Familial Chronic Acidosis due to an Error in Lactate and Pyruvate Metabolism

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THERE have been several reports of children with chronic metabolic acidosis due to elevated blood levels of lactate and pyruvate during the past five years.[1-5] Two further cases of this apparently rare disorder are described herein.

CASE REPORTS

The patients were younger siblings of a patient described previously[3] and were members of a family of North American Indians who live in a remote and relatively inaccessible area of Northern Ontario. The family history is recorded, in as much detail as could be obtained, in Table I. Eight of the children

TABLE I.—SUMMARY OF FAMILY HISTORY

		Sex	Year of birth	Age at death (months)	Symptoms or present conditions
Father		M	1919	—	Tall, lean, in good health
Mother		F	1929	—	Tall and very obese, otherwise in good health. Blood lactate and pyruvate levels normal
Children	1	M	1945	16	Tachypnea, muscular twitching, episodes of coma, vomiting and cough
	2	F	1947	5	" "
	3	M	1949	18	" "
	4	M	1950	3	" "
	5	M	1952	—	"Ill as a baby"—since then has been well. Tall and obese. Normal intelligence
	6	F	1954	6	Diarrhea for two weeks before death. Hospital diagnosis: bronchopneumonia and gastroenteritis
	7	F	1956	—	Healthy, normal intelligence. "Big for her age"
	8	M	1958	—	Healthy, normal intelligence
	9	F	1960	6	Tachypnea, muscular twitching, episodes of coma, vomiting, cough
	10	F	1961	23	Chronic hyperlactatemia. Israels *et al.* Case 1[3] (R.P.)
	11	M	1964	16	Chronic hyperlactatemia. Present Case 1 (C.P.)
	12	M	1966	—	Chronic hyperlactatemia. Present Case 2 (J.P.)

died before 2 years of age. The symptoms preceding death in the first, second, third, fourth and ninth children were described by the mother as being remarkably similar—rapid breathing, convulsions, episodes of unconsciousness, occasional vomiting and cough. These were also the main symptoms exhibited by the tenth, eleventh and twelfth children with proved hyperlactatemia and it seems reasonable to postulate that these other five children may have had the same disorder. The sixth child, according to the mother, did not show the same symptoms and was well until the onset of diarrhea two weeks before her death in Sioux Lookout Indian Hospital, Ontario. The hospital records state that she died of gastroenteritis and bronchopneumonia.

When the mother was seen in 1964, she was very obese but otherwise appeared healthy. Her blood lactate and pyruvate levels* were 0.7 and 0.08 mM. per litre, respectively. It has not been possible to examine the father and the three older surviving children.

CASE 1

This boy (C.P.), the eleventh child, developed pneumonia in the neonatal period from which he rapidly recovered. The birth history and birth weight were not available. At 3 months of age he was admitted to a local hospital because of pneumonia. He responded poorly to treatment and was transferred to the Winnipeg Children's Hospital.

He was an obese child who was acutely ill and markedly dehydrated. His weight was 7.3 kg., length 63.5 cm. and head circumference 44.4 cm. His respirations were laboured and deep at a rate of 45 to 50 per minute, and there were scattered adventitious sounds throughout the chest. Athetoid movements of the limbs were noted.

Laboratory Investigations: The hemoglobin was 8.7 g. per 100 ml., and the white blood count 16,200 per c.mm., with a preponderance of neutrophils. The urine contained acetone and acetoacetic acid but no phenylketones. The serum sodum was 137 mEq. per litre, potassium 4.6 mEq. per litre, chloride 111 mEq. per litre, CO_2 content 9.3 mEq. per litre, blood pH 7.23, PCO_2 29.0 mm. Hg, bicarbonate 13.8 mEq. per litre, whole blood lactate 8.3 mM. per litre, blood glucose 59 mg. per 100 ml., and blood urea nitrogen 9 mg. per 100 ml. Two days after admission the blood lactate level was 11.7 mM. per litre and pyruvate 0.5 mM. per litre.

The serum lactic dehydrogenase was 395 units and the glutamic oxaloacetic transaminase 40 units. Radiographs of the chest showed a minor infiltration in the upper lobe of the right lung; radiographs of the skull were negative. The cerebrospinal fluid was normal. An electroencephalogram showed an excess of very slow wave activity, more in the left posterior areas.

A few days after admission the glycemic responses to adrenalin and glucagon were tested and were normal. An intravenous glucose tolerance test was also normal. The urine contained a generalized increase of amino acids and from 940 to 1014 mg. lactate per 100 ml.

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*Blood lactate was estimated by either a chemical[6] or an enzymatic[7] method, both methods giving very comparable results (normal range: 0.5 to 2.0 mM. per litre). Blood pyruvate was estimated by the method of Friedemann and Haugen[8] (normal range: 0.05 to 0.20 mM. per litre).

The patient was initially treated with antibiotics and intravenous fluids, containing sodium bicarbonate. After 24 hours he showed some clinical improvement, although the metabolic acidosis was unaltered. At this time neurological examination showed generalized muscular hypotonia, choreoathetotic movements of the upper and lower extremities, an impaired level of consciousness, and retarded general motor performance.

The intravenous fluid therapy was maintained for five days, by which time the acidosis was fairly well corrected but he showed hypernatremia (serum sodium 168 mEq. per litre) as a result of excessive infusion of sodium. He also had transient hypocalcemia (serum calcium 3.3 mEq. per litre) and anemia (hemoglobin 5.9 g. per 100 ml.) for which he was given a blood transfusion. From this time he was maintained on oral sodium bicarbonate, 4 to 8 g. daily.

For the next four months he was fairly well, apart from two episodes of respiratory infection. The neurological signs remained unchanged. The acidosis was also controlled, although blood lactate levels remained greatly elevated. During this interval a number of additional investigations were performed which will be described below. An attempt was also made to assess the effect of a low-glucose, high-galactose diet which was reported by Erickson[4] to result in lowering of the blood lactate level in one patient with lactic acidosis. Our patient was maintained on a diet containing 45% galactose for 10 days. During this time blood lactate levels ranged from 5.2 to 8.0 mM. per litre and showed no tendency to decline.

Four months after admission to the hospital, the effect of stopping the bicarbonate was observed. After three days he showed signs of acidosis and had a convulsion. He rapidly recovered with intravenous fluid therapy; sodium bicarbonate was restarted.

At 9 months of age, after having been in hospital for six months, he was discharged to a foster home in Winnipeg, only to be readmitted six days later in acute acidosis. Finally, at the age of 15 months, he was considered well enough to be transferred to a hospital nearer his home. He had shown almost no sign of development maturation during the year since his original admission, although he would smile to social overtures. Head control was minimal; there was no effective reaching and only momentary retention of anything put into his hands. The generalized choreoathetosis persisted.

A month later he developed an acute episode of acidosis and died. An autopsy was performed but the results are not available to us.

CASE 2

The twelfth child (J.P), a boy, was born in 1966. He appeared normal at birth and weighed 3.84 kg., but within a few hours developed rapid, grunting respirations. Because of the possibility that he might have the same disorder as his siblings, he was transferred to the Winnipeg Children's Hospital. On arrival, he did not appear ill and there were no physical abnormalities, but on investigation he was found to have a mild compensated metabolic acidosis. The blood lactate level was 6.8 mM. per litre, pyruvate 0.56 mM. per litre.

He received therapy with intravenous fluids containing sodium bicarbonate and showed rapid clinical recovery with restoration of the serum electrolytes to normal.

Laboratory Investigations: Following correction of the initial electrolyte imbalance, blood pH values and serum electrolyte concentrations remained generally within the normal range except during the test of muscle function, as will be described later. Serum calcium and magnesium levels were also normal. Resting blood lactate concentrations ranged from 2.4 to 4.4 mM. per litre and blood pyruvate 0.22 to 0.44 mM. per litre with lactate/pyruvate ratios 8.6 to 14.0. Total plasma lipids were 480 mg. per 100 ml. and free fatty acids 0.42 mEq. per litre. The urine contained ketones on admission but never subsequently. A urine amino acid chromatogram showed a generalized increase of most amino acids. The urine became acidified to a pH of 5.5 during a period of mild acidemia. An oral glucose tolerance test was normal. Skull radiographs were normal. An electroencephalogram at 2 months of age was abnormal with paroxysmal bursts of spike and slow wave complexes sometimes on the left side and sometimes on the right. Other special tests are described below.

The infant remained generally well until 1 month of age, when he developed pneumonia which responded rapidly to treatment, and at the age of 6 weeks he began to have minor motor seizures, with occasional grand mal convulsions. These were not appreciably affected by anticonvulsant drugs.

Although he had occasional episodes of hyperventilation, often before a convulsion, repeated blood pH and bicarbonate estimations were always within the normal range. He was given sodium bicarbonate by mouth for a short time, but this had no effect on the convulsions and it was discontinued.

He gained weight rapidly, weighing 4.5 kg. at 1 month of age and 7.3 kg. at 3 months of age, at which time he showed obesity which was also observed in his similarly affected siblings. In spite of his physical growth, he showed no developmental maturation. At 5 months of age a developmental assessment indicated that he was functioning at the newborn level. He was hypotonic, had a persistent tonic neck reflex, complete head lag and showed no visual following. At the time of writing he is 7 months old and his condition remains unchanged.

SPECIAL INVESTIGATIONS

Muscle Function and Metabolism

In Case 1 (C.P.), nerve conduction velocity was tested in the left peroneal muscle and was normal. Electromyography showed no gross abnormality although the motor units in the left biceps were somewhat slowed.

TABLE II.—LACTATE AND PYRUVATE LEVELS, OXYGEN SATURATION AND pH IN FEMORAL ARTERY, FEMORAL AND HEPATIC VEIN BLOOD AT REST, EXERCISE AND RECOVERY IN CASE 2 (J.P.) AND 3 CONTROL PATIENTS. (FOR THE CONTROLS, MEAN AND RANGE ARE GIVEN. FIGURES IN PARENTHESES INDICATE NUMBER OF OBSERVATIONS.)

	Case 2					*Controls*				
	Lactate (mM./l.)	*Pyruvate (mM./l.)*	*Lactate pyruvate*	*Oxygen saturation (%)*	*pH*	*Lactate (mM./l.)*	*Pyruvate (mM./l.)*	*Lactate pyruvate*	*Oxygen saturation (%)*	*pH*
Resting										
Femoral artery....	2.7	0.30	9.0	96	7.42	0.9 (2) 0.8 - 1.0	0.14 (2) 0.11 - 0.16	7.1 (2) 5.0 - 9.1	91.0 (3) 84 - 95	7.315 (2) 7.31 - 7.32
Femoral vein.....	2.6	0.30	8.7	72	7.38	1.2 (3) 0.9 - 1.4	0.13 (3) 0.12 - 0.14	9.2 (3) 7.5 - 10.0	74.0 (2) 73 - 75	7.31 (1)
Hepatic vein.....	2.4	0.30	6.0	—	—	0.7 (2) 0.6 - 0.8	0.14 (2)	5.0 (2) 4.3 - 5.7	—	—
Exercise No. 1										
Femoral artery....	3.1	0.28	11.1	97	7.41	1.4 (3) 1.3 - 1.6	0.15 (3) 0.13 - 0.16	9.9 (3) 8.1 - 10.8	83.7 (3) 65 - 94	7.300 (2) 7.29 - 7.31
Femoral vein.....	4.2	0.25	16.8	34	7.25	3.2 (3) 2.4 - 3.8	0.18 (3) 0.13 - 0.22	18.1 (3) 15.9 - 20.0	27.7 (3) 19 - 42	7.155 (2) 7.15 - 7.16
Hepatic vein.....	3.2	0.29	11.0	—	—	2.2 (1)	0.21 (1)	10.5 (1)	—	—
Recovery										
Femoral artery....	6.5	0.44	14.8	—	—	1.9 (3) 1.5 - 2.1	0.21 (2) 0.20 - 0.22	8.4 (2) 6.8 - 10.0	82.0 (3) 59 - 94	7.31 (2)
Femoral vein.....	8.0	0.30	26.7	69	7.16	3.5 (3) 2.5 - 4.7	0.22 (3) 0.14 - 0.27	16.3 (3) 13.6 - 17.9	67.5 (2) 53 - 82	7.25 (1)
Hepatic vein.....	—	—	—	—	—	1.6 (2) 1.5 - 1.7	0.19 (2)	8.4 (2) 7.9 - 8.9	—	—
Exercise 2										
Femoral artery....	7.5	0.29	25.9	89	7.25	2.4 (2) 2.1 - 2.8	0.18 (2) 0.12 - 0.24	14.6 (2) 11.7 - 17.5	92 (1)	7.29 (1)
Femoral vein.....	10.4	0.25	41.6	34	7.07	4.6 (2) 3.6 - 5.6	0.21 (2) 0.13 - 0.28	23.8 (2) 20.0 - 27.7	31.5 (2) 30 - 33	7.120 (2) 7.09 - 7.15
Hepatic vein.....	—	—	—	—	—	3.5 (1)	0.27 (1)	13.0 (1)	—	—
Recovery										
Femoral artery....	7.8	0.49	15.9	—	—	2.3 (2) 1.7 - 2.8	0.19 (2) 0.15 - 0.24	11.5 (2) 11.3 - 11.7	93 (1) —	7.31 (1) —
Femoral vein.....	8.5	0.40	21.2	—	—	4.2 (2) 3.9 - 4.5	0.25 (2) 0.18 - 0.31	18.1 (2) 14.5 - 21.7	64 (1)	7.13 (1)
Hepatic vein.....	—	—	—	—	—	2.8 (1)	0.25 (1)	11.2 (1)	—	—

In the patient reported by Hartmann *et al.*[1, 2] an abnormality in the lactic dehydrogenase isozyme pattern of skeletal muscle was described. The lactic dehydrogenase isozymes of a fragment of the vastus lateralis of C.P. were qualitatively assessed by electrophoresis on agar.[9] Qualitative visual comparison with the patterns obtained in the muscles removed from the same site from two control patients of approximately the same age showed no significant difference.

In Case 2 (J.P.) the effect of muscle stimulation on venous and arterial lactate and pyruvate levels was observed. Three patients, aged 4, 11 and 28 months, undergoing cardiac catheterization for acyanotic congenital heart disease were tested in an identical manner and served as controls. The femoral artery was cannulated and blood from the femoral and hepatic veins was sampled through a heart catheter. Following removal of samples of blood from the femoral artery and vein and hepatic vein for lactate and pyruvate, oxygen saturation and pH determinations, the lower leg on the same side was stimulated electrically for three minutes. After five to eight minutes' rest, further blood samples were obtained and the leg was stimulated for a further three minutes. Femoral arterial and venous blood, and hepatic venous blood from one control patient, was obtained at the end of the second exercise period and after five minutes' rest. The results are shown in Table II and Fig. 1.

The following striking differences in blood lactate and pyruvate responses between J.P. and the controls were observed:

1. Although the initial venous blood lactate rise was comparable in J.P. and controls (1.6 and 2.0 mM. per litre respectively), the lactate level in J.P. continued to increase rapidly during the first rest period, whereas in the controls the levels increased much less.

2. Venous and arterial pyruvate concentrations in J.P. declined during both exercise periods and increased during the rest periods, whereas in the controls pyruvate levels increased, as expected, during the exercise periods.

3. Arterial pyruvate levels in J.P. were invariably greater than in the venous blood. This arterial-venous difference was particularly marked at the end of the first rest period (0.14 mM. per litre).

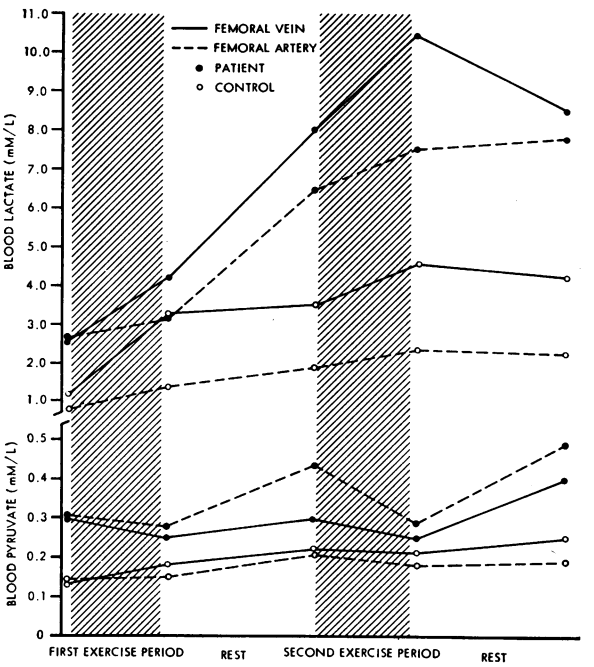

Fig. 1.—Femoral arterial and venous blood lactate (above) and pyruvate levels (below) in J.P. and three control patients (means) during rest, muscular stimulation and recovery. Continuous lines represent venous levels, interrupted lines arterial levels. Closed circles indicate J.P. and open circles the controls.

A similar test was attempted in C.P., but difficulties were encountered and the muscle stimulation was insufficient to produce a significant rise in lactate or a decrease in the oxygen saturation of the femoral venous blood. However, from the limited results available, the trend in the response of the blood pyruvate concentrations appeared to be similar to those in J.P., namely a decline in the pyruvate level during exercise and a positive arterial-venous difference.

No cardiac or circulatory abnormalities were detected in C.P. or J.P. during heart catheterization.

Lactate and Pyruvate Tolerance Tests

In two previous cases of hyperlactatemia, infusion of sodium lactate resulted in high and prolonged elevations of the blood lactate concentration.[3] C.P. received 67 ml. of 1/6 molar sodium lactate intravenously over a period of 1½ hours; 100 ml. of the same solution was infused into J.P. over a one-hour period. Fig. 2 shows the effects of these infusions on blood lactate levels compared with three control subjects of comparable age and the two previously reported cases (G.C. and R.P.). In C.P. the blood lactate level had not returned to the preinfusion level of 18 mM. per litre two hours after the termination of the infusion. The preinfusion blood lactate concentration in J.P. was only slightly

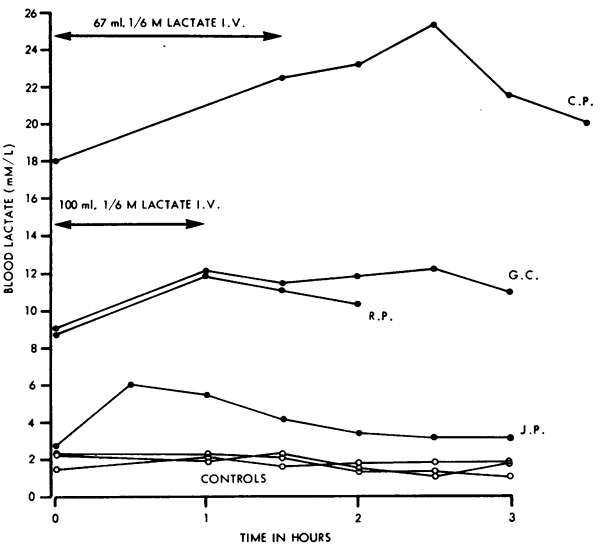

Fig. 2.—Blood lactate levels during and after the slow intravenous infusion of 1/6 molar sodium lactate in four patients and three control subjects

above the normal range, but during and following the infusion it rose considerably and did not return to the baseline level for one to two hours. In this patient blood pyruvate and glucose levels were estimated simultaneously with the lactate level. The blood pyruvate rose with the lactate but not to a comparable degree, resulting in an increase in the lactate/pyruvate ratios from a resting value of 10.9 to 17.3 at one-half hour and then declining to 16.1 at one hour, 14.8 at one and one-half hours and 13.5 at two hours. The blood glucose rose from a preinfusion value of 75 mg. per 100 ml. to 92 mg. per 100 ml. at one-half hour, 100 mg. per ml. at one hour, 101 mg. per 100 ml. at one and one-half hours, 94 mg. per 100 ml. at two hours and 96 mg. per 100 ml. at three hours.

In J.P. the effects of rapid intravenous injection of lactate and pyruvate were also observed. After a four-hour fast, the patient was given a sedative dose of chloral hydrate, and 1 g. of sodium pyruvate or sodium lactate as a 25% aqueous solution was injected within a four-minute period. Capillary blood samples for lactate and pyruvate estimations were taken before the infusion and 10, 15, 20, 25, 30, 45 and 60 minutes thereafter. Three pyruvate tolerance tests were performed in the patient and in three different controls of comparable age. The results are shown in Fig. 3. One intravenous lactate tolerance test was performed in the patient and in a control, and the curves of the lactate and pyruvate levels were very similar to those following the intravenous injection of pyruvate.

The logarithms of the blood lactate and pyruvate levels were plotted against time from

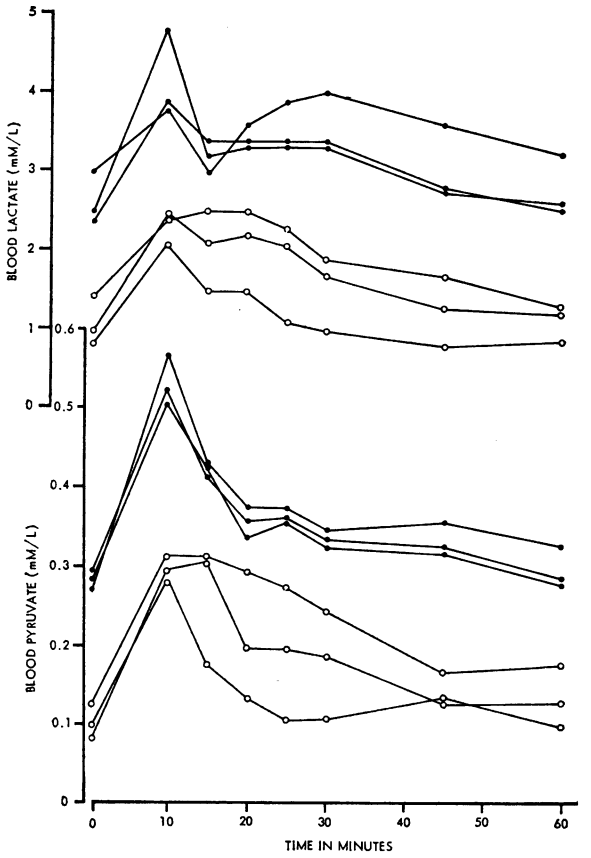

Fig. 3.—Blood lactate levels (above) and pyruvate levels (below) after the rapid intravenous injection of 1 g. sodium pyruvate into J.P. on three occasions and into three control subjects. Closed circles indicate J.P. and open circles the controls.

10 to 30 minutes after the lactate and pyruvate injections. A linear decline was found in the lactate and pyruvate concentrations of the control and in the pyruvate concentration in J.P. after lactate injections and lactate and pyruvate levels of one control after pyruvate injection. From these figures the decay constants ("K") were calculated in the conventional way, indicating the proportion of the blood lactate and pyruvate disappearing each minute. Pyruvate disappearance rates in the two controls were 2.1 and 1.4% per minute and in the patient 0.85% per minute. Control lactate disappearance rates were 2.4 and 3.6% per minute. It can be noted in Fig. 3 that lactate levels in the patient did not show a linear decline on any occasion.

Glycolysis in Shed Blood

Lactate and pyruvate production were measured in the blood cells of C.P. and in the blood of control patients of similar age. Blood was also incubated with sodium oxamate in a concentration of 0.01 molar solution. The results were quite variable from one experiment to another, and no differences between patient and controls could be demonstrated.

α-Ketoglutarate Excretion

R.P., the sister of these patients, was shown to excrete a greatly increased amount of α-ketoglutarate in the urine and when glutamic acid was fed by mouth, the amount of α-ketoglutarate excreted was still further increased[3] (glutamic acid is transaminated to α-ketoglutarate). It was suggested that these findings might indicate a block in the metabolism of α-ketoglutarate which undergoes a process of decarboxylation similar to that of pyruvate. In C.P., blood and urinary α-ketoglutarate* was estimated on a number of occasions and the results were very variable. Blood levels ranged from 0.14 to 44.7 mg. per 100 ml. and the urinary excretion ranged from 13.4 to 229 mg. per 24 hours. Urinary α-ketoglutarate content was not constantly elevated, and glutamic acid feeding on two occasions did not result in a sustained or reproducible increase in the excretion of this metabolite. In J.P., urinary α-ketoglutarate was measured on one occasion and was 55.2 mg. per 24 hours.

DISCUSSION

Including the two patients described here, nine patients with idiopathic chronic hyperlactatemia and hyperpyruvicemia have so far been reported in detail. We also have knowledge of one other case (K.O. Schärer—personal communication). In seven of these patients the symptoms dated from early infancy and consisted of spells of hyperventilation, generalized muscular hypotonia, severe mental retardation and occasional convulsions. Two of the children developed scaly erythematous eruptions on the face. The four patients seen by us showed generalized obesity, but this was apparently not a feature of the other cases. Our patients were also prone to lower respiratory tract infections.

J.P. has in some ways shown less severe manifestations of the disorder. With the exception of the episode of metabolic acidosis on the first day of life which resulted in his admission to hospital, he has not so far shown the severe electrolyte disturbances which were characteristic of the other patients and he has not required continuous treatment with sodium bicarbonate. Blood pyruvate and lactate levels in the resting state have often been only a little above the normal range and yet the various tests of lactate and pyruvate metabolism were very

*Estimated by chromatography of its 2, 4-dinitrophenylhydrazone. The range of normal values in blood is 0.13-0.24 mg. per 100 ml. and in urine 0.9-2 mg. per 100 ml.[10, 11]

abnormal. He is also severely mentally retarded, suggesting that the brain abnormality in this disorder is not directly related to the degree of acidosis or hyperlactatemia, but that mental and chemical disorders may be unrelated, or, more likely, that they are both the result of the same underlying basic abnormality.

The two brothers with lactic acidosis described by Worsley *et al.*[5] presented somewhat differently. They developed fairly normally for the first year of life but between the first and second year showed convulsions, episodes of hyperventilation, ataxia, involuntary movements and mental deterioration, and they died after about six months. At autopsy one of these children had widespread degenerative lesions in the brain and spinal cord, with demyelinization and necrosis of nerve cells. We did not find comparable changes in the one patient of ours in whom autopsy findings are available (Israels *et al.*, Case 2[3]).

Whether the nine cases are all examples of a single disease entity is not known. They showed some differences in the age of onset of symptoms, as mentioned above, and also in their biochemical findings, although the latter may be partly the result of differing interpretations and this will be discussed later.

The disorder is clearly familial. Three of our patients were siblings and five other children in the family died in infancy with symptoms suggesting that they may have had the same disorder. Unfortunately, owing to their inaccessibility in Northern Ontario, our knowledge of the family is incomplete. Erickson's[4] two patients were siblings and there was a history of infant deaths and mental retardation in other members of the family. There is not yet sufficient evidence to form an opinion as to the mode of inheritance of the disorder.

The present patients, like the others, showed no evidence of the recognized causes of hyperlactatemia such as liver glycogen disease or chronic hypoxia. Both children were capable of acidifying their urine and renal function appeared to be normal apart from a generalized aminoaciduria. The lactate/pyruvate ratios were generally within the normal range, showing that the lactic dehydrogenase system was functioning normally; and the elevation of the blood lactate level could be accounted for by the elevation of blood pyruvate, although ratios in venous and capillary blood were at times elevated as they were in the cases of Erickson.

In a previous publication[3] we suggested that the most likely pathogenesis was a defect, perhaps a partial metabolic block, in the metabolism of pyruvate. Others have interpreted the findings in their patients as suggesting increased lactate production. Increased erythrocyte glycolysis was reported by Hartmann *et al.*[1] and Worsley *et al.*[5], the latter suggesting that some lactate was produced from non-glucose sources such as phosphorylated intermediates of glycolysis. In our experience measurement of glucose disappearance and lactate and pyruvate production from the *in vitro* incubation of blood can give very variable results from one experiment to another, and we could not demonstrate differences between our patient and controls of similar ages.

Hartmann *et al.*[1, 2] reported evidence suggesting a metabolic defect in muscle resulting in excessive production of lactate. The muscle of their patient contained about twice the normal content of active phosphorylase, and the blood lactate increased from a resting level of 5.75 mM. per litre to 22.75 mM. per litre after walking. A control of the same age showed an increase of blood lactate from 1.65 to 4.55 mM. per litre after walking. Erickson[4] also reported increases of venous lactate concentrations during mild exercise with increased arteriovenous lactate differences. However, the sequence of his observation is not entirely clear and the results are therefore difficult to interpret.

Another muscle defect found by Hartmann *et al.*[2] was an abnormal pattern of muscle lactic dehydrogenase (LDH) isozymes. The biological and clinical significance of lactic dehydrogenase isozymes has recently been well reviewed by Zinkham, Blanco and Kupchyk.[12] It will only be mentioned here that there are five isozymes (LDH 1-5) in body tissues which all catalyze the reversible reaction pyruvate ↔ lactate but having rather differing characteristics with regard to substrate inhibition. In heart muscle the predominant isozyme is LDH 1 (or "H" type). In muscle, on the other hand, LDH 5 ("M" type) predominates. In the muscle of the patient described by Hartmann *et al.*[2] a preponderance of LDH 5 was found. Through the courtesy of Dr. Hulda Wohltmann, isozymes were examined qualitatively in the muscle of a previous patient with lactic acidosis (Israels *et al.*, Case 2[3]) and the same abnormality was found. In C.P. the muscle isozymes showed a normal distribution compared to muscle from a control patient of the same age. At present the significance of Hartmann's finding is uncertain.

Investigation of the present cases has provided further information about the metabolic error in these patients, but the nature and site of the defect still remain unknown. The evidence suggests that in the resting state the patients have

a partial inability to dispose of pyruvate. Pyruvate levels are chronically elevated in the blood, and lactate levels are proportionately increased with a normal lactate/pyruvate ratio. Pyruvate and lactate tolerance tests suggest a delay in the removal of these metabolites from the blood. In J.P. the blood glucose level increased during the infusion of lactate, suggesting that gluconeogenesis from lactate was taking place. The most likely site of the metabolic defect in the disposal of pyruvate would seem to be in its oxidation within the mitochondria. The increased urinary excretion of ∝-ketoglutarate would also suggest a lesion involving the tricarboxylic acid cycle.

The most probable interpretation of the apparently very abnormal blood lactate and pyruvate response to muscular exercise is that pyruvate was shunting to lactate in the muscle. The positive arteriovenous differences in blood pyruvate concentrations and the negative arteriovenous differences in lactate across the leg with greatly elevated lactate/pyruvate ratios strongly suggest that muscle was taking up pyruvate from the arterial blood and releasing it into the venous blood as lactate. This must indicate a degree of intracellular hypoxia resulting in insufficient oxidation of reduced nicotinamide adenine dinucleotide during exercise. A portion of muscle from one of the patients investigated showed normal histology on light microscopy but this does not exlude a functional defect within the cell.

In a unified hypothesis to explain all the abnormalities found, one could postulate that in these patients at rest the tricarboxylic acid cycle is sufficiently active to oxidize enough reduced nicotinamide adenine dinucleotide to permit a normal equilibrium of the lactic dehydrogenase reaction pyruvate ↔ lactate. However, a defect in the oxidation of pyruvate would deprive the muscle cell of substrate with which to form the additional energy required during exercise. This would result in the ratio of reduced nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide being increased and the shunting of pyruvate to lactate.

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Summary A North American Indian family is described in which three of the children were mentally retarded, and had convulsions, other neurological abnormalities, muscular hypotonia, obesity and signs and symptoms of metabolic acidosis. On laboratory investigation there were signs of chronic metabolic acidosis of varying degree and elevations of the blood lactate and pyruvate levels. Two of the children died, the other is still alive. Five other children in the family died before 2 years of age with symptoms suggestive of the same disorder. The basic etiology of the metabolic disorder is unknown, but investigation of lactate and pyruvate metabolism, described in this report, suggests that these patients have a partial inability to oxidize pyruvate.

Résumé Trois enfants d'une famille d'indiens d'Amérique du Nord souffraient d'arriération mentale, de convulsions, d'autres anomalies neurologiques, d'hypotonie musculaire, d'obésité et présentaient les signes et symptômes de l'acidose métabolique.

Les analyses de laboratoire ont mis en évidence une acidose métabolique chronique à des degrés variables et une augmentation des concentrations sanguines de lactate et de pyruvate.

Deux de ces enfants sont morts, le troisième est encore vivant. Cinq autres enfants de la même famille sont morts avant d'avoir atteint 2 ans et leur symptomatologie permettait de croire qu'ils souffraient du même trouble.

On ignore l'étiologie profonde de cette pathologie, mais l'étude du métabolisme du lactate et du pyruvate à laquelle il a été procédé ici, laisse supposer que ces malades ont une incapacité partielle d'oxyder le pyruvate.

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