Metabolism

LACTIC ACIDOSIS

MEDICAL GRAND ROUNDS

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HISTORICAL CONSIDERATIONS

Lactic acid was first isolated from sour milk by Scheele in 1780. Subsequently, lactic acid was identified in muscle by Breselius in 1807. However, the role of lactate in carbohydrate metabolism in vivo was not appreciated until the nature of glycolysis was described first by Bernard in 1877. Subsequent to Bernard's description, major work in the area of glycolysis was contributed by Lapine in 1909, Fletcher and Hopkins in 1906, Warburg in 1923, Hill in 1927, and Meyerhof in 1930. At about the time that glycolysis was being described, clinical observations by several investigators described the presence of diabetic coma with acidosis in patients who had no ketone bodies present in their urine.

The modern era of interest in lactic acidosis began with the studies of Huckabee (1-3) who carried out a systematic examination of lactate and pyruvate concentrations in a number of hospitalized patients with a wide variety of illnesses. Huckabee classified hyperlactatemia into three groups: Group I consisted of patients with an elevated lactate but a proportionately elevated pyruvate so that the lactate/pyruvate ratio remained normal. These patients did not exhibit a significant acidosis. The second group of patients, Huckabee's Group IIA, had classical lactic acidosis secondary to either recent hypoxia of fairly severe intensity or circulatory failure. The third group, Huckabee's Group IIB, included patients with lactic acidosis of no apparent etiology. As we shall see this classification scheme has been modernized and replaced with two categories: lactic acidosis Type A and Type B.

CHEMICAL AND PHYSICAL PROPERTIES OF LACTIC ACID

The chemical formula for lactic acid is $C_3H_6O_3$. It has a molecular weight of 90.08 and is a relatively strong acid with a pKa at 25° of 3.79. This pKa insures that virtually all lactate in physiologic fluids is present as the lactate anion. There are two optical isomers of lactic acid, the L and the D form. The L form is the normal metabolite in mammals, although the D form has been shown to be metabolized by various mammalian tissues (4-6). In man, D lactic acid is very slowly metabolized compared with the L isomer (7).

Although more detailed discussion of glycolysis will follow, it should be pointed out that lactic acid is not the product of anaerobic glycolysis. Table I lists the two reactions occurring in anaerobic glycolysis. In the first reaction, glucose plus ADP and inorganic phosphate yields two molecules of lactate, 2 ATPs and water. The protons from anaerobic glycolysis are actually derived from the second equation which illustrates the hydrolysis of ATP into ADP, inorganic phosphate, and a proton. Thus, for the appearance of lactic acid in the extracellular fluid, both lactate and protons must leave the cells in which they are manufactured. Although much is known about the metabolic production and fate of lactate much less is known about the transport of lactate into and out of various cell types.

Lactate transport has been characterized in two cell types. First, in red blood cells, there is a specific anion transporter that excretes a proton with each lactate (8). The proton gradient from inside the red cell to outside is maintained by a chloride-bicarbonate exchanger. Therefore, when chloride enters the red blood cell and bicarbonate ions move out the proton gradient stimulates lactate excretion from the cell. When chloride ions leave the red blood cell and the intracellular milieu becomes

TABLE I

ORIGIN OF H^+ IN ANAEROBIC GLCOLYSIS

1. $C_6H_{12}O_6 + 2ADP^{3-} + 2Pi^{2-} \rightarrow 2CH_3CHOHCOO^- + 2ATP^{4-} + 2H_2O$

2. Hyrolysis of ATP:

$$RCH_2OPOPOPO^{-} + H_2O \rightarrow RCH_2OPOPO^{-} + HOPO^{-} + H^+$$

(O⁻ O⁻ O⁻ on the left; O O O on the left; O⁻ O⁻ on the first product; O⁻ on the second product; O O on the first product; O on the second product)

more alkaline lactate excretion is inhibited. The second cell type in which lactate transport has been examined is the Erhlich-ascites tumor cell (9). The lactate/H^+ symport mechanism in the Erhlich-ascites tumor cell is very similar to that of the red blood cell. It is unclear, mostly due to lack of effort to examine this question, whether lactate transport in other cells involves a similar mechanism. Although the lactate anion and the small amount of lactate that exists in the form of lactic acid can diffuse across cell membranes, the magnitude of this process is unknown. Because of the extremely low concentration of lactic acid in normal body fluids the role of nonionic diffusion in lactate transport is minimal despite claims to the contrary (10).

It is of interest that recent studies on muscles stimulated to accumulate lactate and then observed for the rates of lactate and proton efflux from the cells demonstrate a time lag between the efflux of protons and the efflux of lactate from the muscle cell. The differing kinetics of proton and lactate efflux suggest that their transport is not tightly coupled (11).

MEASUREMENT OF BLOOD LACTATE LEVELS

Normal levels of lactate in human subjects range between 0.4 and 1.5 mM. However, it should be noted that there are at least three ways in which to obtain falsely high measurements. First, drawing venous blood with a tourniquet and thus promotion of venous stasis will result in blood lactate levels that are falsely high. Second, even blood drawn without stasis but from a subject who is standing or contracting trunk muscles while holding an arm stationary will result in blood lactate levels 2 to 3 times normal. Finally, after collection of blood it should be put on ice immediately or mixed with cold prochloric acid immediately to prevent continued release of lactate derived from red and white blood cell glycolysis.

LACTATE METABOLISM

Lactate is produced and consumed in only one biochemical reaction:

(1) $(\text{Pyruvate}^-) + \text{NADH} + \text{H}^+ \rightleftharpoons (\text{Lactate}^-) + \text{NAD}^+$

Since this reaction is normally close to the equilibrium it can be rearranged to:

$$(2)\quad [\text{Lactate}^-] = K \times \frac{[\text{Pyruvate}] \times [\text{NADH}] \times [\text{H}^+]}{[\text{NAD}^+]}$$

where K is the equilibrium constant. If we rearrange equation 2:

$$(3)\quad \frac{[\text{Lactate}^-]}{[\text{Pyruvate}^-]} = K \times \frac{[\text{NADH}]}{[\text{NAD}^+]} \times [\text{H}^+]$$

Thus, the lactate to pyruvate ration (which is normally 10) is a direct function of the NADH/NAD^+ ratio or the oxidation reduction potential of the cell. These equations predict two major points:

1. Cytosolic lactate$^-$ concentration is a function of the oxidation reduction (redox state) of the cell--NADH/NAD.

2. Cytosolic lactate$^-$ concentration is a function of the pyruvate$^-$ concentration. Pyruvate, of course, is a compound that is central in intermediary metabolism and is produced or consumed by several reactions. Figure 1 schematically summarizes these reactions.

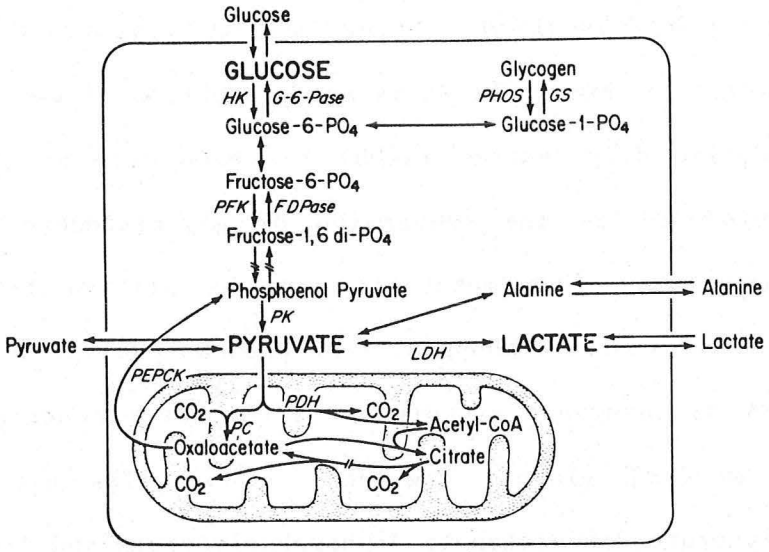

Figure 1. Schematic outline of metabolic pathways for interconversion of glucose and lactate in a cell of the liver or the proximal renal tubule. Abbreviations: HK, hexokinase, G-6-Pase, glucose-6 phosphatase; PHOS, phosphorylase; GS, glycogen synthetase; PFK, phosphofructokinase; FD Pase, fructose diphosphatase; PK, pyruvate kinase; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; PC, pyruvate carboxylase; PEPCK, phospho-enol, pyruvate carboxykinase.

Lactate production rates in normal man are approximately 15-20 mEq$\cdot$ kg$^{-1}\cdot$day^{-1} (12). Compare this with the total amount of nonskeletal buffer

readily available which is 10-15 $mEq \cdot kg^{-1}$ and with normal net acid excretion by the kidney which is approximately 1 $mEq \cdot kg^{-1} \cdot day^{-1}$. Thus, enough lactate is normally produced to totally deplete extracellular buffer and to exceed by over 15-fold the kidney's normal acid excretion. These observations point to the obvious importance of the metabolism of lactate to maintain acid-base balance. It is interesting to note that normal proton production is approximately 150 moles per day. In fact proton turnover in the normal human exceeds that of any metabolite. As is true for the case of lactate, the production and consumption of protons are normally very closely matched.

As shown in Figure 1, the enzymes involved in anaerobic glycolysis are located in the cell cytoplasm. There are two important results of the anaerobic glycolytic pathway. First is the production of two moles of reduced nicotinamide adenine dinucleotide (NADH) for each mole of glucose degraded. The NADH is produced in the conversion of glyceraldehyde 3-phosphate to 1,3-diphosphoglycerate. This metabolic step is omitted from figure 1 but occurs between fructose 1,6 diphosphate and phospho-enol pyruvate. The second important result of anaerobic glycolysis is the net production of 2 moles of ATP for each mole of glucose degraded. These ATPs are generated from 1,3-diphosphoglycerate conversion to 3-phosphoglycerate and from phospho- enol pyruvate conversion to pyruvate.

There is marked tissue heterogeneity in the glycolytic capacity. Table II illustrates the glycolytic capacity of various tissues expressed as microliters of CO_2 displaced by acid formation in the bicarbonate buffer per mg of dry tissue in 1 hr at 37°C.

Figure 2 illustrates the normal daily lactate production as a function of tissue type in man. Note that the major producers of lactate include the skin 29%, red blood cells 24%, brain 17%, muscle 16% and gastrointestinal mucosa 8%.

TABLE II

THE GLYCOLYTIC CAPACITY OF VARIOUS RAT TISSUES EXPRESSED AS MICROLITERS OF CO_2 DESPLACED BY ACID FORMATION IN A BICARBONATE BUFFER PER mg OF DRY TISSUE IN 1 HR AT 37°C

Tissue	Q_M	Tissue	Q_M
Kidney		Intestinal mucosa	14
(1) cortex	3	Adrenal gland	4
(2) medulla	28	Pituitary gland	13
Liver	3	Red cell	0·35
Brain cortex	18	Leukocyte	22
Retina	88	Platelets	26
Lung	10	Skin	7
Spleen	8		

From Cohen and Woods, 1976.

In contrast to the distribution of tissues which produce lactate, outlined on Figure 3 are the normal tissue lactate uptakes as a percent of daily total. The liver, kidney, and heart are responsible for virtually all lactate uptake.

Lactate can have several fates (Figure 4). First, lactate can be a substrate for gluconeogenesis. This, of course, first requires its conversion to pyruvate. Gluconeogenesis is a function of only the liver and kidneys. The second possible fate of lactate is oxidation via the tricarboxylic acid cycle to carbon dioxide and water. This fate also first requires the conversion of lactate to pyruvate. The rate at which lactate is oxidized via the tricarboxylic acid, however, is critically dependent on the activity of the enzyme pyruvate dehydrogenase (see Figure 1). Pyruvate dehydrogenase is a mitochondrial enzyme which is reversibly inactivated by a phosphorylation step via a specific pyruvate dehydrogenase kinase and reactivated via dephosphorylation by a specific pyruvate dehydrogenase phosphatase (14). The enzyme is also inhibited by acetyl CoA (15).

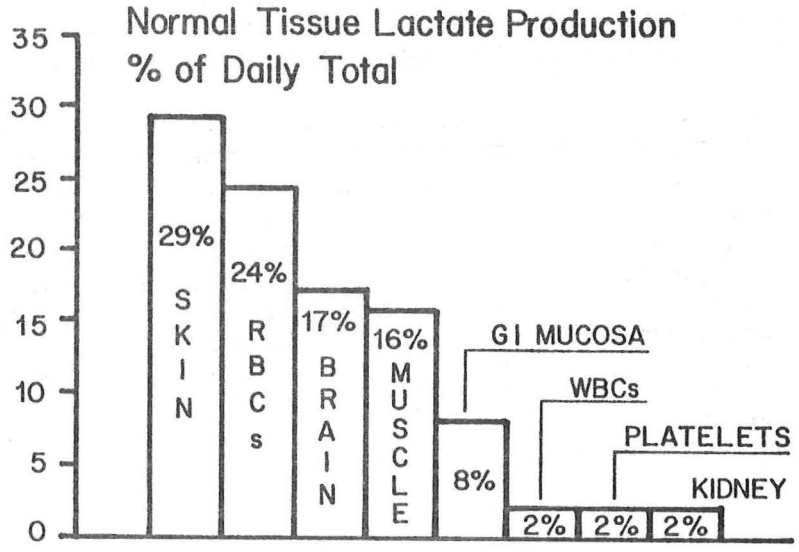

Figure 2

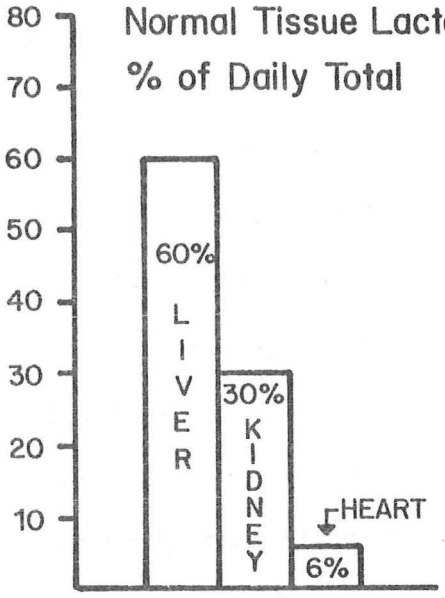

Figure 3

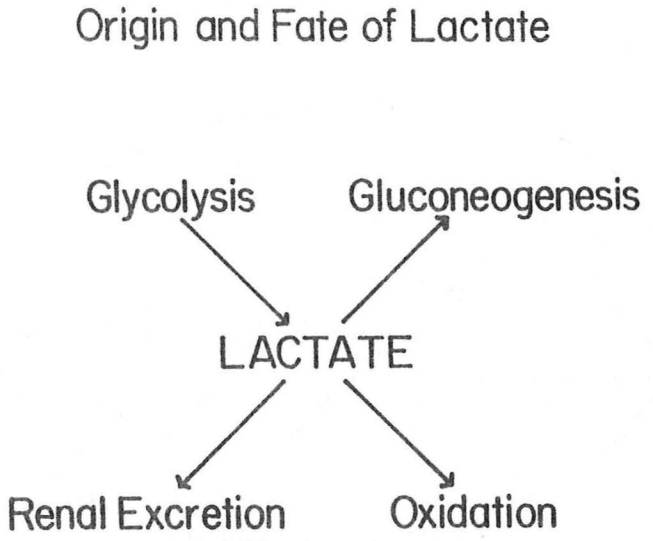

Figure 4

The third possible fate of lactate applies only to the kidney and that is renal excretion. Normal urinary lactate excretion is less than 1 mM and therefore constitutes less than 1/2 to 1/3 of 1% of the daily turnover.

Thus, combining both the production and utilization of of lactate we in essence describe the Cori cycle (Figure 5).

LABORATORY DIAGNOSTIC CONSIDERATIONS

Before discussing the pathophysiology and clinical features of lactic acidosis, it is appropriate to review some aspects of differential diagnosis of acid-base disorders. Lactic acidosis is a classical example of an increased anion gap acidosis. It should be recalled that the anion gap represents the presence in the serum of negative charges that are not measured by the usual laboratory tests. Under normal circumstances these unmeasured anions represent the negative charge on serum proteins, organic anions such as lactate, citrate, acetate, pyruvate, and ketone bodies, and divalent anions

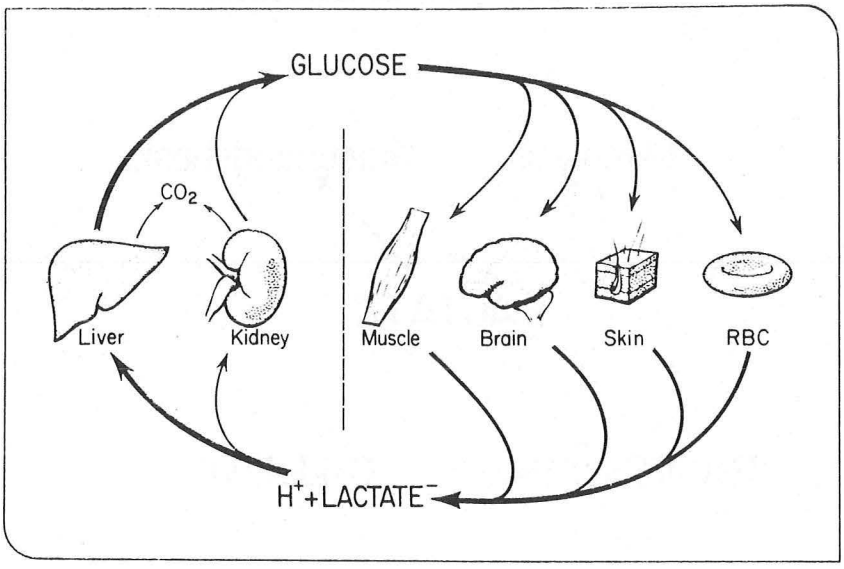

Figure 5. Schema of the Cori cycle. Glucose is converted by glycolyzing tissues to lactic acid, which is then reconverted to glucose (or oxidized to CO_2) by the liver and the kidney cortex.

such as sulfate. The usual calculation of the anion gap is accomplished by subtracting the sum of the chloride and bicarbonate concentrations from the sodium concentration as determined by the measurement of serum electrolytes. Even though phosphate is ordinarily measured on most automated blood chemistry analyses, note that the method of calculating the anion gap includes phosphate as an unmeasured anion. Figure 6 schematically summarizes the ionic anatomy of serum.

When there is addition of strong acid to body fluids, sodium bicarbonate and extracellular fluid is consumed and the bicarbonate is replaced with the anion from the strong acid. As illustrated in Figure 7 this reaction is responsible for the generation of a high anion gap acidosis. It should be noted that lactic acidosis is only one of numerous causes of an increased anion gap.

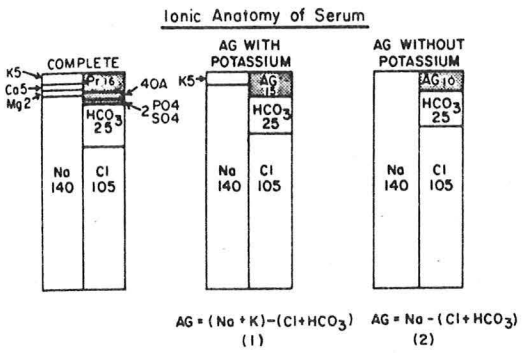

Figure 6. Normal serum electrolyte pattern and the calculation of the anion gap (AG). OA: organic acids. Pr: proteins. Numbers refer to serum concentration in mEq/L. From Emmett M, Narins RG. Medicine 56:38-54, 1977

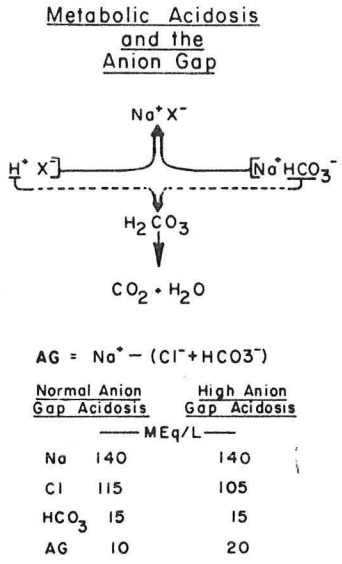

Figure 7. Schematic view of the effect of strong acids on the serum electrolyte pattern. From Emmett M, Narins RG. Medicine 56:38-54, 1977.

Table III summarizes the differential diagnosis of disorders producing a high anion gap metabolic acidosis. The present review will not deal any further with high anion gap acidoses other than lactic acidosis.

TABLE III

CAUSES OF A HIGH ANION GAP
METABOLIC ACIDOSIS

1.	Lactic acidosis
2.	Uremia
3.	Ketoacidosis
4.	Salicylate intoxication
5.	Methanol ingestion
6.	Ethylene glycol ingestion
7.	Paraldehyde ingestion

Although there is some disagreement in evaluation of published reports of lactic acidosis unaccompanied by shock, there appears to be a trend for the blood lactate level in mM/L to exceed the anion gap. This is graphically represented in Figure 8. It is apparent from this figure that in the majority

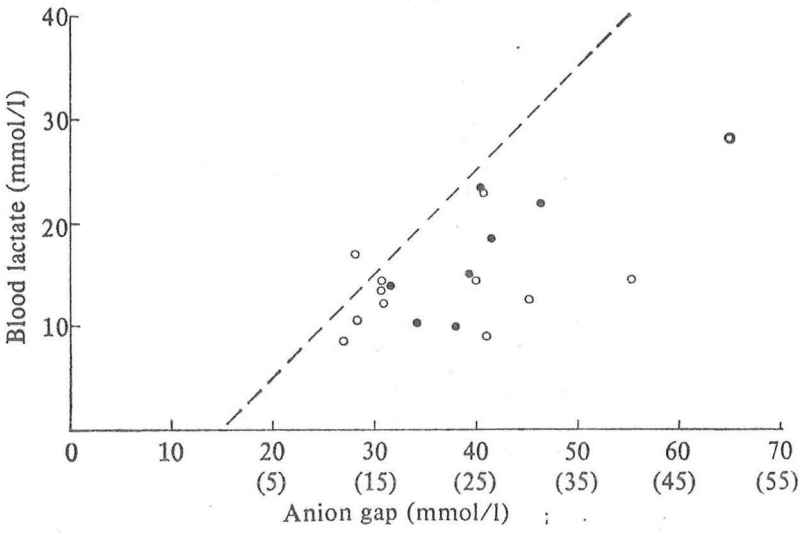

Figure 8. Relation between plasma anion gap and blood lactate. On the abscissa the figures in parentheses are increments in anion gap above the mean normal value, calculated as (measured anion gap--15). The dotted line is the line of equality between the increment thus calculated and the blood lactate. From Cohen & Woods, 1976, p. 62.

of patients the anion gap exceeded the measured blood lactate level. The reason behind this descrepancy between anion gap and blood lactate level is not totally clear.

It should be noted that plasma protein concentration and the titration of plasma proteins in response to pH changes effect the magnitude of the anion gap (Table IV). It is evident that acidification of plasma results in a decrease in the anion gap attributable to the negative charge of serum protein (17). A possible contributor to the observed difference between the anion gap and the plasma lactate levels in lactic acidosis could be the effects of lactic acidosis on serum phosphorous level.

TABLE IV

ROLE OF PLASMA PROTEIN CONCENTRATION
AND TITRATION OF PLASMA PROTEINS
IN THE ANION GAP

1.	Net negative charge assuming A/G ratio of 1.6 is 2.41 meq/liter per g% of protein.
2.	Between pH 6.8 and 7.8 Δcharge per gram of protein is 0.11 meq/liter per pH unit. Therefore, if plasma pH increases from 7.4 to 7.8 and serum protein is 6 g% (60 g/liter), then Δcharge is 0.4 x 0.11 x 60 or 2.64 meq/liter.

Lactic acidosis as well as other organic acid acidoses such as beta hydroxy, butyric acidosis, produce a significant increase in plasma phosphorous concentration. Figure 9 from Reference 18 illustrates experimental metabolic acidoses of several types in dogs. It is apparent that the infusion of an

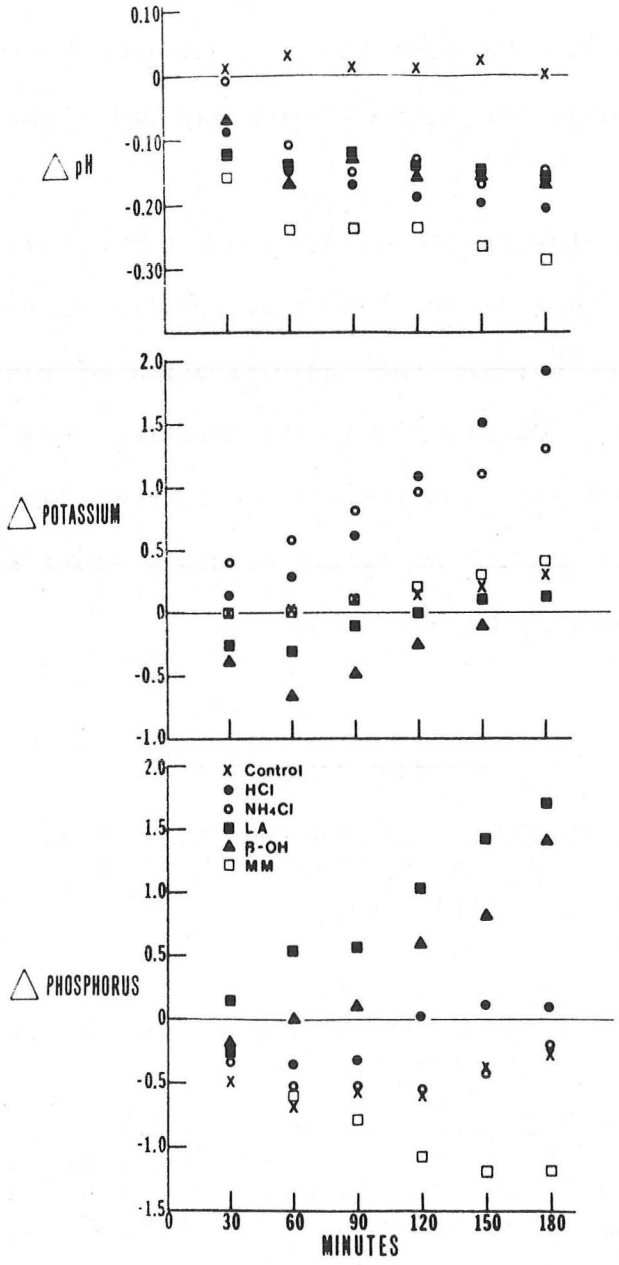

Figure 9. Change in pH, serum $[K^+]$, and serum $[PO_4^=]$ in response to the infusion of several different acids. From Oster et al, 1978.

organic acid results in a significant elevation of the serum phosphorous in contrast to the effects observed when hydrochloric acid or ammonium chloride are infused. It should be noted that at the 180 min time of acid infusion in these studies the arterial blood pH was 7.1 in the hydrochloric-acid-infused and 7.16 in the lactic-acid-infused animals. In support of these animal studies are clinical observations of an inordinate increase in serum phosphate in lactic acidosis as compared to diabetic ketoacidosis (Figure 10) (19).

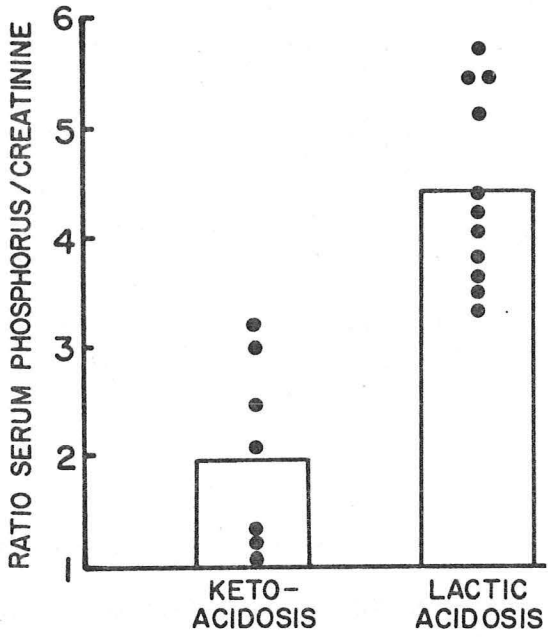

Figure 10. Calculated ratio of serum inorganic phosphate (phosphorus) to serum creatinine for all patients studied. From O'Connor et al, 1977.

In addition to the apparent trend of lactic acidosis to be associated with an anion gap higher than the expected value from serum lactate measurements there is a trend for the plasma CO_2 tension to be inappropriately low. Table 5 summarizes certain rules of thumb with respect to blood gases in patients with acute metabolic acidosis (20).

A final feature thought to be somewhat characteristic of lactic acidosis is the absence of significant hyperkalemia in this disorder as compared to other metabolic acidoses (21,22). Figure 11 demonstrates the effects of various forms of acute metabolic acidosis in the dog on plasma potassium concentration. As can be seen there is a major increase in serum potassium

TABLE V

RULES OF THUMB IN BLOOD GASES
OF PATIENTS WITH ACUTE METABOLIC ACIDOSIS

Assume metabolic acidosis reduces serum [HCO_3] to 10 mm; then:

1. pCO_2 in mmHg = (1.5 HCO_3 + 8) ± 2
   or = 23 ± 2

2. ΔpCO_2 = 1.0 to 1.2 × $\Delta[HCO_3]$
   or = 22 to 25

3. pCO_2 = last two digits of pH (7.24)
   or = 24 (7.24 = 6.1 + log 10/0.72)

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with hydrochloric acid and ammonium chloride induced metabolic acidosis while lactic acidosis and acidosis induced by methylmalonic acid are not associated with a change in plasma potassium.

PATHOPHYSIOLOGY OF LACTIC ACIDOSIS

As will be discussed in more detail later, lactic acidosis is classified into Type A and Type B depending upon the presence or absence of shock. While the various disorders associated with lactic acidosis have their unique features, it is clear that the development of lactic acidosis has common features in all clinical circumstances. Development of lactic acidosis is inevitable when lactate production exceeds lactate utilization. This can be accomplished by either a primary reduction in metabolic production of lactate or a primary reduction in the metabolic clearance of lactate. In many clinical circumstances lactic acidosis results from a combination of both increased production and decreased clearance. Figure 12 schematically

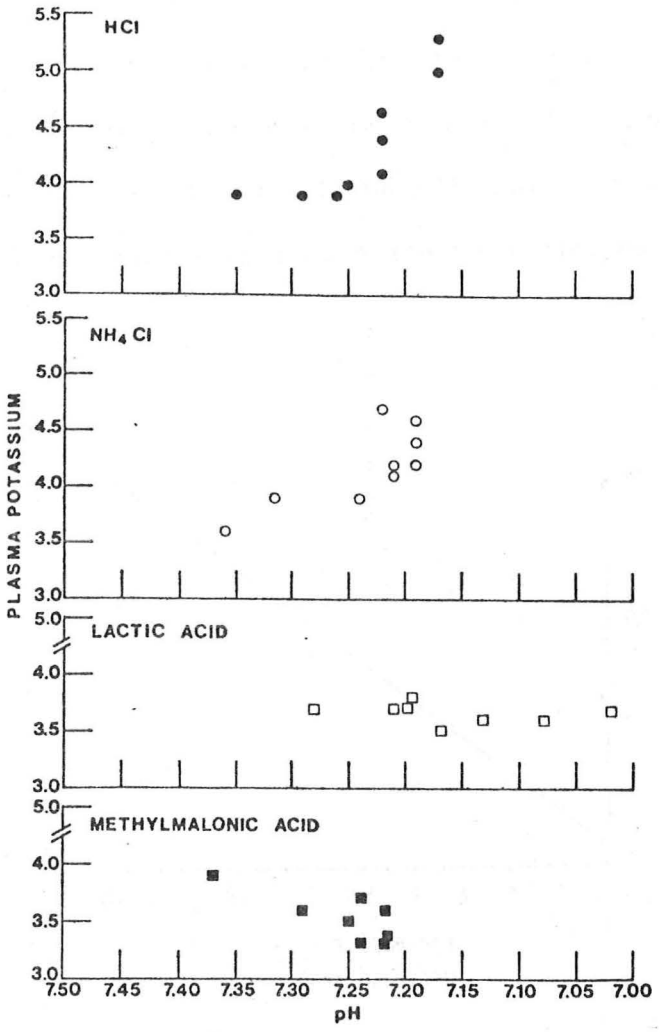

Figure 11. Typical response of plasma potassium to experimentally-induced metabolic acidosis in individual dogs. 3-hour infusion of the mineral acids HCl and NH_4Cl resulted in progressive increments in potassium whereas administration of the organic acids lactic acid and methylmalonic (and beta-hydroxybutyric -- not shown) did not result in increases in potassium and, in fact, produced initial decreases in the majority of animals. From Peretz et al, 1981.

summarizes these considerations. Depending on the specific etiology of the lactic acidosis the change in lactate synthesis can be found in several

tissues including, as we shall see, neoplastic tissue. However, any effect of a change of lactate clearance is predominantly a manifestation of changes in hepatic or renal lactate metabolism. Documentation for increased lactate and hydrogen ion production for a specific clinical circumstance or tissue would require measurement of regional blood flow to the tissue and the determination of arterial-venous lactate concentration differences. A few such studies are available in man.

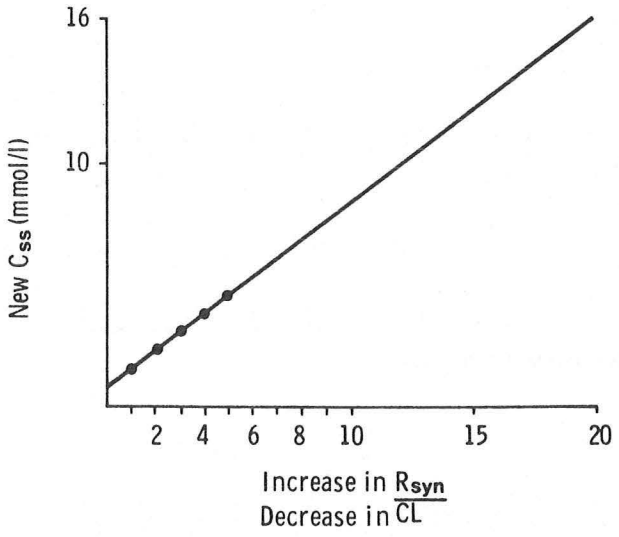

Figure 12. The effect of increasing the synthesis rate, or decreasing the clearance, of lactate on the steady-state lactate concentration in blood. The graph shows the new steady-state lactate concentration (C_{ss} in mmol l^{-1}) resulting either from a progressive increase in synthesis rate (R_{syn}) when the clearance (Cl) is kept constant, or from a progressive decrease in CL when R_{syn} is kept constant. The figures on the x axis represent the factor by which R_{syn} is increased or CL is decreased in the calculation.

Table VI summarizes some data on the effects of burns and sepsis on limb lactate production. As can be seen, measurements of lactate turnover in

TABLE VI

EFFECTS OF LIMB BURN AND SEPSIS ON PERIPHERAL METABOLISM

	Control[a] *(n = 4)*	*Burned*[a] *(n = 8)*	*Septic (n = 6)*
Limb blood flow ($ml \cdot 100\,ml\ limb^{-1} \cdot min^{-1}$)	2.62 ± 0.23	8.71 ± 0.68	6.07 ± 0.68
Systemic lactate concentration ($mg\ 100\,ml^{-1}$)	11.6 ± 2.1	15.8 ± 2.9	19.6 ± 4.1
Limb O_2 consumption ($ml \cdot 100\,ml\ limb^{-1} \cdot min^{-1}$)	0.124 ± 0.036	0.275 ± 0.039	0.110 ± 0.019
Systemic O_2 consumption ($ml \cdot m^{-2} \cdot min^{-1}$)	126 ± 3	255 ± 13	147 ± 15
Lactate production ($mg \cdot 100\,ml\ limb^{-1} \cdot min^{-1}$)	0.017 ± 0.059	0.197 ± 0.071	0.138 ± 0.014
Glucose uptake ($mg \cdot 100\,ml\ limb^{-1} \cdot min^{-1}$)	0.105 ± 0.36	0.236 ± 0.08	0.332 ± 0.08

From Burns et al: Metabolic acidosis in the critically ill. Metabolic Acidosis. Ciba, Pitman, Great Britain, 1982, pp. 293-306.

forearm muscle of patients demonstrate that in 6 septic patients the lactate production increased over 800% above control and even more impressively in burned limbs, the lactate production was increased by almos_ 1200% above control. Similarly, shown on Table VII are measurements of lactate concentrations at the level of the renal vein, hepatic vein, lower inferior vena cava, and aorta, which demonstrate that at times both the kidney and the liver may contribute to the development of lactic acidosis in shock. Note that in some patients in this study the liver and the kidney, which normally are responsible for clearing lactate, actually provide additional lactate to the circulation. We will discuss the role of the liver in more detail subsequently.

TABLE VII

TOTAL REGIONAL LACTATE METABOLISM IN SHOCK IN MAN

Sampling sites	Relative lactate concentrations
Renal vein (RV) & Aorta (A)	RV > A in 4 out of 8
Hepatic vein (HV) & Aorta (A)	HV > A in 2 out of 4
Low inferior vena cava (IVC) & Aorta (A)	IVC > A in 3 out of 3

(From Sriussadaporn & Chon, 1968.)

It has long been appreciated that there is an increase in lactate production in response to primary hypocapnia (24-28). While in dogs exposed to prolonged hyperventilation and severe degrees of hypocapnia the elevation in plasma lactate concentration and the associated proton production actually resulted in overcompensation of the respiratory alkalosis and the development of a significant metabolic acidosis (24), this has never been a convincing etiology for clinically significant lactic acidosis in man. This well-known observation of lactate generation in response to hypocapnia is a result of pH effects on the activity of the enzyme phosphofructokinase. In intact cells or cell-free systems phosphofructokinase demonstrates a marked pH sensitivity (29-31). Figure 13 summarizes the effect of ATP concentrations on phosphofructokinase activity at various pHs (30). Activity of phosphofructokinase is normally inhibited by low concentrations of ATP. It is evident from this figure that increasing pH markedly blunts the inhibitory effect of ATP on phosphofructokinase activity. It is believed that this general reaction is an adaptive response of intermediary metabolism to maintain cell pH when pCO_2 falls. In healthy humans voluntary hypoventilation to pCO_2 levels of 20 mm Hg are accompanied by elevations of blood lactate levels but only to levels

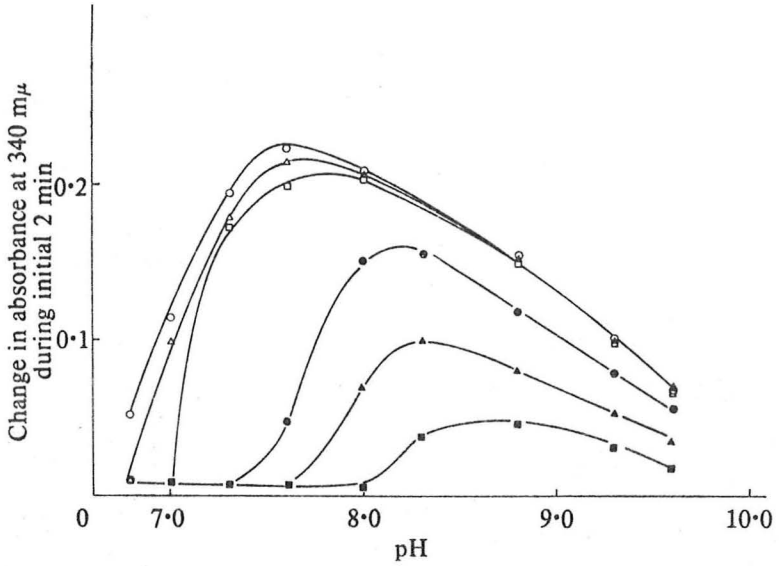

Figure 13. Effect of pH on rat skeletal muscle phosphofructokinase activity in vitro at various concentrations of ATP. o——o, 0·1 mmol/l ATP; ●——●, 3 mmol/l ATP; ■——■, 8 mmol/l ATP. Other symbols represent intermediate concentrations of ATP (From Ui, 1966).

of approximately 2 mM (32). In patients with acute illnesses such a stroke and pulmonary emboli, as well as more chronic illnesses like Wernicke's encephalopathy, the associated prolonged pathologic hyperventilation is accompanied by elevations of blood lactate level to as high at 22 mM (33,34). Thus, as mentioned above, there is no evidence that significant metabolic acidosis can result as overcompensation for hypocapnia.

There are two commonly observed situations in which transient lactic acidosis may occur that is clinically not significant. These include strenuous exercise and seizures. Figure 14 summarizes the time course of blood lactate concentration and arterial pH and pCO_2 at rest and during recovery from 1 min of maximal exercise. As can be seen from this figure, a very significant elevation of blood lactate and reduction of arterial pH is observed in normal healthy humans undergoing maximal exercise. Restoration of normal pH, pCO_2, and lactate concentrations occur rapidly but still require a significant period of time.

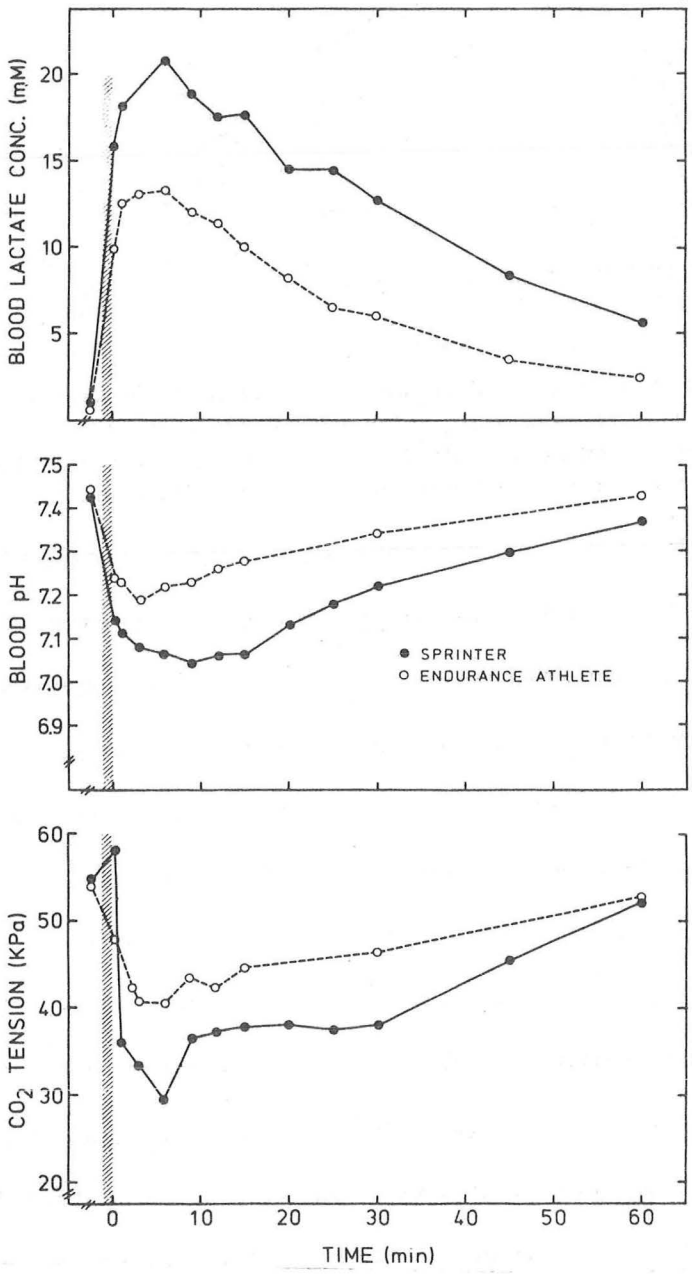

Figure 14. Time-course of blood lactate concentration, arterial pH and pCO_2 at rest and during recovery (from time 0) from 1 min of maximal exercise.

A similar observation can be found in the setting of seizures. Table VIII summarizes data from a study by Oringer et al (35). As with subjects undergoing maximal exercise, seizures can result in a major increase in blood lactate and a reduction in arterial pH with restoration of both to normal levels within one hour post-seizure.

TABLE VIII

SEIZURE-INDUCED LACTIC ACIDOSIS

	Time			
	0	15	30	60
pH	7.14	7.24	7.31	7.38
Na^+	140.0	138.0	137.0	137.0
K^+	3.8	3.8	3.9	3.9
Cl^-	99.0	98.0	98.0	98.0
HCO_3^-	17.1	17.5	20.0	23.6
Lactate	12.7	8.9	9.5	6.6
Anion Gap	25.0	22.0	18.0	14.0

From: Orringer, et al. NEJM 297:796-799, 1977

As mentioned earlier, both the liver and kidney are the major organs responsible for clearance of a lactate load. In experimental studies of the contribution of the kidney to removal of lactic acid it was demonstrated that in rats with normal blood pH the apparent contribution of the kidneys to

removal of a lactic acid load is approximately 30%. The vast majority of the kidney's handling of this lactate is via metabolism, with only a minor fraction being excreted (36). In the same study, bilaterally nephrectomized rats made acidotic by the administration of ammonium chloride demonstrated a progressively decreased rate of lactate removal in response to increasing metabolic acidosis. This decreased rate of removal of lactic acid was not seen in rats with intact kidneys. Thus, it appears that the normal kidney has an increased ability to remove lactate during metabolic acidosis and thus is, in part, responsible for compensation in this disorder.

In contrast to those observations in the kidney, the liver, while it possesses the major capacity for lactate removal, does not appear to increase its ability to do so in the setting of metabolic acidosis. Figure 15 illustrates the effect of functional hepatectomy on blood lactate concentration in dogs. The closed points on this figure represent acutal measurements while the line represents the mathematically-predicted value of blood lactate concentration, assuming a production or unchanged and the liver is responsible for 92% of lactate removal. The open circle represents the predicted steady-state concentration of plasma lactate in the absence of liver metabolism. Note the close fit of the observed values with those predicted.

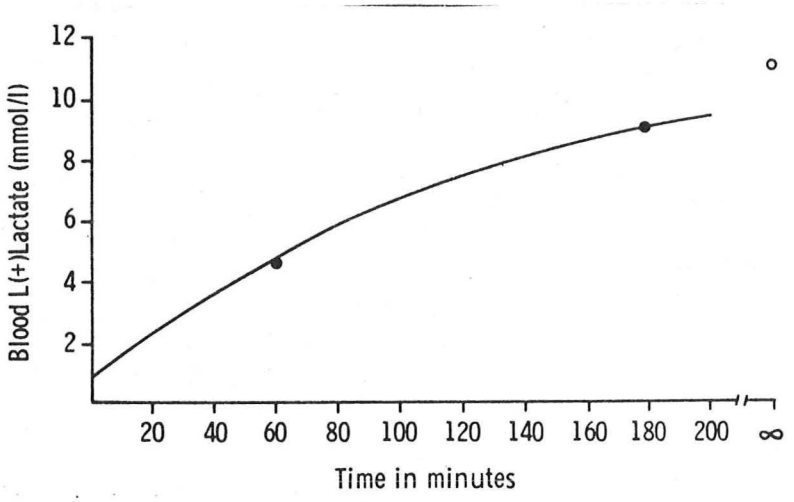

Figure 15. Increase in blood lactate concentration following functional hepatectomy in dogs. From Arieff et al, 1980.

It is apparent that major reduction in overall functioning liver mass would be a possible contributor to the development of lactic acidosis.

In addition to the role of destruction or replacement of functioning liver tissue in the development of lactic acidosis, there are numerous observations on the effects of metabolic acidosis and perfusion of the liver which are importantly related to the role of the liver in lactic acidosis. Lloyd et al (38) examined the effects of simulated metabolic acidosis on the intracellular pH and lactate metabolism in the isolated perfused liver of the rat. They demonstrated several interesting points. First, as outlined in Figure 16 from their studies, intracellular pH of liver cell, as determined by the distribution of the pH sensitive marker [^{14}C DMO], is normally slightly lower than that of arterial blood. However, as the perfusion pH of the

liver was gradually reduced by reducing the bicarbonate concentration of the perfusate, intracellular pH gradually fell. However, the decline in intracellular pH was lower than the reduction in pH of the perfusion fluid. Thus, when perfusate pH was reduced to 7 and 6.85, the liver intracellular pH still remained at approximately 7.1. Intracellular pH did not fall below 7 until the perfusate

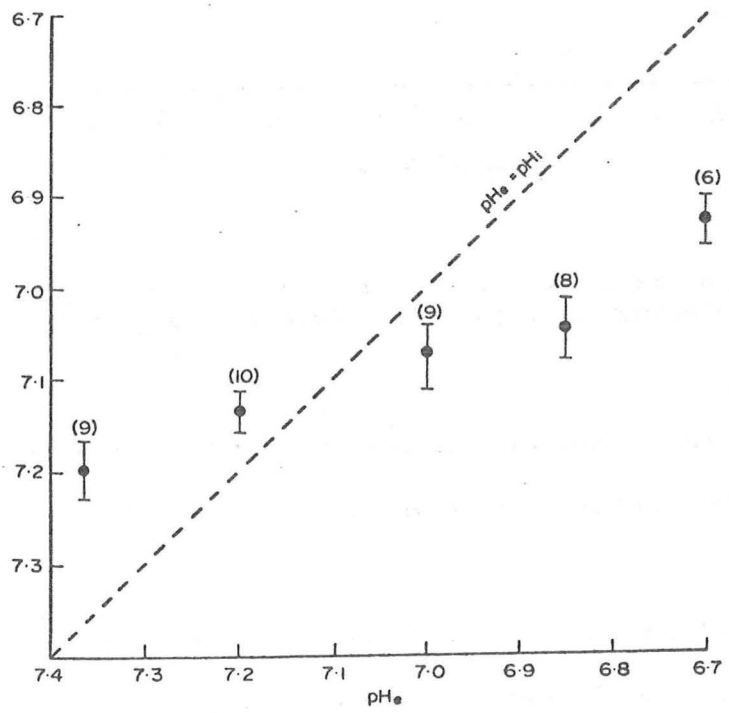

Figure 16. The relationship between pH_e and pH_i. The pH values represent the mid-points of the pH ranges 7.44-7.3, 7.3-7.1, 7.1-6.9, 6.9-6.8 and 6.8-6.6. pH_i is represented as mean ± SEM. The numbers in each group are given in parentheses. (From Lloyd et al 1973)

pH was below 6.7. Simultaneous with the measurements of intracellular pH, these investigators examined the relationship between pH and liver uptake of

lactate. Illustrated in Figure 17 are their observed relationships between intracellular pH and lactate uptake. Note that the liver takes up lactate until intracellular pH falls below 7.0 at which point it

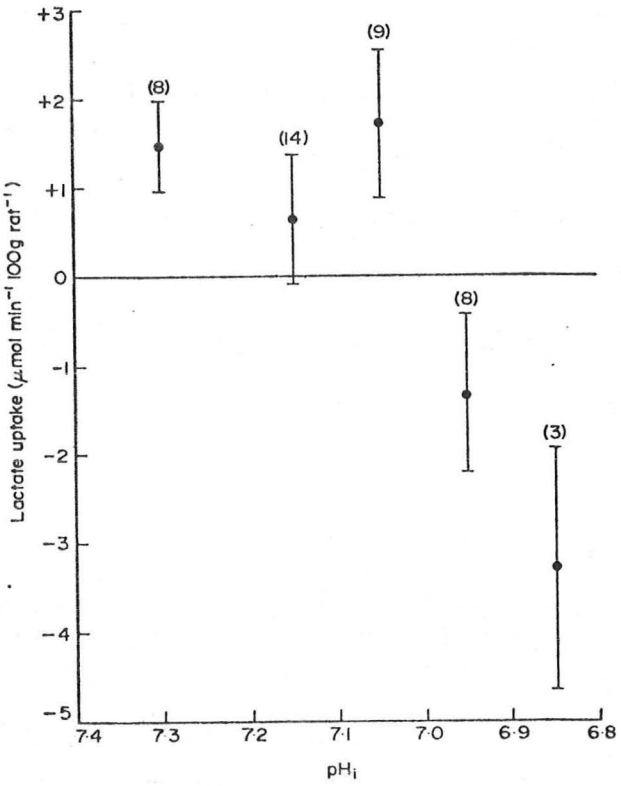

Figure 17. The relationship between pH_i and lactate uptake. The pH_i values represent the mid points of the pH ranges 7.4-7.2, 7.2-7.1, 7.1-7.0, 7.0-6.9 and 6.9-6.8. The numbers in each group are given in parenthesis. (From Lloyd et al, 1973.)

begins to add lactate to the perfusate. In a more recent study from these investigators the effect of combined acidosis and ischemia on lactate uptake and gluconeogenesis was examined (39). Table 9 summarizes these results. In these studies perfusate at both pHs contained equivalant amounts of lactate. When in vitro perfusion flow rate of the liver was normal, lactate uptake and

gluconeogenesis were significantly higher at perfusate pH 7.38 as opposed to pH 7.1. In addition, intracellular pH of the perfused liver cells was significantly higher during perfusion with alkaline perfusate. When the flow was reduced by 50% intracellular pH fell both during perfusion with 7.38 pH solutions as well as 7.1 pH solutions. With both perfusates lactate uptake fell significantly at 50% flow rate but was still higher in those livers perfused with a solution pH of 7.38. Finally, when flow rate was reduced to 20% of normal, there was a dramatic fall in intracellular pH of livers perfused with both 7.38 and 7.1 pH solutions. Coincident with this fall was a major drop in the lactate uptake and glucose output with both parameters being comparable in the livers perfused at both 7.38 and 7.1 pH.

TABLE IX

EFFECT OF PERFUSATE pH AND FLOW RATE ON INTRACELLULAR pH LACTATE UPTAKE AND GLUCOSE OUTPUT BY THE LIVER

	Normal Flow	50% Flow	20% Flow
At Perfusate pH 7.38			
Intracellular pH	7.37	7.28	7.09
Lactate Uptake $\mu mol \cdot min^{-1} \cdot 100\ g^{-1}$	6.9	4.5	1.6
Glucose Output	3.5	2.9	1.1
At Perfusate pH 7.1			
Intracellular pH	7.16	7.10	6.78
Lactate Uptake $\mu mol \cdot min^{-1} \cdot 100\ g^{-1}$	5.6	3.0	1.9
Glucose Output	2.2	2.2	1.1

From Iles RA, et al. Clin. Sci. 60:537-542, 1981.

The enzyme pyruvate carboxylase is a key enzyme in gluconeogenesis. It catalyzes the following reaction:

$$\text{Pyruvate} + \text{ATP} + HCO_3 \xrightarrow[Mg^{++}]{\text{Acetyl Coa}} \text{oxaloacetate} + \text{ADP} + P_i$$

Acetyl CoA appears to be an obligatory allosteric activator of this enzyme. It has been demonstrated that the activation of pyruvic carboxylase by acetyl CoA is extremely pH dependent. Figure 18 summarizes this finding. It is thought that this observation is in a major way responsible for the effects of intracellular pH on hepatic gluconeogenesis.

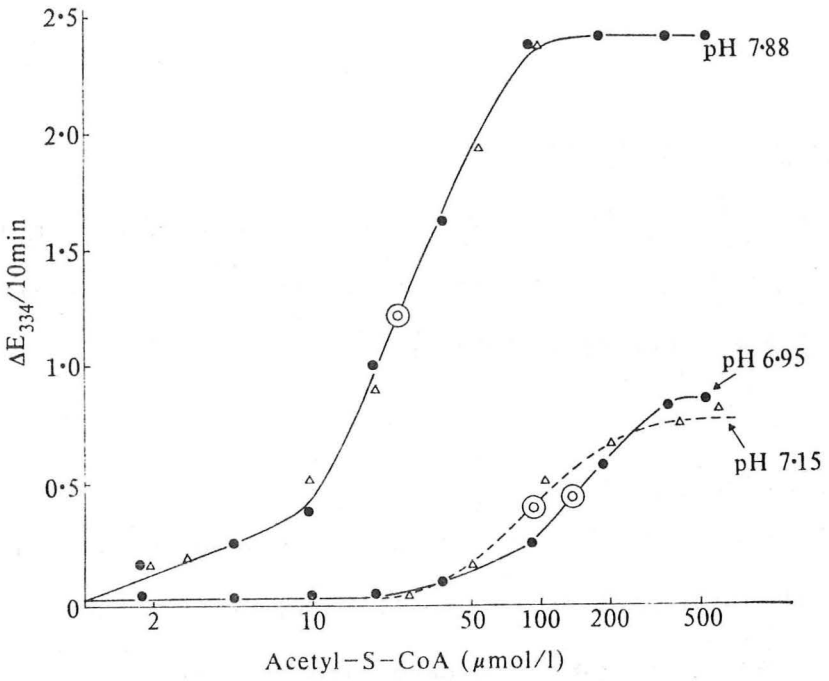

Figure 18. Activation of pyruvate carboxylase from rat (Δ···Δ) and guinea-pig (●——●) liver by acetyl-CoA at different pH values at 30°C. The reaction mixture contains HCl, 100 mmol/l; pyruvate, 10 mmol/l; ATP, 2.5 mmol/l; $MgCl_2$, 7 mmol/l; $NaHCO_3$, 20 mmol/l; NADH, 0.25 mmol/l; malate dehydrogenase, 1 μg/ml and 0.15 mgm protein/ml of the pyruvate carboxylase preparation. The ordinate is proportional to the activity of the enzyme. The bigger circles indicate the point of half-maximal velocity. (From Kleineke & Soling, 1971.)

No matter what the initiating factors in the generation of lactic acidosis are, an additional major pathophysiologic component may be related to the effects of lactic acidosis on the performance of the left ventricle (41-47). Studies on the dog left ventricle response to lactic acid demonstrate significant depression of ventricular contractility at extracellular pHs of 7.1 and 6.8 (41). In addition, the ionotropic response of the ventricle to norepinephrine was reduced by lactic acidosis. This observation coupled with the observations on the effects of extracellular pH on liver metabolism of lactate are important in that they emphasize the importance of attempting to maintain a pH above 7.1 when treating patients with lactic acidosis.

CLASSIFICATION OF LACTIC ACIDOSIS

As mentioned earlier, the initial classification scheme of Huckabee has been modified. Currently, lactic acidosis is divided into two types: Type A and Type B. These are outlined on Table 10.

CLINCAL PRESENTATION

Since by definition Type A lactic acidosis is seen in patients with shock or asphyxiation, the presentation is usually obvious. In these patients the lactic acidosis is secondary to inadequate tissue perfusion and an imbalance between lactate production and utilization. Regardless of the etiology, whether myocardial infarction, hemorrhage, gram-negative sepsis, or trauma, lactic acidosis is an integral part of the shock syndrome. This presentation will not deal with Type A lactic acidosis.

Type B lactic acidosis has been subdivided into three categories. In none of these categories is there clinical evidence of poor tissue perfusion.

TABLE X

CLASSIFICATION OF LACTIC ACIDOSIS

Type A - Poor tissue perfusion--poor oxygenation of arterial blood.

1. Shock of any type
2. Asphyxia
3. Carbon monoxide poisoning

Type B - No evidence of poor tissue perfusion

1. Common disorders
   a. diabetes mellitus
   b. renal failure
   c. liver disease
   d. infections
   e. leukemia and other malignancies

2. Drug or toxin ingestion
   a. phenformin
   b. ethanol
   c. fructose
   d. sorbitol
   e. xylitol
   f. methanol
   g. salicylate
   h. dithiazinine
   i. ethylene glycol
   j. streptozotocin

3. Hereditary
   a. decreased gluconeogenesis
      1) glucose-6-pohsphate deficiency
      2) fructose 1,6, diphosphatase deficiency
      3) pyruvate carboxylase deficiency
   b. decreased lactate oxidation
      1) pyruvate dehydrogenase deficiency
      2) defect in oxidative phosphorylation

The first category includes diseases with which lactic acidosis is commonly associated although the exact pathogenesis of the lactic acidosis in these diseases may not be clear. We will briefly review pertinent features of these common disorders. The second subgroup under Type B lactic acidosis is that induced by drug or toxin ingestion. We will also discuss examples from this subgroup. The final subgroup under Type B lactic acidosis is the inherited disorders of metabolism. These are basically subdivided into two groups: those consisting of a defect in gluconeogenesis as a pathway for disposition of lactate and those consisting of decreased ability to metabolize lactate via oxidation.

Cohen and Woods (13) summarized the most common presenting symptoms and physical findings in patients with Type B lactic acidosis. These are summarized on Table XI. It is apparent that these symptoms and signs are very nonspecific. Compare this summary of Cohen-Woods to the characteristics of 76 patients with lactic acidosis described by Ritz and Heidland (48) as outlined in Table XII.

TABLE XI

MOST COMMONLY RECORDED SYMPTOMS AND PHYSICAL FINDINGS IN 65 CASES OF TYPE B LACTIC ACIDOSIS

	No. of cases	% incidence
Hyperventilation or dyspnoea	44	69
Stupor or coma	24	38
Vomiting	14	22
Drowsiness	13	20
Abdominal pain	5	8

From Cohen and Woods 1976.

Because of the non-specific nature of these signs, it is most important for the physician to anticipate the presence of significant lactic acidosis based on the clinical circumstances. In this regard, Cohen and Woods (13) have

TABLE XII

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS IN 76 PATIENTS WITH LACTIC ACIDOSIS

Clinical	Percent
Altered level of consciousness	47
Gastrointestinal problems (nausea, vomiting, abdominal pain, diarrhea)	83
Hypotension (<100 mm Hg systolic)	39
Kussmaul respiration	78
Hypothermia (<36.5° rectal)*	55
Extracellular fluid volume contraction (Dehydration and/or transiently elevated BUN)	65
Laboratory	
pH 7.32-7.11	33
pH 7.1 or less	66
Diminished renal function**	90
Blood glucose <100 mg/100 ml	46
<60 mg/100 ml***	28
Leukocytosis (>12000/ml)****	80

*lowest reported temperature 26.7°C rectal
**serum creatining >1.4 mg/100 ml/ BUN >20 mg%
***lowest value 5 mg/100 ml
****highest value 60,000/ml
From Ritz and Heidland, 1977.

also catalogued the incidence of those clinical circumstances most commonly associated with lactic acidosis. These are summarized in Table 13. Note the relatively frequent occurrence of uremia as well as hepatic disease and acute infection.

The majority of patients with lactic acidosis will have blood lactate levels in the 10-20 mM range with values from 5 to 35 mM reported. Similarly, the lactate/pyruvate ratio (normal range 6-15) is generally in the 20-40 range. Plasma bicarbonate concentration is generally 5-15 mM and there is some correlation between the anion gap and the fall in plasma bicarbonate, although the increased anion gap tends to be larger than the fall

TABLE XIII

COMMON ASSOCIATED FACTORS IN LACTIC ACIDOSIS

	Total	A. Without obvious circulatory failure	B. With circulatory failure	C. Indeterminate cardiovascular status
Diabetes	73			
With phenformin	57	28	22	7
Without phenformin	16	10	5	1
Phenformin	59	32	20	7
Uraemia (blood or plasma urea >45 mg/100 ml)	55	37	18	
Hepatic disease	32	23	9	
Acute ethanolism	7	4	3	
Infections	38	27	11	
Acute pyelonephritis	13	10	3	
Other	25	17	8	

From Cohen and Woods, 1976.

in plasma bicarbonate. Cohen and Woods (13) have analyzed the distribution of these various parameters, i.e., blood lactate, lactate to pyruvate ratio, and arterial pH, in a group of patients with lactic acidosis. Their data is presented in Figures 19-21.

DIABETES MELLITUS

As mentioned earlier, it has long been appreciated that in diabetic patients ketonemia occasionally does not fully explain the magnitude of the metabolic acidosis. There clearly is a higher incidence of lactic acidosis in patients with diabetes mellitus. However, this association occurs for multiple reasons. First and foremost is the obvious increased incidence in the diabetic population of clinical disorders associated with lactic acidosis.

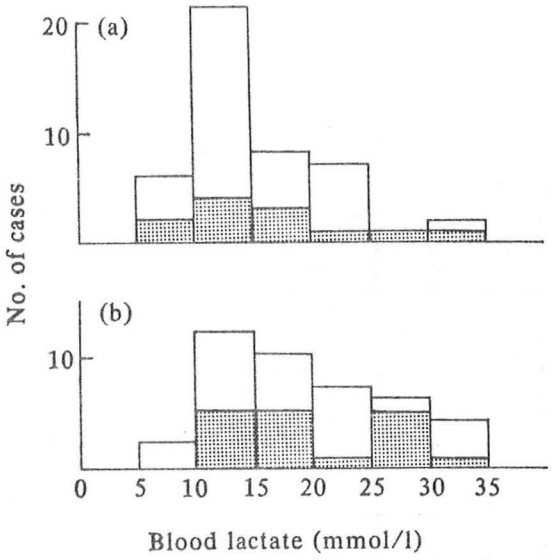

Figure 19. Distribution of blood lactate values in 82 recorded cases of lactic acidosis. Where more than one value has been recorded in a particular case the highest has been selected. The lower half of the figure (b) refers to phenformin-associated cases and the upper half (a) the remainder. The shaded areas refer to cases judged by our criteria to be of the Type A variety, the remainder being Type B. From Cohen and Woods, 1976.

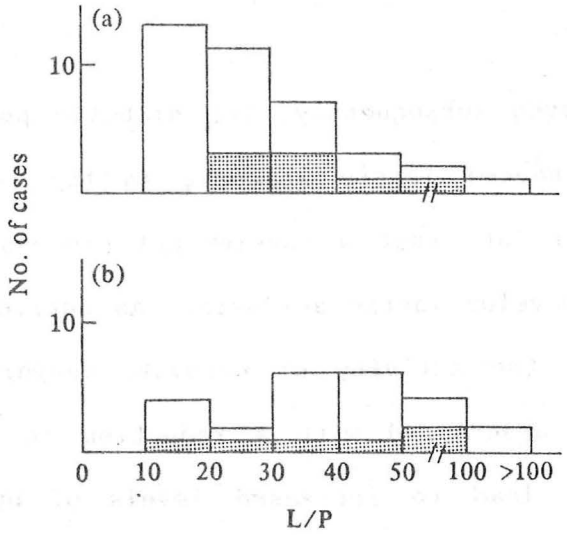

Figure 20. Distribution of values of blood L/P in 58 recorded cases of lactic acidosis. (a) Unassociated with phenformin; (b) phenformin associated. Shading as in Figure 19. From Cohen and Woods, 1976.

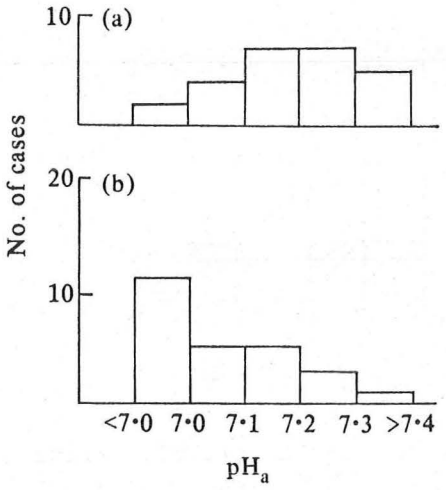

Figure 21. Distribution of arterial pH in Type B lactic acidosis. (a) Unassociated with phenformin; (b) phenformin-associated. The values selected are generally the lowest obtained. (From Cohen and Woods, 1976.)

Second, as will be discussed subsequently, the diabetic population has had major exposure to drug-induced lactic acidosis in the form of biguanide treatment. Third, there is at least a theoretical propensity for patients with lack of insulin to develop lactic acidosis. As outlined in Figure 22, insulin has an effect on the activity of pyruvate dehydrogenase with the absence of insulin being associated with a reduction in activity of this enzyme (49). This would lead to increased levels of pyruvate and thus increase substrate for lactate formation. In addition, insulin, by inhibiting the triacylglycerol lipase, prevents the release of free fatty acids which are substrates in the liver for acetyl CoA formation. Increased levels of acetyl CoA will inhibit the conversion of pyruvate to acetyl

Possible Mechanisms for Beneficial Effect of Insulin Treatment in Lactic Acidosis

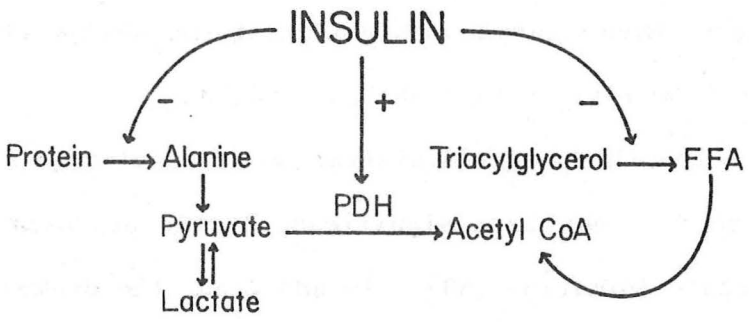

Figure 22

coenzyme A. Thus, effects of insulin on lipid metabolism affect the amount of pyruvate available for lactate formation. Finally, insulin's effect on preventing gluconeogene_ sis from protein results in decreased availability of alanine for pyruvate synthesis. In spite of the theoretic potential for diabetic patients to develop significant lactic acidosis by this last mechanism, they indeed do not tend to do so. It is generally agreed that the blood lactate concentration is not raised in stable diabetic patients (2,50-52). In contrast, though, there is general agreement that the blood lactate level is elevated in acutely ill diabetic patients prior to therapy (53-58). As pointed out by Narins et al (20), even the modest elevation of blood lactate of 5 mmol/liter observed in some acutely ill diabetics can be very significant when superimposed on an already existing metabolic acidosis. Several studies have demonstrated a significant incidence of elevation of blood lactate above 5 mmol/liter in diabetics (54,58).

It should be noted that the administration of insulin to a hyperglycemic diabetic patient who does not have significant lactic acidosis results in an acceleration of lactate formation (59). In addition, the provision of insulin to the media perfusing an isolated animal heart accelerates the rate of lactate formation (60,61). Presumably, this effect of insulin is secondary to its action on cell membranes making more glucose available for metabolism.

RENAL DISEASE

Renal failure is also frequently associated with the development of lactic acidosis. However, just as with diabetes mellitus, the association of

renal failure with lactic acidosis is most frequently not a cause and effect relationship. That is, patients who develop lactic acidosis are in certain clinical conditions which also are associated with the development of renal failure. In spite of this, it should be recalled that the kidneys may play a role in the development of lactic acidosis in two ways. First, the kidney is a significant organ with respect to gluconeogenesis. In addition, it also functions as a major organ for the extraction and metabolism or excretion of lactate. Finally, the kidneys are obviously involved in the metabolic response to any acid-base disorder with respect to their ability to alter excretion of net acid.

It should be recalled that the effect of acidosis on renal lactate removal is opposite to that in the liver. The absolute rate of removal of a lactate load by the kidneys is progressively increased by acidosis. Studies in the acidotic rat demonstrate that after a few hours of acidosis renal phosphoenol pyruvate carboxykinase activity is increased (62). Hepatic phospho- enol pyruvate carboxykinase in these studies was unaffected by acidosis (63). Since phosphenol pyruvate carboxykinase is an essential enzyme for gluconeogenesis its increased activity in acidosis may play a role in the renal adaptation to lactic acidosis. However, the clinical significance of these observations remain to be determined.

Since 1970 there have been numerous case reports of spontaneous hypoglycemia in patients with renal failure. In these patients, lactic acidosis has been a common observation (63-65). Frequently, these patients are anephric and on hemodialysis (63). Possible etiologies for this hypoglycemia and lactic acidosis include: defects in hepatic gluconeogenesis; limited availability of gluconeogenic substrates as a consequence of hemodialysis-related losses of alanine (66); and excessive glucose utilization by

inappropriate hyperinsulinism. The lactic acidosis and hypoglycemia in these patients can be quite severe and, although the number of cases reported in the literature is small, the mortality rate is near 50%. Recognition of this disorder should alert the physician to search for hypoglycemia and lactic acidosis in any chronic renal failure patient who presents with altered mental status.

LIVER DISEASE

The role of the liver in the pathophysiology of lactic acidosis has been discussed in some detail. In addition, a later section of this presentation will discuss the role of the liver in several experimental models of lactic acidosis in dogs. Early studies demonstrated the development of lactic acidosis in dogs that were vigorously hyperventilated, placed into shock by the infusion of Arfonads, or placed into shock by rapid bleeding through an arterial cannula (67). In these studies, the hyperventilation was vigorous enough to result in a decline of blood pressure, hepatic blood flow, and hepatic vein oxygen tension, and an increase in hepatic vein lactate to pyruvate ratio. Simultaneously, lactate and glucose output from splanchnic bed increased dramatically. Similarly, hemorrhagic shock resulted in an increase in aortic, vena cave, and hepatic vein lactate concentration. These observations are summarized in Figures 23 and 24.

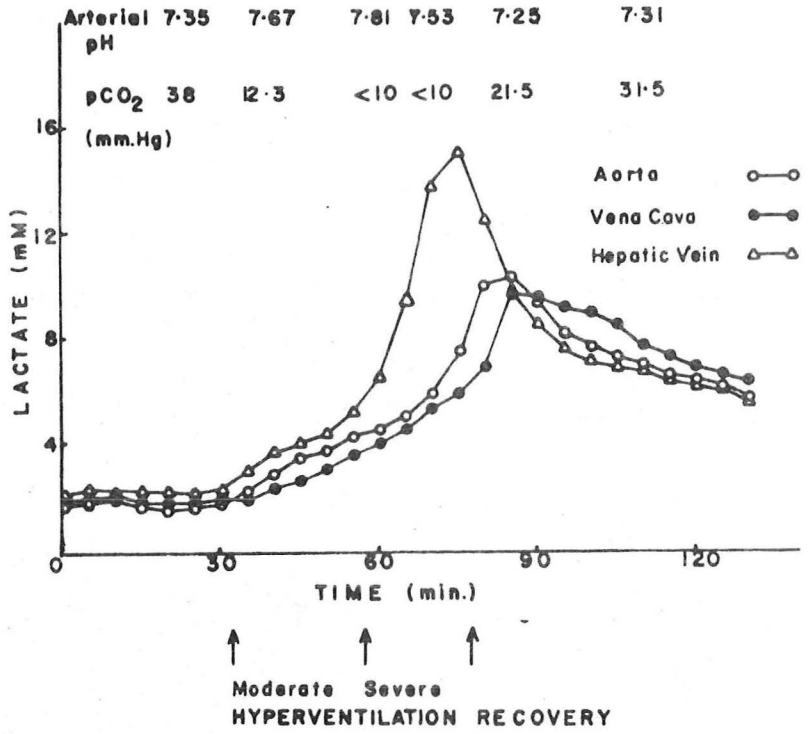

Figure 23. The effect of hyperventilation on aortic, vena caval, and hepatic vein lactate levels. From Berry and Scheuer, 1967.

Lactic acidosis has been described frequently in patients with liver disease (68-71). In one study patients were divided into two groups, those with chronic liver disease and those with acute hepatic failure (71). In the group of patients with chronic hepatic disease usually an acute precipitating event was identified as the major etiologic factor in the development of lactic acidosis. Seven out of 9 patients experienced a precipitating event, 4 of whom had sepsis and 3 of whom had major gastrointestinal bleeding. In these patients, although they had evidence of chronic liver disease, the results of most tests of hepatic function were not dramatically altered. Of importance is that none of these patients survived. In contrast, the patients

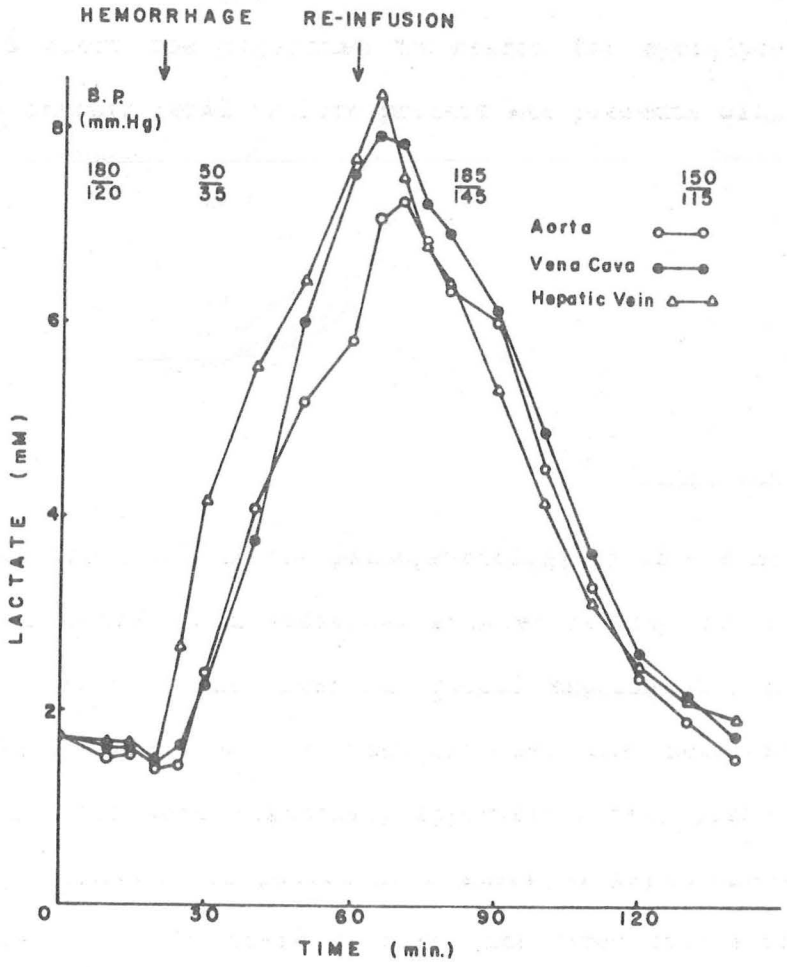

Figure 24. Effect of hemorrhagic shock on aortic, vena caval and hepatic vein lactate levels. From Berry and Scheuer 1967.

with acute hepatic failure had major alterations in their hepatic function tests with prolongation of the prothrombin time. Three of the 7 patients in the group with acute hepatic failure survived. As expected, hypoglycemia was seen in patients from both groups (7;). Table XIV summarizes the results of

TABLE XIV

EFFECT OF GLUCOSE INFUSION IN ACUTE HEPATIC INSUFFICIENCY AND LACTIC ACIDOSIS

Time	serum glucose mg%	glucose infusion g/hr	arterial lactate mM	arterial pyruvate mM	pH
0	25	0	14.6	0.65	7.24
2 h	98	10			7.29
4 h	212	10	6.3	0.41	7.30
12 h	236	7.5	2.7	0.12	7.38

From: Hernig, R.E., et al: Arch. Intern. Med. 139:1229-1232, 1979.

glucose infusion in one of the patients with acute hepatic insufficiency and lactic acidosis.

INFECTIONS

Sepsis commonly is associated early on with hyperventilation and respiratory alkalosis followed by development of lactic acidosis (72). While the etiology of lactic acidosis is not a secret when patients develop severe hypotension and compromised organ perfusion, the appearance of lactic acidosis while blood pressure is normal and arterial oxygen content maintained is suggestive of a pathophysiologic process that is not typical of Type A lactic acidosis. The specific mechanisms responsible for lactic acidosis in this early phase of infection are not known. It is not uncommon, however, that the appearance of an increased anion gap is the first clue to the presence of a serious infection.

LEUKEMIA AND OTHER MALIGNANCIES

The relationship between malignancy and lactic acidosis has become striking. It has long been appreciated that tumors have high rates of glycolysis (73). While the significance of this altered metabolism in tumors is beyond the scope of the present discussion, it has been postulated that at least in one tumor cell type, the Ehrlich ascites tumor cell, the high rate of glycolysis is due to a defect in the plasma membrane which results in defective operation of the sodium potassium pump (74). An interesting review of the role of hydrogen ions in cancer has recently been published (75). In a detailed study on the glycolytic rates of various rat hepatoma cell lines it was demonstrated that a significant correlation existed between in vivo hepatoma growth rate and in vitro rate of anaerobic glycolysis (76).

While originally the observations of lactic acidosis and cancer were made almost exclusively in patients with acute leukemia (77,78), subsequent studies of patients with cancer have described this disorder in Hodgkin's disease (79), large cell carcinoma of the lung without involvement of the liver (80), colon and lung cancer metastatic to the liver (81,82), and osteogenic sarcoma without evidence of liver involvement (83). Using data from reference 77, Table 15 summarizes the calculation of lactate production in patients with a significant load of leukemic cells.

Although treatment will be discussed subsequently, it is of interest that in one report of a patient with an anaplastic large cell tumor involving the bone marrow (80), the infusion of massive amounts of bicarbonate over a period of several days resulted in no significant change in blood lactate level. Indeed, blood lactate level fell when bicarbonate infusion was stopped. The time course of these observations are listed in Figure 25 and on Table 16. It is evident from Table 16 that bicarbonate infusion was

TABLE XV

POSSIBLE ORIGIN OF LACTIC ACIDOSIS
IN PATIENTS WITH LEUKEMIA

1. In vitro lactabe production of leukemic cells from patients with acute lymphocytic leukemia--50 μmoles/ hr/10^9 cells.*

2. Assume 10^{13} cells tumor load then 500 mmoles lactate produced/hr.

3. Depending on what proportion of lactate is converted to pyruvate and what proportion is fully metabolized to CO_2 and H_2O, oxygen consumption would increase 40-400%. BMR of leukemics is increased 35-70%.**

*From Field M, et al. Amer. J. Med. 40:528-547, 1966.

**From Garren LD and Lipsett MB. J. Clin Endocrinol. 21:1248-1254, 1961.

TABLE XVI

EFFECT OF HCO_3 ON URINARY ACID EXCRETION
IN PATIENTS WITH METASTATIC LUNG CANCER

HCO_3 Infusion (400-1000 meq per day x 5)	Net Acid Excretion (in mmol/h)	Urinary Lactate
50	7.38	37.2
None	0.70	0.235
50	5.30	7.07

From Fraley et al, N. Engl. J. Med. 1980

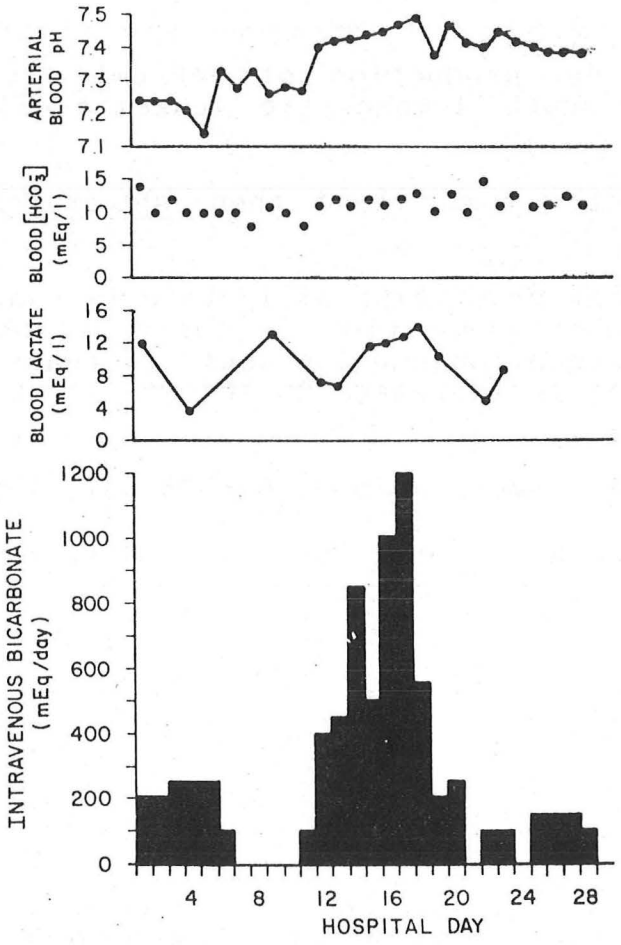

Figure 25. Changes in arterial blood pH and in bicarbonate and lactate levels in a patient in whom intravenous bicarbonate was administered on each day of hospitalization. HCO_3^- deontes bicarbonate. From Fraley et al. NEJM, 1980.

associated with an increase in urinary lactate excretion. This is presumptive evidence for increased lactate production in response to bicarbonate infusion.

DRUG- OR TOXIN-INDUCED LACTIC ACIDOSIS

Biguanides

Until its removal from the market in the United States in 1977, phenformin had been implicated as a major etiologic factor in lactic acidosis in diabetics (84-86). Since these agents are no longer in use in the United States they will not be discussed in this presentation. For interest, Tables 17 and 18 summarize data from studies of 330 and 306 patients respectively in whom biguanide therapy for diabetes resulted in lactic acidosis.

Ethanol

It has long been known that ethanol increases the blood lactate concentration secondary to a reduction in the hepatic metabolism of lactate. Ethanol is metabolized in the liver to acetaldehyde by alcohol dehydrogenase (87). The acetaldehyde is further oxidized to acetate by aldehyde dehydrogenase. These reactions occur in the cell cytoplasm and result in a significant increase in NADH. The increased NADH lowers the redox potential of the cell and is reflected by an increase in the lactate to pyruvate ratio (88,89). In addition, Krebs et al (90) demonstrated that ethanol inhibits gluconeogenesis from lactate in the perfused livers of starved rats. A 66% inhibition occurred at ethanol concentrations well below the level of legal intoxication. This is thought to occur via a decrease in the pyruvate concentration through an increase in the lactate to pyruvate ratio. Since the concentration of pyruvate is a critical factor in determining the rate of gluconeogenesis the latter is reduced in response to ethanol intake (91). Also, the removal of a lactate load in man is impaired after ethanol administration (92). These changes in response to alcohol ingestion have been further documented by experiments of Kriesburg et al (93).

TABLE XVII

LACTIC ACIDOSIS IN DIABETICS TAKING BIGUANIDES

	Phenformin	Buformin	Metformin
pH	6.95 ± 0.12	6.98 ± 0.35	7.10 ± 0.58
HCO_3	6.6 ± 0.3	7.5 ± 1.1	7.8 ± 0.7
Lactate	17.3 ± 0.6	16.1 ± 1.6	12.8 ± 1.4
Anion Gap	37.4 ± 1.1	45.1 ± 8.8	34.3 ± 5.7
Creatinine	2.9 ± 0.2	4.3 ± 0.6	6.3 ± 1.1
Urea N	114.0 ± 4.0	160.0 ± 20.0	111.0 ± 29.0
Glucose	176.0 ± 9.6	150.0 ± 24.0	172.0 ± 50.0
Mortality	52% (128/246)	50% (13/26)	18% (2/11)

From: Luft D, et al: Diabetologia 14:75-87.

TABLE XVIII

TREATMENT OF PHENFORMIN ASSOCIATED LACTIC ACIDOSIS

	All Patients	Insulin	Dialysis
No. of Patients	306 (100%)	26 (100%)	31 (100%)
No. Recovered	150 (49%)	21 (81%)	16 (52%)
No. Died	129 (42%)	4 (15%)	15 (48%)
Unknown	27 (9%)	1 (4%)	0 (0%)
Lactate	18.5	15.9	20
pH	6.96	6.96	6.96

From Misbin RI. Ann. Intern. Med. 87:591-595, 1977.

Severe acidosis due only to lactic acid is uncommon in alcoholics. More frequently these patients demonstrate a mixed lactic acidosis and nondiabetic ketoacidosis (94). The relative proportions of lactic acid and keto acids in these patients vary with the lactate predominating in some and ketones in others. The clinical history of alcoholic lactic acidosis is usually that of recent acute prolonged alcohol intake superimposed on a background of poor nutritional intake, anorexia, nausea, vomiting, and volume depletion. In addition, these patients often present at the beginning stages of alcohol withdrawal and manifest hyperventilation and tremulousness. Since the redox potential of the liver cells in these patients is reduced even the ketoacidosis associated with this disorder is frequently undetected because of the presence of betahydroxybutyric acid as the major ketone body. It should be recalled that the standard acetest tablets are insensitive to betahydroxybutyric acid and mostly sensitive to acetocetic acid.

It should be noted that the alteration of redox potential by the metabolism of alcohol appears initially to take place in the cytoplasm. However, when the acetaldehyde is oxidized to acetic acid there is an increase in mitochondrial NADH (95). The majority of the increased mitochondrial NADH is derived from a decrease in oxidation of mitochondrial generated NADH (96-98) rather than from enhanced movement of cytoplasmic NADH into the mitochondria (99). The exact mechanism for this inhibition in mitochondrial NADH oxidation is unclear but it may be related to a depressant effect of acetaldehyde (95).

Table 19 summarizes certain of the pathophysiologic features of the Type B lactic acidoses.

CONGENITAL LACTIC ACIDOSIS

The third subgroup under Type B lactic acidosis includes various enzyme deficiencies. The major categories are summarized under Table 20. An

TABLE XIX

PATHOPHYSIOLOGY OF LACTIC ACIDOSIS TYPE B

Disorder	↑ Lactate Production	↓ Lactate Utilization
Diabetes	Muscle, ↓ PDH	Liver, ↓ redox
Liver disease	RBC, alkalosis	Liver, ↓ perfusion or extraction
Biguanides	Gut	Liver, ↓ pH
Ethanol		Liver, ↓ redox
Fructose	Gut, fructolysis	
Cancer	Tumor cells	

extensive discussion of these disorders is beyond the scope of this presentation and the reader is referred to references 100-107.

TABLE XX

CONGENITAL LACTIC ACIDOSIS

DEFECTS IN GLUCONEOGENESIS
1. Deficiency of glucose-6-phosphatase (Type I glycogen-storage disease)
2. Deficiency of fructose-1, 6-diphosphatase
3. Deficiency of pyruvate carboxylase

DEFECTS IN OXIDATION OF PYRUVATE
1. Deficiency of pyruvate dehydrogenase
2. Defects in oxidative phosphorylation

EVALUATION OF EXPERIMENTAL LACTIC ACIDOSIS IN DOGS

Before discussing the treatment and prognosis of lactic acidosis it is pertinent to review a series of studies by Arieff and colleagues (108-110). In the first paper of the series diabetes was induced in dogs by surgical pancreatectomy and the animals were maintained on insulin and oral pancreatic extract. Insulin was withheld 2 days before experiments. Normal and diabetic dogs were anesthetized and administered phenformin intravenously at a dose of 13 mg/kg/hr. Numerous measurements of lactate concentrations in blood samples as well as determinations of intracellular pH in muscle and liver were made.

Figure 26 represents the redox potential of the livers of normal and diabetic and diabetic dogs infused with phenformin. Liver redox potential was determined from liver lactate, pyruvate, intracellular pH and extracellular space. Table 21 summarizes the arterial blood gases and various lactate concentrations of these animals. It is evident from Figure 26 and Table 22 that 1) the induction of diabetes significantly reduces the liver cell redox potential but more importantly the superimposition of phenformin treatment on diabetic animals results in a marked reduction
of this potential.

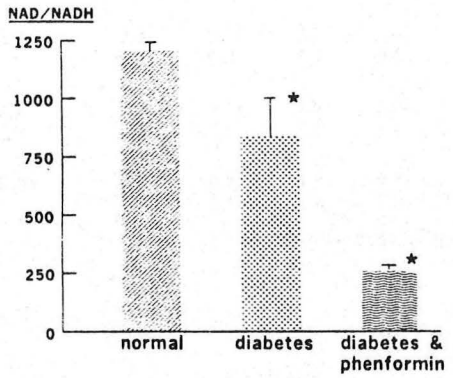

Figure 26. Cytosolic redox state in liver of normal and diabetic dogs (Group 2) and of dogs infused with phenformin (Group 6b). In diabetic dogs, liver redox state is significantly less than normal. In dogs infused with phenformin, liver redox state is significantly less than that in both normal and control diabetic dogs. * $P<0.01$. From Arieff, et al, 1980.

TABLE XXI

ARTERIAL BLOOD GASES AND LACTATE CONCENTRATIONS
IN NORMAL, DIABETIC, AND DIABETIC + LACTIC ACIDOSIS DOGS

	pH	$[HCO_3^-]$	$[Lactate^-]$
Normal	7.38	19.5	1.2
Diabetic	7.40	20.6	2.1
Diabetic + phenformin	7.08	10.0	9.0

From Arieff et al, 1980.

TABLE XXII

SYSTEMIC EFFECTS OF LACTIC ACIDOSIS AND ITS TREATMENT

	Blood					Cardiac Output, liter/min	pH_i			HPV Flow, $ml \cdot kg^{-1} \cdot min^{-1}$	Survival Time, min
	Arterial pH	Arterial HCO_3, mM	Arterial lactate, mM	HPV lactate, mM	HV lactate, mM		Liver	Muscle	Erythrocytes		
Diabetes (*group 1*, $n = 9$)											
Mean	7.40	19.9	1.87	2.46	1.93	2.84	7.05	6.98	7.30	19.2	
±SE	0.01	0.6	0.19	0.28	0.15	0.25	0.04	0.03	0.05	1.4	
Lactic acidosis (*group 2*, $n = 12$)											
Mean	7.15	10.9	6.7	8.2	7.5	1.26	6.82	6.93	7.20	10.9	
±SE	0.03	0.5	0.4	0.7	0.4	0.18	0.02	0.02	0.03	0.9	
$NaHCO_3$ therapy (*group 3*, $n = 12$)											
Mean	7.18	10.2	13.6	17.2	16.6	0.88	6.72	6.86	7.12	8.9	122
±SE	0.03	1.0	1.5	2.6	2.0	0.31	0.05	0.06	0.06	0.9	33
NaCl therapy (*group 4*, $n = 6$)											
Mean	7.13	10.1	9.1	11.0	10.5	1.12	6.79	6.86	7.16	11.2	114
±SE	0.07	1.1	1.2	1.1	1.8	0.20	0.06	0.07	0.02	0.8	37
No therapy (*group 5*, $n = 8$)											
Mean	7.07	9.6	8.7	8.6	8.5	<0.20				<2.0	96
±SE	0.05	0.7	0.7	1.2	1.0						8

HPV, hepatic portal vein; HV, hepatic vein; pH_i, intracellular pH.

From Arieff et al, 1980.

Associated with this marked reduction in the ratio of NAD to NADH in the phenformin treated animals is the development of a significant lactic acidosis in this experimental group (Table 21).

Shown in Figure 27 are the measurements of blood lactate levels from various sites in the diabetic dogs treated with phenformin. It is apparent that there is a significant increase in the lactate level in both hepatic portal vein as well as hepatic vein. These observations suggest increased production of lactate in extrahepatic splanchnic beds.

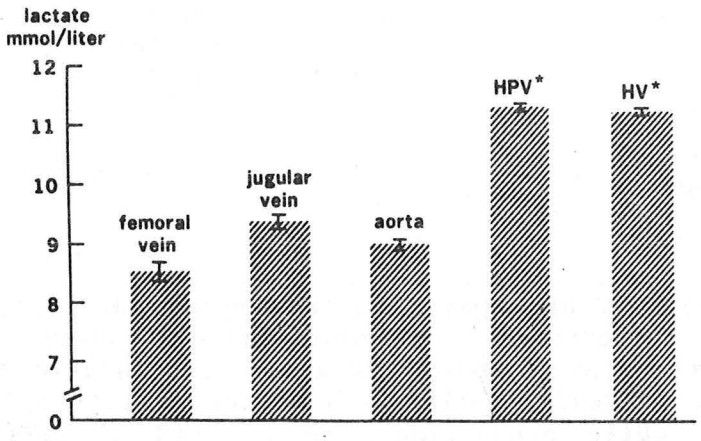

Figure 27. Blood lactate level simultaneously measured in aorta, femoral vein, jugular vein, hepatic vein (HV), and hepatic portal vein (HPV) in diabetic dogs with phenformin-induced lactic acidosis. From Arieff et al, 1980.

In addition, the absence of a significant difference in hepatic portal vein and hepatic vein lactate levels suggest that the liver was unable to remove the increased lactate load. Figure 28 summarizes the hepatic lactate extraction as well as splanchnic lactate production in the diabetic dogs, diabetic dogs treated with phenformin, and diabetic dogs with normal systemic pH infused with lactic acid. The last group had an

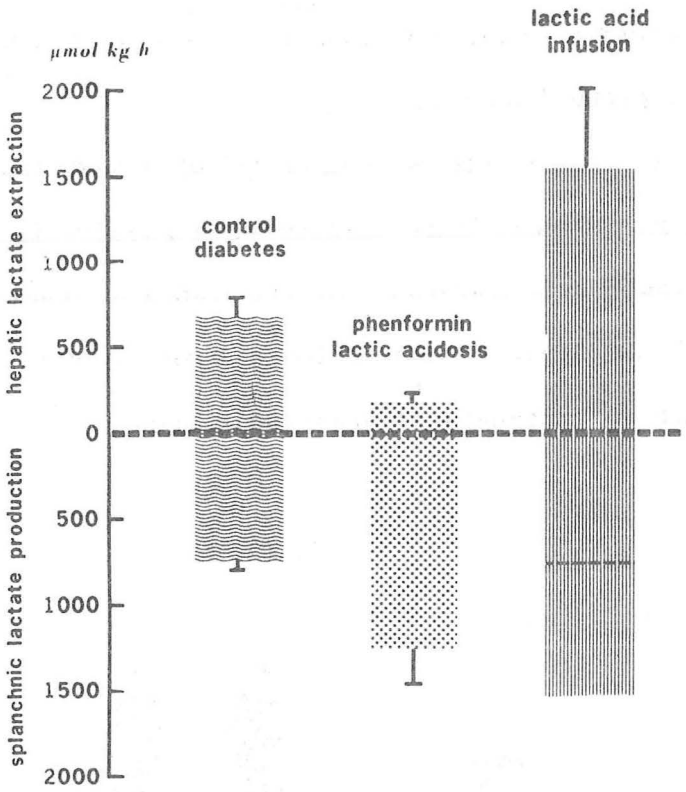

Figure 28. Comparison of hepatic lactate uptake and extrahepatic splanchnic lactate production. In control diabetic dogs, uptake and production of lactate are similar. However, in diabetic dogs with phenformin lactic acidosis, lactate extraction fell to only 22% of base-line value, while production rose to 166% of control. In diabetic dogs infused with L-lactic acid, liver lactate extraction (1,530 μmol/kg/h) was not different from sum of basal production (755 μmol/kg/h) plus the amount infused (800 μmol/kg/h). From Arieff et al, 1980.

arterial ph of 7.33, a plasma bicarbonate concentration of 13.7 and a plasma lactate concentration of 6.8 mmol. In the animals with diabetes, hepatic lactate extraction matched splanchnic lactate production. However, in animals with phenformin induced lactic acidosis superimposed on diabetes, hepatic lactate extraction was less than 25% of splanchnic lactate production. In contrast, the diabetic dogs not treated with phenformin increased hepatic lactate extraction in response to lactic acid infusion.

Finally, using the technique of distribution of [^{14}C] DMO both liver and muscle intracellular pH were determined in diabetic dogs diabetic dogs in which lactic acidosis was induced by phenformin. Figure 29 summarizes these results.

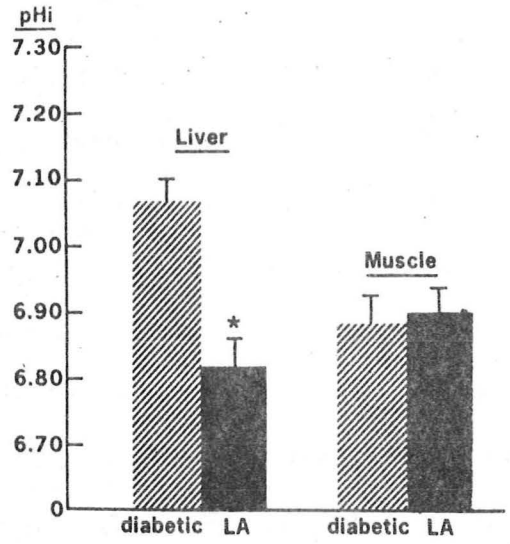

Figure 29. Effects of phenformin-induced lactic acidosis on intracellular pH (pHi) in liver and skeletal muscle. There is a significant fall in pHi of liver, but no effect on pHi of sleketal muscle. * P <0.001. LA, lactic acidosis. From Arieff et al, 1980.

It is apparent that phenformin therapy had no effect on intracellular pH of muscle whereas it markedly reduced the intracellular pH of liver cells.

The second paper of this series of studies reports observations on the effects of sodium bicarbonate treatment in the experimental model of lactic acidosis (109). In this study, the infusion of sodium chloride was compared to that of sodium bicarbonate in dogs with phenformin-induced lactic acidosis. Five groups of dogs were observed: 1) a diabetic group, 2) a diabetic group with lactic acidosis secondary to phenformin treatment, 3) dogs similar to

group 2 except treated with an infusion of sodium bicarbonate, 4) dogs similar to those in group 2 except treated with an infusion of sodium chloride, and 5) dogs similar to those in group 2 who received no therapy. Table 22 summarizes measurements of blood gases, lactate concentrations, cardiac output, intracellular pH, and survival times in these 5 groups. While there was no significant difference in the survival time of the sodium bicarbonate vs sodium chloride treated animals, there were significant differences with respect to other parameters. Blood lactate level was significantly higher in the sodium bicarbonate treated animals and also was significantly higher than that in animals untreated lactic acidosis. Similarly, cardiac output and hepatic portal vein flow were lower in the sodium bicarbonate treated group. Figure 30 graphically represents measurements of intracellular pH in the various experimental groups. It can be seen that sodium bicarbonate treatment of lactic acidosis resulted in significant decrease in intracellular pH of the liver. Finally, Figure 31 illustrates the relationship between hepatic lactate extraction and splanchnic lactate production in the various groups. Sodium chloride treatment had no effect on either lactate extraction or lactate production, whereas sodium bicarbonate therapy resulted in a significant increase in splanchnic lactate production.

The last paper in this series of studies on experimental lactic acidosis examines the effects of treatment of two different models of Type B lactic acidosis in diabetic dogs: hepatectomy-induced lactic acidosis and phenformin-induced lactic acidosis. In phenformin-induced lactic acidosis in diabetic dogs treatment with dichloroacetate resulted in a mortality of 22% versus 89% mortality observed in those animals treated with sodium bicarbonate infusion. Dichloroacetate treatment resulted in an increase in arterial pH and bicarbonate concentration, an increase in liver intracellular pH, an

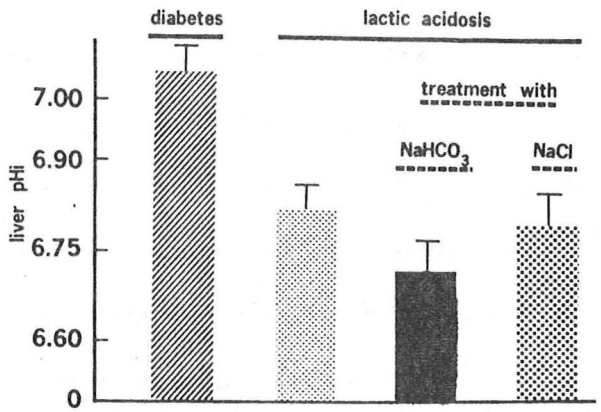

Figure 30. Liver intracellular pH (pHi) is shown in 4 groups of dogs. In dogs with lactic acidosis, there was a significant decrement ($P<0.01$) in liver pHi compared with control diabetic animals. Liver pHi was unaffected by NaCl treatment but decreased significantly ($P<0.01$ vs. dogs with lactic acidosis before treatment) after therapy with $NaHCO_3$. From Arieff et al, 1982.

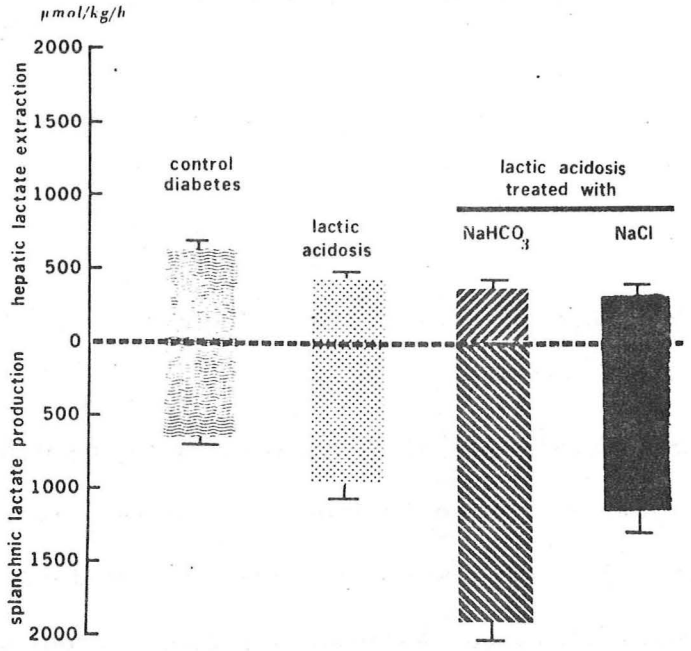

Figure 31. Extrahepatic splanchnic lactate production and liver lactate uptake are shown in 4 groups of dogs. In dogs with lactic acidosis, there were significant decrements of both lactate production and uptale of lactate by the liver ($P<0.01$). Liver lactate uptake was unaffected by treatment with either NaCl or $NaHCO_3$. However, treatment with $NaHCO_3$ resulted in a highly significant increase in both extrahepatic and net splanchnic lactate production ($P<0.01$), whereas treatment with NaCl did not. From Arieff et al, 1982.

increase in cardiac index, increase in liver lactate uptake, and a fall in plasma lactate levels. In contrast, sodium bicarbonate therapy resulted in a decrease in cardiac index, a decrease in liver intracellular pH, and an increase in extrahepatic splanchnic lactate production. In dogs with lactic acidosis induced with by hepatectomy, pretreatment with dichloroacetate resulted in stabilization of cardiac index, fall in plasma lactate, and a 17% mortality. In contrast, sodium bicarbonate therapy was associated with a continuous decline in cardiac index, a rise in blood lactate, and a 67% mortality. Hepatectomized dogs treated with sodium chloride demonstrated a mortality of 33% while dogs pretreated with dichloroacetate demonstrated 100% survival. The results of these studies are graphically displayed in Figures 32-35.

TREATMENT OF LACTIC ACIDOSIS

Numerous treatment modalities of varying efficacy have been proposed as therapy for lactic acidosis. These include: 1) sodium bicarbonate or other buffer administration; 2) hemodialysis or peritoneal dialysis; 3) glucose or glucose and insulin administration; 4) administration of sodium nitroprusside; 5) administration of pyridoxine alpha ketoglutarate; and 6) administration of dichloroacetate.

First and foremost in the treatment of lactic acidosis is its prevention or at least early management via recognition of the risk factors for its development. However, assuming that lactic acidosis has been established a treatment regimen must be formulated.

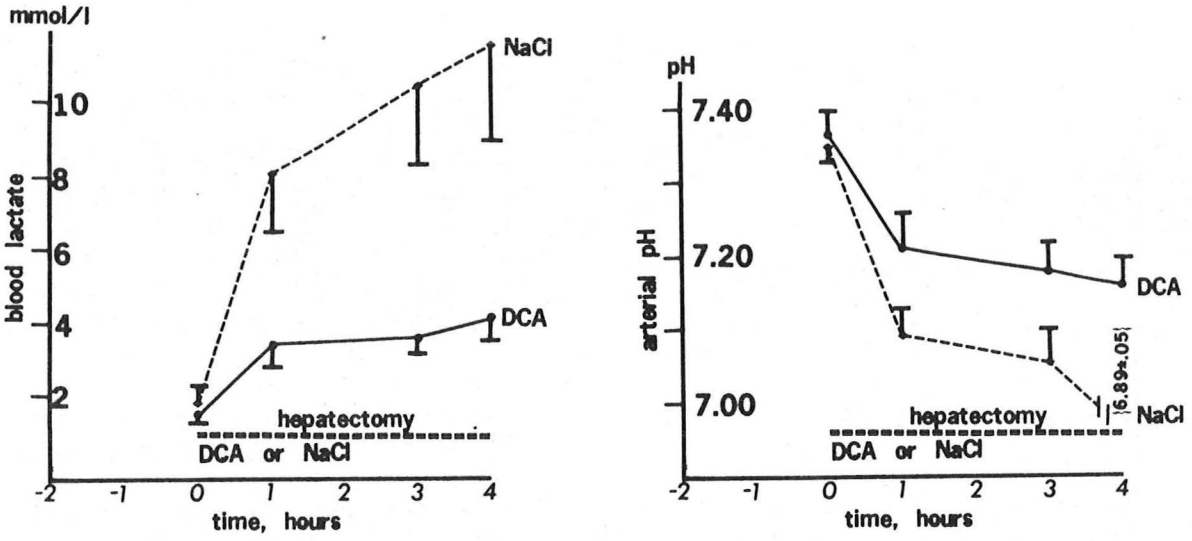

Figure 34. Two groups of dogs with hepatectomy-lactic acidosis (groups 6 and 7) were pretreated with either NaCl or DCA for 2 h before hepatectomy. The animals continued to receive either NaCl or DCA for the duration of hepatectomy, and arterial pH and lactate were compared in the two groups. At intervals of 1, 2, 3, and 4 h, arterial pH was significantly greater ($P<0.01$) and lactate significantly less ($P<0.01$) in DCA-treated dogs vs. those treated with NaCl. From Park and Arieff 1982.

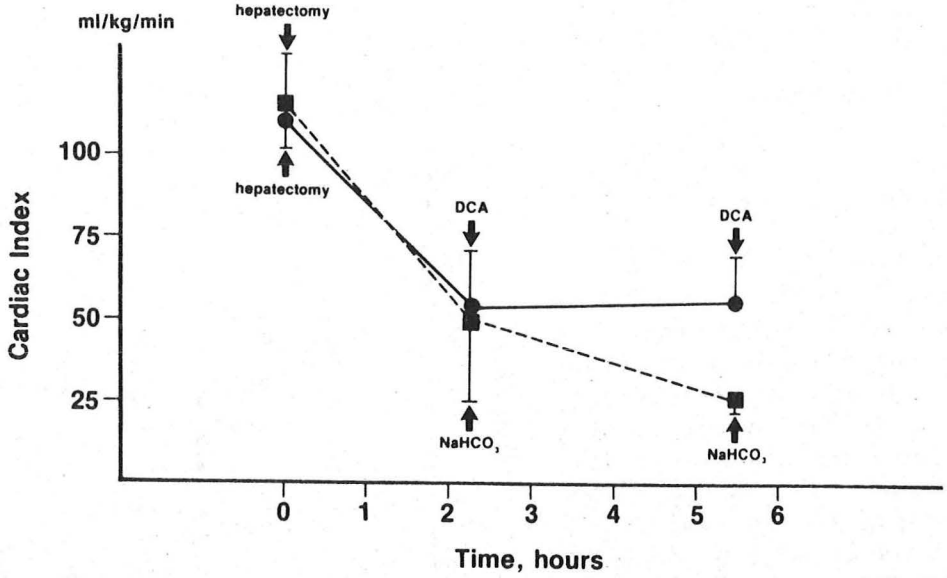

Figure 35. The effects on cardiac index of therapy with DCA vs. $NaHCO_3$ in dogs with hepatectomy-lactic acidosis. After 135 min of functional hepatectomy, cardiac index was reduced to 46% of the control value. In dogs treated with DCA, there was no further change in cardiac index, while in $NaHCO_3$-treated animals cardiac index continues to deteriorate. The 4-h survival was 83% in DCA-treated dogs vs 33% in those treated with $NaHCO_3$. From Park and Arieff, 1982.

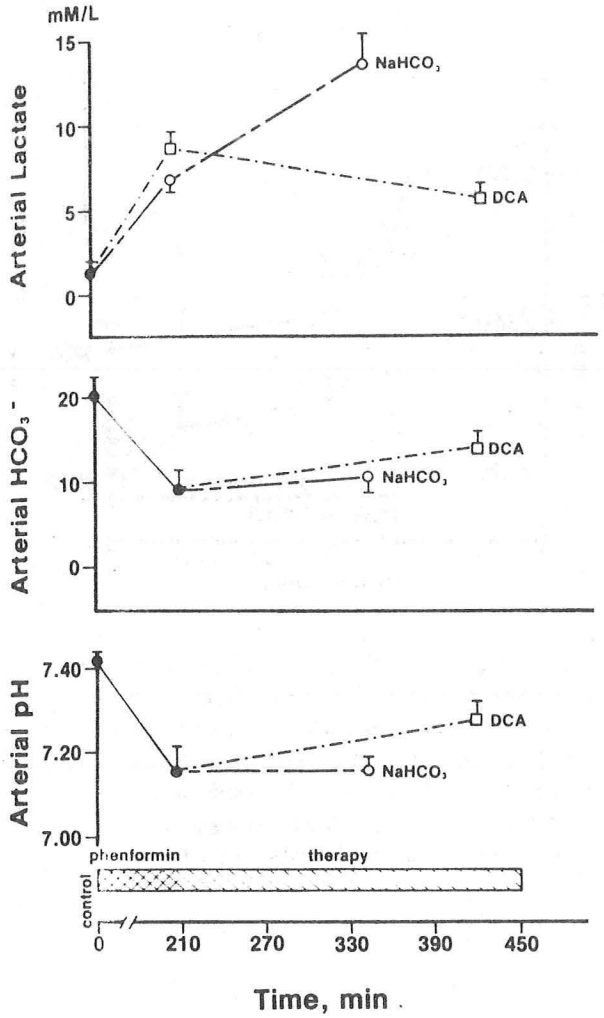

Figure 32. The effects of intravenous DCA vs. $NaHCO_3$ in dogs with phenformin-lactic acidosis are compared. 2 groups of diabetic dogs were given intravenous phenformin for a mean of 210 min (groups 3 and 4) and then half received DCA (group 4) while the other half was given $NaHCO_3$ (group 3) for a maximum of 240 m. In the DCA treated animals arterial lactate was significantly lower ($P<0.01$) while arterial pH and HCO_3 were significantly higher ($P<0.01$), despite the fact that the HCO_3 treated dogs had received an average of 73 meq of $NaHCO_3$ vs none for the DCA treated animals. From Park and Arieff, 1982

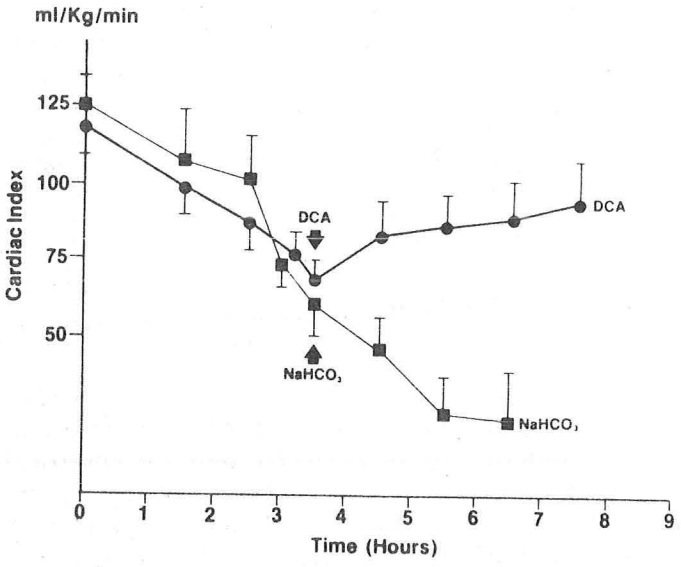

Figure 33. The effects of $NaHCO_3$ vs DCA treatment on cardiac index in dogs with phenformin lactic acidosis. After 4 h of intravenous DCA, cardiac index is not significantly different from the control value. During treatment with $NaHCO_3$, cardiac index progressively diminished, leading to an eventual 91% mortality vs a 22% mortality in DCA treated dogs. From Park and Arieff, 1982.

Alkali Therapy

The administration of sodium bicarbonate has been the mainstay in the treatment of lactic acidosis. It is reasonable to take the following approach. Because of the demonstration that a systemic pH significantly below 7.1 results in a direct effect of the acidosis on myocardial performance, it is reasonable to administer sufficient alkali to bring systemic pH to 7.1. There is growing concern, based on the studies in experimental animals, that attempts to raise systemic pH above this level provides no significant advantage. Indeed, one must be cautious, for the liberal use of sodium bicarbonate therapy is not without its hazards (Table 23).

TABLE XXIII

HAZARDS OF $NaHCO_3$ THERAPY

1.	Sodium and volume overload
2.	Hyperosmolality
3.	Anomalous cerebrospinal fluid acidosis with cerebral depression
4.	Decreased oxygen release from hemoblobin due to alkalinization
5.	Post-correction metabolic alkalosis

Attempts to calculate bicarbonate deficits are difficult due to the very large scatter in the apparent distribution space of bicarbonate in this organic acidosis.

It should be noted that in patients with lactic acidosis associated with cancer the lactic acidosis is frequently chronic and stable. Thus, unless there is an intercurrent acute medical problem or the extent of the steady-state acidosis is severe (systemic pH below 7.1 to 7.2) there is no urgent need to treat the patient with parenteral alkali.

Not all physicians believe that the use of alkali therapy should be tempered. Indeed, some have argued that extracellular pH should be brought to within normal via alkali therapy within approximately 6 hours (13). The rationale for this aggressive alkali therapy is based on the requirement to restore liver intracellular pH to levels that do not inhibit gluconeogenesis. However, it should be pointed out from the more recent studies by Arieff and colleagues that sodium bicarbonate therapy might not have the desired effect on hepatic intracellular pH. To be sure, there has been no controlled clinical study on the comparison of sodium bicarbonate versus sodium chloride infusion in lactic acidosis. If alkali therapy is chosen, it is probably best to administer this as isotonic sodium bicarbonate as opposed to boluses of hypertonic sodium bicarbonate.

Hemodialysis or Peritoneal Dialysis

Since the major problem of lactic acidosis is the acidosis and not the actual level of plasma lactate anion, removal of lactate by dialysis is essentially nontherapeutic. The major role for any form of dialytic therapy in treatment of lactic acidosis is to provide a route for the removal of excess amounts of sodium and to, in some instances, provide alkali when dialysis is performed against bicarbonate-containing solutions. There are reports of successful management of lactic acidosis using bicarbonate buffered dialysis fluid (111,112). It should be noted that any form of dialysis should not utilize dialysate fluid that contains lactate. There have been reports of the development of lactic acidosis in patients with acute renal failure dialyzed against lactate containing peritoneal dialysis fluid. Table 24 summarizes the results of peritoneal dialysis with bicarbonate containing dialysate in four patients with lactic acidosis. There has been no controlled

study on the effectiveness of this form of therapy and as can be noted from Table 24, mortality in this small group of patients was 50%.

Glucose or Glucose and Insulin Infusion

In lactic acidosis associated with hypoglycemia the administration of glucose has proven to be life saving (113,114). In addition, it has been reported that both insulin and glucose infusion in patients with combined keto and lactic acidosis complicating malignancy is beneficial (115). Finally, as is evident from the results on Table 18, the administration of insulin in patients with biguanide-induced lactic acidosis and diabetes has some apparent benefit with respect to survival.

Vasodilator Therapy with Sodium Nitroprusside

There have been rare reports of the reversal of lactic acidosis associated with nitroprusside administration in patients with severe congestive heart failure (116). The general effectiveness of such treatment is unknown and must be viewed with caution when one realizes that nitroprusside infusion has been used as part of a model for the development of experimental lactic acidosis (117). In addition, it has been reported that nitroprusside infusion to control accelerated hypertension has been associated with the development of lactic acidosis (118).

Pyridoxine-Alpha-Ketoglutarate

While no human studies are available, pyridoxine-alpha-ketoglutarate has been used in the treatment of experimental lactic acidosis in the rat (119). The rationale behind this therapy is based on the fact that pyridoxine-alpha-ketoglutarate, through the production of malate, supplies gluconeogenic

TABLE XXIV

PERITONEAL DIALYSIS IN LACTIC ACIDOSIS

Patient	pH		pCO_2		HCO_3		Lactate	
	B	A	B	A	B	A	B	A
Diabetes, phenformin	6.93	7.48	14	27	2.7	20.0	17.1	1.9
Liver disease, sepsis	7.05	7.37	24	33	6.3	18.4	42.5	10.2
Liver disease, sepsis*	7.00	7.41	17	36	3.9	23.0	16.7	1.4
Liver disease, sepsis*	7.25	7.39	30	39	12.7	18.2	8.4	7.2
MEAN	7.05	7.39	21	33	6.4	19.9	21.1	5.1

*Died

From Vaziri ND, et al. Amer. J. Med. 67:392-396, 1979.

substrates which are independent of the pyruvate-lactate system. Since the stimulation of gluconeogenesis through this pathway does not consume lactate it is possible that pyridoxine-alphs-ketoglutarate also lowers the production rate of lactate. It should be pointed out that the particular experimental model of lactic acidosis used in this study was acute biguanide intoxication in the rat. Further studies will be required to elucidate the usefulness of pyridoxine-alpha-ketoglutarate in both biguanide-induced and other forms of lactic acidosis. Finally, there has been recent major interest in the use of dichloroacetate in the treatment of lactic acidosis (120-128). Dichloroacetate reduces blood glucose concentrations in both diabetic and fasting animals but not in healthy animals (129-132). The probable mechanism of its action is through activation of the pyruvate-dehydrogenase via direct inhibition of pyruvate dehydrogenase kinase (133,134). Because both lactate and alanine exist in equilibrium with pyruvate, when pyruvate is oxidized, lactate and alanine conversion into pyruvate is increased. Consequently, less lactate and alanine are released from peripheral into the circulation. Figure 36 schematically summarizes the site of action of dichloroacetate (DCA) in pyruvate metabolism and illustrates the resultant anticipated effects on alanine and lactate concentrations.

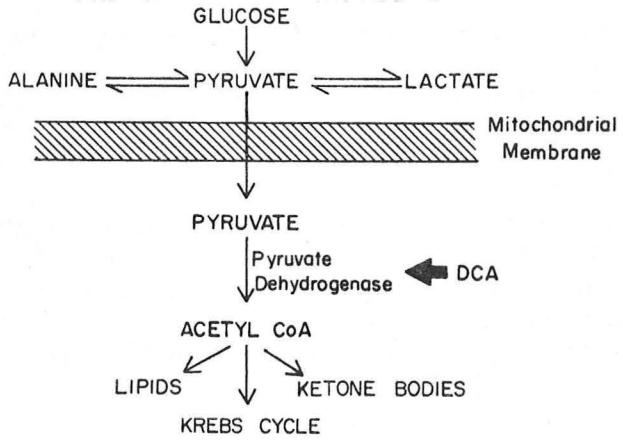

Figure 36. Site of action of dichloroacetate (DCA). From Stacpoole, 1983.

Figure 37 illustrates schematically the mechanism by which dichloroacetate activates the pyruvate dehydrogenase complex. As can be seen from this figure, pyruvate dehydrogenase in its active form is inactivated by a specific kinase and activated by a specific phosphatase. Dichloroacetate stimulates the activity of pyruvate dehydrogenase via inhibition of the kinase reaction.

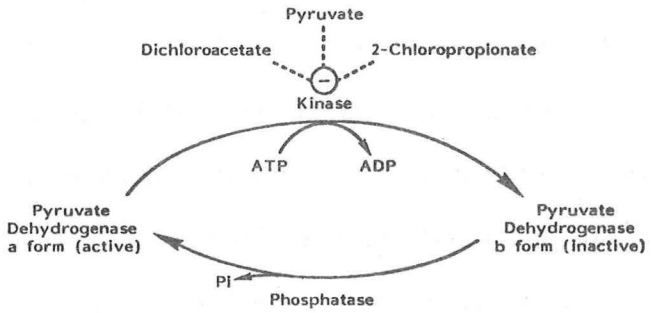

Figure 37. Mechanism by which dichloroacetate activates the pyruvate dehydrogenase complex. From Crabb et al, 1981.

Although there have been numerous studies on the use of dichloroacetate in experimental models of lactic acidosis, there has been a recent publication of the use of this compound in the treatment of bicarbonate resistant lactic acidosis in human subjects (128). The results of this treatment are outlined in Table 25. Listed in this table are the results of the seven patients who demonstrated a biochemical response to the infusion of 35-50 mg/kg of dichloroacetate intravenously. As can be seen there was a major dramatic response of these patients with respect to lowering of their plasma lactate and elevation of their plasma bicarbonate concentrations. The effect of

TABLE XXV

EFFECT OF DICHLOROACETATE (ACUTE INTRAVENOUS) ON "BICARBONATE-RESISTANT" LACTIC ACIDOSIS

	pH		Lactate		HCO_3	
	Pre	Post	Pre	Post	Pre	Post
1)	7.26	7.36	6.8	1.4	15	18
2)	7.23	7.24	9.4	2.4	16	18
3)	7.27	7.37	7.7	6.0	12	13
4)	7.19	7.34	10.6	2.2	17	22
5)	7.29	7.46	25.0	1.8	14	37
6)	7.10	7.42	17.2	4.7	17	21
7)	7.34	7.53	22.4	1.1	8	20
	7.24 ±0.03	7.39 ±0.04	14.2 ±2.8	2.8 ±0.7	14 ±1	21 ±3

From: Stacpoole PW, et al: NEJM 309:390-396.

this compound on survival could not be addressed in this study since all but one patient died of their underlying disease. It should also be recalled that all of these patients had lactic acidosis that was refractory to the administration of large amounts of alkali.

Orally administered dichloroacetate is known to be toxic to mammals. The toxicity of this compound is reviewed in detail in reference 125. While dichloroacetate itself may not be the safest therapeutic agent of this type, its importance lies in the fact that it provides demonstration for possible therapeutic efficacy of control of pyruvate metabolism in the management of lactic acidosis.

PROGNOSIS OF LACTIC ACIDOSIS

It has become increasingly better appreciated that the extent of lactic acidosis under numerous clinical circumstances correlates significantly with survival. For example, Peretz and colleagues in a study of 52 patients with shock of various etiologies including myocardial infarction, hemorrhage, gram negative sepsis, and post-major surgery, demonstrated a significant relationship between mortality and initial blood lactate concentration (135). This relationship is demonstrated in Figure 38. Similar observations have been made in patients with other disorders such as heat stroke (136), and Reye's syndrome (70). It is not surprising that many investigators can demonstrate

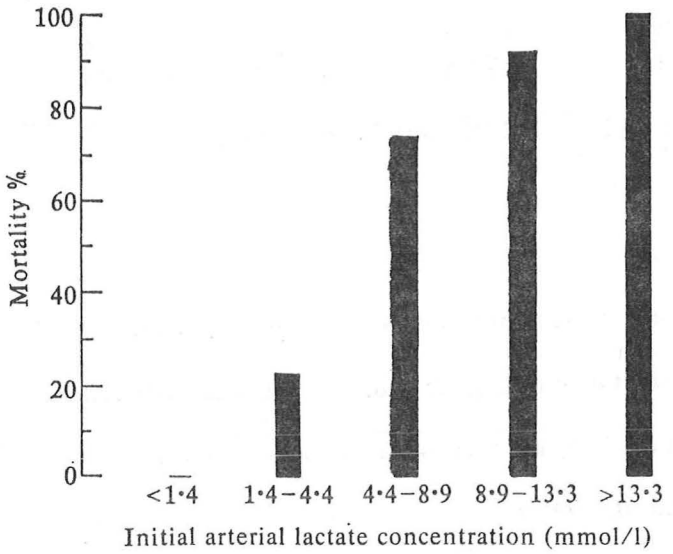

Figure 38. The relationship between mortality and initial blood lactate concentration in patients with chock (Peretz et al, 1965). The figure depicts the relationship between mortality and arterial blood lactate concentrations based on a study of 52 patients.

a relationship between survival and elevation of plasma lactate levels. When one appreciates the significance that elevated plasma lactate levels has with respect to disturbances in normal metabolism, it is apparent that awareness of such a relationship will provide a strong impetus to anticipate the clinical setting in which lactic acidosis occurs and to either prevent its occurrence or intervene as early as possible.

REFERENCES

1. Huckabee WE. Amer. J. Cardiology, November 1963, pp. 663-666.
2. Huckabee WE. Amer. J. Med., June 1961, pp. 833-839.
3. Huckabee WE. Amer. J. Med. June 1961, pp. 840-848.
4. Cori CF, Cori GT. J. Biol. Chem. 81:389, 1929.
5. Huennekens FM, Mahler HR, Nordmann J. Arch. Biochem. 30:66, 1951.
6. Mahler HR, Tomisek A, Huennekens FM. Exptl. Cell Res. 4:208, 1953.
7. Alpert NR. Ann. N.Y. Acad. Sci. 119:995, 1965.
8. Dubinsky WP, Racker E. J. Membrane Biol. 44:25-36, 1978.
9. Spencer TL, Lehninger AL. Biochem. J. 154:405-414, 1976.
10. Pichette C, Bercovici M, Goldstein M, et al. Crit. Care Med. 10:323, 1982.
11. Benade AJS, Heisler N. Respir. Physiol. 32:369-380, 1978.
12. Kreisberg RA, Pennington LF, Boshell BR. Diabetes 19:64, 1970.
13. Cohen RD, Woods HF. Chemical and Biochemical Aspects of Lactic Acidosis. London: Blackwell, 1976.
14. Linn TC, Pettit FH, Reed LJ. Proc. Natl. Acad. Sci. USA 62:234, 1969.
15. Garland PB, Randle PJ. Biochem. J. 91:6c, 1964.
16. Emmett M, Narins RG. Medicine 56:38-54, 1977.
17. Adrogue HJ, Brensilver J, Madias NE. Am. J. Physiol. 235: F291-F297, 1978.
18. Oster JR, Perez GO, Vaamonde CA. Am. J. Physiol. 235: F345-F351, 1978.
19. O'Connor LR, Klein KL, Bethune JE. N. Engl. J. Med. 297:707, 1977.
20. Narins RG, Rudnick MR, Bastl CP. Hosp. Prac. May 1980, p. 125.
21. Perez GO, Oster JR, Vaamonde CA. Nephron 27:233-243, 1981.
22. Fulop M. N. Engl. J. Med. 300:1087, 1979.
23. Sriussadaporn S, Cohn JN. Circulation 37, Suppl. 6, 197, 1968.
24. Eichenholz A, Mulhausen RO, Anderson WE. J. Appl. Physiol. 17:283-288, 1962.

25. Giebisch G, Berger L, Pitts RF. J. Clin. Invest. 34:231, 1955.

26. Bock AV, Dill DB, Edwards HT. J. Clin. Invest. 11:775, 1932.

27. Bolke B, Ellis JP, Jr, Wells JG. J. Appl. Physiol. 12:269, 1958.

28. Huckabee WE. J. Clin. Invest. 37:244, 1958.

29. Trivedi B, Danforth WH. J. Biol. Chem. 241:4110, 1966.

30. Ui M. Biochim. Biophys. Acta 124:310-322, 1966.

31. Burr MJ. Comp. Biochem. Physiol. 41B:687-694, 1972.

32. Eldridge F, Salzer J. J. Appl. Physiol. 22:461, 1967.

33. Huckabee WE. Amer. J. Med. 30:833, 1961.

34. Dossetor JB, Zborowski D, Dixon HB, et al. Ann. N.Y. Acad. Sci. 119:1153, 1965.

35. Orringer, et al. N. Engl. J. Med. 297:796-799, 1977.

36. Yudkin J, Cohen RD. 48:121-131, 1975.

37. Arieff AI, Park R, Leach WJ, et al. Am. J. Physiol. 239:F135, 1980.

38. Lloyd MH, Iles RA, Simpson BR, et al. Clin. Sci. Molec. Med. 45:543-549, 1973.

39. Iles RA et al. Clin. Sci. 60:537-542, 1981.

40. KleinkeJ, Soling HD. In: Regulation of Gluconeogenesis. Georg Thieme Stuttgart, 1971, p. 20.

41. Wildenthal K, Mierzwiak DS, Myers RW, et al. Amer. J. Physiol. 214:1352, 1968.

42. Bendixen HH, Laver MB, Flacke WE. Circulation Res. 13:64-70, 1963.

43. Darby TD, Aldinger EE, Gadsden RH, et al. Circ. Res. 8:1242-1253, 1960.

44. Gremels H, Starling EH. J. Physiol., London 61:297-304, 1926.

45. Lorkovic H. Circ. Res. 19:711-720, 1966.

46. McElroy WT, Jr, Gerdes AJ, Brown EB, Jr. Am. J. Physiol. 195:412-416, 1958.

47. Ng ML, Levy MN, Zieske HA. Am. J. Physiol. 213:115-120, 1967.

48. Ritz E, Heidland A. Clin. Nephr. 7:231, 1977.

49. Park R, Arieff AI. In Advances in Internal Medicine, vol. 25, Chicago, Year Book Medical Publishers, 1980, p. 33.

50. Jervell O. Acta. Med. Scand. Suppl. 24, 1, 1928.

51. Anderson J, Mazza R. Lancet iii:270, 1963.

52. Tranquada RE, Grant WJ, Peterson CR. Arch. Intern. Med. 117:192, 1966.

53. Hartmann AF. Arch. Intern. Med. 56:413, 1935.

54. Watkins PJ, Smith JS, Fitzgerald MG, et al. Brit. Med. J. 1:744, 1969.

55. Marliss EB, Ohman JL, Aoki TT, et al. N. Engl. J. Med. 283:978, 1970.

56. Zimmet PZ, Taft P, Ennis GC, et al. Brit. Med. J. 3:610, 1970.

57. Hockaday TDR, Alberti KGMM. Clin. Endocrinol. Metab. 1:3, 751, 1972.

58. Arieff AI, Carroll HJ. Medicine 51:73, 1972.

59. Tolstoi E, Loebel R, Levine SZ, et al. Proc. Soc. Exp. Biol. Med. 21:449, 1924.

60. Williamson JR, Krebs HA. Biochem. J. 80:540, 1961.

61. Davis EJ. Canad. J. Biochem. 43:1001, 1965.

62. Alleyne GAO, Scullard GH. J. Clin. Invest. 48:364, 1969.

63. Rutsky EA, McDaniel HG, Tharpe DL, et al. Arch. Intern. Med. 138:1364, 1978.

64. Garber AJ, Bier DM, Cryer PE, et al. Diabetes 23:982-986, 1974.

65. Peitzman SJ, Agarwal BN. Nephron 19:131-139, 1977.

66. Ganda OP, Aoki TT, Soeldner JS, et al. J. Clin. Invest. 57:1403-1411, 1976.

67. Berry MN, Scheuer J. Metabolism 16:537, 1967.

68. Record CO, Iles RA, Cohen RD, et al. Gut 16:144, 1975.

69. Mulhausen R, Eichenholz A, Blumentals A. Medicine 46:185, 1967.

70. Tonsgard JH, Huttenlocher PR, Thisted RA. Pediatrics 69:64, 1983.

71. Heinig RE, Clarke EF, Waterhouse C. Arch. Intern. Med. 139:1229, 1979.

72. MacLean LD, Mulligan WG, McLean APH, et al. Ann. Surgery 166:543, 1967.

73. Warburg O: Uber den stoffwechsel des Tumoren. Springer-Verlag, Berlin, 1926.

74. Racker E. J. Cell. Physiol. 89:697, 1976.

75. Harguindey S. Med. Pediatr. Oncol. 10:217, 1982.

76. Burk D, Woods M, Hunter J. J. Nat. Cancer Inst. 38:839, 1967.

77. Field M, Block JB, Levin R, et al. Amer. J. Med. 40:528, 1966.

78. Chen Y-H, Schade SG, Brynes RK. South. Med. J. 73:1656, 1980.

79. Nadiminti Y, Wang JC, Chou S-Y, et al. N. Engl. J. Med. 303:15, 1980.

80. Fraley DS, Adler S, Bruns FJ, et al. N. Engl. J. Med. 303:1100, 1980.

81. Fields LA, Wolman SL, Halperin ML. Cancer 47:2026, 1981.

82. Varanasi UR, Carr B, Simpson DP. Cancer Treatment Reports 64:1283, 1980.

83. Stacpoole PW, Lichgenstein MJ, Polk JR, et al. South. Med. J. 74:868, 1981.

84. Tranquada RE, Bernstein S, Martin HE. JAMA 184:158, 1963.

85. Luft D, Schmulling RM, Eggstein M. Diabetologia 14:75, 1978.

86. Misbin RI. Ann. Intern. Med. 87:591, 1977.

87. Lieber CS, Jones DP, Losowsky HS, et al. J. Clin. Invest. 41:1863, 1962.

88. Seligson D, Waldstein SS, Giges B, et al. Clin. Res. Proc. 1:86, 1953.

89. Seligson D, Stone HH, Nenir P. Surg. Forum. 9:85, 1958.

90. Krebs HA, Cunningham DJC, Stubbs M, et al. Israel J. Med. Sci. 5:959, 1969.

91. Krebs HA. Adv. Enzyme Regul. 6:467, 1968.

92. Daughaday WH, Lipicky RJ, Rasinski DC. N. Engl. J. Med. 267, 1010, 1962.

93. Kreisberg RA, Owen WC, Siegal AM. J. Clin. Invest. 50:166, 1971.

94. Miller PD, Heinig RE, Waterhouse C. Arch. Intern. Med. 138:67, 1978.

95. Cederbaum AI, Lieber CS, Rubin E. Arch. Biochem. Biophys. 161:26, 1974.

96. Williamson JR, Scholz R, Browning ET, et al. J. Biol Chem. 244:5044, 1969.

97. Kiessling KH, Tilander K. Exp. Cell Res. 30:476, 1963.

98. Rubin E, Beattie DS, Toth A, et al. Fed. Proc. 31:131, 1972.

99. Cederbaum AI, Lieber CS, Beattie DS, et al. Biochem. Biophys. Res. Commun. 49:649, 1972.

100. Greene HL, Schubert WK, Hug G. J Pediatr. 76:853, 1970.

101. Kuroda Y, Kline JJ, Sweetman L, et al. Pediat. Res. 13:928, 1979.

102. Cowan MJ, Packman S, Wara DW, et al. Lancet II:115, 1979.

103. Robinson BH, Taylor J, Sherwood WG. Pediatr. Res. 14:956, 1980.

104. Koike M, Koike K. Ann. NY Acad. Sci. 378:225, 1982.

105. Kobayashi Y, Miyabayashi S, Takada G, et al. Eur. J. Pediatr. 139:25, 1982.

106. Sherwood WG, Saunders M, robinson BH, et al. J. Pediatr. 101:546, 1982.

107. Toshima K, Kuroda Y, Hashimoto T, et al. Pediatr. Res. 16:430, 1982.

108. Arieff AI, Park R, Leach WJ, et al. Am. J. Physiol. 239:F135, 1980.

109. Arieff AI, Leach W, Park R, et al. Am. J. Physiol. 242:F586, 1982.

110. Park R, Arieff AI. J. Clin. Invest. 70:853, 1982.

111. Foulks CJ, Wright LF. South. Med. J. 74:1162, 1981.

112. Vaziri ND, Ness R, Wellikson L, et al. Am. J. Med. 67:392, 1979.

113. Maguire LC, Sherman BM, Whalen JE. Am. J. Med. Sci. 276:305, 1978.

114. Miller PD, Heinig RE, Waterhouse C. Arch. Intern. Med. 138:67, 1978.

115. Coleman RA, Sommerville HM, Friedman HS, et al. J. Pediatr. 100:584, 1982.

116. Brazis M, Rowe M, Shalev O. Brit. Med. J. 2:1399, 1979.

117. Whalen JE, DiBona GF. Proc. Soc. Exper. Biol. Med. 158:426, 1978.

118. Mellino M, Phillips DF. Cleve. Clin. Quart. 47:119, 1980.

119. Capretti L, Fici F, Coscelli C, et al. Horm. Metab. Res. 13:472, 1981.

120. Loubatieres AL, Ribes G, Valette G. Proc. B.P.S. September 15-17, 1976, 429P.

121. Cohen RD, Iles RA. N. Engl. J. Med. 298:1364, 1978.

122. Coude FX, Saudubray JM, DeMaugre F, et al. N. Engl. J. Med. 299:1365, 1978.

123. Stacpoole PW, Moore GW, Kornhauser DM. N. Engl. J. Med. 298:526, 1978.

124. Wells PG, Moore GW, Rabin D, et al. Diabetologia 19:109, 1980.

125. Crabb DW, Yound EA, Harris RA. Metabolism 30:1024, 1981.

126. Evans OB, Stacpoole PW. Biochem. Pharmacol. 31:1295, 1982.

127. Blackshear PJ, Fang LS-T, Axelrod L. Diabetes Care 5:391, 1982.

128. Stacpoole PW, Harman EM, Curry SH, et al. N. Engl. J. Med. 309:390, 1983.

129. Lorini M, Ciman M. Biochem. Pharmacol. 11:832, 1962.

130. Stacpoole PW, Felts JM. Metabolism 19:71, 1970.

131. Fichner HL, Stacpoole PW, Forsham PH. Diabetes 23:179, 1974.

132. Blackshear PJ, Holloway PAH, Alberti KGMM. Biochem. J. 142:279, 1974.

133. Whitehouse S, Randle PJ. Biochem. J. 134:651, 1973.

134. Whitehouse S, Cooper RH, Randle PJ. Biochem. J. 141:761, 1974.

135. Peretz DI, Scott HM, Duff J, et al. Ann. NY Acad. Sci. 119:1133, 1965.

136. Hart GR, Anderson RJ, Crumpler CP, et al. Medicine 61:189, 1982.

APPENDIX

CASE PRESENTATION

HW is a 30-year-old black male, IV drug abuser, with end-stage renal disease on hemodialysis, admitted to Parkland Memorial Hospital with a history of recent onset of nausea, vomiting, fever, and somnolence with mental confusion.

The patient presented with the nephrotic syndrome in early 1982 with 18 g protein excretion per 24 h. A renal biopsy at that time failed to provide sufficient tissue for histologic diagnosis. The patient was followed in renal clinic with a presumed diagnosis of focal sclerosing glomerulonephritis secondary to IV drug abuse. In early 1983 the patient was admitted to PMH for initiation of hemodialysis because of progressive renal failure. At that time he had a BUN of 177 and a creatinine of 41. He was followed in the outpatient dialysis center and was admitted in the middle of 1983 with a clotted vascular access. At that time his hematocrit was 27% and he had abnormal liver function tests, but was demonstrated to be hepatis B surface antigen negative. It is presumed that he continued his habit of parenteral administration of illicit drugs. On the day prior to the present admission, he was dialyzed without any apparent complications. However, he had complained of feeling sick when he arrived home from that dialysis with development of nausea and vomiting and progressive lethargy. He was brought to the emergency room responsive only to pain. There was no history of seizures, diarrhea, or bleeding. On admission, he had a temperature of 38.5, BP of 150/80 without a significant change on tilting. His pulse was 120 and regular and his respiratory rate was 18. Physical exam revealed an abscess on his left cheek,

supple neck, clear lungs, the presence of an S_4 gallop, and the presence of a 3 out of 6 systolic ejection murmur at the left sternal border. Abdominal exam was negative as was rectal exam. Stool guaiac was negative. Neurologic exam revealed an obtunded individual with no focal neurologic findings. Initial laboratory data revealed a white blood cell count of 38,000 with a slight left shift, hematocrit of 11%, 295,000 platelets, a prolonged Pro time at 15.6 seconds with control of 13, and a prolonged PTT at 36 seconds with a control of 28. Reticulocyte count was 2.2% and the erythrocyte sedimentation rate was 145 mm/h. The peripheral smear showed a few schistocytes with some splenocytes and rouleaux formation. Most of the red blood cells appeared normal morphologically. White blood cells on smear showed toxic granulation. Serum chemistries showed a Na of 146 mEq/L, K 5.1 mEq/L, Cl 96 mEq/L, total CO_2 15 mEq/L, glucose 41 mg%, BUN 86 mg%, calcium 8.9 mg%, and bilirubin 2.4. The initial anion gap was thus 35 mEq/L. Lactic acid concentration obtained shortly after admission was 136 mg% or 15 mEq/L. Toxicology screen was negative except for the possibility of an amphetamine spike. Fibrin split products were slightly elevated between 10 and 40 and fibrinogen was normal at 350 mg%. Chest x-ray was normal and electrocardiagram showed sinus tachycardia with peak T waves in the lateral precordial leads. The direct Coombs test was negative but an anti-Lewis antibody was found on type and crossmatch. It should be known that all bloods drawn from the patient demonstrated pink plasma which was presumed to be evidence for intravascular hemolysis. Diagnoses on admission included: 1) sepsis, 2) intravascular hemolysis, 3) increased anion gap acidosis of dual etiology including uremic acidosis and lactic acidosis, 4) end-stage renal disease. A central venous line was placed in the right subclavian vein and a peripheral IV was also started. Six blood cultures were taken and a spinal tap was performed which

demonstrated clear spinal fluid that showed no organisms on gram stain. The abscess on the left cheek was drained and cultured and the gram stain of the pus obtained revealed gram positive and gram negative organisms. The patient was started on vancomycin and tobramycin. He was typed and crossmatched and transfused with packed red blood cells. In addition, hydrocortisone 100 mg was given IV. The patient was given glucose and insulin and volume expanded with normal saline. The patient made an uneventful recovery and within 36 hours of admission his sodium was 136, K 4.9, Cl 89, total CO_2 25, glucose 126, and BUN 100. At this time his anion gap was 22 mEq/L.

This patient demonstrates an excellent example of the presentation and management of acute lactic acidosis in a critically ill patient.