for subsequent utilization, through a reaction catalyzed by the enzyme pyruvate dehydrogenase (PDH). Nicotinamide adenine dinucleotide is an important cofactor in this reaction and if insufficient quantities are available the conversion of pyruvate to acetyl CoA will be inhibited and its conversion to lactate will be augmented. The activity of PDH is inhibited by starvation and diabetes mellitus (16, 17), in addition to those conditions that impair mitochondrial reoxidation of NADH to NAD. In liver and kidney pyruvate is predominantly utilized for gluconeogenesis. The first and rate-limiting step in this sequence, the conversion of pyruvate to oxalacetate, is catalyzed by the enzyme PC and requires an adequate supply of ATP. Thus, impairment of mitochondrial function, which interferes with the reoxidation of NADH and the generation of ATP, influences the activity of both PDH and PC, the subsequent metabolism of pyruvate through their respective pathways, and results in the accumulation of lactate.

Because the concentration of pyruvate depends on the balance between pyruvate production and pyruvate utili-
zation, mitochondrial function need not be impaired for increased production of lactate to occur. Rapid glycolysis induced by alkalosis or insulin could generate both pyruvate and NADH more rapidly than they could be utilized so that collectively or individually they could be associated with increased lactate formation. The inhibition of PDH and impairment of pyruvate utilization that occur in starvation and diabetes mellitus could interact with other factors and predispose to the development of lactic acidosis.

Homoeostasis and Quantitative Aspects of Lactate Metabolism

Although lactate is produced by virtually all tissues, brain, erythrocytes, and skeletal muscle account for most of the lactate synthesized; minor contributions are made by leukocytes, platelets, and renal medulla (18, 19). Skin has been thought to be a potential major contributor as well (19). Lactate is utilized predominantly by liver and kidney, although the myocardium and even skeletal muscle, under certain conditions, have the capacity to utilize lactate. The reutilization of lactate for glucose synthesis and the oxidation of lactate for energy purposes are intimately concerned with maintenance of acid-base balance. The oxidation of lactate or its conversion to glucose can also be viewed as generating bicarbonate or utilizing hydrogen ions (13). With utilization, lactate concentrations fall and bicarbonate concentrations rise reciprocally.

Lactic acidosis may be viewed as an imbalance between lactic acid production and lactate utilization (8, 10, 12, 13). The relative importance of these factors in clinical conditions associated with lactic acidosis is controversial. It has been traditional, particularly in situations associated with poor tissue perfusion, to attribute lactic acidosis to the overproduction of lactic acid by hypoxic tissues. Even in the presence of satisfactory cardiovascular performance, the development of lactic acidosis has been attributed to subtle (subclinical) alterations in perfusion and oxygen delivery to tissue. However, because splanchnic as well as peripheral blood flow is reduced in such situations, the delivery of lactate to the liver and kidney, the major sites of utilization, and its extraction would also be expected to be significantly reduced. Thus, overproduction as well as underutilization would contribute to the development or maintenance of lactic acidosis in low flow states. In a variety of situations, both factors may be operative. For example, experimental hyperventilation in animals and pathologic hyperventilation in humans probably produces lactic acidosis by virtue of pH-related changes in lactic acid production and transport as well as by decreased hepatic uptake that results from reduced splanchnic blood flow (28-24).

The precise rate of lactic acid production is not known. By measurement of regional blood flow and arteriovenous lactate concentrations tissue or organ lactate balance can be determined and lactate production assessed. Alternatively, lactic acid turnover can be determined by isotopic dilution techniques. Each appears to have its limitations, the former probably leads to underestimation and the latter to overestimation of lactate production. In postabsorptive man basal lactate production, by isotopic dilution, is to 0.9 to 1.0 mmol/kg·h (19) (20 to 25 mmol/kg·d), whereas that calculated from lactate balance across tissue beds is 0.6 to 0.8 mmol/kg·h (15 to 20 mmol/kg·d) (19).

Isotopic studies in humans show that approximately 15% to 17% of lactate production is derived from alanine (26) and 50% from glucose (19, 25). Thus, 65% to 70% of the lactate turnover is derived from glucose and alanine. Glucose synthesis from lactate and lactate oxidation account for 20% and 70% to 80%, respectively, of the lactate turnover (19, 25).

Postabsorptively in humans, the liver extracts 380 mmol of lactate and 25 mmol of pyruvate per day for a total of 405 mmol (27), representing approximately 20% to 30% of the lactate turnover. The utilization of lactate and pyruvate by the kidney postabsorptively in humans, under basal conditions, is not known. In starvation, renal lactate extraction only accounts for 5% to 10% of the isotopically determined lactate turnover (28). Thus, in both postabsorptive and starved humans extrahepatic and extrarenal sites of lactate utilization are quantitatively most important.

The maximum rate of lactate production can be estimated when there is intense muscle contraction of brief duration. Plasma lactate concentrations may reach 20 to 30 mM after maximum work of short duration (29, 30) representing approximately 20% to 30% of the lactate turnover. The utilization of lactate and pyruvate by the kidney postabsorptively in humans, under basal conditions, is not known. Plasma lactate concentrations during exercise in fed human subjects (33), and a maximum

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projected rate of hepatic lactate uptake of 400 g/d, derived by estimates in rats that were extrapolated to humans (35). These calculations implicate extrahepatic mechanisms for the reestablishment of lactate homeostasis in the postexercise recovery period and refute the proposal that hepatic underutilization of lactate is always central to the development of lactic acidosis (36).

The ability of the liver to augment its uptake of lactate and the time it takes to do so become critical limiting factors in determining the maximum capacity of the liver to metabolize lactate. Unfortunately, the uptake of lactate by the liver has never been related to the concentration of lactate, even in Rowell and associates' exercise study (33), so that the projected rate of maximum lactate utilization, derived with blood lactate concentrations of 5 to 8 mM may be considerably less than the rates that would be found with higher lactate concentrations.

Having said the above, it still seems reasonable that inhibition of lactate utilization could produce lactic acidosis in a relatively brief period. Basal lactate production of 0.9 mmol/kg·h would generate approximately 60 to 70 meq each of hydrogen ion and the lactate anion per hour for the 70-kg reference person. The concentration of lactate in body water under those circumstances would approach 10 mM in 6 h.

Acute studies of lactate metabolism by the liver in the dog do not clarify the matter because of peculiarities of the splanchnic bed and because lactate extraction by the liver cannot always be demonstrated. This may not be the situation in chronic preparations in which vascular catheters have been inserted and the animals allowed to recover. Under these circumstances hepatic extraction of lactate accounts for 50% of the lactate production rate (CHERRINGTON A. Personal communication). These studies also demonstrate that the gastrointestinal tract accounts for 15% of the lactate production rate. The development of lactic acidosis in functionally hepatectomized dogs can be prevented by treatment with dichloroacetate, which inhibits lactate acid production by extrahepatic tissues (37), suggesting that impaired hepatic utilization of lactate is responsible, in this model, for the accumulation of lactate and the acidosis.

An unsettled but important problem involves the capacity of other tissues to utilize lactate and hence buffer the increase in lactate that would occur as a result of impaired hepatic lactate extraction. Although myocardium and kidney can utilize lactate, they are quantitatively relatively unimportant. Under certain circumstances, skeletal muscle has been demonstrated to extract lactate. During profound exercise of a single limb, muscle of the nonexercising extremity can be demonstrated to extract and utilize lactate (36). Even in the exercising limb isotopic studies confirm that contracting skeletal muscle both produces and utilizes lactate (38). In a recent study in which sodium lactate was infused, skeletal muscle was responsible for 35% of the lactate removed and the splanchnic bed for only 10% (39). Other in-vivo and in-vitro studies have established that exercising and resting muscle can utilize lactate. During exercise the capacity to provide glucose to exercising muscles in proportions similar to those used at rest indicates hepatic reutilization of lactate for glucose synthesis (39, 40). However, hepatic extraction and utilization of lactate accounts for only 50% of the lactate produced during exercise (39, 40), indicating that extrahepatic sites of lactate utilization are important and quantitatively equivalent to the liver. Exercise may not be the best situation from which to draw conclusions about hepatic and extrahepatic contributions to the maintenance of lactate homeostasis in low-flow states because blood flow is normal or increased under these circumstances.

Data on the role of the liver in lactate homeostasis in shock do not clarify this issue. The clearance of a lactate load in hemorrhagic shock in dogs and Ringers lactate solution in experimental animals and human subjects after acute trauma appears to be normal (41, 42). In one of two isotopic studies of lactate metabolism in dogs subjected to hemorrhagic shock and in one isotopic study (in which shock was induced by cardiac tamponade, hemorrhage or endotoxin), the increase in plasma lactate was attributed to increased lactic acid production (43-46). There is general agreement that a reduction in hepatic lactate extraction may occur as a result of diminished blood flow or oxygenation of the liver (47, 48), or both. In another study in which a low-flow state was induced in dogs by cardiac tamponade hepatic lactate extraction was impaired (48). An increasing arterial lactate concentration, early in this experiment, that was higher than that in the inferior vena cava indicated that the hyperlactateemia was due to increased hepatic lactate release. During the recovery phase the liver was the only organ or tissue that extracted lactate. In humans with hypotension and in dogs subjected to hemorrhage, liver, skeletal muscle, and kidneys all contribute to the acidosis and the hyperlactateemia (49).

In conclusion, there are currently few firm data by which the roles of skeletal muscle, liver, and kidney in the pathogenesis of lactic acidosis can be assessed. There is little doubt, however, that, in addition to reduced uptake, the liver may be a source of lactic acid production when blood flow, oxygenation, or both, is reduced and thereby contribute to or be responsible for the development of lactic acidosis. Whether impairment of hepatic extraction of lactate can occur as a primary abnormality, independent of alterations in hepatic blood flow or oxygenation, and lead to the development of lactic acidosis is not known but would be of tremendous interest (50).

The contributions of increased production or decreased utilization, or both, to the development of lactic acidosis likely will vary with the species and the underlying cause. Better knowledge of the factors regulating lactic acid production, utilization, interorgan flux, and balance is essential to better understand the pathogenesis of lactic acidosis.

Lactate and the Kidney

The kidney is important in lactate homeostasis, not only because it utilizes lactate but also because it regulates the concentration of lactate in body fluids. The kidney effectively reabsorbs filtered lactate up to plasma con-
centrations of 6 to 10 mM (51). Thus, lactate does not begin to appear in the urine, when renal perfusion is preserved, until these concentrations in plasma are exceeded. The conservation of filtered lactate by the kidney guarantees an adequate supply of substrate from which bicarbonate can be generated when the factors causing its accumulation are reversed. Because substantial quantities of bicarbonate are usually administered to patients with lactic acidosis, rebound alkalosis often ensues when the precipitating factors are corrected.

Definition of Lactic Acidosis

Lactic acidosis is a metabolic acidosis caused by the accumulation of lactate and hydrogen ion and is accompanied by elevated blood lactate concentration. The extent of acidosis, as defined by the pH, and the concentration of lactate required for the diagnosis of lactic acidosis have never been defined. Values for each have been arbitrarily established but no consensus exists (4, 12, 13). The highest blood pH and the lowest lactate still compatible with lactic acidosis, reported in the literature are 7.37 and 1.3 mM, respectively. This would obviously represent the least rigorous definition and, if applied, would include many patients who either did not have lactic acidosis or had inconsequential acidosis. Criteria for blood lactate concentrations in lactic acidosis include "a raised blood lactate level," greater than 1.3 mM, greater than 2.0 mM, and greater than 7.0 mM; whereas the criteria for pH include "a significant lowering," "a lowered arterial pH," less than 7.37 and less than 7.30 (4, 12, 13). Obviously, the reported frequency of lactic acidosis as well as its association with other diseases will be influenced by the criteria that are utilized. Lactic acidosis should not be diagnosed when the lactate concentrations or the pH changes are trivial. In acidosis due to circulatory failure and septic shock lactate concentrations of 4 mM or above are associated with increased mortality (52, 53). Lactate concentrations of 4 to 5 mM or over, with simultaneously and comparably reduced plasma bicarbonate concentrations that are associated with a significant lowering of the arterial pH should permit an accurate presumptive diagnosis of lactic acidosis (13).

Diagnosis of Lactic Acidosis

The diagnosis of lactic acidosis is generally not difficult. While availability of rapid lactate determinations have considerably simplified matters, an accurate presumptive diagnosis can usually be established quickly and with a high degree of certainty on clinical grounds (2). The precipitous development of unexplained severe hyperventilation and the presence of an increased anion-gap metabolic acidosis in a critically ill patient with compromised cardiovascular function—in the absence of ketoacidosis, chronic renal failure or both—will generally permit a firm early diagnosis. The anion gap is determined by subtracting the sum of the plasma chloride and bicarbonate concentrations from the sodium concentration [(Na) - (Cl + HCO₃⁻)] (54). The difference, normally 12 to 15 meq/L, represents unmeasured anions, including albumin, present in plasma. When the anion gap is 25 meq/L or greater, invariably there are increased quantities of unmeasured organic anions. When lactate concentrations are not markedly elevated, the serum bicarbonate may be reduced only slightly, the increase in the anion gap may be marginal, and the diagnosis may be more difficult. In lactic acidosis the increase in the anion gap is usually greater than the decrease in the bicarbonate concentration (55). This is in contrast to diabetic ketoacidosis where the increase in the anion gap is identical to the decrease in bicarbonate. A history of ethylene glycol ingestion, methanol consumption, salicylate overdose, acute alcoholism, fructose administration, and, in the past, of phenformin administration will often permit the identification of noncardiovascular precipitating factors. When noncardiovascular factors are responsible, the onset of the acidosis is usually insidious, hyperventilation is usually appropriate for the degree of acidaemia except when it is related to salicylates (13), and cardiovascular function is usually initially well preserved (2). Only when the acidosis has been permitted to persist does the hemodynamic status deteriorate.

Occasionally, exclusion of diabetic ketoacidosis will be difficult because the nitroprusside color reaction, dependent primarily on acetoacetate, will be weakly positive or negative in the presence of severe ketoacidosis when the predominant ketoacid anion is betahydroxybutyrate. Under these circumstances, and in the absence of quick lactate measurements, the increased anion gap will be falsely attributed to lactate. On the other hand, ketoacidosis and lactic acidosis can coexist, particularly in patients with alcoholic ketoacidosis (56, 57) or patients with diabetic ketoacidosis in whom there is a coexistent renal disease (58). In the absence of lactate measurements these combinations may be difficult to detect. When lactate concentrations do not account for all of the increase in the anion gap and when renal failure is absent, combined ketoacidosis and lactic acidosis should be suspected. The persistence of acidosis in a patient with treated diabetic ketoacidosis should suggest coexistent but previously unidentified lactic acidosis or superimposed lactic acidosis.

The precipitous development of severe metabolic acidosis is often encountered in clinical situations where tissue perfusion is unsatisfactory. Under these circumstances it takes no great insight or diagnostic skill to arrive at a correct presumptive diagnosis. However, with certain drugs and toxins the development of acidosis proceeds more slowly and the rate of development may not be helpful. However, utilization of the anion-gap calculation should permit an accurate assessment of the problem. Should an accurate presumptive diagnosis not be possible, or if the information that is required to make such a diagnosis is not available, lactic acidosis should be suspected when the acidosis is resistant to large quantities of bicarbonate, sudden and unpredictable shifts in acid-base status occur, and when alkalosis develops in the recovery phase (2).

Blood or plasma lactate concentrations normally range from 0.5 to 1.5 mM. Venous concentrations of lactate tend to be higher than arterial concentrations because of
local tissue production of lactate, and may reach 2.0 mM. Stasis of blood should be avoided but is usually only a problem with venous samples. Arterial blood is thus preferred but not required. Blood should be quickly deprotei­nized or processed to prevent the continued metabolism of glucose and the formation of lactate by red blood cells. Failure to adhere to these guidelines will result in spurious lactate elevations. Lactate measurements are becoming available or are readily available in most hospitals and, except for the desirability of obtaining arterial blood and the need for prompt deproteinization, they are neither difficult nor complex. Pyruvate, in contrast, is very labile and unless samples are processed quickly and meticulously will deteriorate rapidly. The samples cannot be stored, even if frozen. Measurement of pyruvate in the neutralized deproteinized supernatant must be undertaken promptly. These problems essentially guarantee spuriously low pyruvate concentrations and falsely elevated L/P ratios. They are of sufficient magnitude to make pyruvate determinations impractical for clinical purposes.

Convulsive Disorders

The lactic acidosis that accompanies grand mal seizures (32) is important because it is self-limited and treatment is unnecessary. It is probably one of the commonest but least appreciated causes of lactic acidosis either because of its transient nature or the infrequency with which systemic pH, lactate, and electrolyte measurements are obtained in patients with seizures or both of these. However, the rapid onset and resolution of severe metabolic acidosis permits evaluation of the relative roles of overproduction or underutilization, or both, under these specific conditions. Severe metabolic acidosis with marked hyperlactatemia was seen in patients who had a single grand mal seizure (32). Within 60 minutes of the seizure, the arterial pH had returned to normal and the plasma lactate concentration had decreased from 12 to 6 mM. Resolution of acidosis was accompanied by a reciprocal change in the lactate and bicarbonate concentrations. In view of the precipitous development of acidosis, it is reasonable to conclude that lactic acid overproduction is the sole factor in this instance. The changes in the concentrations of lactate and in pH in patients with seizures are similar to those seen after maximal exercise of short duration, where plasma lactate concentrations as high as 22 to 32 mM and pH values as low as 6.8 to 6.9 occur and an excellent inverse correlation exists between blood lactate and bicarbonate concentrations.

Of particular importance, however, is that this is a self-limited metabolic acidosis that is rapidly reversed without therapy. The disappearance of lactate is associated with the generation of bicarbonate; the lactate serves as the substrate for the correction of the acidosis.

Diabetes Mellitus

The relation between diabetes mellitus and lactic acidosis has been an intriguing one. Approximately 50% of the reported cases of idiopathic lactic acidosis have occurred in patients with diabetes mellitus (3, 4). Whether an association between these two conditions exists is not clear because, in my experience, idiopathic lactic acidosis in patients with diabetes mellitus has become virtually nonexistent since the removal of phenformin from the market. Diabetes mellitus could predispose to the development of lactic acidosis in various ways. Macrovascular disease; microangiopathy; altered affinity of hemoglobin for oxygen due to decreased 2, 3-diphosphoglycerate or increased quantities of glycosylated hemoglobin, or both; abnormal platelet function; and altered blood viscosity could individually and in combination lead to abnormal perfusion and inadequate tissue oxygenation. That a metabolic lesion may exist in addition to or instead of the above possible causes must also be considered. In experimental diabetes mellitus there is a decrease in PDH activity in muscle, and a 75% reduction in lactate oxidation (17). Studies with radiolabeled lactate in animals and patients with diabetes mellitus show that lactate is metabolized normally but less is oxidized and more is channeled into glucose (59, 60). In addition, there is a twofold greater increase in lactate release from muscle of diabetic animals when compared with normal controls (17). With exercise, the rate of lactate release from muscle is normal but lactate oxidation is still inhibited (by 75%), suggesting diminished PDH activity (17). In patients with diabetes mellitus lactate utilization by skeletal muscle is also reduced, but blood lactate concentrations are normal or only slightly elevated (61), perhaps reflecting increased hepatic lactate extraction and increased gluconeogenesis. Submaximal exercise in partially treated and insulin-deficient patients with juvenile diabetes mellitus produces blood lactate concentrations that are higher than those detected in control subjects (62). Patients with insulin-dependent diabetes mellitus, withdrawn from insulin therapy for 24 hours, have slightly elevated baseline arterial lactate concentrations that increase disproportionately during exercise, despite augmented splanchnic uptake of lactate and increased glucose production (61). Leg lactate production (mmoles per minute) in diabetic patients at rest and after 10 and 40 minutes of exercise is higher by 230%, 180%, and 500%, respectively, than in normal control subjects. Although hepatic extraction of lactate is increased in diabetes it still cannot keep pace with the increased production of lactate by skeletal muscle.

In patients with diabetic ketoacidosis clinically significant lactic acidosis is uncommon (58, 63-66). In one series of patients with ketoacidosis, those with the severest degree of acidosis, hyperglycemia, and hypovolemia, had the highest initial lactate concentrations whereas those with milder abnormalities had lower lactate concentrations (64). With therapy, in the former, lactate concentrations declined while in the latter they increased, but in no instance did clinical lactic acidosis develop. In experimental ketoacidosis blood lactate concentrations are normal or minimally decreased but tend to increase with insulin therapy (67, 68). This increase is attributed to inhibition of gluconeogenesis by insulin, and reduced hepatic extraction of lactate rather than increased extrahepatic lactate production (68).

Recently, an experimental rabbit model for the induc-
tion of lactic acidosis was described that involves the production of diabetes mellitus by alloxan, depletion of NAD by the infusion of betahydroxybutyrate, and then alkalinization with bicarbonate (69). The shift in the oxygen-hemoglobin dissociation curve reduces tissue oxygen delivery and the depletion of NAD prevents the conversion of lactate to pyruvate. Under these circumstances, irreversible lactic acidosis developed in one half of the diabetic animals.

Thus, under certain experimental and clinical circumstances, the diabetic patient may demonstrate a unique biochemical predisposition to the development of lactic acidosis. The increased susceptibility of the older diabetic patient to lactic acidosis may also be explained on the basis of macrovascular or microvascular disease, or both.

**Ethanol**

Even though hyperlactatemia is a well-recognized consequence of ethanol consumption it is seldom severe, and lactate concentrations in excess of 3 mM are rare (70). The hyperlactatemia associated with the use of ethanol is a result of decreased hepatic lactate extraction rather than increased lactate production (70). Lactic acidosis may occasionally be encountered in alcoholic patients with or without elevated blood ethanol concentrations (56, 57). Ethanol interferes with lactate clearance and it is possible that significant lactic acidosis occurs in alcoholics when other factors, such as seizures or hyperventilation, strain homeostatic mechanisms by accelerating lactate production and unmask this inhibition. Obviously, the use of ethanol in the presence of hepatocellular disease could further accentuate defects in lactate utilization by the liver. Lactic acidosis has also been reported after parenteral administration of ethanol (71). Although lactic acidosis usually occurs in the presence of or with the use of ethanol, and ketoacidosis with ethanol withdrawal or abstinence, they occasionally occur together and may be associated with hypoglycemia (56, 57). The development of lactic acidosis or ketoacidosis may depend on underlying nutrition and hepatic glycogen stores. Ethanol is more likely to induce lactic acidosis in diabetic patients than in nondiabetic patients (13). Administration of glucose is generally all that is necessary to reverse ketoacidosis or lactic acidosis, or both, in the alcoholic (57).

**Hepatic Disease**

In view of the proposed role of the liver in lactic acid homeostasis it seems reasonable that hepatic disease would predispose to the development of lactic acidosis. Because of vast functional reserve, basal lactate concentrations are usually within normal limits or only slightly increased (seldom over 2 mM) in patients with liver disease. A recent study of lactate metabolism in patients with alcoholic cirrhosis did not show a defect in hepatic extraction of lactate under basal conditions (72). Decreased hepatic reserve would be unmasked only when stressed by conditions that further decrease the capacity of the liver to extract lactate (such as ethanol) or increase the load of lactate delivered to the liver for reutilization (such as seizures). The occasional concomitant occurrence of hypoglycemia and lactic acidosis (73) supports the suggestion that reduced hepatic uptake of lactate could produce the combined abnormalities.

Although acid-base disturbances are common in patients with cirrhosis of the liver, pure metabolic acidosis due to lactic acidosis is relatively uncommon. In a recently published series of 91 patients with cirrhosis, five patterns of acid-base disturbances were described, two of which are of interest because of the presence of increased lactate concentrations (75). One group, with partially compensated respiratory alkalosis, consisted of 20 patients in whom there were modest elevations in blood lactate and pyruvate concentrations. There was an additional group of 15 patients with completely compensated respiratory alkalosis or frank metabolic acidosis in whom there was marked elevation of blood lactate and pyruvate concentrations (8 mM lactate for the completely compensated group and 16 mM lactate for those with metabolic acidosis). Overall, 35 of 91 patients or 38% demonstrated hyperlactatemia. The relation between increasing blood lactate concentrations and decreasing pH suggests that the development or intensification of lactic acidosis is responsible for these changes and that the differences between the two groups of patients may be primarily due to the intensity of the process or time, or both. The transition from respiratory alkalosis to metabolic acidosis is similar to that observed with sustained hypocapnia produced by mechanical hyperventilation in dogs (22). The mechanism that facilitates lactate accumulation to the point where it is associated with overcompensation is not known, but alkalosis due to persistent central hyperventilation, as discussed earlier, increases lactic acid production, facilitates its transport from the intracellular to the extracellular space, reduces hepatic lactate extraction, and decreases tissue oxygenation. Pathologic hyperventilation, with hypocapnia and alkalosis, has been associated with lactic acidosis in both animals and humans. In patients with liver disease, persistent hyperventilation and hypocapnia seem to be central elements for the development of lactic acidosis, much as they are in salicylate toxicity.

In a recently published series of 28 patients with fulminant hepatic failure metabolic acidemia was present in only four patients (75). Three of these patients had taken overdoses of paracetamol and the acidosis developed before the onset of hepatic failure and was associated with hypoglycemia and hypotension. If these patients are excluded, lactic acidemia was associated with hepatic failure in only one of 25 patients; yet elevated lactate concentrations were also common in this series, occurring in 25 of 65 measurements. Thus, lactic acidosis and hyperlactatemia are common, indicating an abnormality in lactate homeostasis; but lactic acidemia is infrequent, probably because of coexistent metabolic or respiratory alkalosis, or both.

**Hypoglycemia**

Lactic acidosis has occasionally been associated with hypoglycemia, usually in association with enzymic de-
feets in gluconeogenesis or glycogenolysis (13). For the most part this association is confined to pediatric patients and is genetic in origin, but it has also been noted occasionally in adults with either hepatic or renal disease (73, 76, 77). In these patients who are alcoholic or have hepatic disease, or both, the lactic acidosis was considered to be secondary to hypoglycemia as correction of the hypoglycemia resulted in resolution of lactic acidosis (73).

This is curious since it would make better sense if inhibition of lactate uptake was the primary abnormality. A defect in hepatic lactate and in alanine utilization would result in the development of both lactic acidosis and hypoglycemia because of decreased extraction of the major gluconeogenic substrates. In the patients with end-stage renal disease the development of hypoglycemia was also occasionally associated with lactic acidosis that improved upon correction of the hypoglycemia (76, 77).

Insight into the pathogenesis of this abnormality may be gained by consideration of the events that occur in infants with fructose diphosphatase deficiency. Under these circumstances, gluconeogenesis is inhibited because of a defect in a rate-limiting step of glucose synthesis. Inhibition of the conversion of 1,3-diphosphoglyceric acid to glyceraldehyde-3-phosphate results in the accumulation of NADH. Substrate oxidation of NADH by pyruvate increases lactic acid production and interferes with lactate utilization. The more reduced state of the hepatic redox couples is due to the accumulation of glyceraldehyde-3-phosphate, and the resultant inhibition of NADH reoxidation to NAD that is catalyzed by glyceraldehyde phosphate dehydrogenase. Hypoglycemia stimulates the release of counterregulatory hormones that ordinarily would augment glucose production but cannot because of the enzymic defect. The increased flux of 3-carbon glucose "precursors" into the pathway to pyruvate, in the presence of altered hepatic redox, accounts for the accumulation of lactate and the development of lactic acidosis. Thus, the administration of glucose corrects the hypoglycemia, suppresses the release of counterregulatory hormones that are responsible for the increased substrate flux, and corrects the altered hepatic redox, thereby permitting resolution of the lactic acidosis. In children with a deficiency of fructose diphosphatase, the reestablishment of normal pH and lactate concentrations after correction of hypoglycemia (78) would indicate that lactate disposal had occurred via extrahepatic routes. From a therapeutic standpoint the implications seem clear. When hypoglycemia coexists with lactic acidosis the acidosis may not be reversed unless the hypoglycemia is corrected and, at times, glucose may be all that is required.

Malignancy (Neoplasia)

Lactic acidosis has been occasionally associated with acute leukemia (usually lymphocytic, rarely myelocytic), or other advanced neoplasia (79, 80, 81, 82). In most instances the acute leukemia is massive and rapidly progressive but some patients may be in partial remission. The lactic acidosis has been attributed mostly to the overproduction of lactic acid by the tumor and appears to be related to the total body tumor burden. Accelerated aerobic glycolysis in tightly packed, poorly oxygenated marrow cavities has been suggested as the cause of the lactic acid overproduction. On some occasions lactic acidosis has been associated with almost complete replacement of the liver in patients with nonhematologic malignancies and, in these instances, it has been attributed to reduced hepatic lactate uptake. Hepatic arteriovenous or portal-hepatic vein differences have not been measured, however, so that production of lactic acid by the hepatic metastases has not been excluded. Interestingly, reduction of the tumor burden in patients with these disorders has been associated with improvement in the acidosis or reduced alkali requirements, or both. Although such patients often have huge bicarbonate requirements, the lactic acidosis may be chronic and reasonably well tolerated, which is clearly different from the usually fulminating course of this disorder. Acetate has been effectively utilized to generate bicarbonate and treat these patients, suggesting that the oxidative metabolism of non-tumor tissues is normal and that such tissues are not responsible for the development of lactic acidosis.

Phenformin

Phenformin-associated lactic acidosis has recently been reviewed in this journal (83) and will not be discussed. Lactic acidosis in diabetic patients, in the absence of other predisposing factors, virtually disappeared from our medical center since withdrawal of phenformin by the Food and Drug Administration. It obviously should no longer be a problem.

Salicylate

Toxic concentrations of salicylates are seldom of sufficient magnitude to account for more than a minor portion of the increased anion-gap seen in patients with salicylate-induced metabolic acidosis. Lactate is responsible for most of the increase in the anion-gap, and lactic acid is responsible for the metabolic acidosis (84). While the lactic acidosis might be attributed to the impaired electron transport by the cytochrome system and defective oxidative phosphorylation, which can be produced by salicylates, this seems unlikely. Metabolic acidosis occurs late in the time-sequence of events after an overdose of salicylate. If salicylic acid were directly responsible because of its acid properties or its effects on electron transport, metabolic acidosis would be expected at the outset when blood concentration of the drug would be maximum. Hyperventilation, due to direct stimulation of the respiratory center, with resultant respiratory alkalosis, is the primary abnormality in adults and metabolic acidosis is uncommon (85). In animals, if the hypocapnia associated with early hyperventilation is prevented, lactic acidosis does not develop. If hypocapnia is permitted to persist the initial respiratory alkalosis evolves to a mixed acid-base disorder and finally to a pure metabolic acidosis, which is due to the accumulation of lactic acid (84).

Treatment

In most patients the onset of lactic acidosis is abrupt,
and prompt appropriate therapy is required for a successful outcome. In patients with severe heart disease development of lactic acidosis may be more insidious, and there may not be an overt change in cardiac status. When lactic acidosis accompanies malignancy or enzymic defects, the acidosis is chronic and fairly well tolerated over protracted periods.

The most important aspect of the therapy of lactic acidosis is to identify and correct predisposing factors. Where lactic acidosis is associated with hemorrhage, hypovolemia, sepsis, trauma, or a primary alteration of cardiovascular function, or all of these, identification of these factors usually is not difficult and they may even be correctable. Occasionally the clinical evaluation of patients is misleading and does not suggest the presence of a low flow state when tissue oxygenation is in fact impaired. The clinical assessment of tissue perfusion is notoriously inaccurate, and subtle abnormalities in perfusion and oxygenation may not be obvious. Recovery is usually limited by the underlying disorder (that is, myocardial infarction, sepsis, and so forth). The appropriate use of inotropic and vasoactive agents, fluids, colloid, blood, and adequate quantities of bicarbonate is indicated, as intractable and progressive acidosis has an adverse effect on cardiovascular and pulmonary function. Unfortunately, early and accurate assessment does not guarantee success because remedies for some problems are not available. Under these circumstances, treatment of metabolic acidosis is seldom more than a temporizing measure. Frequently a delay in diagnosis permits a potentially reversible problem to become irreversible. As previously discussed, when lactic acidosis coexists with hypoglycemia, correction of hypoglycemia may be all that is necessary.

In idiopathic lactic acidosis and with lactic acidosis associated with drugs or toxic agents, cardiovascular function is usually preserved initially. With protracted or intractable acidosis, myocardial contractility fails, tissue perfusion and oxygenation become inadequate, and the undesirable adverse effects of the low-flow state are realized. The aggressive use of bicarbonate at the onset to maintain hemodynamic stability and performance is warranted but can quickly become a double-edged sword, producing a variety of adverse developments such as volume overload, worsening acidosis, and rebound alkalosis.

Theoretically enhanced lactic acid production is an additional complication associated with the use of bicarbonate and alkalization (83). As pH rises and glycolysis is increased, lactic acid production is facilitated, which may explain the transiently unchanged or rising lactate concentrations seen in successfully treated patients. On the other hand, lactate removal and utilization by the liver, as previously discussed, are also pH dependent and would also be expected to improve. Thus, even if lactate production by peripheral tissues were increased, it would be accompanied by and perhaps offset by enhanced hepatic lactate extraction. The use of bicarbonate to treat experimental phenformin-induced lactic acidosis in diabetic dogs was accompanied by a worsening acidosis and 100% mortality. By contrast, the use of DCA to inhibit lactic acid production was associated with decreased acidosis and 67% survival (86). At present, the dilemma of whether to use or not to use bicarbonate is unresolved. Nonetheless, in the absence of specific therapy and when there cannot be a reasonable expectation for recovery without the use of bicarbonate, withholding it seems irrational.

**Dichloroacetate**

A new area of research of potential importance in the therapy of lactic acidosis involves dichloroacetate (DCA), a chemical that activates PDH in skeletal muscle, myocardium, adipose tissue, kidney and liver, thereby promoting the oxidation of glucose, pyruvate, and lactate (68, 87, 88). In the starved and diabetic rat, DCA reduces the blood glucose, pyruvate, and lactate concentrations (68). Facilitation of the metabolism of pyruvate and lactate in extrahepatic tissues reduces their release and availability to the liver for gluconeogenesis. Similar changes have been reproduced by the administration of DCA to patients with diabetes mellitus (89). Dichloroacetate inhibits hyperlactatemia produced in dogs by phenformin (90, 91), strenuous muscular work, and catecholamines (91) and in rats treated with phenformin, galactosamine, and fructose (92, 93). Dichloroacetate will block the increase in blood lactate concentrations that occur in insulin-treated rats with diabetic ketoacidosis (68). It does not inhibit lactic acidosis produced by hypoxia (92) and thus does not appear to be great potential for its use in lactic acidosis related to inadequate tissue oxygenation, where restoration of blood flow would be essential. Unfortunately, DCA is associated with neurologic complications that currently prohibit its use in human subjects (94). Nonetheless, DCA is an exciting agent with tremendous research potential with regard to defining the pathophysiology of lactic acidosis and disorders of lactate homeostasis.

**Vasodilator Agents**

Vasoactive drugs that reduce peripheral vascular resistance and improve tissue perfusion may be valuable in lactic acidosis. The accumulation of lactic acid in dogs subjected to controlled hemorrhage, who appear hemodynamically intact, has been attributed to subtle alterations in tissue perfusion that are not detectable by clinical assessment or hemodynamic measurements. Whether this occurs in patients who have “idiopathic” lactic acidosis is not known. The use of vasodilator agents could theoretically reverse the metabolic trend simply by decreasing resistance and restoring tissue perfusion. Nitroprusside has been successfully utilized in a single patient to reverse heart failure and metabolic acidosis that was intractable to otherwise aggressive management (95). In most situations such drugs will be effective because they improve cardiac or respiratory performance, or both, and only secondarily improve tissue oxygenation. Nonetheless, a direct effect on tissue perfusion, independent of changes in cardiac function, is a possibility. Excessive and uncontrolled vasodilation could worsen acidosis by decreasing tissue perfusion and oxygenation.
Dialysis

Hemodialysis and occasionally peritoneal dialysis may be useful in managing patients with phenformin-associated lactic acidosis and perhaps others who develop sodium and volume overload (83). The concept that dialysis corrects the acidosis by removing hydrogen ions or lactate is unreasonable. Removal of lactate, however, can minimize or prevent the rebound alkalosis that commonly occurs with lactate reutilization after correction of the acidosis with bicarbonate or acetate. The acidosis is corrected by restoration of the buffer pool with the addition to body fluids of bicarbonate or a substrate (acetate) that is converted to bicarbonate. The fact that acetate can, under these conditions, correct the acidosis indicates that oxidative pathways are largely intact and this should indicate something about the nature of the defect(s) leading to lactic acidosis in these patients. More recently, peritoneal dialysis with a specially formulated dialysate containing bicarbonate instead of lactate has been successful in the treatment of lactic acidosis (96). This approach permits the addition of bicarbonate to body fluids while simultaneously controlling volume and preventing overload.

Requests for reprints should be addressed to Robert A. Kreisberg, M.D.; 236 bicarbonate instead of lactate has been successful in the dialysis with a specially formulated dialysate containing treatment of lactic acidosis (96). This approach permits the addition of bicarbonate to body fluids while simultaneously correcting the acidosis. A change to bicarbonate. The fact that acetate can, under these conditions, correct the acidosis indicates that oxidative pathways are largely intact and this should indicate something about the nature of the defect(s) leading to lactic acidosis in these patients. More recently, peritoneal dialysis with a specially formulated dialysate containing bicarbonate instead of lactate has been successful in the treatment of lactic acidosis (96). This approach permits the addition of bicarbonate to body fluids while simultaneously controlling volume and preventing overload.

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