

Treatment of Lactic Acidosis with Dichloroacetate in Dogs

Robert Park, ... , William Leach, Virginia C. Lazarowitz

J Clin Invest. 1982;70(4):853-862. <https://doi.org/10.1172/JCI110682>.

Research Article

Lactic acidosis is a clinical condition due to accumulation of H⁺ ions from lactic acid, characterized by blood lactate levels >5 mM and arterial pH <7.25. In addition to supportive care, treatment usually consists of intravenous NaHCO₃, with a resultant mortality >60%. Dichloroacetate (DCA) is a compound that lowers blood lactate levels under various conditions in both man and laboratory animals. It acts to increase pyruvate oxidation by activation of pyruvate dehydrogenase. We evaluated the effects of DCA in the treatment of two different models of type B experimental lactic acidosis in diabetic dogs: hepatectomy-lactic acidosis and phenformin-lactic acidosis. The metabolic and systemic effects examined included arterial blood pH and levels of bicarbonate and lactate; the intracellular pH (pHi) in liver and skeletal muscle; cardiac index, arterial blood pressure and liver blood flow; liver lactate uptake and extrahepatic splanchnic (gut) lactate production; and mortality. Effects of DCA were compared with those of either NaCl or NaHCO₃. The infusion of DCA and NaHCO₃, delivered equal amounts of volume and sodium, although the quantity of NaHCO₃ infused (2.5 meq/kg per h) was insufficient to normalize arterial pH.

In phenformin-lactic acidosis, DCA-treated animals had a mortality of 22%, vs. 89% in those treated with NaHCO₃. DCA therapy increased arterial pH and bicarbonate, liver pHi and cardiac index, with increased liver lactate uptake and [...]

Find the latest version:

<https://jci.me/110682/pdf>



Treatment of Lactic Acidosis with Dichloroacetate in Dogs

ROBERT PARK and ALLEN I. ARIEFF with the technical assistance of
WILLIAM LEACH and VIRGINIA C. LAZAROWITZ, *Division of Nephrology,*
Department of Medicine, Veterans Administration Medical Center;
University of California School of Medicine, San Francisco, California 94121

ABSTRACT Lactic acidosis is a clinical condition due to accumulation of H^+ ions from lactic acid, characterized by blood lactate levels >5 mM and arterial pH <7.25 . In addition to supportive care, treatment usually consists of intravenous $NaHCO_3$, with a resultant mortality $>60\%$. Dichloroacetate (DCA) is a compound that lowers blood lactate levels under various conditions in both man and laboratory animals. It acts to increase pyruvate oxidation by activation of pyruvate dehydrogenase. We evaluated the effects of DCA in the treatment of two different models of type B experimental lactic acidosis in diabetic dogs: hepatectomy-lactic acidosis and phenformin-lactic acidosis. The metabolic and systemic effects examined included arterial blood pH and levels of bicarbonate and lactate; the intracellular pH (pHi) in liver and skeletal muscle; cardiac index, arterial blood pressure and liver blood flow; liver lactate uptake and extrahepatic splanchnic (gut) lactate production; and mortality. Effects of DCA were compared with those of either NaCl or $NaHCO_3$. The infusion of DCA and $NaHCO_3$, delivered equal amounts of volume and sodium, although the quantity of $NaHCO_3$ infused (2.5 meq/kg per h) was insufficient to normalize arterial pH.

In phenformin-lactic acidosis, DCA-treated animals had a mortality of 22%, vs. 89% in those treated with $NaHCO_3$. DCA therapy increased arterial pH and bicarbonate, liver pHi and cardiac index, with increased

liver lactate uptake and a fall in blood lactate. With $NaHCO_3$ therapy, there were decrements of cardiac index and liver pHi, with an increase in venous pCO_2 and gut production of lactate.

Dogs with hepatectomy-lactic acidosis were either treated or pretreated with DCA. Treatment with DCA resulted in stabilization of cardiac index, a fall in blood lactate, and 17% mortality. $NaHCO_3$ was associated with a continuous decline of cardiac index, rise in blood lactate, and 67% mortality. In dogs pretreated with NaCl, mortality was 33%, but all dogs pretreated with DCA survived. Dogs pretreated with DCA also had lower blood lactate and higher arterial pH and bicarbonate than did those pretreated with NaCl.

Thus, in either of two models of type B experimental lactic acidosis, treatment with DCA improves cardiac index, arterial pH, bicarbonate and lactate, and liver pHi. The mortality in dogs with type B lactic acidosis was significantly less in DCA-treated animals than in those treated with other modalities.

INTRODUCTION

Lactic acidosis is a clinical syndrome characterized by metabolic acidosis caused primarily by accumulation of hydrogen ions from lactic acid. In general, patients with this disorder have blood lactate levels >5 mM, bicarbonate levels <15 mM, and arterial pH <7.25 (1, 2). The two major forms of lactic acidosis are classified as type A and type B (3). In type A lactic acidosis, there is clear evidence of conditions causing tissue hypoxia, such as shock or hypovolemia; in type B, there is no obvious cause for tissue hypoxia. The mortality in patients with lactic acidosis is $>85\%$ in type A and 50% in type B (1, 4, 5). The therapy of lactic acidosis has consisted primarily of intravenous bicarbonate, frequently in excess of 1,000 meq/d (1-4).

We have recently shown that bicarbonate treatment of animals with experimental phenformin-induced lac-

This work was presented in part at the Annual Meeting of American Federation for Clinical Research (AFCR), San Francisco, CA. (1978. *Clin. Res.* 26: 410a), and at the Annual Meeting, Western Section, AFCR, Carmel, CA. (1979. *Clin. Res.* 27: 48a.).

Dr. R. Park is a Research Associate of the Veterans Administration.

Address all correspondence to Dr. A. I. Arieff, Veterans Administration Medical Center, San Francisco, CA 94143.

Received for publication 29 December 1981 and in revised form 9 March 1982.

tic acidosis decreased cardiac output, increased lactate production by the splanchnic bed, and decreased intracellular pH (pHi)¹ in liver and erythrocytes. Furthermore, bicarbonate therapy had no effect on mortality (83%) when compared with saline treatment (83%) (6). These results, together with the substantial mortality associated with bicarbonate treatment in patients with lactic acidosis (2, 5), suggest that the role of bicarbonate therapy in this disorder should be re-evaluated.

Dichloroacetate (DCA) is a compound that lowers blood levels of glucose, triglycerides, and lactate under fasting or diabetic conditions, in both man and laboratory animals (7–10). In muscle, DCA increases the oxidation of pyruvate and other substrates derived from glucose by activation of pyruvate dehydrogenase (11, 12), the rate-limiting enzyme complex that regulates the entry of pyruvate into the tricarboxylic acid cycle.

The effect of DCA on blood lactate levels suggests that it might be useful in the treatment of type B lactic acidosis (13). This study was therefore designed to evaluate the systemic and metabolic effects of DCA in two different models of experimental type B lactic acidosis in the dog: phenformin-induced lactic acidosis and hepatectomy-lactic acidosis. Previous studies from this laboratory have shown that in dogs with phenformin-lactic acidosis, there is increased production of lactate by the extrahepatic splanchnic vascular bed (gut), along with impaired liver lactate uptake, low liver pHi, and decreased cardiac output (14). In hepatectomy-lactic acidosis, cardiac output also decreased (15). In this study, we evaluated the effects of DCA on the aforementioned abnormalities.

METHODS

Animal groups. Studies were carried out in eight groups of adult mongrel dogs of both sexes, mean weight (\pm SD) 23.9 \pm 6.3 kg fasted for 16 h. The groups of dogs were: (a) control diabetic dogs subjected to 180 min of general anesthesia; (b) phenformin-lactic acidosis; (c) phenformin-lactic acidosis treated with NaHCO₃; (d) phenformin-lactic acidosis treated with DCA; (e) hepatectomy-lactic acidosis; (f) hepatectomy-lactic acidosis treated with NaCl; (g) hepatectomy-lactic acidosis treated with DCA. Group 8 consisted of 10 dogs with hepatectomy-lactic acidosis treated with either NaHCO₃ (group 8a) or DCA (group 8b). In this group, measurements were made only of cardiac index and arterial pH and lactate.

Experimental procedures. Diabetes was induced by surgical pancreatectomy (14). Diabetic dogs, plasma glucose at least 17.5 mM, were then maintained for 9–20 d on Purina dog chow (Ralston Purina, Co., St. Louis, MO), NPH insulin (5–15 U/d to maintain plasma glucose between 8 and 16

mM), oral pancreatic extract (Entozymme, A. H. Robbins, Richmond, VA) (3 pills/d), and vitamin K (Aquamephyton, Merck, Sharp & Dohme, West Point, PA) (10 mg every other day). 2 d before the experiments insulin was withdrawn. At experiment time arterial levels of bicarbonate, acetoacetate, and β -hydroxybutyrate were normal. The animals were anesthetized with pentobarbital 18–20 mg/kg i.v., intubated, and mechanically ventilated with a Harvard large animal respirator (16) (Harvard Apparatus Co., S. Natick, MA). In all animal groups, arterial pCO₂ was adjusted to \sim 35 mmHg by small adjustments in the tidal volume.

In groups 2, 3, and 4, the abdomen was opened via a midline abdominal incision, and, when appropriate, polyethylene cannulas were placed in the aorta via the femoral artery, the inferior vena cava via the femoral vein, in the hepatic portal (HPV) vein via a branch of the splenic vein, and in the hepatic vein (HV) via the jugular vein. Both the HPV and hepatic artery (HA) were enclosed via a Statham flowmeter (Gould Statham blood flowmeter, model SP 2202, Gould, Inc., Medical Products Div., Oxnard, CA) cuff that was used to measure hepatic and splanchnic blood flow. A catheter was inserted into the pulmonary artery to measure cardiac output via thermodilution, using a cardiac output computer (No. 601, Instrumentation Laboratories, Inc., Lexington, MA).

Lactic acidosis was induced in groups 2–4 by infusion of phenformin hydrochloride (kindly supplied by Ciba-Geigy Corporation, Ardsley, NY), 7.5 mg/kg per h for a mean of 210 min (14). All dogs had arterial lactate levels >5 mM, pH <7.25, and bicarbonate <12 mM. Dogs in group 2 were killed after the 210 min of infusion. Dogs in group 3 were then treated with intravenous 8.4% NaHCO₃ infused at a rate of 2.5 meq/kg per h for a maximum of 4 h (mean rate of infusion = 60 meq/h). Dogs in group 4 were given DCA in 5.8% NaCl, 50 mg i.v. as a bolus followed by sustained infusion at a rate of 25 mg/kg per h (mean infusion = 4 meq/h), also for a maximum of 4 h. The rate of infusion of fluid and sodium were the same in groups 3 and 4. The DCA was administered as the sodium salt. Experiments were terminated either after 4 h of therapy, or before 4 h if either mean arterial pressure fell below 60 mmHg or cardiac index fell below 50% of the pretreatment value. Data in Table I for groups 3 and 4 were obtained at the termination of experiments.

Lactic acidosis was induced in groups 5, 6, 7, and 8 via functional hepatectomy produced in the following manner: a polyethylene catheter was inserted into the vena cava via the right femoral vein. Through a midline abdominal incision, the HPV was mobilized for 2–3 cm caudal to its entry into the liver. The HPV was ligated and then cannulated caudally. The HPV and vena cava catheters were connected with bayonet-style attachments so that HPV flow was completely diverted into the inferior vena cava. The total time required to complete diversion of HPV flow was <3 min. The HA was then identified and ligated.

Dogs in group 5 were given intravenously 154 mM NaCl, 0.4 meq/kg per h, beginning at the completion of hepatectomy and continuing for the duration of the experiment, which averaged 201 \pm 31 min. Dogs in group 6 received NaCl as above, beginning 2 h before hepatectomy. These animals were studied for a maximum of 4 h after hepatectomy. Group 7 dogs were pretreated with DCA beginning 2 h before hepatectomy. The dogs received a continuous infusion of DCA, 300 mg/kg per h for a maximum of 360 min. Group 8 dogs were given intravenously NaCl (0.4 meq/kg per h) beginning at the time of hepatectomy and continuing for 150 min. They then received either NaHCO₃ at a rate of 2.5

¹ Abbreviations used in this paper: DCA, dichloroacetate; HA, hepatic artery; HPV, hepatic portal vein; HV, hepatic vein; pHi, intracellular pH.

meq/kg per h or DCA as a bolus of 50 mg i.v. followed by a continuous infusion of 25 mg/kg per h (groups 8a and 8b). The studies continued for a maximum of 390 min. For group 7 and 8b dogs, the DCA was administered as the sodium salt following partial neutralization with NaOH to pH 6–6.5. The DCA was administered intravenously through an in-line 0.4- μ m filter (Millipore Corp., Bedford, MA) at a concentration of 7.5–12.5 mg/ml for group 8 dogs, and 90–150 mg/ml in group 7 animals. The DCA was dissolved in 5.8% NaCl and administered such that the rate of total sodium and volume delivery was similar in NaCl or NaHCO₃ vs. DCA-treated dogs (groups 6 vs. 7 and 8a vs. 8b).

Tissue and blood samples. In all groups, serial studies were made in arterial and HPV blood of pH, pCO₂, pO₂, bicarbonate, glucose, lactate, and pyruvate. In groups 1, 2, 3, and 4, the above were also measured in the HV and vena cava.

Intracellular pH (pHi) was measured in both liver and skeletal muscle using ¹⁴C-labeled 5,5'-dimethyl-oxazolinedione (DMO, New England Nuclear, Boston, MA) as previously described (16, 17).

Serial determinations of cardiac output using thermodilution technique were done in groups 1–5, 8a, and 8b, and serial measurements of HPV flow were done in groups 1–4.

The techniques for measurement in blood of lactate, pyruvate, glucose, pH, pCO₂, pO₂, and bicarbonate have been described (14, 16).

Calculations. Data are presented as mean \pm SE. For statistical analysis, the unpaired *t* test was used with the appropriate control, as indicated in the text. The paired *t* test was used only where indicated in the text.

In our measurements, the HA blood flow in seven normal dogs subjected to 180 min of anesthesia was 10.2 \pm 3.9 ml/kg per min, while that in HPV was 30.6 \pm 6.4 ml/kg per min. These values were not different after 1, 2, or 3 h of anesthesia. Thus, HA flow was 25% of total liver blood flow, a value that agrees closely with published values (18). HA flow was not measured in all studies, and when HPV flow was measured alone, HA flow was assumed to be a constant fraction (25%) of total liver blood flow. For all subsequent calculations of total liver lactate load and fractional liver lactate uptake, liver blood flow was calculated assuming HPV flow to represent 75% of total liver blood flow.

The lactate load presented to the liver was calculated as the sum of (HPV lactate) (HPV blood flow) + (HA lactate) (HA blood flow). Fractional hepatic lactate uptake was calculated as lactate extracted by the liver divided by lactate load presented to the liver. Hepatic lactate uptake was calculated as follows: hepatic lactate uptake = 0.75 (HPV lactate) + 0.25 (HA lactate) – (HV lactate) \times (HA + HPV blood flow).

RESULTS

Controls and dogs with phenformin-lactic acidosis. The values for arterial blood pH, pO₂, bicarbonate, lactate, and pHi of muscle and liver, are shown in Table I. Compared with control diabetic dogs, those with phenformin-lactic acidosis (phenformin infusion for 210 min) had metabolic acidosis (pH = 7.08 \pm 0.05) and hyperlactatemia (lactate = 8.2 \pm 0.7 mM). The pH, lactate, and bicarbonate were not different from values in groups 3 and 4 before therapy. The cardiac index was 58.3 \pm 9.5 ml/kg per min, vs. the control of 112 \pm 8.7 ml/kg per min (*P* < 0.01). The pHi of liver (6.81 \pm 0.05)

was also significantly below the control value (7.08 \pm 0.04, *P* < 0.01).

Dogs with phenformin-lactic acidosis were then treated with either intravenous NaHCO₃ (group 3) or DCA (group 4). Before treatment the values for arterial pH, lactate, and bicarbonate were 7.15 \pm 0.03, 7.0 \pm 0.5 mM, and 9.5 \pm 0.5 mM in group 3, and in group 4 arterial pH was 7.14 \pm 0.04, lactate was 8.6 \pm 0.9 mM and bicarbonate was 9.6 \pm 1.6 mM. None of the values were significantly different in group 3 vs. group 4 dogs. The pretreatment values in Fig. 1 represent pooled values for groups 3 and 4. The dogs were studied for up to 4 h from the time treatment with either DCA or NaHCO₃ was begun. The 4-h mortality was 91% in 11 group 3 dogs treated with NaHCO₃, while the mortality was 22% in 9 dogs receiving DCA. The cardiac indexes in the two groups of animals are shown in Fig. 2. During treatment with NaHCO₃, mean cardiac index decline from 62.4 \pm 10.4 ml/kg per min to 26.4 \pm 14.9 ml/kg per min in 3 h (*P* < 0.01). In the nine DCA-treated animals (group 4), cardiac index steadily rose from 68.6 \pm 7.0 ml/kg per min to 95.5 \pm 13.2 ml/kg per min after 4 h (control = 112 \pm 8.7 ml/kg per min, NS).

As shown in Fig. 1 and Table I, the changes in cardiac index were accompanied by corresponding changes in arterial pH, bicarbonate, and lactate. There was no change in arterial pH in bicarbonate-treated dogs, but a significant rise occurred (from 7.08 to 7.29, *P* < 0.01) in DCA-treated dogs. Similarly, blood bicarbonate was unaltered in bicarbonate-treated animals, but there was a significant increment (from 9.7 to 14.1 mM, *P* < 0.01) in DCA-treated dogs. The arterial pCO₂ was 32 \pm 3 mm Hg in group 4 dogs, and after DCA it was unaltered (32 \pm 3 mm Hg). However, in group 3 animals, arterial pCO₂ rose from 30 \pm 1 mm Hg to 35 \pm 3 mm Hg (*P* < 0.01 by paired *t* test). A more substantial change was observed in mixed venous (inferior vena cava) pCO₂. Venous pCO₂ was unaltered (37 \pm 3 mm Hg) after DCA treatment but after bicarbonate therapy, it rose to 55 \pm 5 mm Hg (*P* < 0.001). The most dramatic changes in arterial blood were seen in the lactate values. After NaHCO₃ therapy, blood lactate almost doubled (from 8.6 to 13.6 mM, *P* < 0.01). By contrast, DCA treatment resulted in a significant decrement of lactate (from 8.6 to 5.2 mM, *P* < 0.01, Fig. 1). The liver pHi, which was significantly decreased in dogs with lactic acidosis, fell still further (from 6.81 to 6.71, *P* < 0.01) following NaHCO₃ (Table I). However, after DCA, there was an increment of hepatocellular pHi (to 6.90) such that the value was significantly greater (*P* < 0.01) than in NaHCO₃-treated dogs.

Thus, DCA therapy resulted in normalization of cardiac index, with improvement in arterial pH, bicarbonate, lactate, and liver pHi, whereas bicarbonate

TABLE I
Effects of DCA vs. NaHCO₃ in Dogs with Phenformin-Lactic Acidosis

	Arterial pH	Arterial HCO ₃	Arterial lactate	HPV lactate	HV lactate	HPV flow ml/kg/min	HLU	HLU	EHSLP	Liver pHi	Muscle pHi
							%		μmol/kg/h		
Normal + 3-h anesthesia (group 0, n = 12)											
Mean	7.38	19.9	1.23	1.41	1.34	30.6	+8.8	+295	330	7.00	6.87
±SE	0.01	0.8	0.16	0.20	0.14	6.4		11	16	0.04	0.01
Control diabetic (group 1, n = 9)											
Mean	7.43	20.6	1.64	2.01	1.71	19.5	+10.5	+312	433	7.08	6.88
±SE	0.01	1.6	0.16	0.22	0.11	1.9		26	21	0.04	0.02
Phenformin-lactic acidosis (group 2, n = 8)											
Mean	7.08	9.7	8.2	9.8	9.6	10.6	-2.1	-170	1,018	6.81	6.87
±SE	0.05	1.6	0.7	0.6	1.0	1.2		52	112	0.05	0.03
Phenformin-lactic acidosis + NaHCO ₃ (group 3, n = 11)											
Mean	7.12	10.9	13.9	17.1	16.0	9.6	+1.8	+230	1,890	6.71	6.90
±SE	0.03	1.0	1.8	1.9	1.5	1.1		56	216	0.07	0.04
Phenformin-lactic acidosis + DCA (group 4, n = 9)											
Mean	7.29	14.1	5.6	7.2	6.3	12.3	+7.4	+492	1,181	6.90	6.86
±SE	0.04	1.7	0.9	1.2	1.1	1.6		67	148	0.03	0.04

HLU, hepatic lactate uptake; EHSLP, extrahepatic splanchnic lactate production; HPV flow is in ml/kg per min.

therapy was associated with a decrement of cardiac output and liver pHi, an increase in both arterial pCO₂ and lactate, and venous pCO₂, with no change in blood pH or bicarbonate. The mean survival time for DCA-treated animals (group 4) was 212±21 min, while that in bicarbonate-treated dogs was 132±31 min (*P* < 0.01). The survival times are calculated from the initiation of therapy. Survival times >4 h were counted as 4 h. Three dogs in group 4 were evaluated for extended survival after 4 h of DCA therapy. These three dogs had their laparotomy incision closed and were observed overnight. All three were alert and ambulatory the next day. The dogs were then sacrificed without additional studies being done.

Dogs with hepatectomy-lactic acidosis. Lactic acidosis was induced by functional hepatectomy, and dogs were treated with either NaCl, DCA, and NaHCO₃. In 10 untreated dogs (group 5) with hepatectomy-lactic acidosis, arterial pH was 7.05±0.04 (control = 7.38±0.01, *P* < 0.01) after 3 h of hepatectomy. The arterial lactate and bicarbonate were 9.1±0.9 and 8.3±1.1 mM, respectively. Mean arterial

pressure was 76±6 mm Hg (control = 94±10 mm Hg), and cardiac index was 52.4±22.2 ml/min (control = 115±7.8 ml/min, *P* < 0.01).

The controls for group 7 (pretreatment with DCA) were pretreated with 154 mM NaCl (group 6) so that volume status in the two groups was identical. After 3 h, the arterial pH, lactate, and bicarbonate in group 6 were 7.06±0.04, 10.6±2.2 mM, and 7.6±0.6 mM, respectively (Fig. 3). Mean arterial pressure was 79±1 mm Hg. After 4 h, arterial pH was 6.89±0.05, bicarbonate was 5.1±0.7 mM, and lactate was 11.7±2.6 mM. Four of six dogs survived 4 h after hepatectomy was performed.

Dogs in group 7 were pretreated with DCA (300 mg/kg i.v. sustained infusion) and observed for up to 4 h. After 3 h, arterial lactate was 3.8±0.5 mM while bicarbonate and pH were 11.4±1.3 mM and 7.18±0.04 respectively (Fig. 3). Mean arterial pressure was 79±8 mm Hg. All of the values were significantly different from both untreated dogs and saline-treated dogs (Fig. 3). After 4 h of DCA, arterial lactate was 4.3±0.6 mM, arterial pH was 7.16±0.04, and bicarbonate was

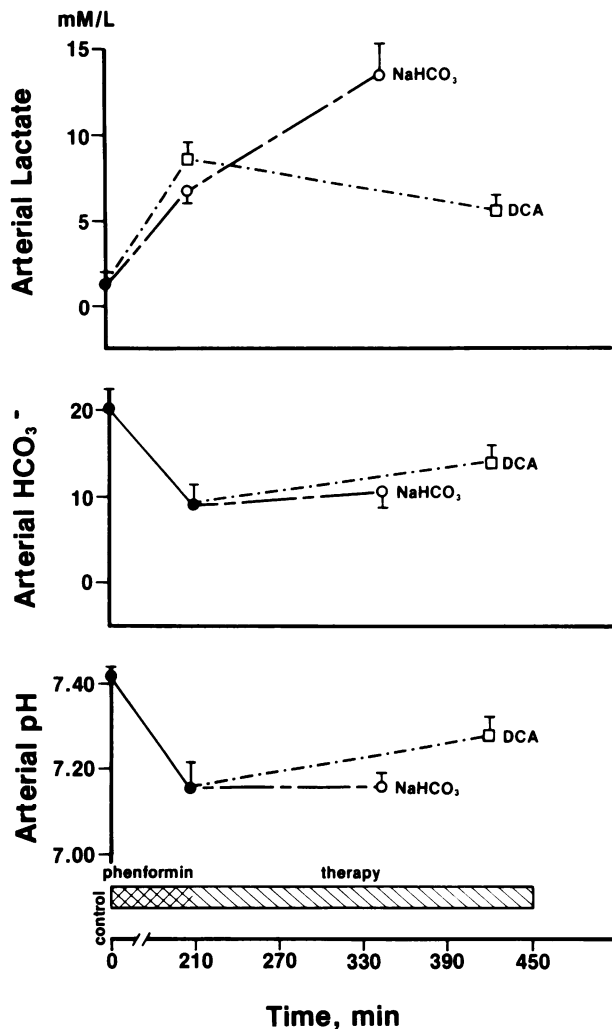


FIGURE 1 The effects of intravenous DCA vs. NaHCO₃ in dogs with phenformin-lactic acidosis are compared. Two groups of diabetic dogs were given intravenous phenformin for a mean of 210 min (groups 3 and 4) and then half received DCA (group 4) while the other half was given NaHCO₃ (group 3) for a maximum of 240 min. In the DCA-treated animals arterial lactate was significantly lower ($P < 0.01$) while arterial pH and bicarbonate (HCO₃⁻) were significantly higher ($P < 0.01$), despite the fact that the bicarbonate-treated dogs had received an average of 72 meq of NaHCO₃, vs. none for the DCA-treated animals.

11.0±1.1 mM (Fig. 4). All six dogs treated with DCA survived 4 h, at which time mean arterial pressure was 68±6 mm Hg.

In a separate group of dogs with hepatectomy-lactic acidosis, effects of DCA vs. NaHCO₃ therapy were evaluated on cardiac index only (groups 8a and 8b). After 2.5 h of hepatectomy-lactic acidosis, arterial pH

was 7.06±0.05 and lactate was 10.1±1.1 mM. Cardiac index had fallen to 52.4 ml/kg per min vs. the control value of 115 ml/kg per min ($P < 0.01$) (Fig. 4). At this point, half of the dogs were given NaHCO₃ and half were given DCA. Experiments were terminated when mean arterial pressure fell below 50 mm Hg or at the end of 4 h if the dogs survived.

Among dogs treated with NaHCO₃, the cardiac index fell from 53.6 to 26.0 ml/kg per min during therapy (Fig. 4) and only two of the six bicarbonate-treated dogs survived 4 h. The mean survival time was 147±37 min. At the time experiments were terminated, arterial pH was 7.34±0.04 and lactate was 11.1±1.4 mM.

Among dogs treated with DCA, the mean survival time was 220±20 min significantly longer than the time in NaHCO₃-treated dogs ($P < 0.05$) and five of six survived 4 h. However, in contrast to the results in bicarbonate-treated dogs, cardiac index did not decline during DCA therapy (Fig. 4). The blood lactate in DCA-treated dogs was 6.4±1.2 mM, significantly less ($P < 0.01$) than the value in NaHCO₃-treated animals. Arterial pH was 7.21±0.04, a value not significantly different from that in NaHCO₃ treated dogs ($P = 0.07$).

DISCUSSION

These data demonstrate that in dogs with two different types of type B experimental lactic acidosis, treatment with DCA significantly improves survival when compared with conventional therapy with either NaCl or NaHCO₃. In addition to improved survival, therapy with DCA results in significant improvement of several biochemical and physiological entities. In particular, treatment with DCA results in either an increase (Fig. 2) or stabilization (Fig. 4) of cardiac output; a decrement of blood lactate and an increase of blood pH and bicarbonate (Fig. 1); and a rise in liver pH (Table I).

In normal fasted dogs, DCA does not appear to increase lactate uptake by the liver (20). However, we evaluated the effects of DCA in dogs with phenformin-lactate acidosis, where fractional hepatic lactate extraction was actually negative (-2.1% vs. control value of 7.4%). Following treatment, absolute hepatic lactate uptake was twice the value in DCA vs. NaHCO₃-treated animals (492 vs. 230 μmol/kg per h, Table I). In terms of fractional removal of lactate, DCA-treated dogs extracted 7.4% of the calculated lactate load presented to the liver (492 of 6,691 μmol/kg per h) vs. only 1.8% of the total (230 of 12,518 μmol/kg per h) removed in NaHCO₃-treated dogs. Thus, the effects of DCA on blood lactate appear to be mediated in part by increased removal by the liver. The fractional he-

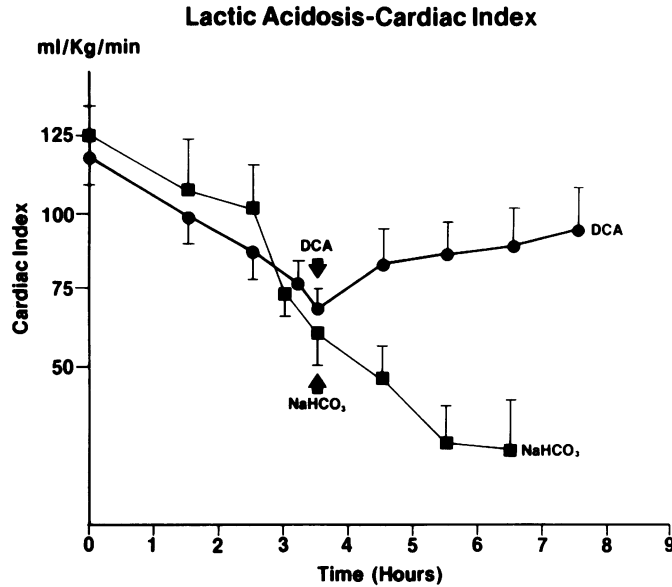


FIGURE 2 The effects of NaHCO₃ vs. DCA treatment on cardiac index in dogs with phenformin-lactic acidosis. After 4 h of intravenous DCA, cardiac index is not significantly different from the control value. During treatment with NaHCO₃, cardiac index progressively diminished, leading to an eventual 91% mortality, vs. a 22% mortality in DCA-treated dogs.

patic lactate extraction in diabetic dogs with phenformin-lactic acidosis receiving DCA (7.4%) was similar to the control diabetic value (10.5%) but less than the fractional extraction previously reported in fasted dogs treated with DCA infusion (20%) (20).

In dogs with hepatectomy-lactic acidosis, pretreatment with DCA resulted in a significantly lower blood lactate than did pretreatment with NaCl (Fig. 4). Since the liver was not present in this preparation, the observed effect of DCA on blood lactate had to be due to a decrease in extrahepatic lactate production.

There was no observed effect of DCA on gut production of lactate (extrahepatic splanchnic lactate production, Table I). Gut production of lactate in dogs with phenformin-lactic acidosis was 1,018 $\mu\text{mol/kg}$ per h (control = 433 $\mu\text{mol/kg}$ per h, $P < 0.01$) and this value was unaffected by DCA (Table I). Effects of DCA on gut lactate production have not previously been evaluated in lactic acidosis, but studies in normal fasting dogs have also shown that DCA has no effect (20).

Liver pHi, which is decreased in dogs with phenformin-lactic acidosis, was significantly increased by DCA, and lowered by NaHCO₃ (Table I). It has been shown that under a variety of physiological conditions that encompass an extracellular pH (pHe) range of 7.66–7.09, hepatic pHi does not change (16). In animals with phenformin-lactic acidosis, both in vivo (dog) and in vitro (isolated perfused guinea pig liver),

hepatic pHi is decreased (14, 21). The fall in pHi may have any of several possible important functional consequences.

One of the major substrates for hepatic gluconeogenesis is lactate. One of the rate-limiting enzymes for glucose synthesis from lactate is pyruvate carboxylase (22). This enzyme catalyzes the conversion of pyruvate to oxaloacetate and is markedly pH sensitive. At pH below ~ 6.90 , both enzyme activation and reaction velocity fall markedly (22–24). In this study, hepatic pHi was 6.81 (control = 7.08, $P < 0.01$) and this was associated with marked impairment in liver lactate uptake. It is possible that impaired activity of pyruvate carboxylase was a factor in the decreased liver lactate uptake.

The lactate load presented to the liver in dogs with phenformin-lactic acidosis was 7,952 $\mu\text{mol/kg}$ per h, but hepatic uptake was actually negative ($-170 \mu\text{mol/kg}$ per h, Table I). We have previously shown that the normal dog liver can extract at least 19% of the lactate load presented (2.3 of 12.2 mmol/kg per h), (16) and data from other laboratories are similar (20). DCA resulted in an increment of liver pHi to 6.90. Liver lactate extraction after DCA infusion increased from -2.1% to 7.4% of the delivered load, whereas with NaHCO₃ administration, extraction was only 1.8%. The rate of volume expansion was identical in the two groups. It may be that the increased lactate uptake following DCA was at least in part responsible for the

increment in hepatocellular pHi. Cohen and associates (24, 25) have presented evidence that for each lactate metabolized by the liver a proton is consumed, resulting in generation of a base equivalent that results in an increment of liver pHi. There may also be a direct action of DCA on liver pHi. Such an effect has not previously been evaluated and the present study provides no additional specific data. However, DCA also has a number of additional effects on the liver, both in vivo and in vitro, many of which appear unrelated to pyruvate dehydrogenase activation (26). The effects include amino acid transamination, production of oxalate and glyoxylate, and stimulation of fatty acid synthesis (26). These or other actions may in part explain the effect of DCA on liver pHi.

In comparing the effects of therapy with DCA vs. NaHCO_3 , it should be pointed out that we were not able to normalize arterial pH with NaHCO_3 (Fig. 2). It may be that if arterial pH had been normalized, the effects on lactic acidosis might have been different. In reviewing the literature, one sees that it has been possible to normalize arterial pH with NaHCO_3 in some individuals with lactic acidosis but not in others (2, 27-30). In 102 patients with phenformin-lactic acidosis, infusion of a mean of 527 meq of NaHCO_3 normalized arterial pH in 66% of patients (28). However, infusion of 500-1,200 meq/d of NaHCO_3 had no effect on arterial pH in five patients with other forms of lactic acidosis (2, 29, 30). Our dogs were potentially different from patients with lactic acidosis in several respects. In patients, the acidosis is often more severe (28), the patients are usually able to hyperventilate and to lower arterial pCO_2 (ventilation is fixed to maintain a constant arterial pCO_2 in the dogs), and it is often possible to normalize arterial pH with NaHCO_3 (28). Thus, it may not be possible to draw conclusions about the relative efficacy of DCA vs. effective alkalization. However, it must be pointed out that the quantity of bicarbonate infused (2.5 meq/kg per h) would be the equivalent of infusing 3,600 meq/d to a 60-kg human. Such a quantity of NaHCO_3 would raise serum sodium to >200 meq/liter, a condition which in itself carries a mortality >80% (31). In addition, infusion of bicarbonate resulted in production by the gut of an almost stoichiometric quantity of lactic acid (6). Thus, in this animal model, as well as in several reported cases, effective alkalization was not possible (2, 27, 29, 30). The most important factor in determining survival in patients with lactic acidosis may well be the presence of shock. With either clinical shock or arterial pH <6.9, mortality from phenformin-lactic acidosis is >70% (27, 28).

The effects of DCA on cardiac index were among the most important results observed in the current

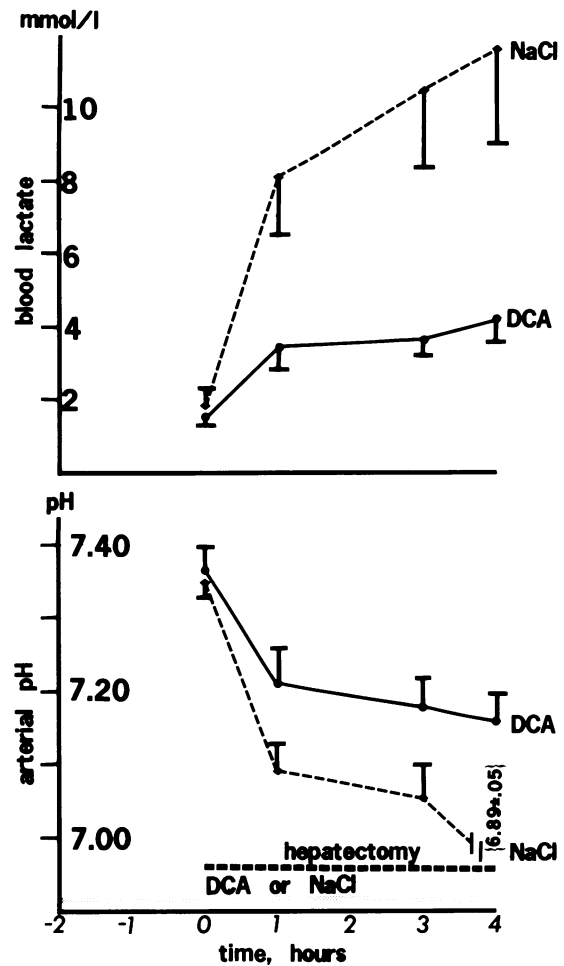


FIGURE 3 Two groups of dogs with hepatectomy-lactic acidosis (groups 6 and 7) were pretreated with either NaCl or DCA for 2 h before hepatectomy. The animals continued to receive either NaCl or DCA for the duration of hepatectomy, and arterial pH and lactate were compared in the two groups. At intervals 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.

study (Figs. 2 and 4). In dogs with phenformin-lactic acidosis, we have previously shown that cardiac index is significantly decreased (6, 15). The low cardiac index is not a result of metabolic acidemia (15, 32) and is not restored by volume expansion with NaCl or by NaHCO_3 infusion. The low cardiac index may be due to a low cardiac pHi (33). In addition, NaHCO_3 infusion further decreased cardiac index (Fig. 2). Bicarbonate has been shown to lower pHi, both in vitro and in vivo under selected conditions (6, 28). The NaHCO_3 infusion may have elevated blood pCO_2 , leading to a decrement of heart pHi (33, 34). Such an

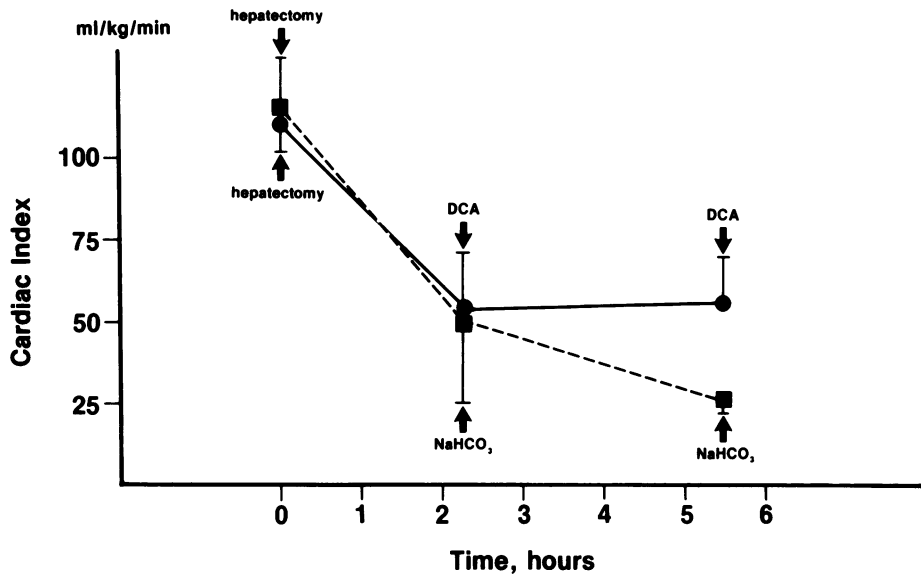


FIGURE 4 The effects on cardiac index of therapy with DCA vs. NaHCO_3 in dogs with hepatectomy-lactic acidosis. After 135 min of functional hepatectomy, cardiac index was reduced to 46% of the control value. In dogs treated with DCA, there was no further change in cardiac index, while in NaHCO_3 -treated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

effect could be expected to further depress myocardial contractility (33). In fact, although myocardial pH was not evaluated, mixed venous pCO_2 did increase from 37 ± 3 to 55 ± 5 mm Hg after NaHCO_3 infusion ($P < 0.001$).

After 4 h of DCA infusion, cardiac index was not significantly different from control values (Fig. 2). The reasons for improvement in cardiac function following DCA are unclear. Studies by McAllister and associates (11) in dogs showed that DCA increased lactate extraction by the heart whereas previous studies have demonstrated that myocardial extraction of both lactate and oxygen are impaired in dogs with phenformin-lactic acidosis (15). Furthermore, such dogs develop electrocardiogram abnormalities compatible with an acute ischemic injury current (15). In another model of acute myocardial ischemic injury, Mjos and associates (35) have evaluated effects of DCA infusion. In dogs with experimental coronary artery occlusion, intravenous DCA reduced the degree of ST-segment elevation, concomitant with increased myocardial extraction of glucose and decreased FFA extraction. These effects of DCA in the ischemic heart may also be operative in dogs with phenformin-lactic acidosis or hepatectomy-lactic acidosis.

We have also previously shown that in dogs with hepatectomy-lactic acidosis, cardiac index gradually decreases, and that this functional deterioration is not

due to metabolic acidemia per se (15). Others have documented cardiovascular collapse in liver failure, both in patients (36) and hepatectomized dogs (37). DCA administered to dogs with hepatectomy-lactic acidosis prevented further deterioration of cardiac index (Fig. 4). Pretreatment with DCA in dogs who subsequently underwent hepatectomy resulted in significantly improved survival, as well as lower blood lactate with higher arterial pH (Fig. 3).

Thus, DCA administration is associated with either biochemical, electrocardiographic or functional improvement of the heart in dogs with any of three different causes of myocardial deterioration: hepatectomy lactic acidosis (Fig. 4); phenformin-lactic acidosis (Table I, Fig. 2); or coronary artery occlusion (35). The relationship between these findings and known effects of DCA on the heart is not yet established (11, 26, 33).

Data from the present study (Figs. 1 and 3) and previous investigations (7-10, 20, 36, 38) show that intravenous DCA infusion can lower blood lactate levels under a variety of circumstances. In lactic acidosis due to either hepatectomy or phenformin, DCA infusion also results in improvement of blood pH and bicarbonate and an increase or stabilization of cardiac index (Figs. 1-4). The aforementioned effects of DCA are also associated with significantly improved 4-h survival in both phenformin-lactic acidosis (78% survival

with DCA vs. 9% survival with NaHCO₃ treatment) and hepatectomy-lactic acidosis (92% survival with DCA vs. 50% combined survival with NaCl or NaHCO₃). These effects of DCA may be unique to only these two forms of lactic acidosis and it is possible that DCA would be ineffectual in other forms of lactic acidosis. Additionally, as has been suggested (39), DCA may lower blood lactate in some forms of lactic acidosis but have no effect on the course of the associated illness (38).

There are some toxic effects of DCA that have been described after chronic administration. There include limb paralysis, cataracts, increased urinary oxalate excretion, testicular degeneration, neuropathy, mutagenicity, and changes in central nervous system white matter (26). Most such toxic effects result from long term oral administration of DCA, with few if any side effects reported with short-term intravenous use (26). Short-term administration to human subjects orally or intravenously has not resulted in any serious side effects (9, 38, 40). With the aforementioned reservations in mind, clinical trials of DCA as adjunctive therapy of lactic acidosis are probably indicated (13).

ACKNOWLEDGMENTS

The authors thank Mr. David Burlew for excellent secretarial and administrative assistance.

This study was supported by a grant from the Kroc Foundation, Santa Ynez, CA, a grant from the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health (RO1 AM18350) and by the Research Service of the Veterans Administration.

REFERENCES

1. Oliva, P. B., 1970. Lactic acidosis. *Am. J. Med.* **48**: 209-225.
2. Waters, W. C. III, J. D. Hall, and W. B. Schwartz. 1963. Spontaneous lactic acidosis. *Am. J. Med.* **35**: 781-793.
3. Cohen, R. D., and H. F. Woods. 1976. *Clinical and Biochemical Aspects of Lactic Acidosis*. Blackwell Scientific Publications, Oxford, England. 40-76.
4. Misbin, R. I. 1977. Phenformin-associated lactic acidosis: pathogenesis and treatment. *Ann. Intern. Med.* **87**: 591-595.
5. Park, R., and A. I. Arieff. 1980. Lactic acidosis. *Adv. Intern. Med.* **25**: 33-68.
6. Arieff, A. I., R. Park, W. Leach, and V. C. Lazarowitz. 1982. Systemic effects of NaHCO₃ in experimental lactic acidosis in dogs. *Am. J. Physiol.* **242**: F586-F591.
7. Blackshear, P. J., P. A. H. Holloway, and K. G. M. Alberti. 1974. The metabolic effects of sodium dichloroacetate in the starved rat. *Biochem. J.* **142**: 279-286.
8. Loubatieres, A. L., G. Ribes, and G. Valette. 1976. Pharmacological agents and acute experimental hyperlactatemia in the dog. *Br. J. Pharmacol.* **58**: 429P.
9. Stacpoole, P. W., G. W. Moore, and D. M. Kornhauser. 1978. Metabolic effects of dichloroacetate in patients with diabetes mellitus and hyperlipoproteinemia. *N. Engl. J. Med.* **298**: 526-530.
10. Merrill, G. F., E. J. Zambraski, and S. M. Grassl. 1980. Effect of dichloroacetate on plasma lactic acid in exercising dogs. *J. Appl. Physiol. Resp. Environ. Exercise Physiol.* **48**: 427-431.
11. McAllister, A., S. P. Allison, and R. J. Randle. 1973. Effects of dichloroacetate on the metabolism of glucose, pyruvate, acetate, 3-hydroxybutyrate, and palmitate in rat diaphragm and heart muscle in vitro and on extraction of glucose, lactate, pyruvate, and free fatty acids by dog heart in vivo. *Biochem. J.* **134**: 1067-1081.
12. Whitehouse, S., R. H. Cooper, and P. J. Randle. 1974. Mechanism of action of pyruvate dehydrogenase by dichloroacetate and other halogenated carboxylic acids. *Biochem. J.* **141**: 761-774.
13. Relman, A. D. 1978. Lactic acidosis and a possible new treatment. *N. Engl. J. Med.* **298**: 564-566.
14. Arieff, A. I., R. Park, W. J. Leach, and V. C. Lazarowitz. 1980. Pathophysiology of experimental lactic acidosis in dogs. *Am. J. Physiol.* **239**: F135-F142.
15. Arieff, A. I., E. D. Gertz, R. Park, W. Leach, and V. C. Lazarowitz. 1982. Lactic acidosis and the cardiovascular system in the dog. *Clin. Sci. (Oxf.)*. In press.
16. Park, R., W. J. Leach, and A. I. Arieff. 1979. Determination of the liver intracellular pH in vivo and its homeostasis in acute acidosis and alkalosis. *Am. J. Physiol.* **236**: F240-F245.
17. Park, R., W. J. Leach, and A. I. Arieff. 1980. Measurement of the liver extracellular space in vivo in dogs. *Horm. Metab. Res.* **12**: 680-684.
18. Greenway, C. V., and R. D. Stark. 1971. Hepatic vascular bed: Hepatic flows. *Physiol. Rev.* **51**: 26-29.
19. Park, R., W. J. Leach, and A. I. Arieff. 1979. Dichloroacetate decreases extrahepatic lactate production in diabetic dogs. *Clin. Res.* **27**: 374a.
20. Diamond, M. P., R. C. Rollings, L. Erlendson, P. E. Williams, W. W. Lacy, D. Rabin, and A. D. Cherrington. 1980. Dichloroacetate—its in vivo effects on carbohydrate metabolism in the conscious dog. *Diabetes.* **29**: 702-709.
21. Lloyd, M. H., R. A. Iles, B. Walton, C. A. Hamilton, and R. D. Cohen. 1975. Effect of phenformin on gluconeogenesis from lactate and intracellular pH in the isolated perfused guinea pig liver. *Diabetes.* **24**: 618-624.
22. Scutton, M. D., and M. F. Utter. 1967. Pyruvate carboxylase: Some properties of the activation by certain acyl derivatives of coenzyme A. *J. Biol. Chem.* **242**: 1723-1735.
23. Relman, A. S. 1972. Metabolic consequences of acid-base disorders. *Kidney Int.* **1**: 347-359.
24. Cohen, R. D., R. A. Iles, D. Barnett, M. E. O. Howell, and J. Strunin. 1971. The effect of changes in lactate uptake on the intracellular pH of the perfused rat liver. *Clin. Sci. (Oxf.)* **41**: 159-170.
25. Baron, P. G., R. A. Iles, and R. D. Cohen. 1978. Effect of varying pCO₂ on intracellular pH and lactate consumption in the isolated perfused rat liver. *Clin. Sci. Mol. Med.* **55**: 175-181.
26. Crabb, D. W., E. A. Yount, and R. A. Harris. 1981. The metabolic effects of dichloroacetate. *Metab. Clin. Exp.* **30**: 1024-1039.
27. Fulop, M., and H. D. Hoberman. 1976. Phenformin-associated metabolic acidosis. *Diabetes.* **25**: 292-296.
28. Luft, D., R. M. Schmulling, and M. Eggstein. 1978. Lac-

- tic acidosis in biguanide-treated diabetics. *Diabetologia*. **14**: 75-87.
29. Fraley, D. S., S. Adler, F. J. Bruns, and B. Zett. 1980. Stimulation of lactate production by administration of bicarbonate in a patient with a solid neoplasm and lactic acidosis. *N. Engl. J. Med.* **303**: 1100-1102.
 30. Fields, A. L. A., S. L. Wolman, and M. L. Halperin. 1981. Chronic lactic acidosis in a patient with cancer: therapy and metabolic consequences. *Cancer (Phila.)*. **47**: 2026-2029.
 31. Covey, C. M., and A. I. Arieff. 1978. Disorders of sodium and water metabolism and their effects on the central nervous system. In *Contemporary Issues in Nephrology*, Vol. I. B. M. Brenner and J. H. Stein, editors. Churchill Livingstone, New York. 212-241.
 32. Downing, S. E., J. C. Lee, and J. C. Werner. 1981. Effects of insulin on ventricular function in diabetic lambs with acidosis. *Am. J. Physiol.* **24**: H401-H407.
 33. Steenbergen, C., G. Deleeuw, T. Rich, and J. R. Williamson. 1977. Effects of acidosis and ischemia on contractility and intracellular pH of rat heart. *Circ. Res.* **41**: 849-858.
 34. Cohen, R. D., B. R. Simpson, F. J. Goodwin, and L. Strunin. 1967. The early effects of infusion of sodium bicarbonate and sodium lactate on intracellular hydrogen ion activity in dogs. *Clin. Sci. (Oxf.)*. **33**: 233-247.
 35. Mjos, O. D., N. E. Miller, R. A. Riemersma, and M. F. Oliver. 1976. Effects of dichloroacetate on myocardial substrate extraction, epicardial ST-segment elevation, and ventricular blood flow following coronary occlusion in dogs. *Cardiovasc. Res.* **10**: 427-436.
 36. Trewby, P. N., R. A. Chase, M. Davis, and R. Willaims. 1977. The role of the false neurotransmitter octopamine in the hypotension of fulminant hepatic failure. *Clin. Sci. Mol. Med.* **52**: 305-310.
 37. Mattson, W. J., and J. C. Turcotte. 1969. Survival and metabolism in experimental endogenous hepatic coma. *Surg. Gynecol. Obstet.* **128**: 557-564.
 38. Coude, F. X., J. M. Saudubray, F. DeMaugre, C. Marsac, and J. P. Leroux. 1978. Dichloroacetate as treatment for congenital lactic acidosis. *N. Engl. J. Med.* **299**: 1365-1366.
 39. Cohen, R. D., and R. A. Iles. 1978. Dichloroacetate and the treatment of lactic acidosis. *N. Engl. J. Med.* **298**: 1364.
 40. Wells, P. G., G. W. Moore, D. Rabkin, G. R. Wilkinson, J. A. Oates, and P. W. Stacpoole. 1980. Metabolic effects and pharmacokinetics of intravenously administered dichloroacetate in humans. *Diabetologia*. **19**: 109-113.