In the name of God

دانشگاه علوم پزشکی و خدمات بهداشتی درمانی ایران

Approach to Lactic Acidosis

Understanding the Causes, Diagnosis, and Management

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What Is Lactic Acidosis?

A condition characterized by an elevated lactic acid level in the blood

➡ Results in an excessively low pH (Metabolic Acidosis)

Lactic acidosis

Carbohydrate metabolism defects interfere with the conversion of:

- Pyruvate to glucose via the pathway of gluconeogenesis

- To carbon dioxide and water via the mitochondrial enzymes of the Krebs cycle

Pathophysiology

Lactic Acid Production:

- Produced during anaerobic metabolism.

Normal Metabolism:

Occurs in the liver and kidneys to convert lactate back to energy.

Normal Metabolism:

- Occurs when production exceeds clearance.

Causes of Lactic Acidosis

Type A (Hypoxic):

- Caused by tissue hypoxia or decreased oxygen delivery.
- Examples: Shock, severe anemia, respiratory failure.

Type B (Non-hypoxic):

- Not related to oxygen delivery.
- Examples: Liver failure, sepsis, medications/toxins (e.g., metformin, propofol), malignancies.

Mechanisms Leading to Lactic Acidosis in Inborn Errors of Metabolism

Impaired Glycolysis:

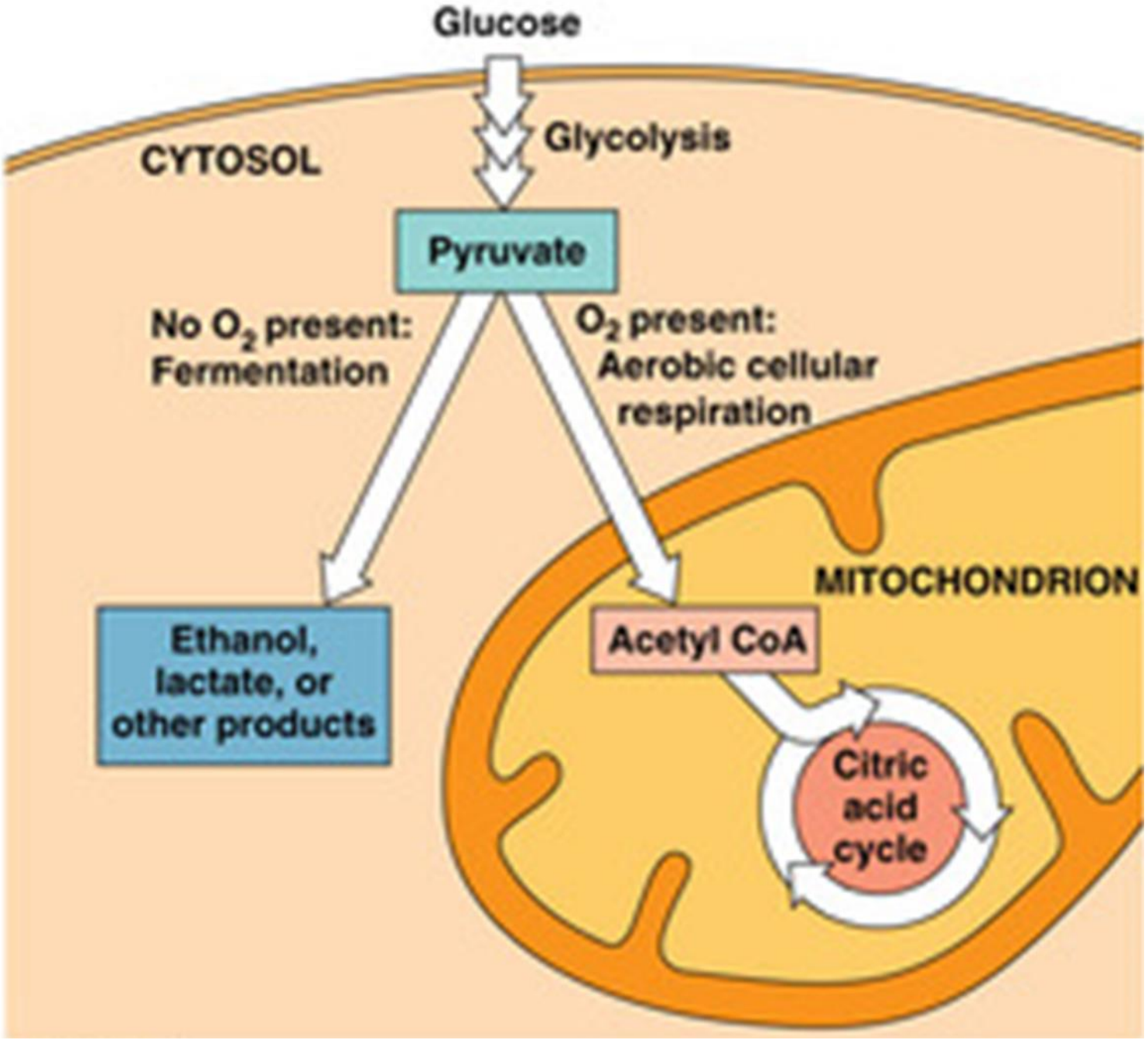
- Defects in enzymes like pyruvate kinase.

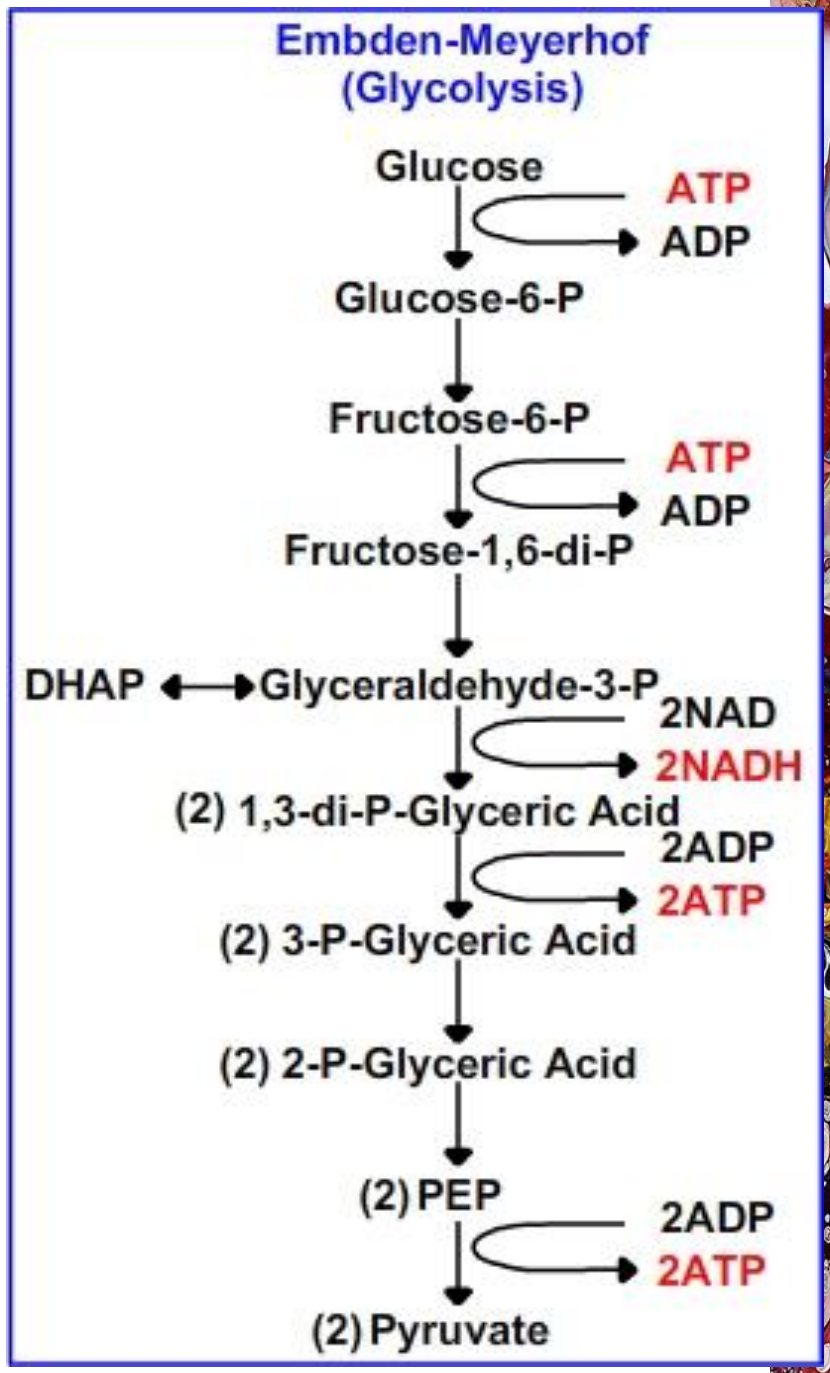
Mitochondrial Dysfunction:

- Disorders affecting the electron transport chain leading to decreased ATP production.

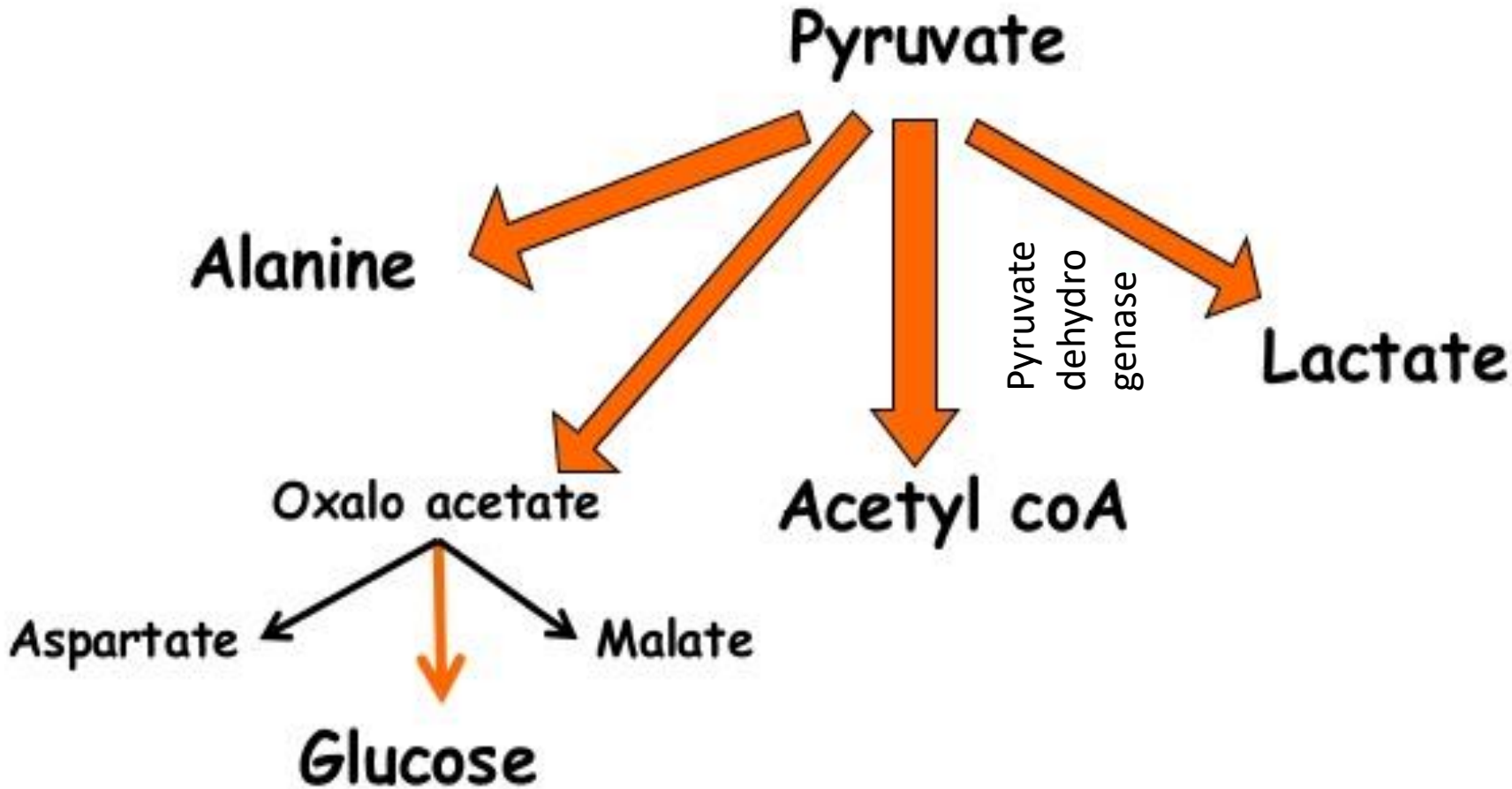
Defective Lactate Clearance:

- Impaired hepatic or renal function affecting lactate metabolism.


Glucose
CYTOSOL
Glycolysis
Pyruvate
No O_2 present:
Fermentation
O_2 present:
Aerobic cellular
respiration
MITOCHONDRION
Ethanol,
lactate, or
other products
Acetyl CoA
Citric
acid
cycle

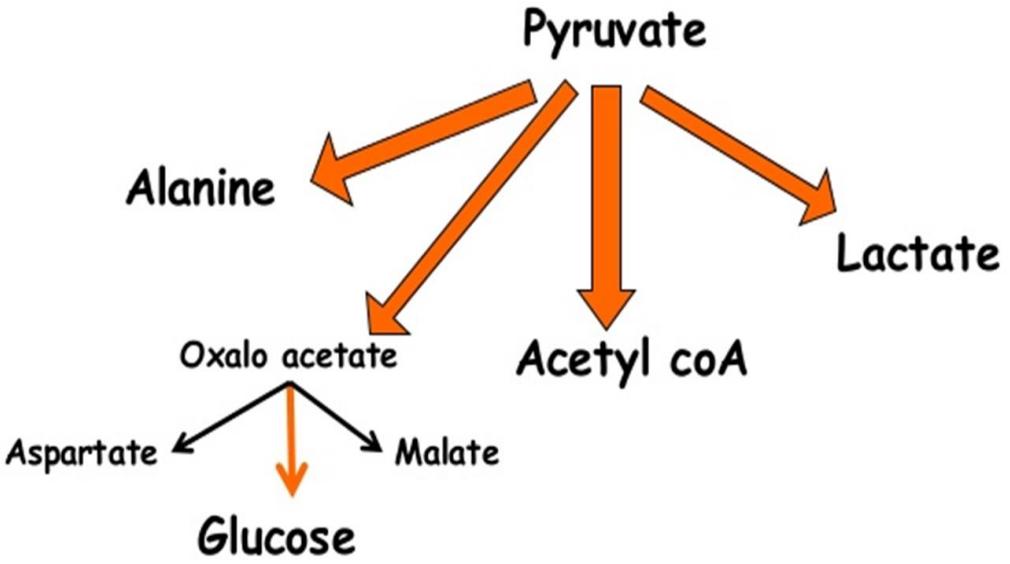

Embden-Meyerhof
(Glycolysis)
Glucose
ATP
ADP
Glucose-6-P
Fructose-6-P
ATP
ADP
Fructose-1,6-di-P
DHAP
Glyceraldehyde-3-P
2NAD
2NADH
(2) 1,3-di-P-Glyceric Acid
2ADP
2ATP
(2) 3-P-Glyceric Acid
(2) 2-P-Glyceric Acid
(2) PEP
2ADP
2ATP
(2) Pyruvate

Metabolic Fate of Pyruvate



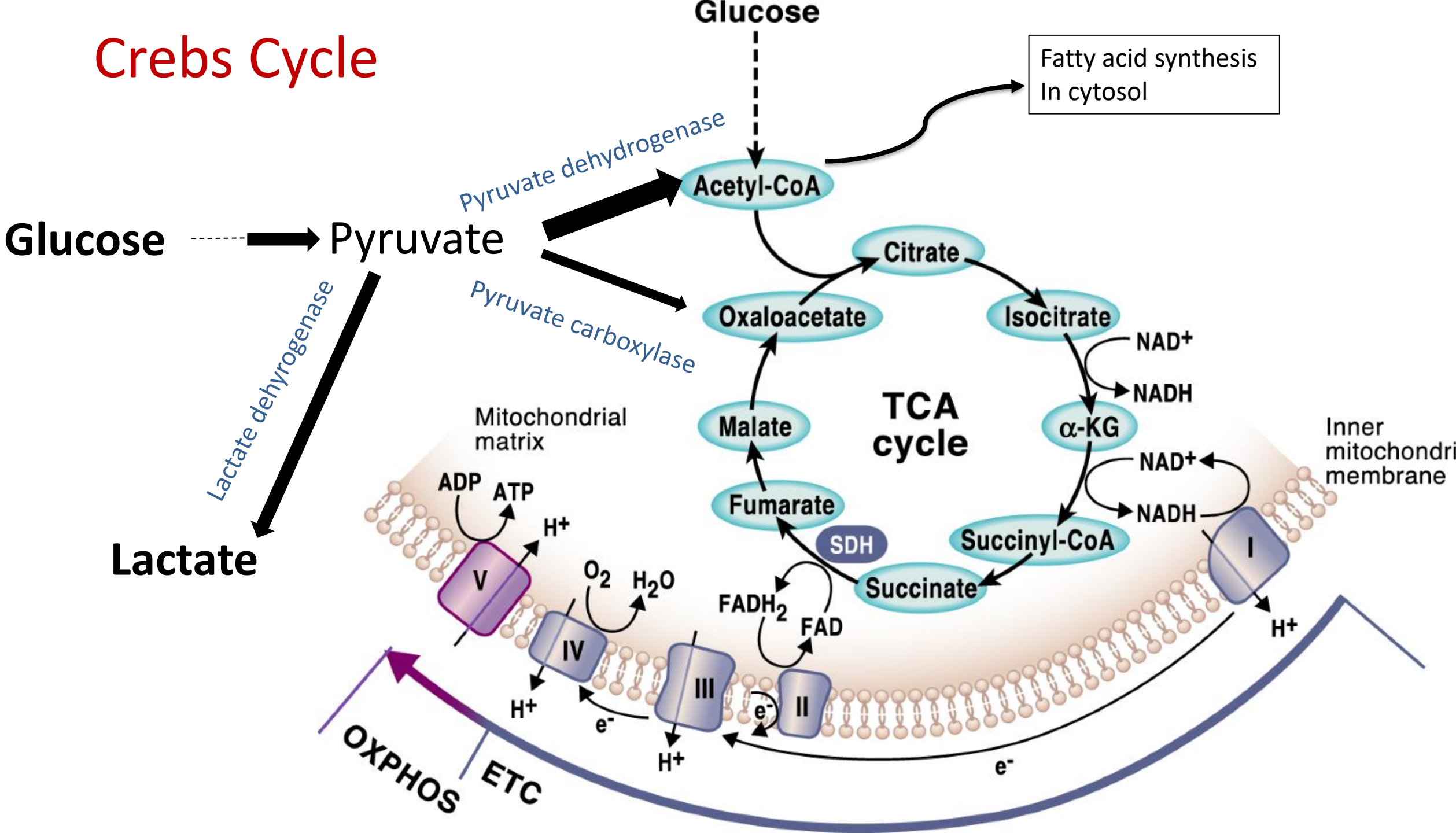
Pyruvate is metabolized through 4 main enzyme systems

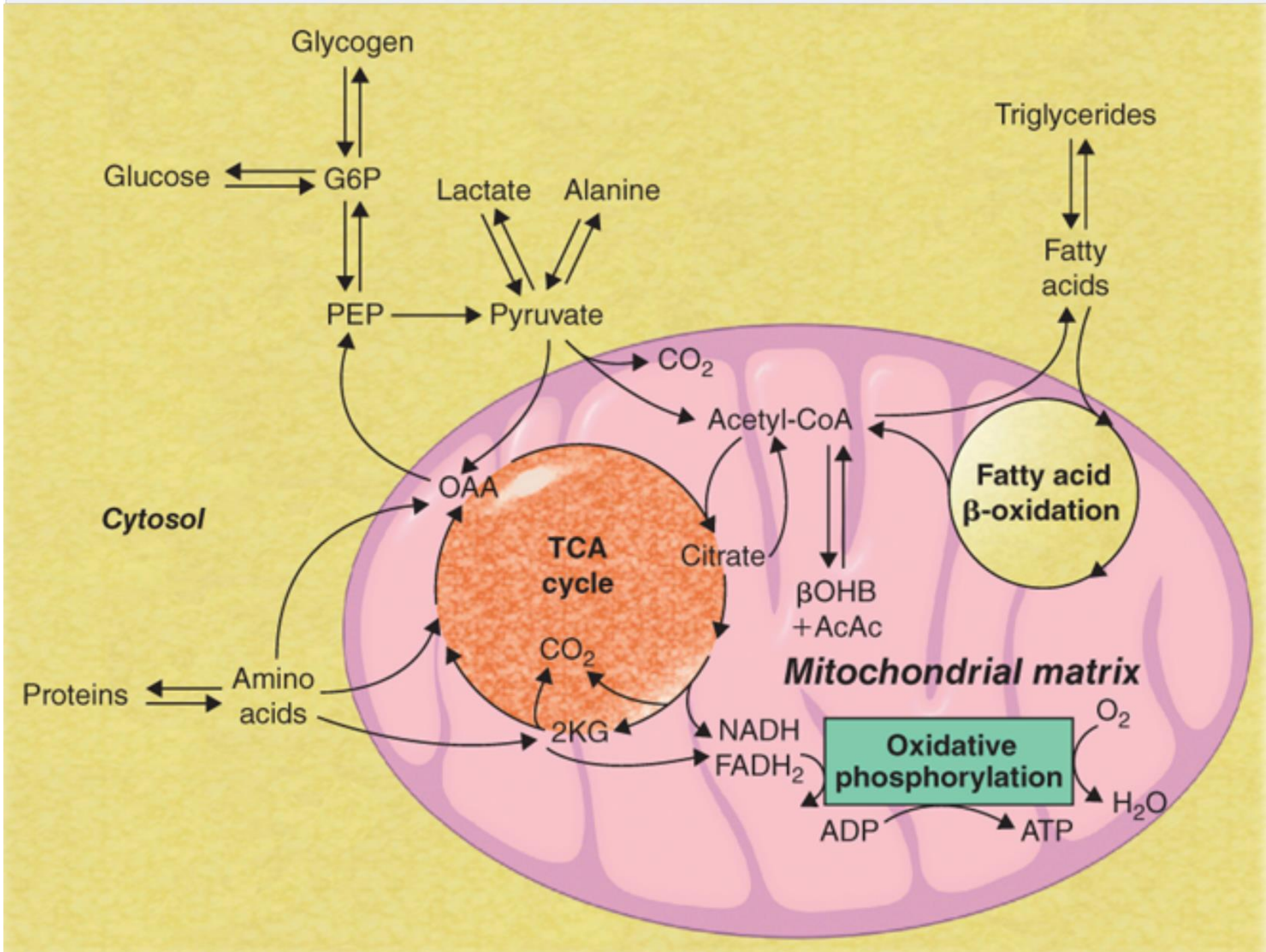
- Lactate dehydrogenase
- Alanine aminotransferase
- Pyruvate carboxylase
- Respiratory chain defects
- Pyruvate dehydrogenase complex

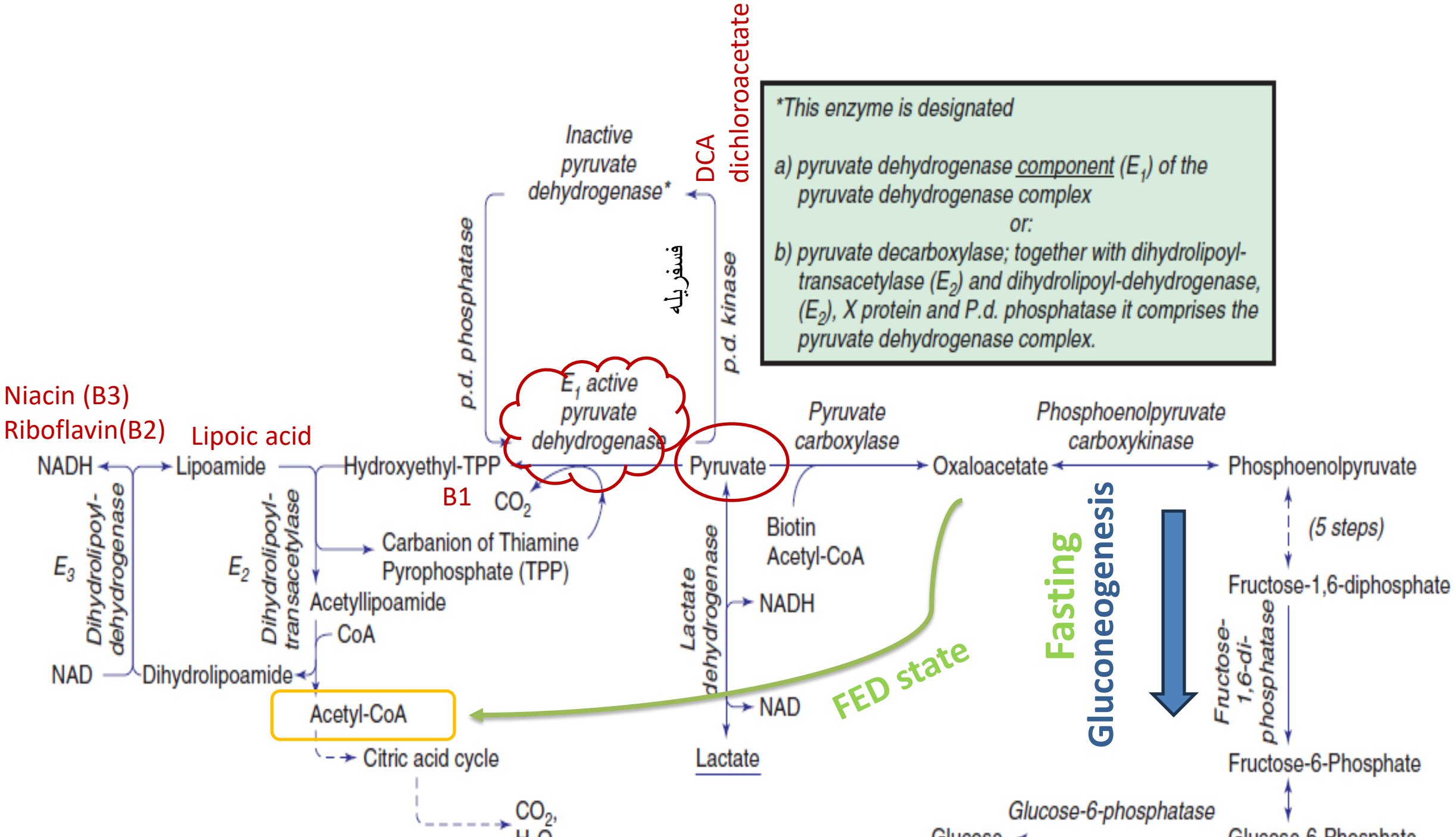


Deficiency of the M subunit of lactate dehydrogenase causes exercise intolerance and myoglobinuria

Crebs Cycle

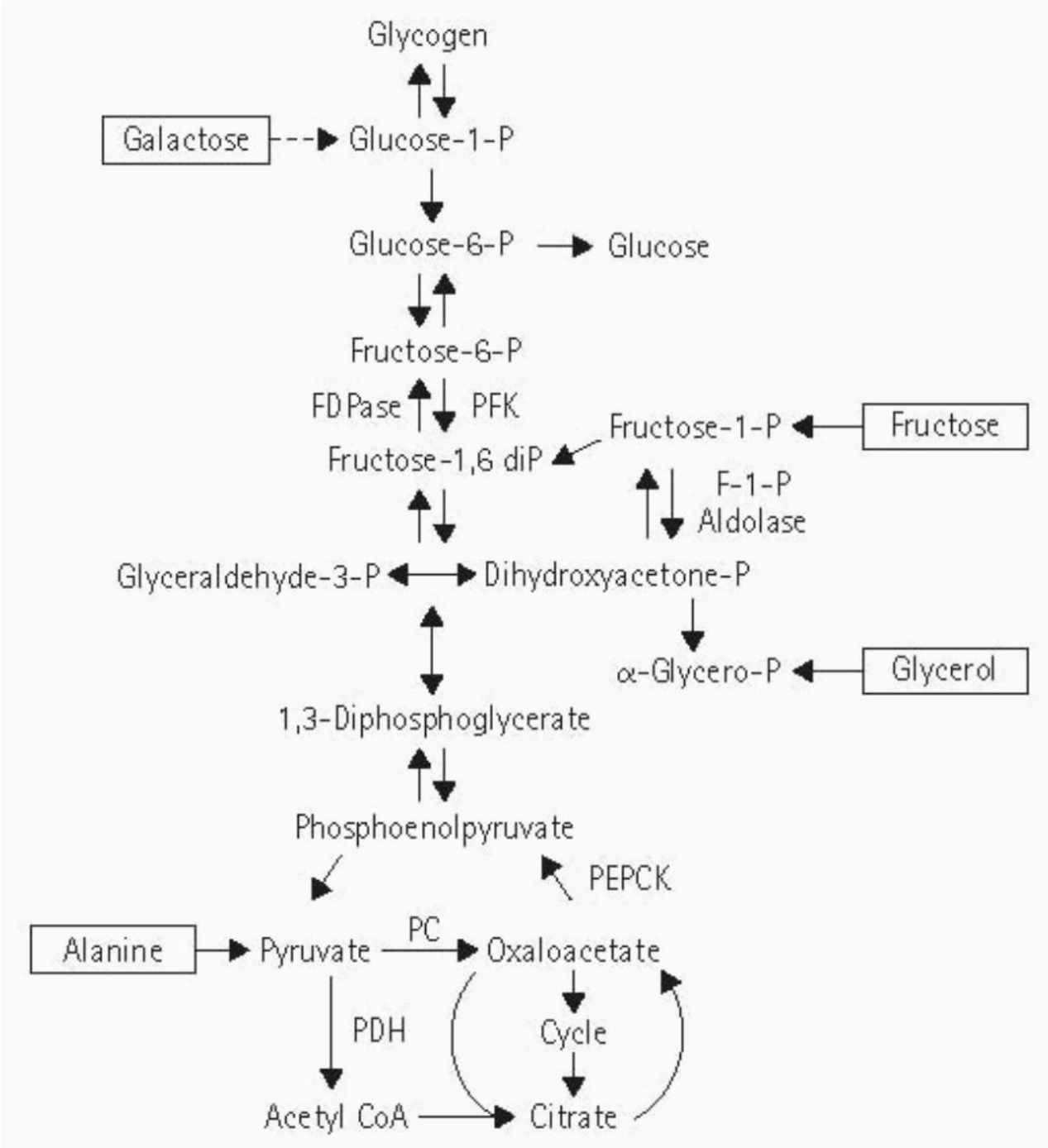

Glucose
Fatty acid synthesis
In cytosol
Pyruvate dehydrogenase
Glucose
Pyruvate
Acetyl-CoA
Citrate
Oxaloacetate
Isocitrate
NAD+
NADH
Pyruvate carboxylase
Lactate dehyrogenase
Mitochondrial matrix
TCA cycle
Malate
α-KG
Inner mitochondri membrane
NAD+
NADH
ADP
ATP
H+
Fumarate
SDH
Succinyl-CoA
I
V
O2
H2O
Succinate
FADH2
FAD
IV
III
II
H+
e-
e-
H+
H+
e-
OXPHOS
ETC
Lactate


Glycogen
Glucose
G6P
Lactate
Alanine
Triglycerides
Fatty acids
PEP
Pyruvate
CO_2
Acetyl-CoA
OAA
Cytosol
TCA cycle
Citrate
Fatty acid β-oxidation
βOHB +AcAc
CO_2
Mitochondrial matrix
Proteins
Amino acids
2KG
NADH
$FADH_2$
Oxidative phosphorylation
O_2
H_2O
ADP
ATP


*This enzyme is designated
a) pyruvate dehydrogenase component (E_1) of the pyruvate dehydrogenase complex
or:
b) pyruvate decarboxylase; together with dihydrolipoyl-transacetylase (E_2) and dihydrolipoyl-dehydrogenase, (E_2), X protein and P.d. phosphatase it comprises the pyruvate dehydrogenase complex.
Inactive pyruvate dehydrogenase*
DCA
dichloroacetate
p.d. phosphatase
فسفريله
p.d. kinase
E_1 active pyruvate dehydrogenase
Niacin (B3)
Riboflavin(B2)
Lipoic acid
NADH
Lipoamide
Hydroxyethyl-TPP
B1
CO_2
Pyruvate
Pyruvate carboxylase
Oxaloacetate
Phosphoenolpyruvate carboxykinase
Phosphoenolpyruvate
(5 steps)
Fructose-1,6-diphosphate
Fructose-1,6-di-phosphatase
Fructose-6-Phosphate
Glucose-6-phosphatase
Glucose
Glucose-6-Phosphate
E_3
Dihydrolipoyl-dehydrogenase
E_2
Dihydrolipoyl-transacetylase
Carbanion of Thiamine Pyrophosphate (TPP)
Acetyllipoamide
CoA
NAD
Dihydrolipoamide
Acetyl-CoA
Citric acid cycle
CO_2,
Biotin
Acetyl-CoA
Lactate dehydrogenase
NADH
NAD
Lactate
FED state
Fasting
Gluconeogenesis

Pathways of metabolism for pyruvate through gluconeogenesis and oxidation.

Boxes highlight compounds that have been used in tests to elucidate defects in gluconeogenesis.



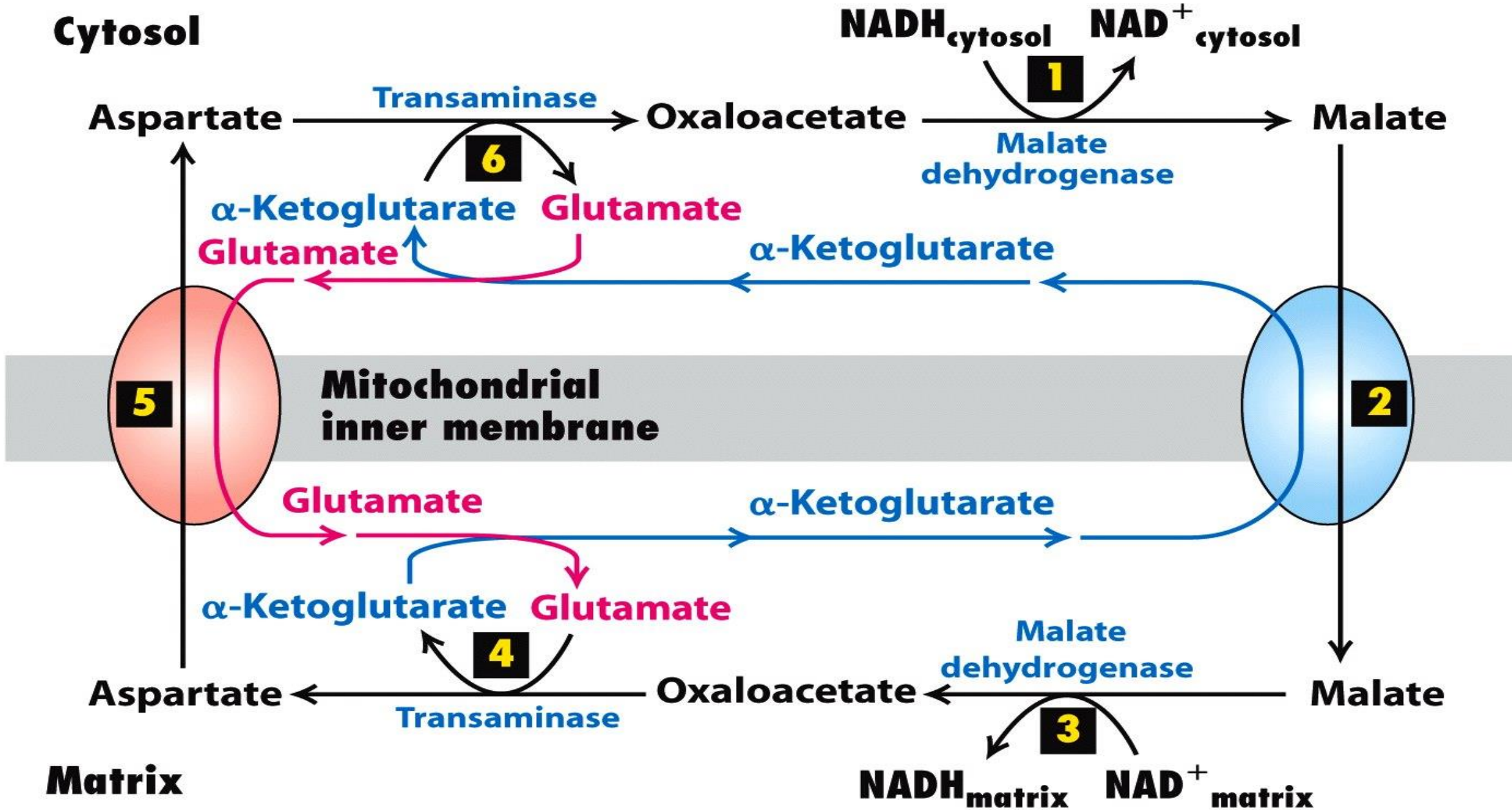
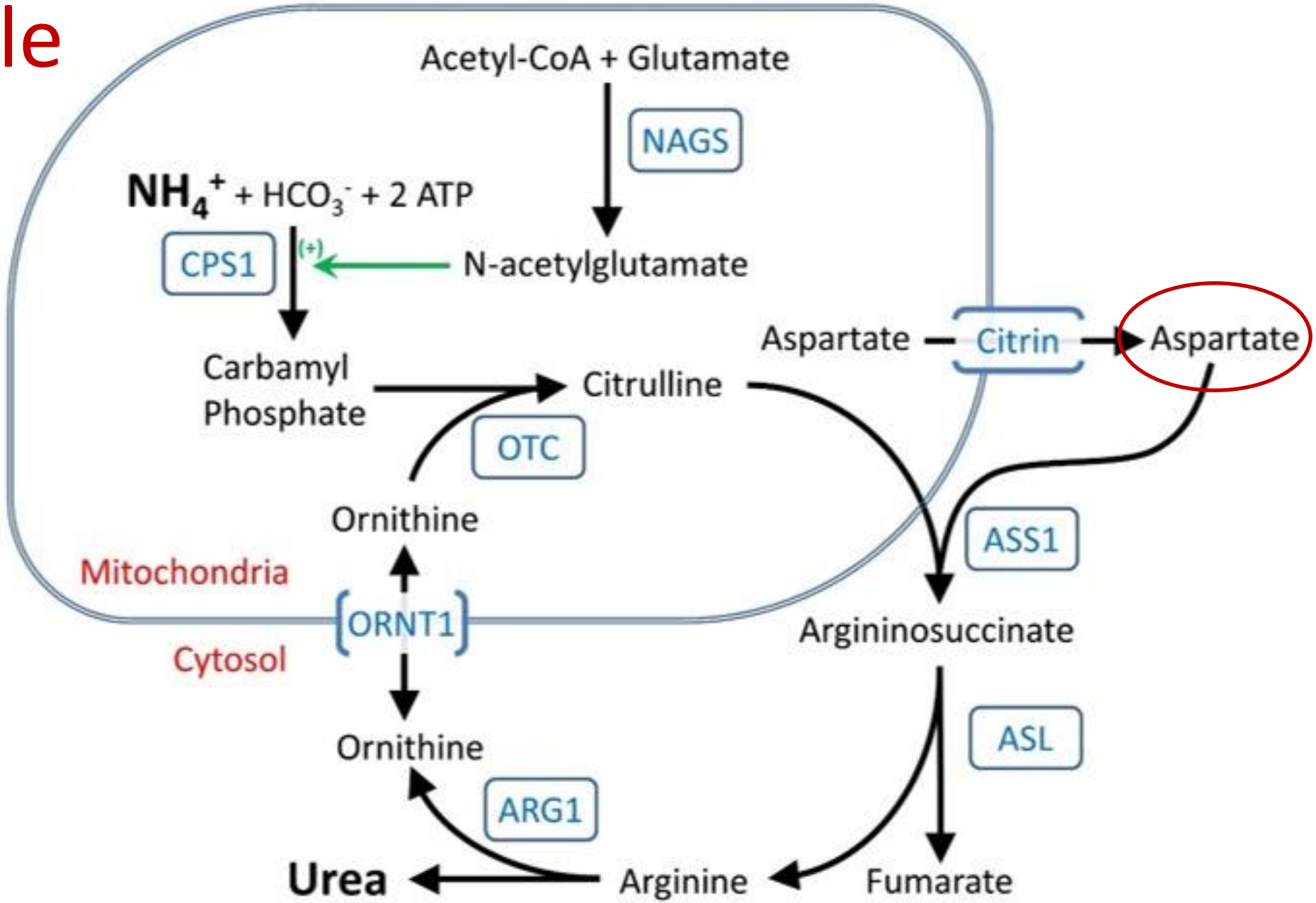
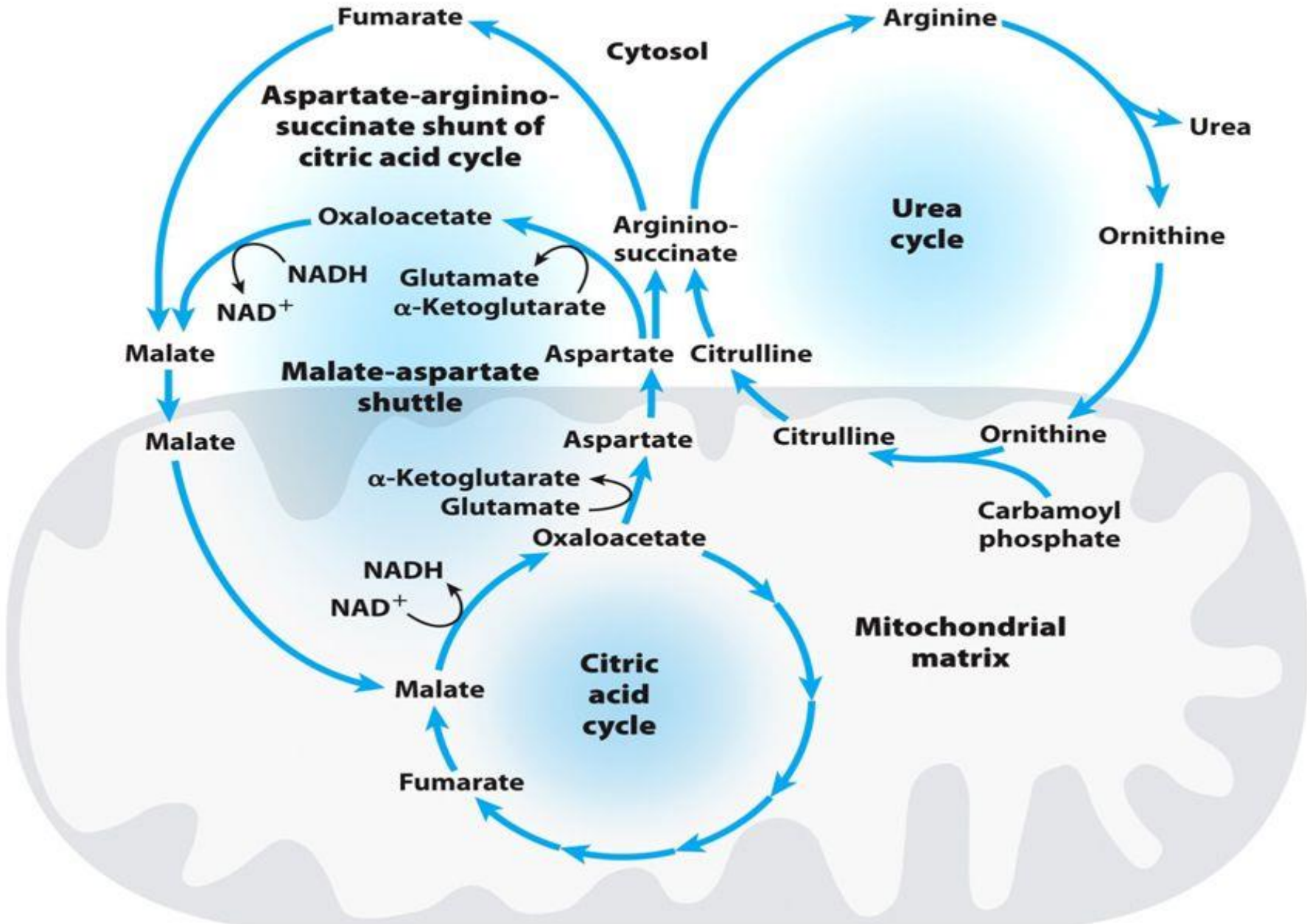


Figure 12-11
Molecular Cell Biology, Sixth Edition

Urea cycle


Acetyl-CoA + Glutamate
NAGS
$NH_4^+ + HCO_3^- + 2$ ATP
CPS1
(+)
N-acetylglutamate
Aspartate
Citrin
Aspartate
Carbamyl Phosphate
Citrulline
OTC
Ornithine
ASS1
Mitochondria
ORNT1
Argininosuccinate
Cytosol
Ornithine
ASL
ARG1
Urea
Arginine
Fumarate

The Citric Acid and Urea Cycles Can Be Linked



Lactic acidosis can also occur

Defects of:

- Fatty acid oxidation
- Organic acidurias
- Biotin utilization diseases

These disorders are easily distinguishable by the presence of :

- Abnormal acylcarnitine profiles,
- Amino acids in the blood,
- Unusual organic acids in the urine.

Clinical Presentation

Symptoms

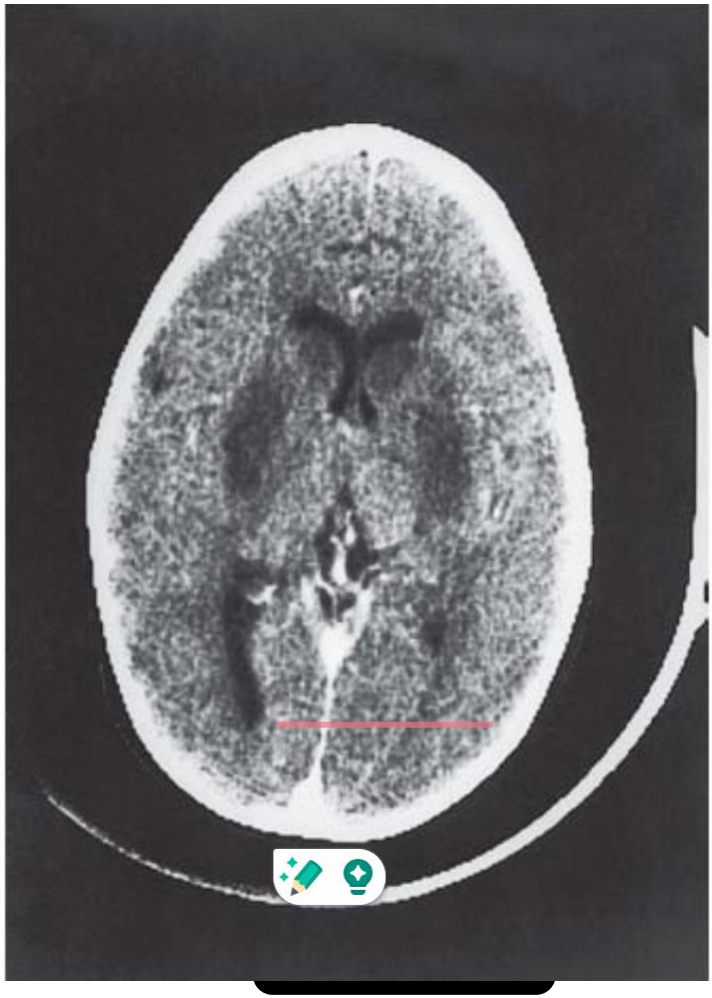
- Poor feeding
- Nausea & vomiting
- Lethargy
- Metabolic acidosis+respiratory alkalosis

Signs

- Tachypnea
- Hypotension
- Hypoperfusion signs
- Respiratory distress
- Hypoglycemia and seizures
- Altered mental status
- Ataxia

Neurologic presentation

- Leigh syndrome, or subacute necrotizing encephalomyelopathy
- The neuropathologic picture resembles Wernicke encephalopathy in the basal ganglia, brain stem, and cerebellum, but in contradistinction to the picture in Wernicke disease, the mammillary bodies are usually spared.
- Spongiform degeneration is seen, as are increased vascularity and glial proliferation.
- (CT) or (MRI) scans now provide the neuroimaging counterpart of the histology with hypodensity in the caudate and putamen
- Ultimately, the patient develops spasticity often with Babinski signs.
- Seizures occur in about a third of such patients.
- Blindness , retinal pigment epithelium changes
- Late in the course, deep tendon reexes may be absent.
- Tracheostomy and artificial ventilation may be required.



First Step !

- Is lactic acid in the blood real!?
- The most common reason for the elevated concentration of lactic acid in blood is an **improper technique**, the use of a tourniquet, or a real struggle in obtaining a sample
- levels are variable even in patients with known disease
- The first step is to document: elevated levels of **lactic acid**, **pyruvic acid**, and/or **alanine** in the blood.
- The concentration of lactate in the CSF may also be elevated.
- The lactic acidemias are disorders of pyruvate metabolism!
- Concentrations of pyruvate are determined, but large elevations of pyruvate are seldom seen
- Concentrations of alanine are not raised factitiously by problems of technique, but they too are variable in patients with known enzymatic defects.

The next step!

Is to exclude the conditions that lead to secondary elevations in concentrations of lactic acid.

- Hypoxia
- Hypoventilation
- Shock, or hypoperfusion

These situations are seen in patients with:

- Sepsis
- Cardiac and pulmonary disease
- Hepatic disease
- Severe anemia.

- *Anaerobic exercise also produces lactic acidemia, but this is seldom an issue clinically, except in the patient who has just had convulsions*.

Metabolic Disease With Lactic Acidemia:

See particularly at times of acute illness

- Propionic acidemia
- Methylmalonic acidemia
- Isovaleric acidemia
- 3-hydroxy-3-methyl glutaric aciduria
- Pyroglutamic aciduria
- Multiple carboxylase deficiency as a direct *consequence of the defect in pyruvate carboxylase.*
- Disorders of fatty acid oxidation
- Mitochondrial disorders

WORK UP OF A PATIENT WITH CONGENITAL LACTIC ACIDEMIA

- Search for mutation in mitochondrial DNA
- Determine the acylcarnitine profile by tandem mass spectrometry.
- Patients judged to have congenital lactic acidemia and not found to have an abnormality in mitochondrial DNA fall into two categories
    - ✓ Those with defects in gluconeogenesis
    - ✓ Those with defects in oxidation

- An intravenous catheter is inserted to facilitate the drawing of samples.
- Prior to the initiation of fasting, blood is obtained for **glucose**, **lactate**, **pyruvate**, and **alanine**.
- After 6 hours of fasting, 0.5 mg of glucagon is given intramuscularly, and the glucose response is determined at 15, 30, 45, 60, and 90 minutes.

The response to glucagon should be a sizable increase in glucose, except in glycogenosis type i .

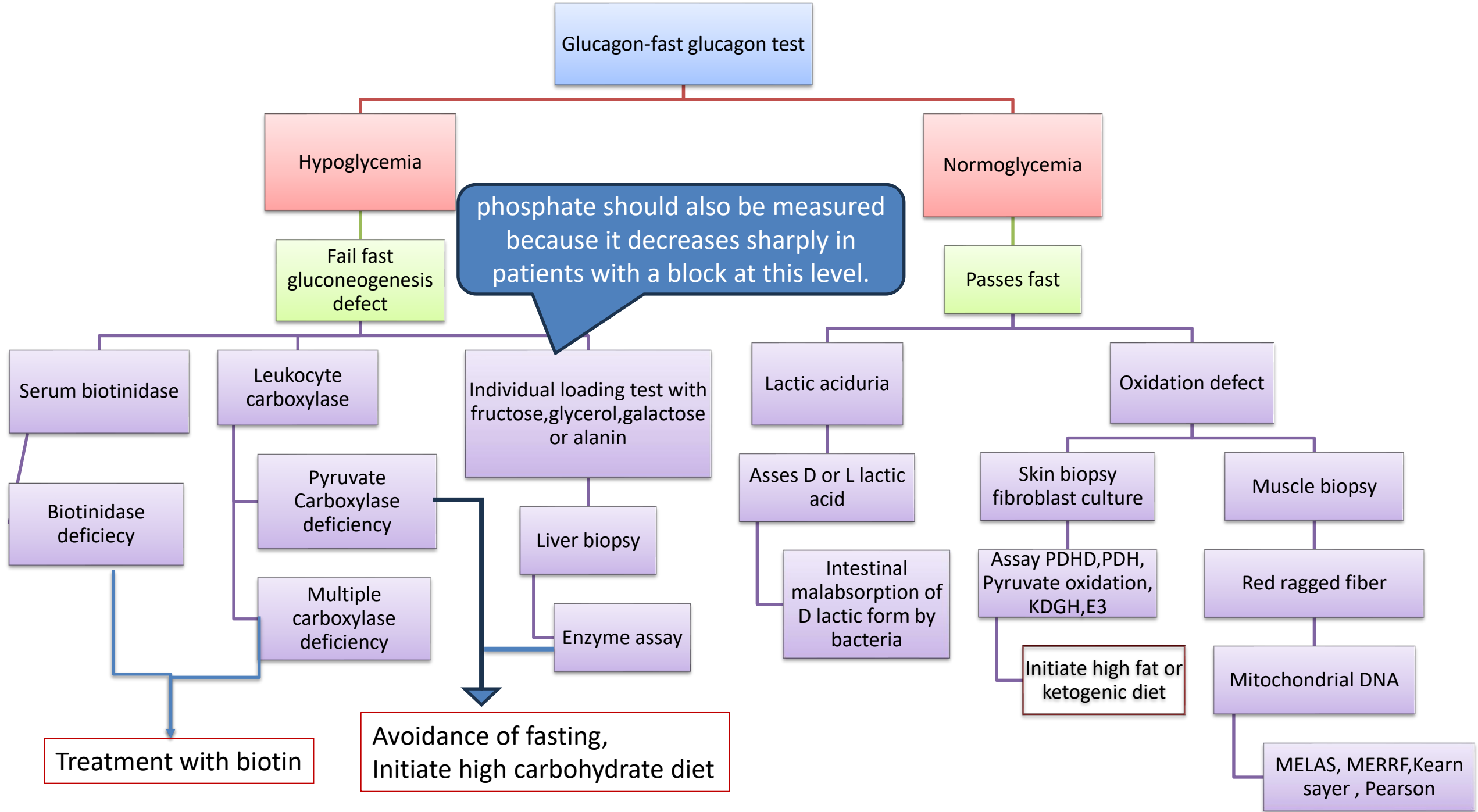
The fast is then continued for 24 hours if the patient remains euglycemic.

The blood concentration of glucose is monitored by determination at the bedside and quantitative determinations are carried out at intervals and in the presence of an abnormal test or symptoms of hypoglycemia.

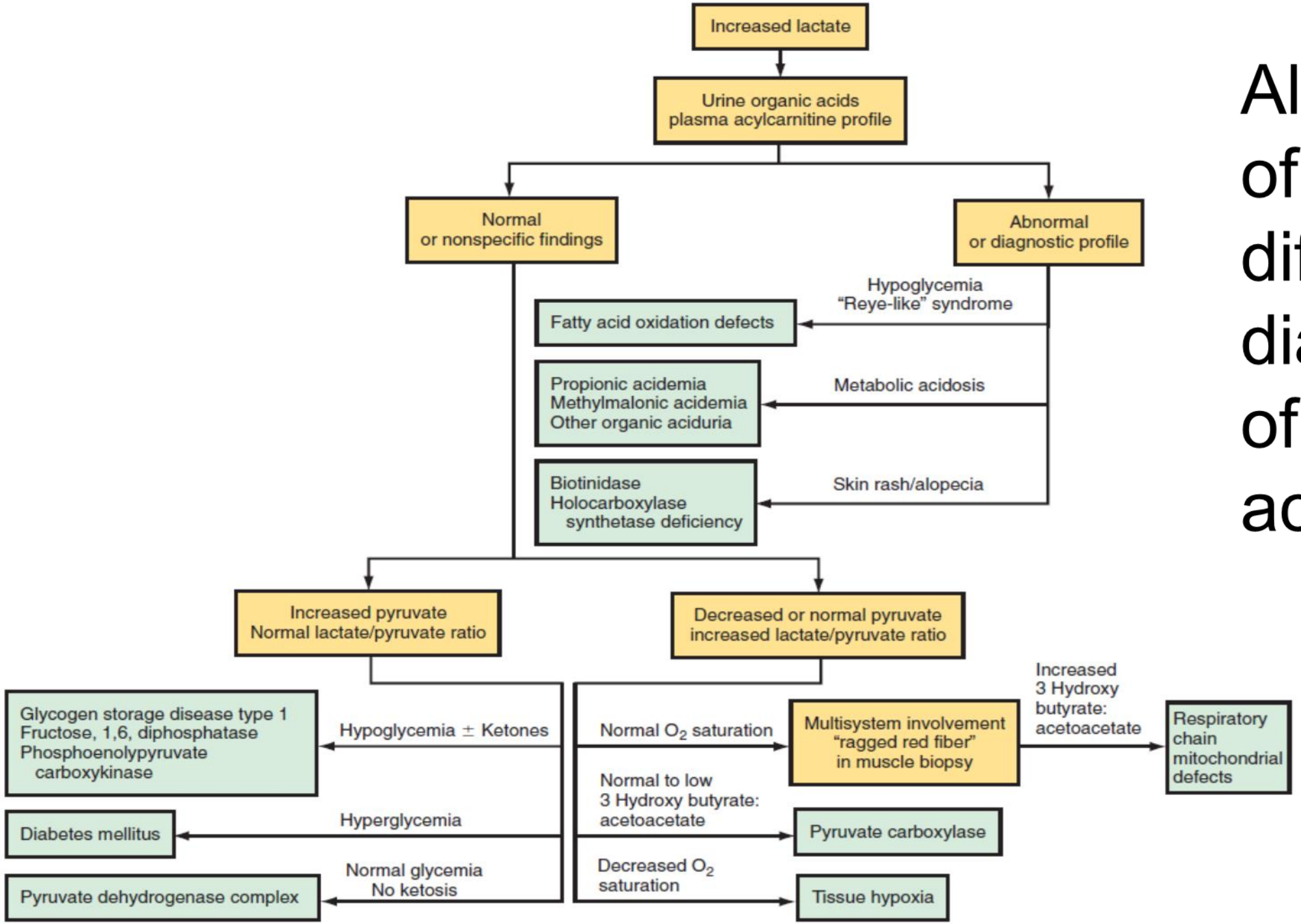
If hypoglycemia develops at any time, the fast is concluded and glucagon given. The intravenous catheter ensures the prompt intravenous administration of glucose to restore normoglycemia.

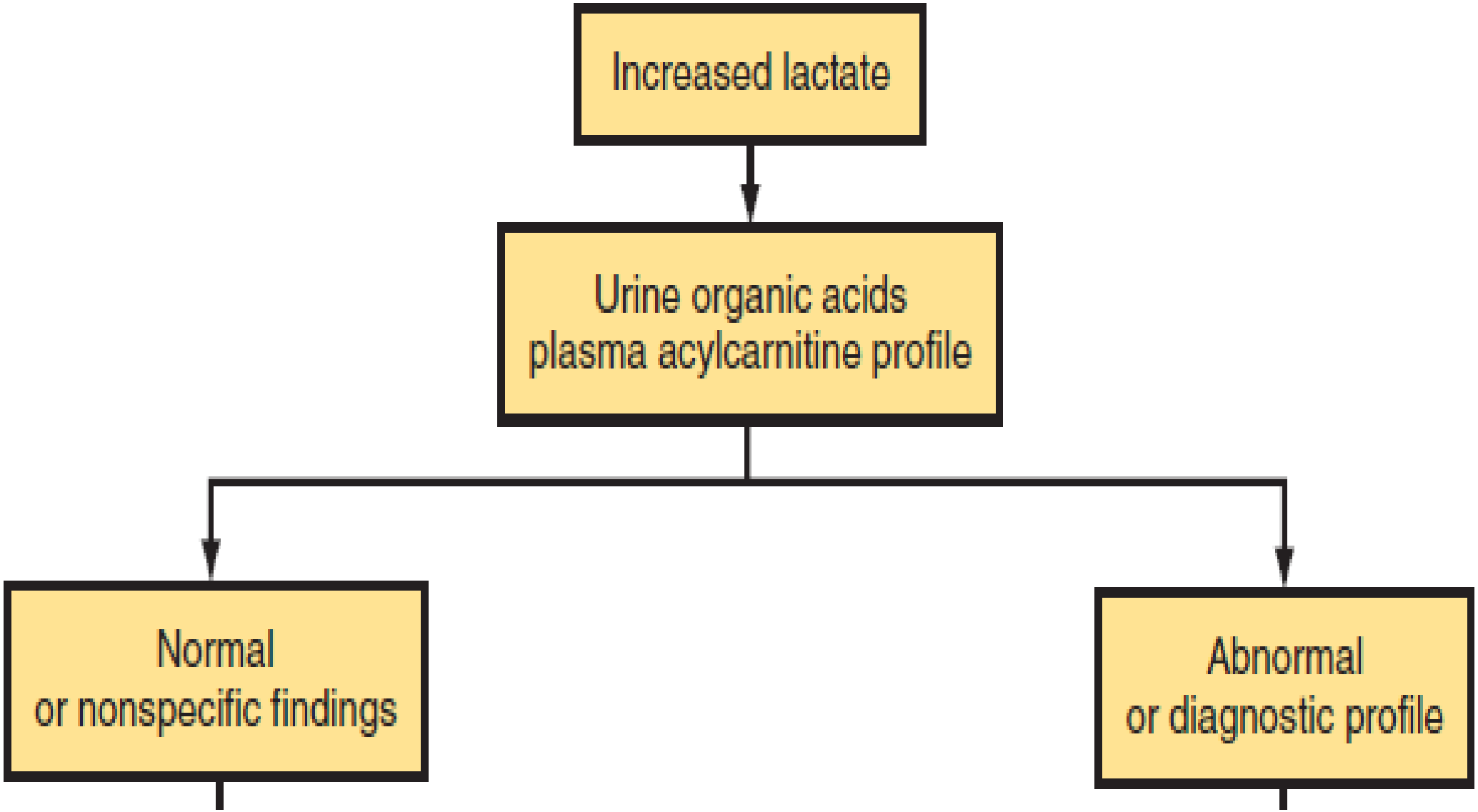
Concentrations of **lactic** and **pyruvic** acids and **alanine** are obtained at the end of the fast prior to the administration of glucagon.

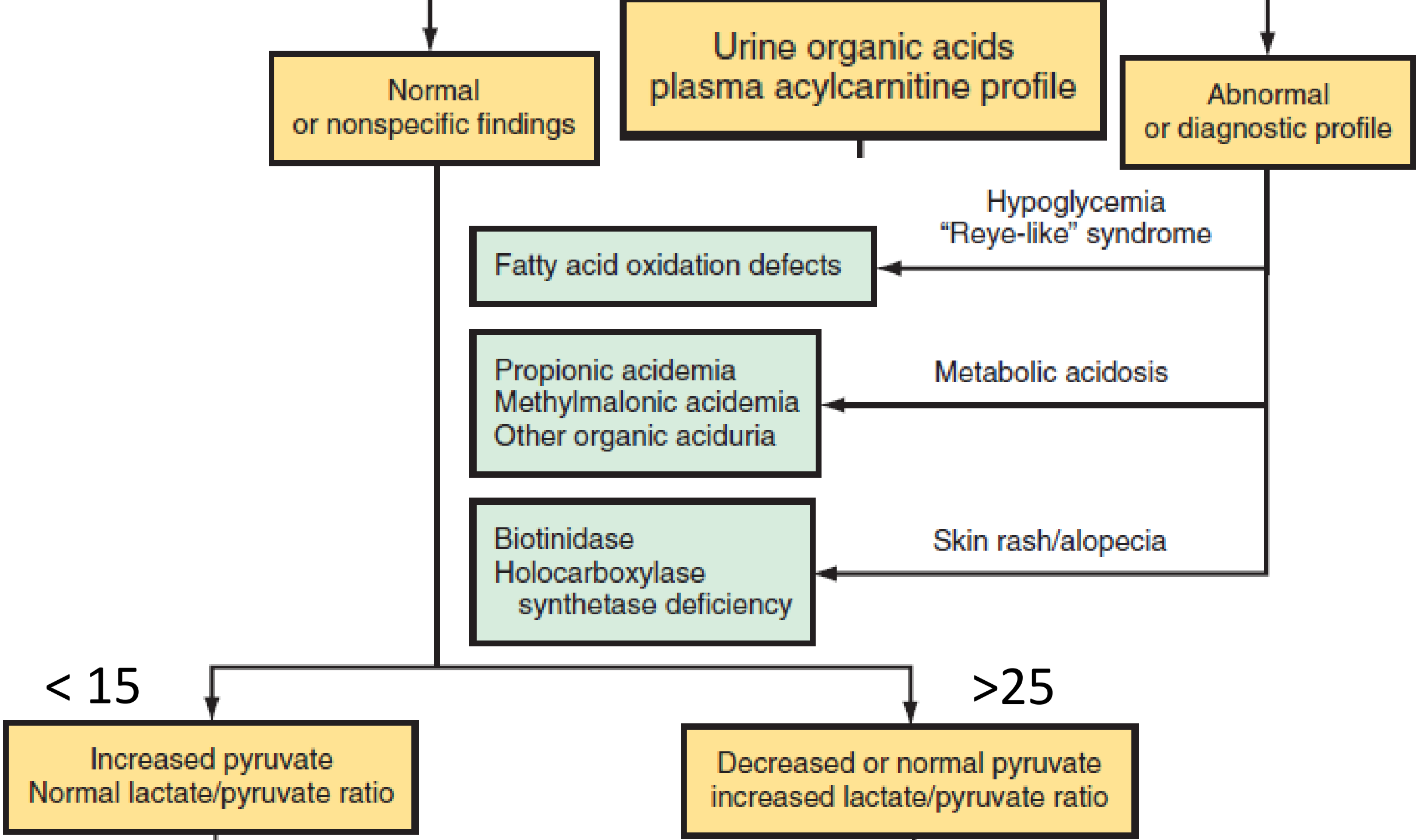
In a hypoglycemic patient, levels of **insulin**, **growth hormone**, and **glucagon** are also obtained if this information is not available from prior testing

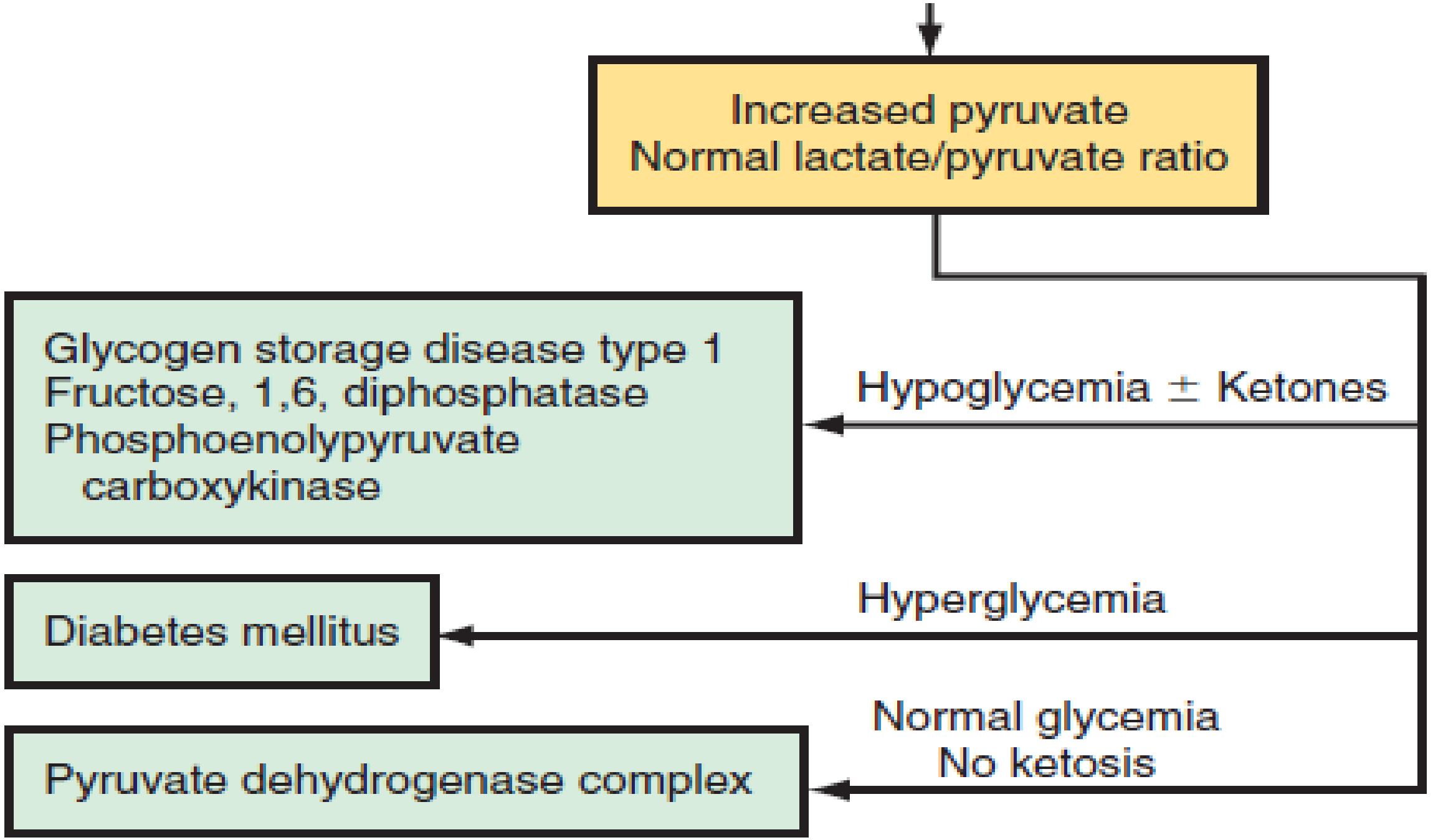

Glucagon-fast glucagon test
Hypoglycemia
Normoglycemia
phosphate should also be measured because it decreases sharply in patients with a block at this level.
Fail fast gluconeogenesis defect
Passes fast
Serum biotinidase
Leukocyte carboxylase
Individual loading test with fructose,glycerol,galactose or alanin
Lactic aciduria
Oxidation defect
Biotinidase deficiecy
Pyruvate Carboxylase deficiency
Liver biopsy
Asses D or L lactic acid
Skin biopsy fibroblast culture
Muscle biopsy
Multiple carboxylase deficiency
Enzyme assay
Intestinal malabsorption of D lactic form by bacteria
Assay PDHD,PDH, Pyruvate oxidation, KDGH,E3
Red ragged fiber
Initiate high fat or ketogenic diet
Mitochondrial DNA
MELAS, MERRF,Kearn sayer , Pearson
Treatment with biotin
Avoidance of fasting,
Initiate high carbohydrate diet

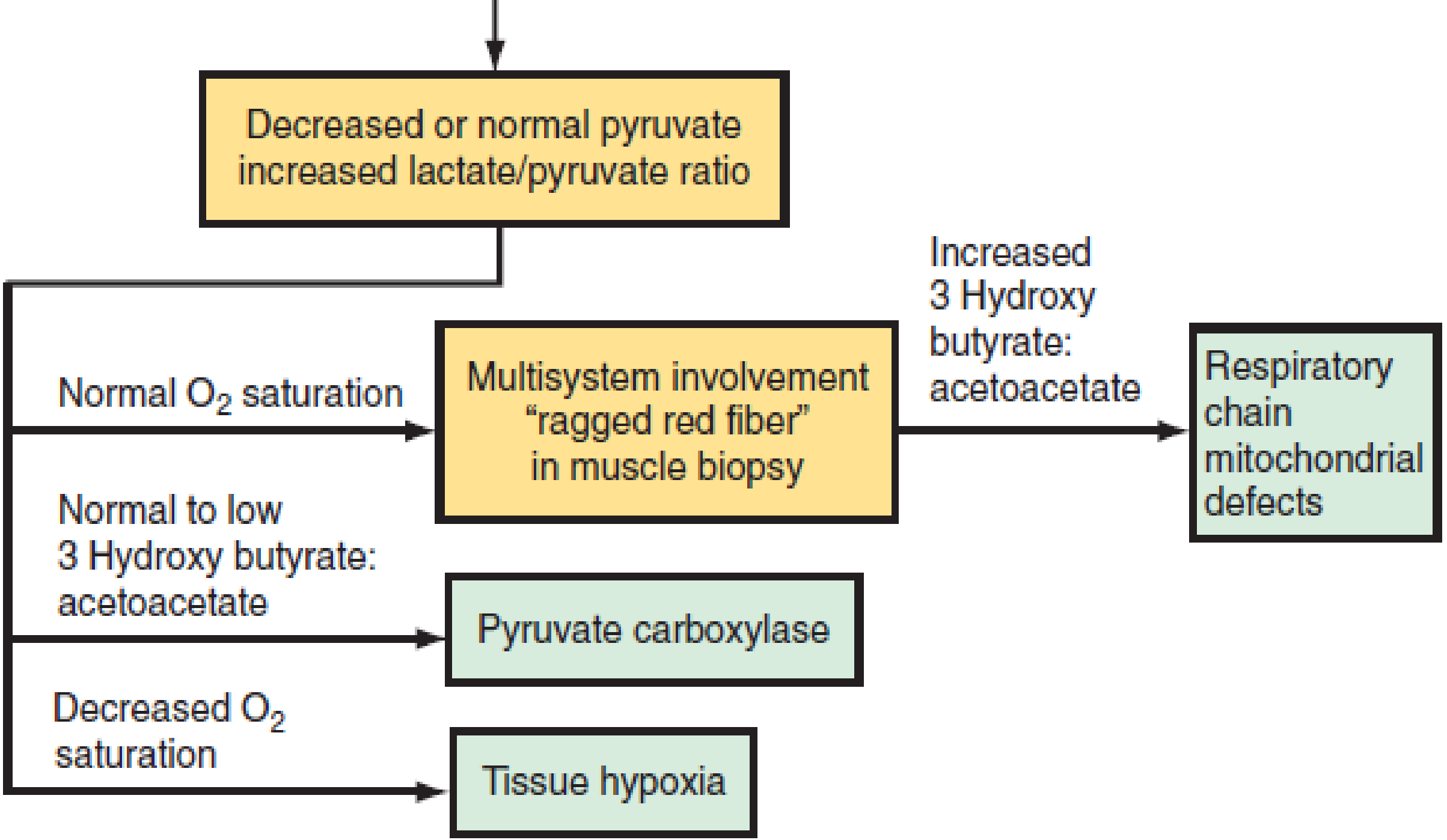
Algorithm of the differential diagnosis of lactic acidosis



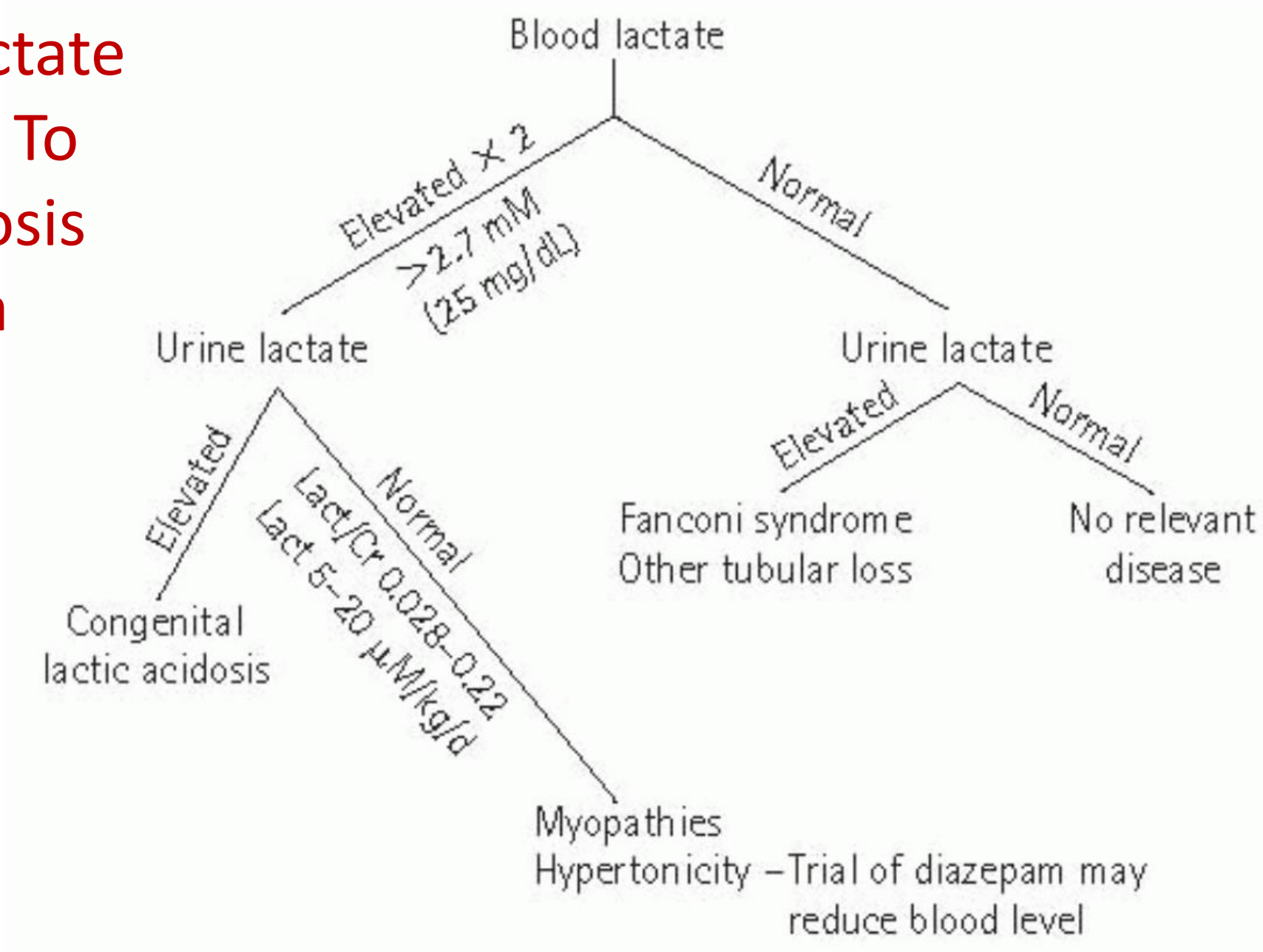

Increased lactate
Urine organic acids
plasma acylcarnitine profile
Normal
or nonspecific findings
Abnormal
or diagnostic profile


Urine organic acids
plasma acylcarnitine profile
Normal
or nonspecific findings
Abnormal
or diagnostic profile
Hypoglycemia
"Reye-like" syndrome
Fatty acid oxidation defects
Propionic acidemia
Methylmalonic acidemia
Other organic aciduria
Metabolic acidosis
Biotinidase
Holocarboxylase
synthetase deficiency
Skin rash/alopecia
< 15
>25
Increased pyruvate
Normal lactate/pyruvate ratio
Decreased or normal pyruvate
increased lactate/pyruvate ratio


Increased pyruvate
Normal lactate/pyruvate ratio
Glycogen storage disease type 1
Fructose, 1,6, diphosphatase
Phosphoenolypyruvate
carboxykinase
Hypoglycemia ± Ketones
Diabetes mellitus
Hyperglycemia
Pyruvate dehydrogenase complex
Normal glycemia
No ketosis


Decreased or normal pyruvate
increased lactate/pyruvate ratio
Normal O_2 saturation
Multisystem involvement
"ragged red fiber"
in muscle biopsy
Increased
3 Hydroxy
butyrate:
acetoacetate
Respiratory
chain
mitochondrial
defects
Normal to low
3 Hydroxy butyrate:
acetoacetate
Pyruvate carboxylase
Decreased O_2
saturation
Tissue hypoxia

Assessment Of Lactate In Urine As An Aid To Deferential Diagnosis Of Lactic Acidemia



TREATMENT

- **Acute treatment** of metabolic acidosis may require large amounts of sodium bicarbonate.
- Sodium citrate may be ineffective in a patient with an oxidative defect because citric acid cycle function is impaired.
- **Chronic treatment**
  - Patients with disorders of gluconeogenesis should avoid fasting and require intravenous glucose during intercurrent illnesses in which the oral route is not available, as in the vomiting patient.
  - A diet high in carbohydrate is therapeutic and cornstarch supplementation may be helpful.

Treatment

- Patients with disorders of oxidation are, in contrast, often glucose-sensitive and respond with reduction in lactate concentrations to a diet **high in fat.**
- Diets employed contain 50 percent or more of the calories from fat. They do not have to be ketogenic.
- Lactate levels can be lowered in some patients by the administration of **dichloroacetate (DCA),** regardless of the cause.
- It is not generally recommended in disorders of gluconeogenesis, because DCA can itself produce hypoglycemia.
- Dichloroacetate activates the PDHC by inhibiting PDH kinase. In vivo, this compound reduces concentrations of lactate, pyruvate, and alanine and increases the percentage of the active form of PDHC in brain, liver, and muscle. It has been used to treat congenital lactic acidosis and levels of lactic acid have been improved.
- Neurologic improvement has been elusive in most patients reported, but there have been some successes. Peripheral neuropathy can be expected to worsen with DCA, and some patients develop peripheral neuropathy


THANK YOU !