February 4, 1965

LACTIC ACID ACIDOSIS

Case #1. [redacted]

This 81 year old [redacted] male was discovered to have diabetes mellitus in 1949. He was treated with diet and small doses of insulin until 1956 at which time Orinase therapy was started. Response was good with blood sugars in the range of 150-170 mgs% until 1960, when, because of increasing hyperglycemia, DBI was added to his treatment at a level of 50 mgs per day. This was gradually increased until he was taking 50 mgs three times daily without difficulty but with blood sugars of approximately 250 mgs%. In May 1962 the drug was stopped for reasons which are not clear, Orinase being continued at a dose of 3.0 grams daily. In [redacted] 1962 DBI was restarted in amounts of 50 mgs daily and in February 1963 was increased to 100 mgs daily. The patient apparently did well during this entire period and at no time had symptoms of hypoglycemia or ketosis.

Four days prior to his final admission at [redacted] the patient developed nausea and vomiting subsequent to ingestion of canned sardines. He came to the emergency room where physical examination was said to be normal. A diagnosis of viral gastritis was made and the patient was discharged on Compazine therapy, 10 mg tid. His vomiting ceased but he ate little over the next three days while continuing to take DBI but not Orinase. The day of admission he complained of left upper quadrant abdominal pain and was noted to be mentally dull by the family. He was brought to the hospital and in the emergency room was found to be dehydrated with a blood pressure of 90/50 (4 days previously B.P. was 170/85). In addition he was breathing 40 times a minute. While being x-rayed he suddenly collapsed unconscious. He was given 50 cc's of 50% glucose and seemed to respond with return of consciousness. Unfortunately a blood sugar was not obtained. Following this a liter of balanced salt solution was administered intravenously. The patient improved markedly and was described as being alert and talking to the family. At this time, however, initial laboratory work drawn on arrival was returned and showed the following:

BUN - 81 mgs%
CO_2 - 4.8 mEq/liter
Na - 115 mEq/liter
Cl - 81 mEq/liter
K - 5.9 mEq/liter

He was admitted to the ward where physical examination showed a B.P of 90/40. Respirations were shallow and rapid with a respiratory rate of 36. The nailbeds were described as pink. Early bilateral cataracts were noted but the retinas were normal. The neck was unremarkable and the thyroid not palpable. The lungs and heart were completely normal as was the abdomen. Extremities showed no abnormalities and neurological examination was normal.

Laboratory data revealed a hemoglobin of 13.1 G and a hematocrit of 43. WBC was 17,000 with a left shift. Urinalysis showed 2+ sugar and a trace of acetone. Serum acetone was negative. Blood sugar was 302 mgs%. Chest x-ray and KUB were normal.

Blood was drawn for methyl alcohol and lactic acid determinations and the patient started on 1000 mls of 1/6 M lactate with 40 mEq of $NaHCO_3$ added. After completion of this infusion in a two hour period, electrolytes were drawn and a repeat infusion of isotonic lactate with added bicarbonate was started. At this point the patient suddenly became unresponsive and blood pressure was unobtainable. Vasopressors, including angiotensin, were administered but the patient expired without regaining consciousness. ECG was normal except for bradycardia minutes before the patient died. Electrolytes shortly before death showed a sodium of 125 mEq/liter, potassium of 5.9 mEq/liter, CO_2 of 5.7 mEq/liter, and a chloride of 73 mEq/liter. Blood methyl alcohol was subsequently reported as negative. Blood lactic acid was 12.8 mEq/liter (normal 1 mEq/liter).

At autopsy the patient had hyalinized islets of Langerhans and diabetic glomerulosclerosis. Early hemorrhagic infarction of the bowel was noted, without vascular obstruction. Tissues were noted to be well hydrated and there were no signs of necrosis in the brain or heart. No obvious cause of death was found.

Case #2. [redacted].

This 44 year old Nego woman was admitted to [redacted] with a 5 month history of severe rectal bleeding against a background for many years of modest difficulty with hemorrhoids. During this 5 month period the blood frequently filled the toilet bowl when the patient was at stool. Coincident with the increased bleeding she began to note fatigue and dyspnea on exertion. The latter progressed to paroxysmal nocturnal dyspnea and two weeks prior to admission she became bedridden with definite orthopnea present. One week prior to admission she developed edema of feet, legs and finally abdomen.

On arrival at the hospital the patient was noted to be tachypneic, pale and in major distress. B.P. was 160/90, pulse was 88 and respirations 40 per minute. Head, eyes, ears, nose and throat examination was normal except for pallor. The neck was supple and venous distension was not present. The lungs were clear to percussion and auscultation. The heart was grossly enlarged to the anterior axillary line, but the rhythm was regular and there were no murmurs. The liver was palpable 8 cm below the costal margin, but ascites was absent. The extremities showed 3+ edema. No cyanosis or clubbing was noted.

Initial laboratory work showed a hemoglobin of 1.7 grams% with a hematocrit of 8. WBC was 15,000 with a normal differential. Urinalysis was free of sugar and acetone. BUN was 23 mgs%, glucose 88 mgs%, sodium 135 mEq/liter, potassium 5.1 mEq/liter and CO_2 2.3 mEq/liter. Venous blood lactate was 11.4 mEq/liter. Circulation time was 95 seconds and venous pressure was 37 mm of water. Chest x-ray showed cardiomegaly but no pulmonary congestion. ECG was normal.

The patient was treated with careful transfusion of packed cells with excellent response. No alkalinizing solutions were administered. The early course is shown by the following laboratory data:

	Admission	3 hrs	24 hrs
Bicarbonate	2.3 mEq	9.64 mEq	18.5 mEq
CO_2 tension	13.7 mm	17.0 mm	29.7 mm
pH	7.25	7.38	7.42
Lactate	11.4 mEq	7.4 mEq	2.0 mEq
Na	135 mEq		141
K	5.1 mEq		3.5
BUN	23 mgs%		18 mgs%

She delivered her edema without digitalization. In addition to blood the patient was treated with parenteral and oral iron. She was discharged asymptomatic after refusing surgery for her giant hemorrhoids.

CAUSES OF HYPERLACTATEMIA

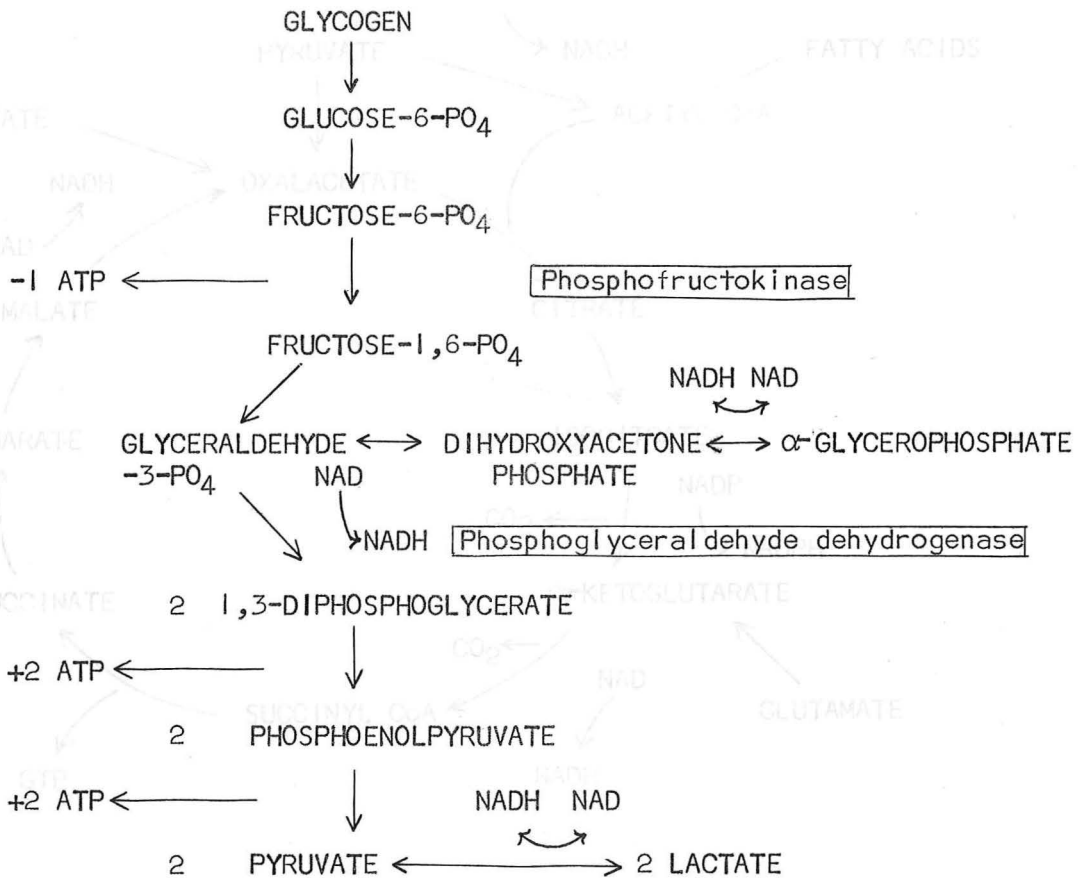
Type I. Hyperlactatemia with proportionate hyperpyruvatemia (no "excess" lactatemia)

1. Glucose infusion; glucose + insulin
2. Drugs and hormones
   a. Epinephrine
   b. Glucagon
   c. Monamine oxidase inhibitors
3. Alkalosis
   a. Respiratory
   b. Metabolic
4. Glycogen storage disease, type I (glucose-6-phosphatase deficiency)
5. Thiamine deficiency
6. Congenital defect with Mongolism

Type II. Hyperlactatemia with no proportionate increase in pyruvate ("excess" lactatemia)

1. "Excess" lactatemia with obvious cause
   a. Muscular exercise
      (1) Hypothermia
   b. Extra-corporeal circulation
   c. Hypoxia
      (1) Anemic
      (2) Circulatory
      (3) Pulmonary
2. "Excess" lactatemia without obvious cause

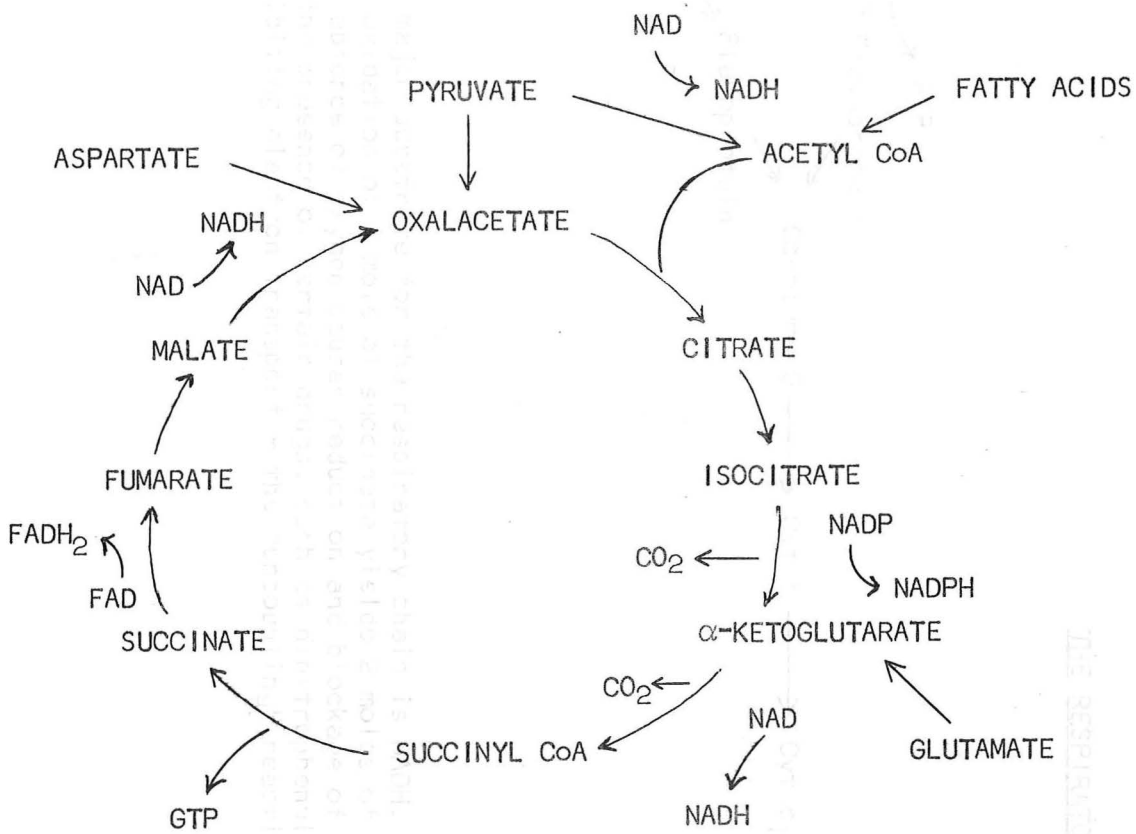
GLYCOLYSIS



Summary

1. The rate limiting enzyme is phosphofructokinase which is the mediator of the Pasteur effect. It is inhibited by ATP and activated by ADP, AMP, cyclic AMP, and Pi.
2. The net energy gain from 1 mole of glucose arising in glycogen is 3 moles of ATP in the absence of oxygen.
3. Glycolysis stops at the phosphoglyceraldehyde dehydrogenase reaction if NADH is not oxidized in the cell.

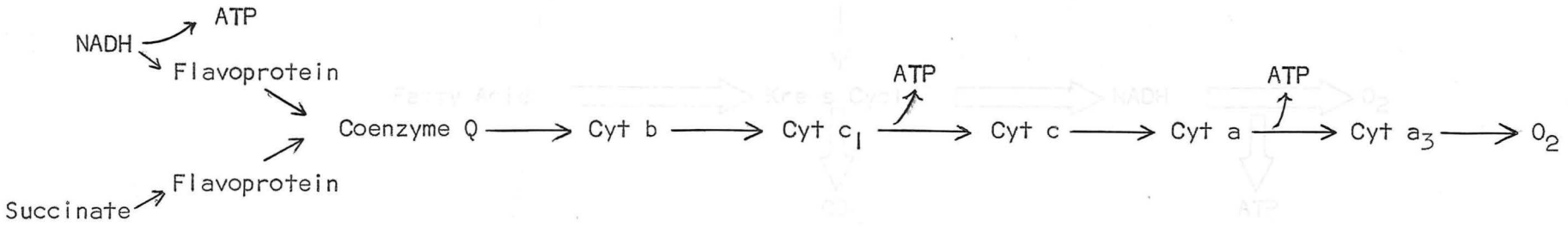
KREBS CYCLE



Summary

1. In the presence of oxygen the main fate of pyruvate is oxidation in the Krebs cycle via acetyl CoA or CO_2 fixation to oxalacetate or malate.
2. Fatty acids furnish substrate for oxidation via acetyl CoA and proteins via aminoacids such as glutamate and aspartate.
3. Only 1 mole of high energy phosphate, GTP formed at the succinyl CoA ——> succinate step, results directly from oxidation of 1 mole of pyruvate or acetyl CoA in the cycle. All other energy depends on oxidation of NADH and NADPH in the electron transport chain with coupled phosphorylation.
4. Failure of oxidation of NADH blocks the cycle.

THE RESPIRATORY CHAIN

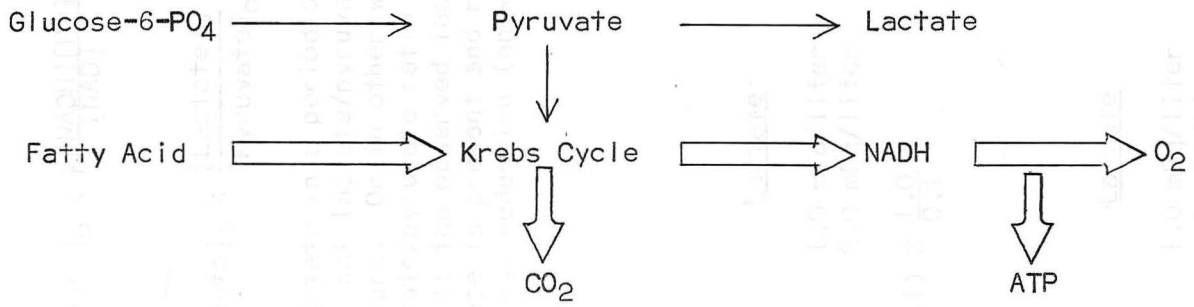


Summary

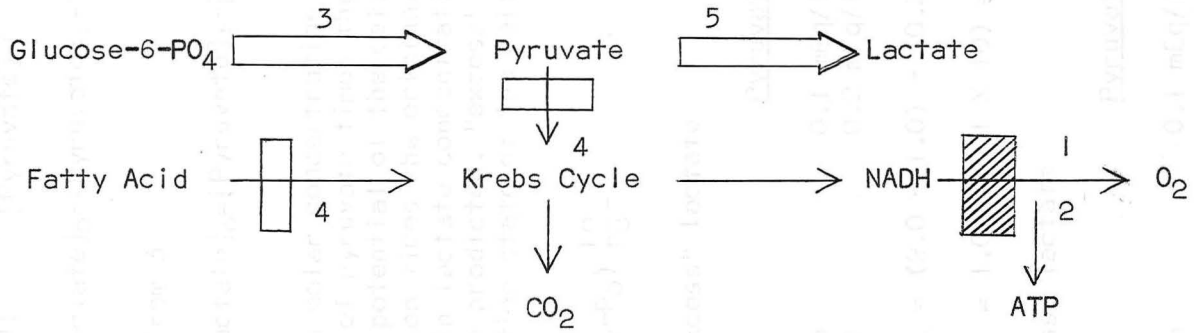
1. The major substrate for the respiratory chain is NADH. Oxidation of 1 mole of NADH yields 3 moles of ATP.
2. The oxidation of 1 mole of succinate yields 2 moles of ATP.
3. The absence of oxygen causes reduction and blockage of the entire cytochrome system and ATP formation.
4. In the presence of certain drugs, such as dinitrophenol, it is possible to inhibit ATP production without inhibiting electron transport - the "uncoupling" reaction.

THE SEQUENCE OF EVENTS IN ANOXIA

1. Normal



2. Anoxia



Summary

1. Oxygen deficiency causes reduction of the respiratory chain and failure of oxidation of NADH.
2. ATP synthesis decreases and cellular stores of ATP break down to ADP, AMP, and Pi.
3. Phosphofructokinase is stimulated by ADP, AMP, and Pi and glycolysis is activated.
4. Krebs cycle activity is inhibited by excess NADH and oxidation of pyruvate and fatty acid is therefore blocked.
5. Oxidation of cytoplasmic NADH is accomplished by formation of lactate from pyruvate, allowing glycolysis to continue.

THE CONCEPT OF "EXCESS" LACTATE AS AN INDICATOR OF CELLULAR ANOXIA

1. $\text{Pyruvate} + \text{NADH} + H^+ \rightleftharpoons \text{Lactate} + \text{NAD}$

2. $K = \dfrac{[\text{Lactate}][\text{NAD}]}{[\text{Pyruvate}][\text{NADH}][H^+]}$

3. $[\text{Lactate}] = [\text{Pyruvate}] \times K\dfrac{[\text{NADH}][H^+]}{[\text{NAD}]}$

$$\left(\text{note: } K\frac{[\text{NADH}][H^+]}{[\text{NAD}]} = \frac{[\text{Lactate}]}{[\text{Pyruvate}]}\right)$$

4. $[\text{Lactate}]_t - [\text{Lactate}]_o = [\text{Pyruvate}]_t - [\text{Pyruvate}]_o \times K\dfrac{[\text{NADH}][H^+]}{[\text{NAD}]}$

5. Substituting from 3

$$[\text{Lactate}]_t - [\text{Lactate}]_o = [\text{Pyruvate}]_t - [\text{Pyruvate}]_o \times \frac{[\text{Lactate}]_o}{[\text{Pyruvate}]_o}$$

This states that the change in molar concentration of lactate in a period of time equals the molar change in concentration of pyruvate times the original lactate/pyruvate ratio provided no change in the ratio (redox potential of the cell) occurs. Or in other words, the increase in pyruvate concentration times the original lactate/pyruvate ratio gives the theoretically expected increase in lactate concentration. If the observed lactate concentration at time t is greater than predicted, "excess" lactate is present and represents a change in the oxidation reduction state of the cell towards reduction (anoxia).
Thus

6. $XL = (L_t - L_o) - (P_t - P_o)\ \frac{L_o}{P_o}$

Example 1. No "excess" lactate

	Pyruvate	Lactate
time o	0.1 mEq/liter	1.0 mEq/liter
time t	0.2 mEq/liter	2.0 mEq/liter

$$XL = (2.0 - 1.0) - (0.2 - 0.1) \times \frac{1.0}{0.1}$$

$$= 1.0 - (0.1 \times 10) = 0$$

Example 2. "Excess" lactate

	Pyruvate	Lactate
time o	0.1 mEq/liter	1.0 mEq/liter
time t	0.2 mEq/liter	5.0 mEq/liter

$$XL = (5.0 - 1.0) - (0.2 - 0.1) \times \frac{1.0}{0.1}$$

$$= 4.0 - (0.1 \times 10) = 3.0 \text{ mEq/liter}$$

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