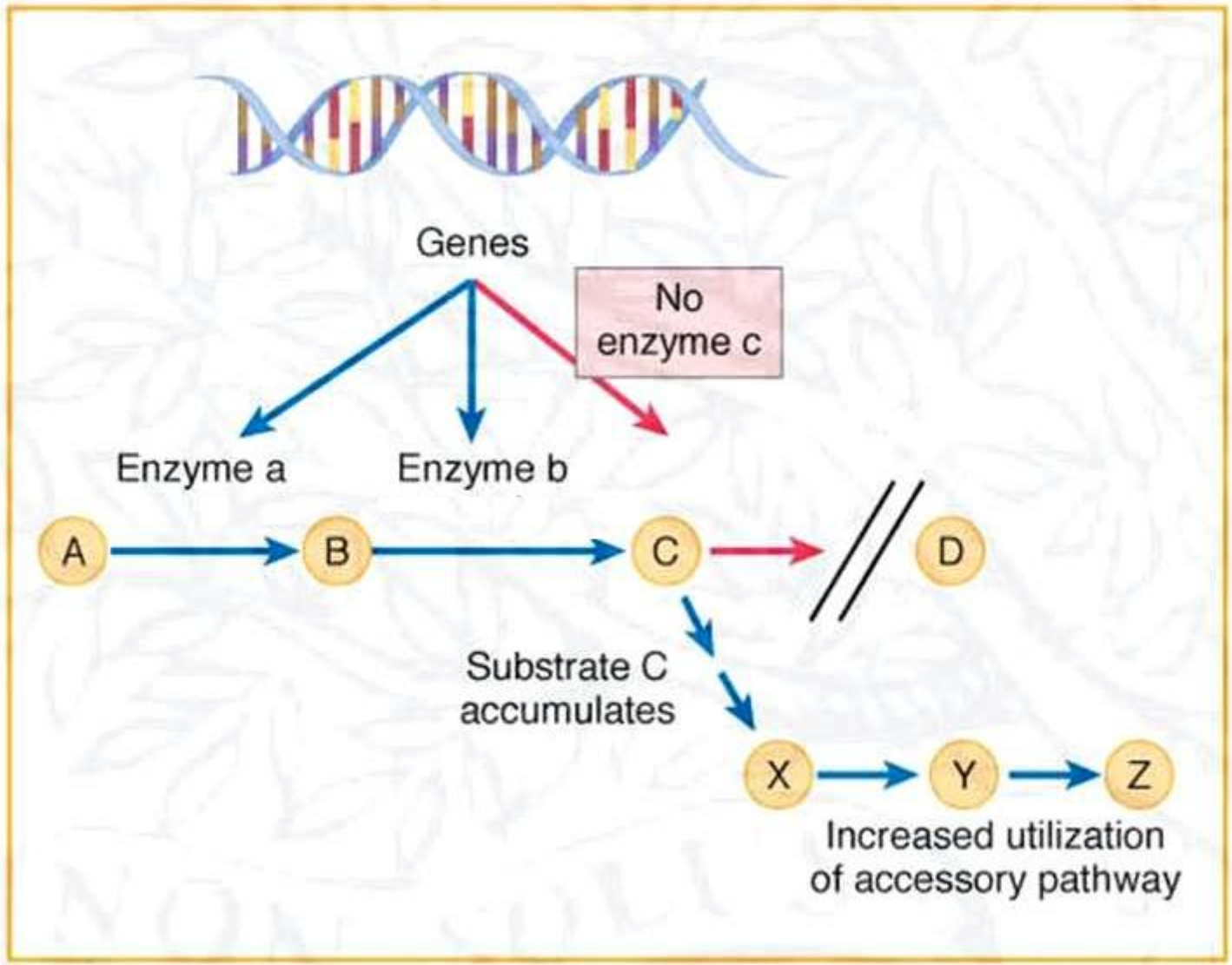
Hereditary metabolic disorders

Biochemistry of metabolic disorders



Newborn screening in Hungary

- Started in 1968 with screening of phenylketonuria and galactosemia at the Pediatric Health Center in Szeged (Guthrie's microbial test)
- Opening of the Budapest Screening Center in 1975 permitted nationwide screening of phenylketonuria and galactosemia
- During the 1980s congenital hypothyreosis (1984) and biotinidase deficiency (1989) were added to the list of screened disorders .
- Since 2007 the microbial screening method has been replaced by MS/MS and the screening of altogether 26 metabolic disorders became compulsory

Newborn screening of metabolic disorders in Hungary

Group of diseases	Disorders	Frequency (HU) *
Aminoacidopathies	Phenylketonuria	28:200 000
	Thyrosinaemia	1:200 000
	Maple syrup disease	1:200 000
	Homocystinuria	1:200 000
	Citrullinaemia	1:200 000
	Arginosuccinate aciduria	1:200 000
Organic acid disorders	Malonic-acidaemia	3:200 000
	Propionic acid / methylmalonic acidaemia	3:200 000
	Isovaleric acid-acidaemia	1:200 000
	Glutaric acidaemia (I, II, III)	1:200 000
	Methylcrotonyl-CoA carboxylase deficiency	2:200 000
	3-hydroxy-3-methylglutaryl-CoA lyase deficiency	16:200 000
	Biotinidase deficiency	3:200 000
Fatty acid oxidation disorders	Short chain acyl-CoA dehydrogenase deficiency	31:200 000
	Medium-chain acyl-CoA dehydrogenase deficiency	13:200 000
	Long chain hydroxyacyl-CoA dehydrogenase deficiency	1:200 000
	Very long chain acyl-CoA dehydrogenase deficiency	2:200 000
Disorders of carnitine transport	Disorder of carnitine transport	2:200 000
	Carnitine palmitoyl transferase deficiency (I, II)	2:200 000
Disorders of Carbohydrate metabolism	Galactosaemia	16:200 000
Endocrine diseases	Congenital hypothyroidism	75:200 000

* 2007. 10.01.-2012.11.10.
Szeged: ~ 200.000 newborns

Based on: *Szabó E, Balogh L, Szabó A, Szatmári I. [Diagnostics of inborn errors of metabolism: laboratory approaches]. Orv Hetil. 2017; 158(48): 1903–1907.*

Newborn screening worldwide

USA

- Started in 1963 with screening of phenylketonuria in 4 states
- Between 1963 and 2005 six disorders were screened
- Since 2005 the number of screened disorders increased to 47 (MS/MS)
- Currently screened disorders:
  - 34 primary conditions
  - 26 secondary conditions
- The actual list of screened disorders slightly differs state by state

United kingdom

- Started in 1969
- Currently 9 disorders are screened
- Participation in the screening program is not compulsory
- The National Screening Committee revises the list of screened conditions every 3 years

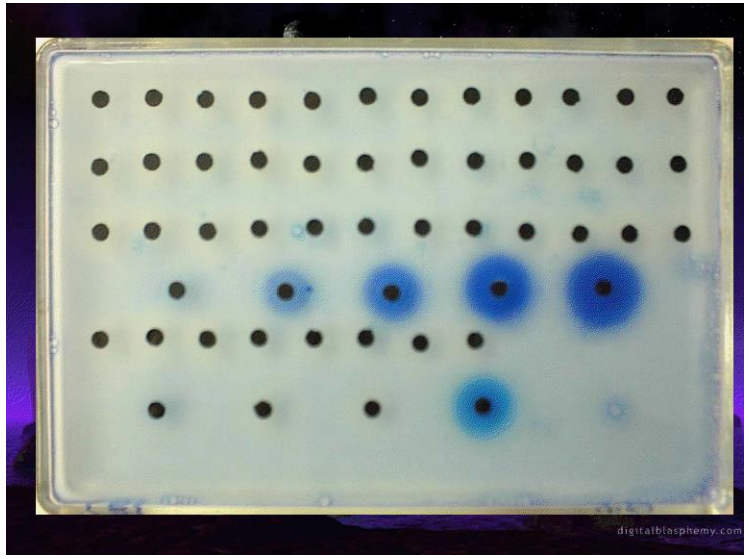
Germany

- Started in 1969
- Currently 16 disorders are screened

Schematic diagnostic algorythm

- Newborn screening:
  - -Guthrie test
  - -Tandem Mass Spectrometry
- Blood and urine analysis
- Enzyme activity analysis
- Molecular genetic testing

Guthrie card



Guthrie bacterial inhibition assay

General features of metabolic disorders

Inheritance: - mostly autosomal recessive

Causes

- Buildup of often toxic intermediates
- Lack of essential intermediates

Possible symptomes

- poor appetite
- nausea
- vomiting
- diarrhea
- fever
- irritability
- extreme sleepiness
- metabolic acidosis
- hyperammonemia
- hypoglycemia
- enlarged organs
- coma

Possible consequences

- organ disfunction/ failure
- developmental delay
- mental retardation
- death

Factors that most frequently trigger the symptoms of inherited metabolic disorders

Triggering factors	Disorders
Stop breastfeeding	Fructose intolerance Fructose diphosphatase deficiency Urea cycle disorders Lysinuria protein intolerance Maple syrup disease Organic acid disorders
Administration of fructose	Fructose intolerance Fructose diphosphatase deficiency
Administration of galactose	Galactosaemia
Protein intake	Urea cycle disorders Lysinuria protein intolerance Maple syrup disease Organic acid disorders Hyperinsulinism
Carbohydrate intake	Pyruvate dehydrogenase deficiency Respiratory chain disease Hyperinsulinism
Infection, catabolism, fever, starvation	Amino acid metabolism disorders Organic acid disorders Disorders of fatty acid oxidation Urea cycle disorders Glycogenoses
Anesthesia, surgery	Thromboembolic complications in homocystinuria, malignant hyperthermia
Medications	Porphyria Glucose-6-phosphate dehydrogenase deficiency

Therapeutic considerations

- Hydration/nutrition/acid-base management
- Elimination of toxic metabolites
- Treatment of coexisting/precipitating factors
- Cofactor replacement
- Long-term care

Classification of hereditary metabolic disorders

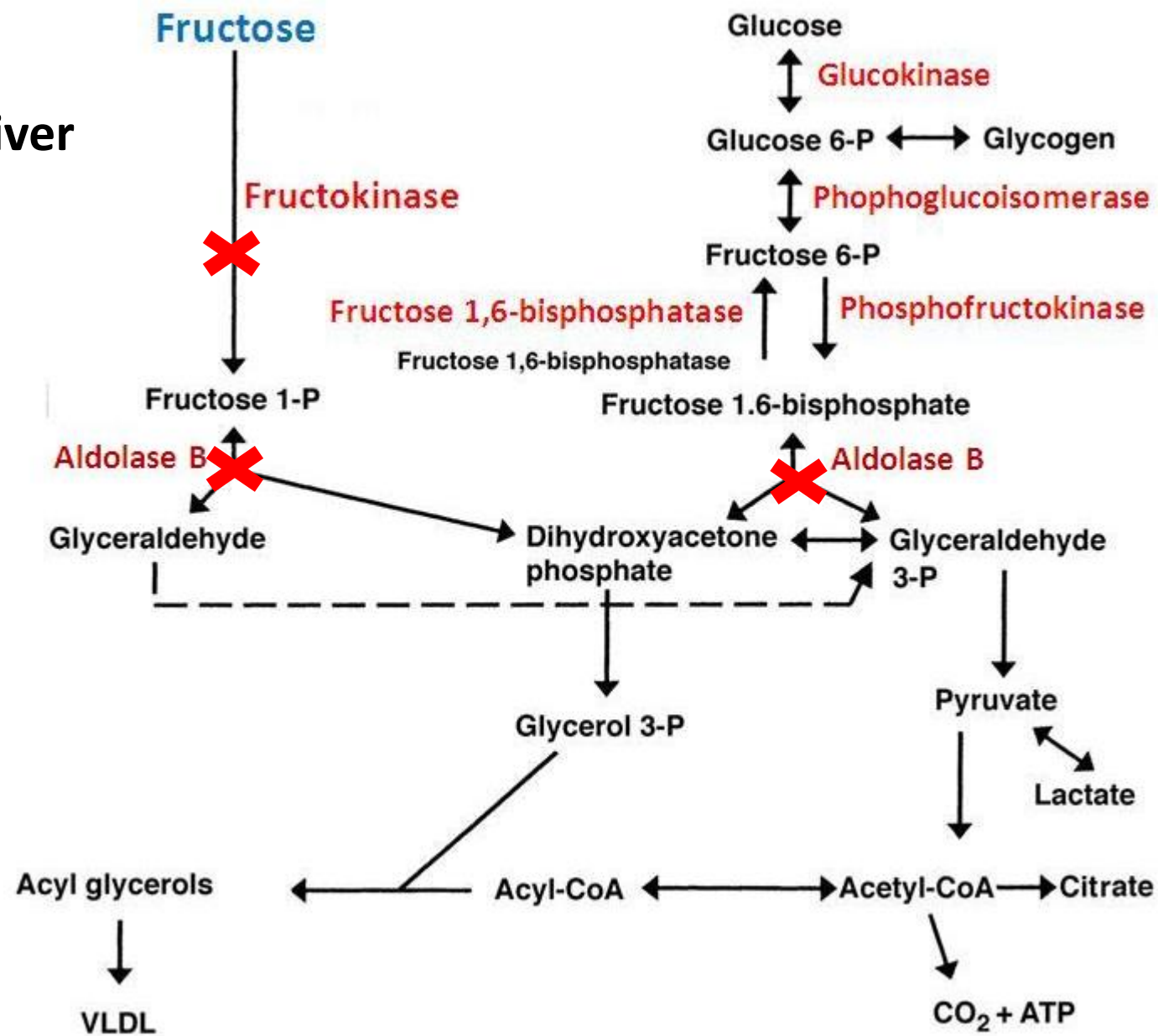
- Disorders of carbohydrate metabolism
- Disorders of amino acid metabolism
- Disorders of organic acid metabolism
- Disorders of fatty acid oxidation and mitochondrial metabolism
- Disorders of porphyrin metabolism
- Disorders of purine or pyrimidine nucleotide metabolism
- Disorders of steroid metabolism
- Disorders of mitochondrial function
- Disorders of peroxisomal function
- Lysosomal storage disorders

Hereditary disorders of carbohydrate metabolism

- Disorders of pyruvate metabolism →IV. semester - pH regulation lecture
- Disorders of fructose metabolism
- Galactosemia
- Lactose intolerance
- Glucose-6-phosphate dehydogenase deficiency →III. semester-Pentose
- phosphate pathway lecture
- Glycogen storage disorders
- Mucopolysaccharidoses (e.g. Hunter, Hurler, Morquio syndromes)

Fructose metabolism disorders

Fructose breakdown in the liver



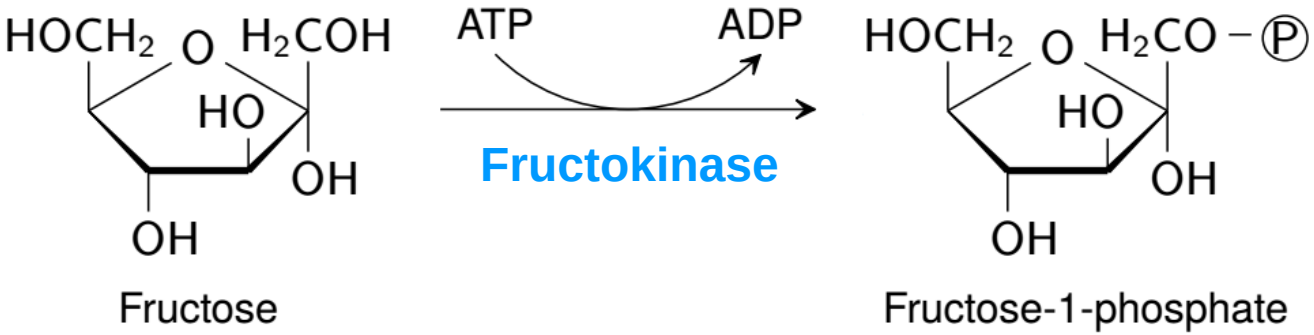
Fructosuria

Fructokinase deficiency

- benign condition

Symptomes:

- fructose is excreted in the urine



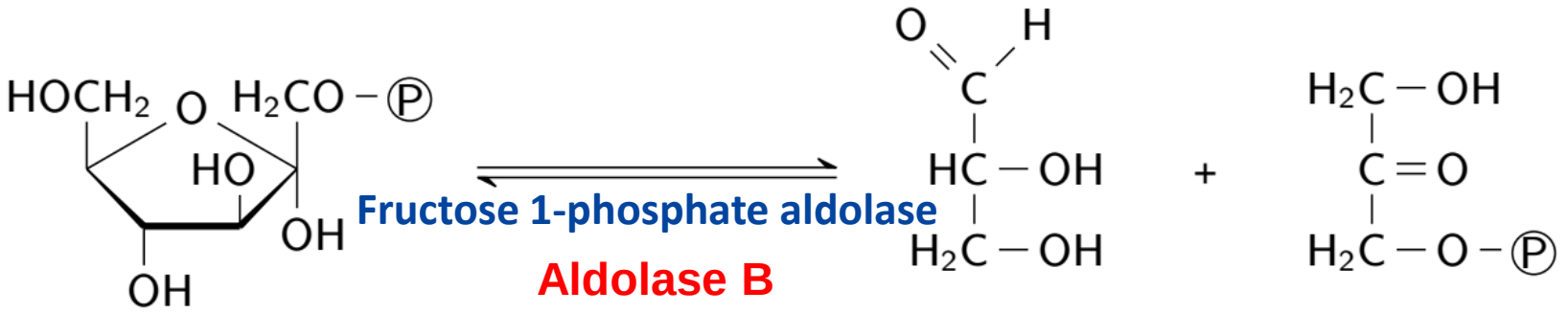
Fructose

Fructose-1-phosphate

Fructose intolerance (Fructosaemia)

Fructose 1-phosphate aldolase (Aldolase B) deficiency

Incidence: 1:20 000



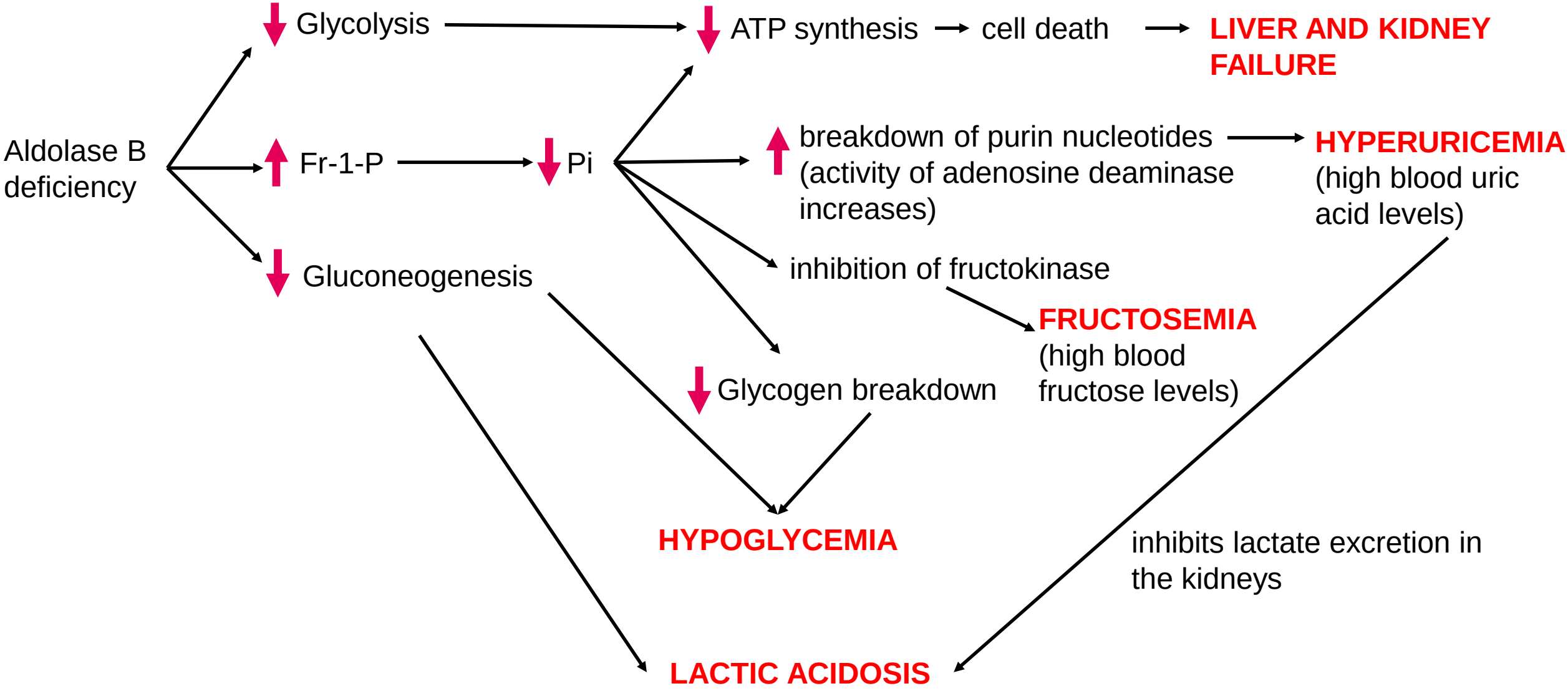
Fructose-1-phosphate

Glyceraldehyde

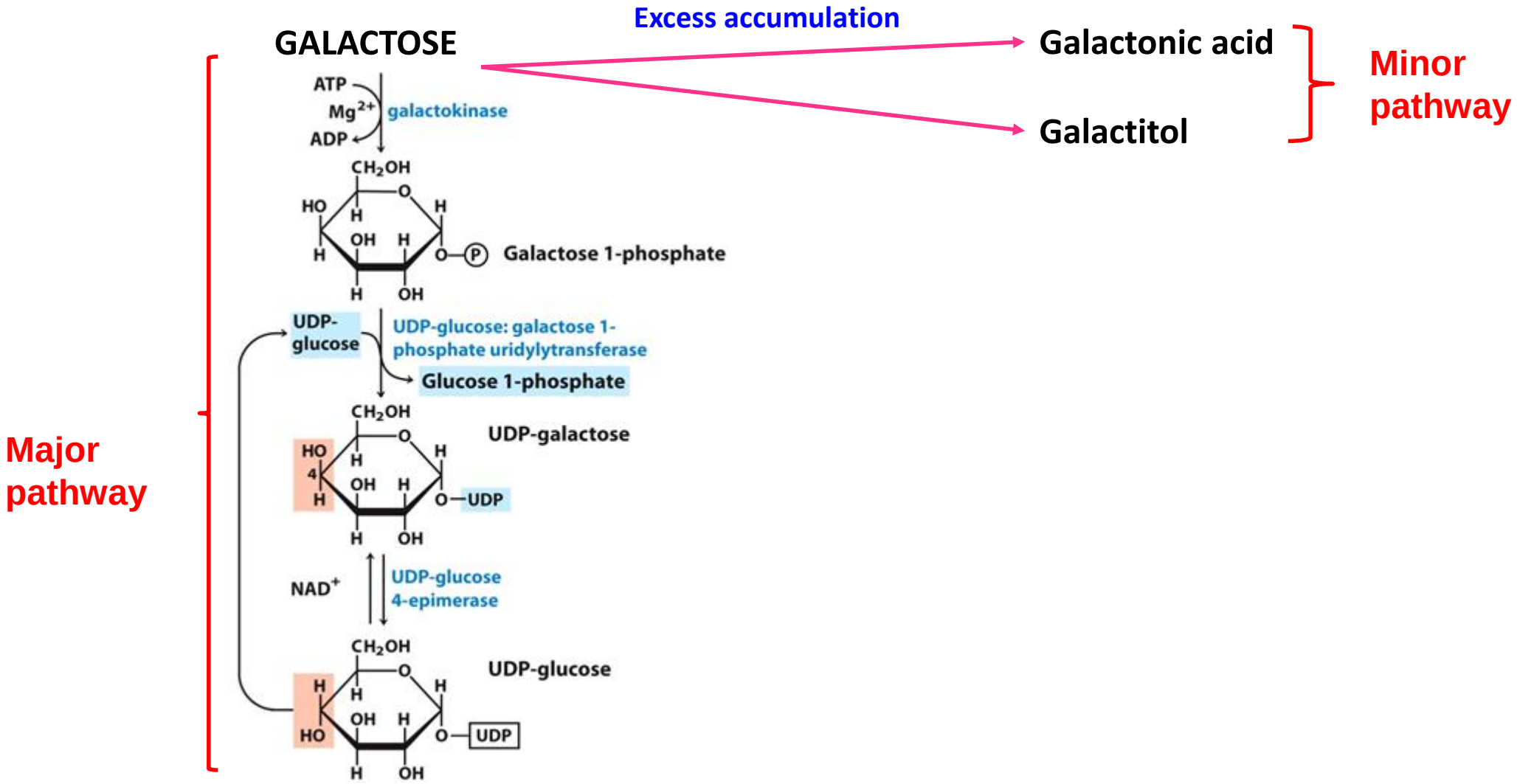
Dihydroxyaceton phosphate

Fructose intolerance (Fructosaemia)

Fructose 1-phosphate aldolase (Aldolase B) deficiency



Galactosemia



Galactosemia

Incidence: 1:60 000 (classic galactosemia)

Types:

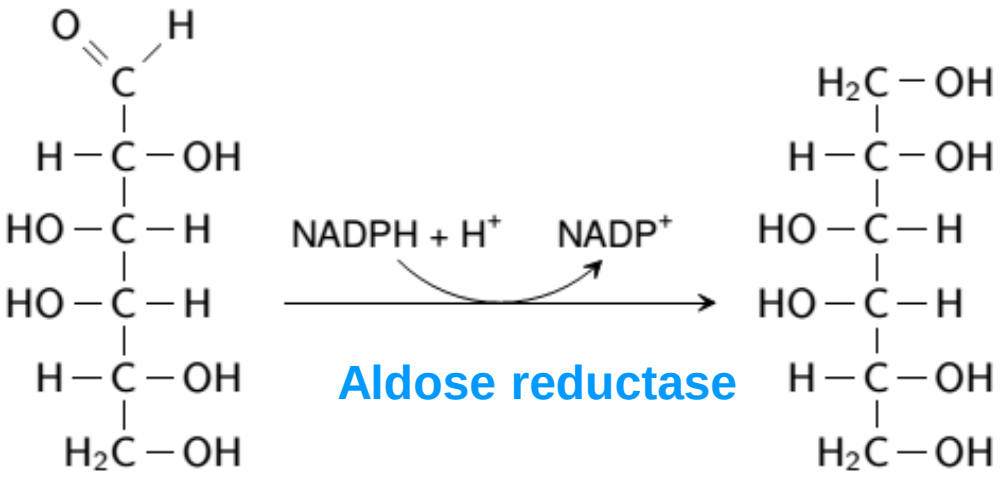
-Classic Galactosemia = Galactose-1-phosphate uridyl transferase (GALT) deficiency

-Galactokinase (GALK) deficiency

-Galactose epimerase (GALE) deficiency

Symptomes:

- developmental delays
- food intolerance
- hepatocellular damage
- cataracts



Galactose **Galactitol**

Catarakt formation

Lactose intolerance

(Milk sugar intolerance)

Lactase (β-galactosidase) deficiency

It is NOT milk protein allergy!

(Adverse immune reaction to one or more of the milk proteins)

Symptoms:

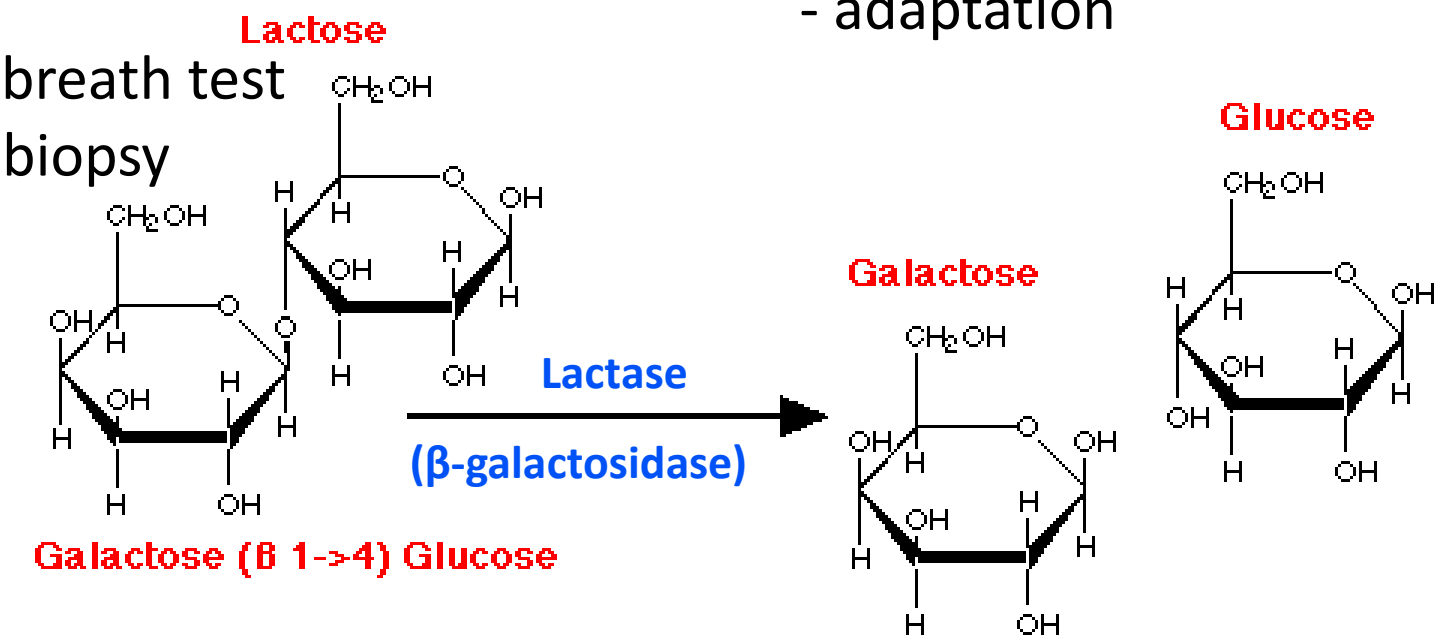
- osmotic diarrhea
- abdominal discomfort, bloating, flatulence

Diagnosis:

- hydrogen breath test
- intestinal biopsy

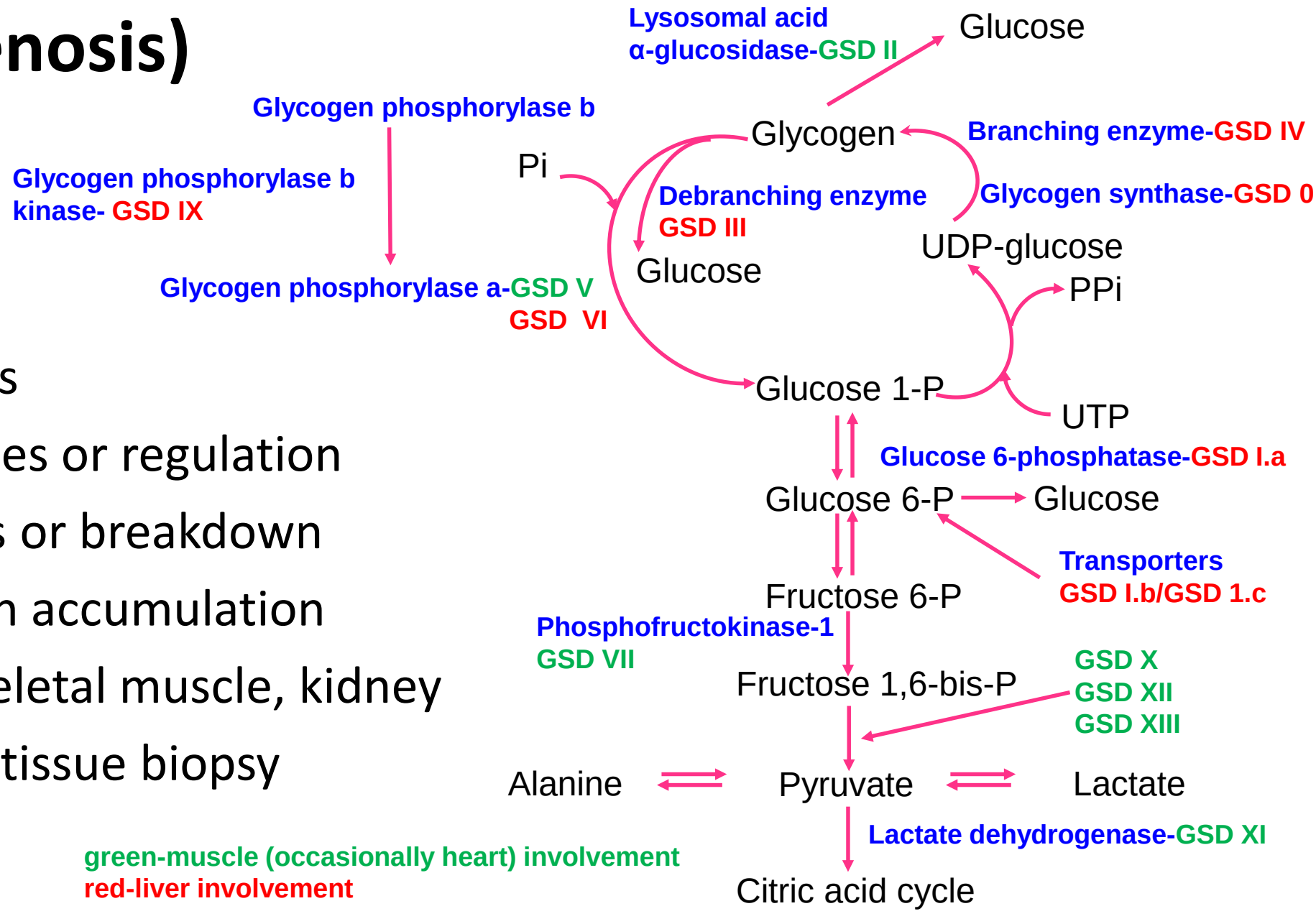
Treatment:

- lactose reduced diet
- lactase supplementation (pure enzyme or bacteria)
- adaptation



Glycogen storage disorders (Glycogenosis)

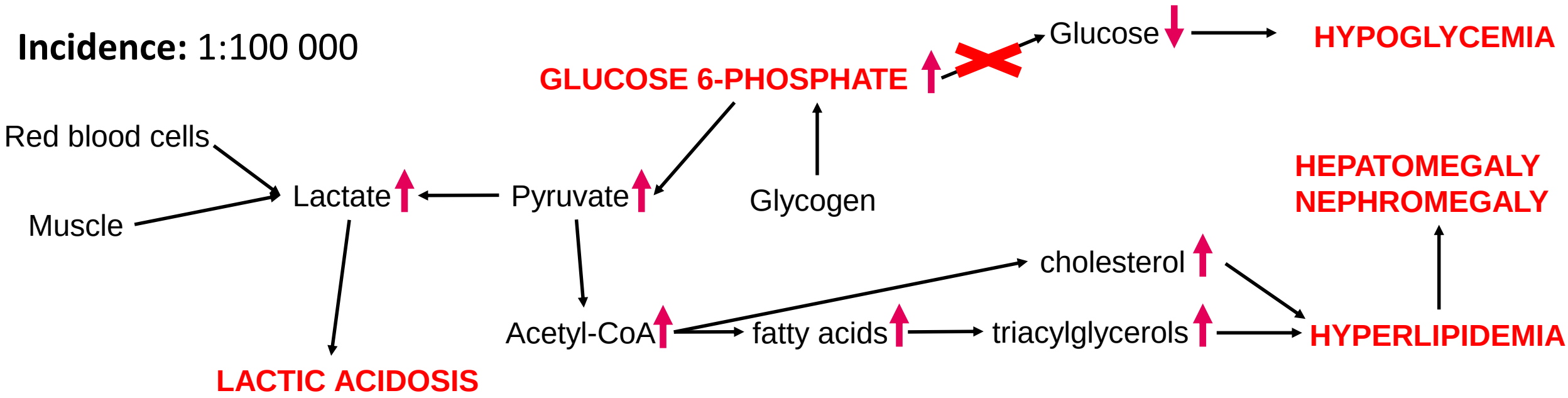
- 12 different disorders
- defects in the enzymes or regulation of glycogen synthesis or breakdown
- Pathological glycogen accumulation in the liver, heart, skeletal muscle, kidney
- Definitive diagnosis: tissue biopsy

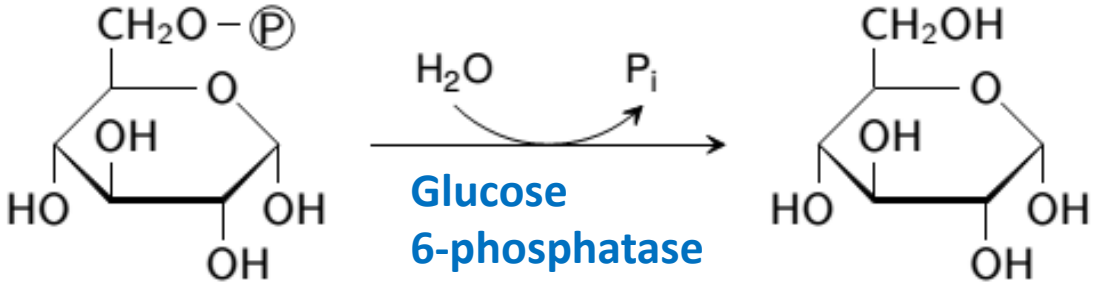


Type I.a: von Gierke's disease

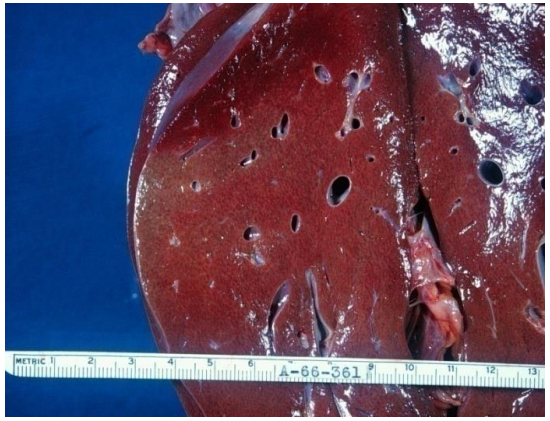
Glucose 6-phosphatase deficiency

Incidence: 1:100 000

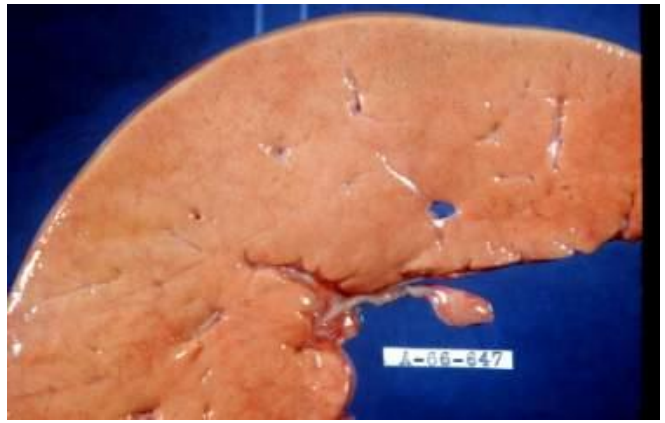




Glucose 6-phosphate **Glucose**



Healthy liver



Liver in von Gierke's disease

Type III: Cori's disease

Deficiency of amylo-1,6-glucosidase = debranching enzyme

Incidence: 1:5400-1:100 000

Symptoms:
- hepatomegaly
- liver disfunction
- hypoglycemia
- hyperlipidemia

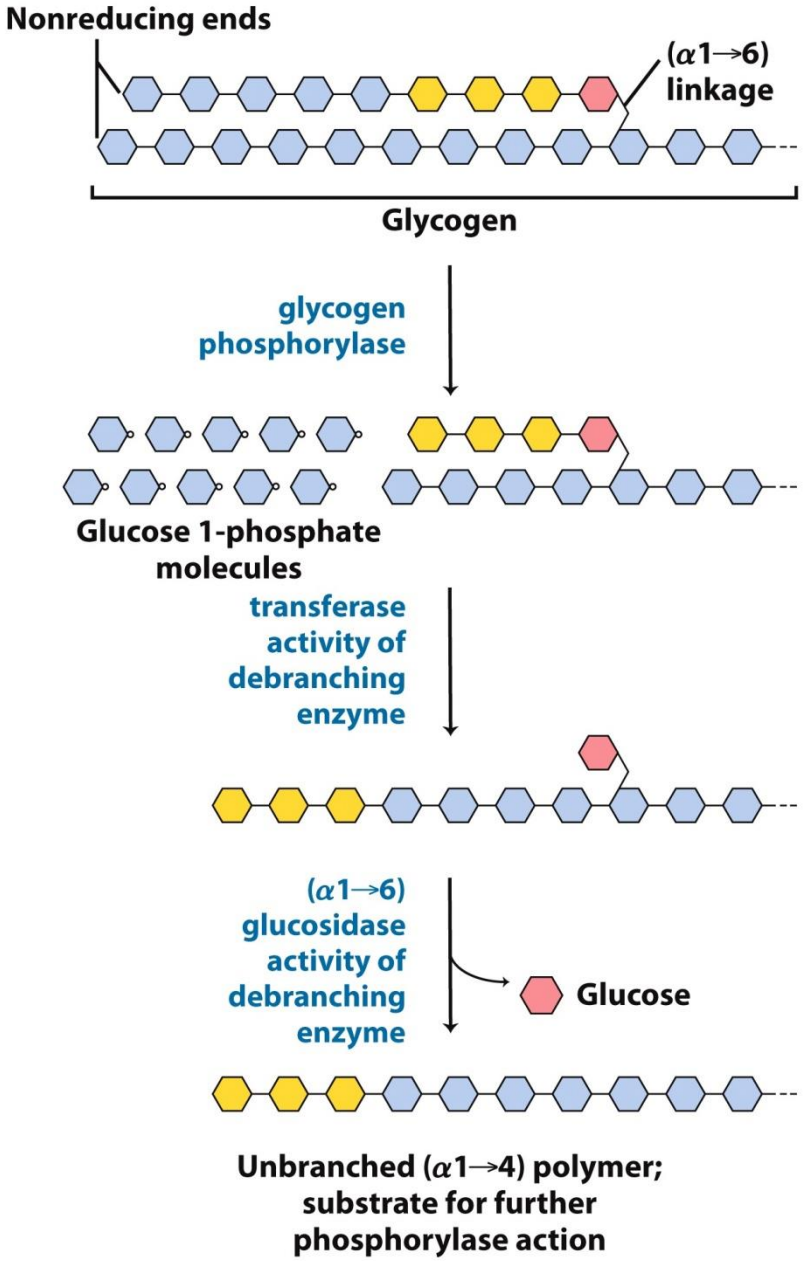


Figure 15-28
Lehninger Principles of Biochemistry, Sixth Edition

Type V: McArdle's disease

Glycogen phosphorylase deficiency in the muscle

Incidence: 1:100 000

Symptoms:

- muscle pain, cramps, weakness and stiffness
- resting improves the symptoms and the exercise tolerance ("second wind")

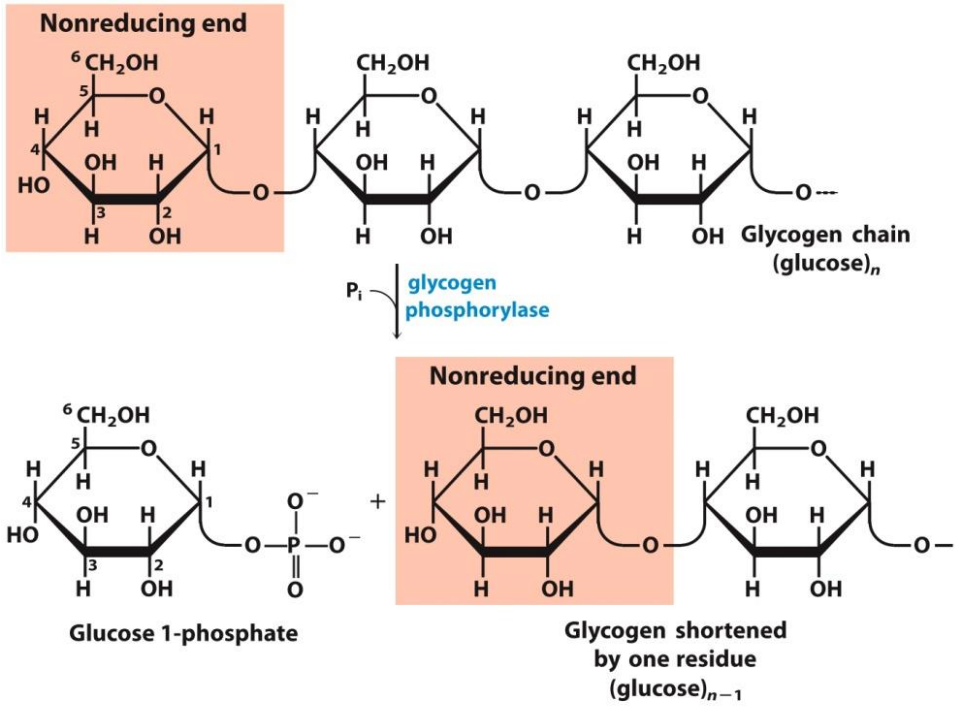


Figure 15-27
Lehninger Principles of Biochemistry, Sixth Edition
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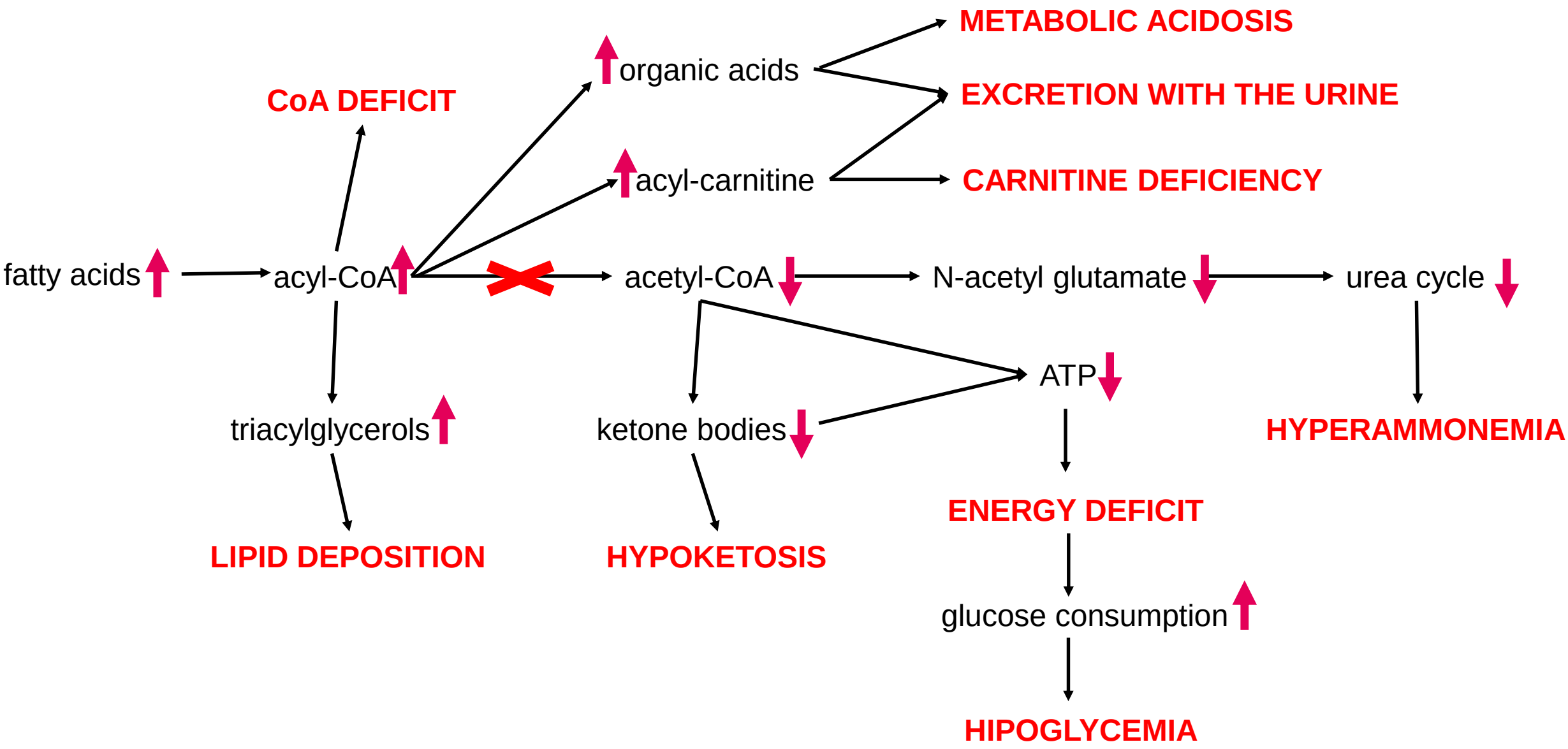
Muscle cramps and weakness after exercise

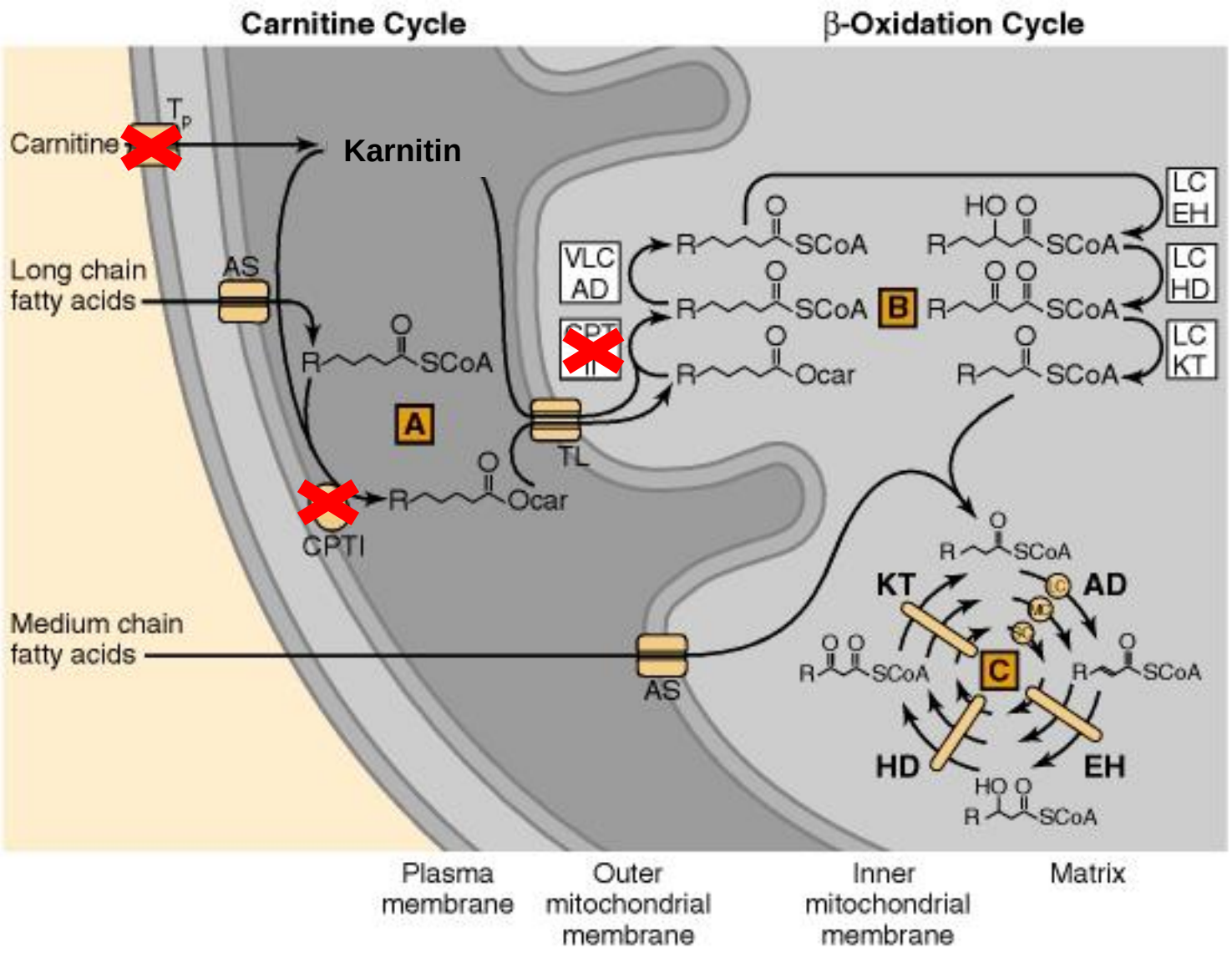
Disorders of fatty acid breakdown

- Carnitine transporter deficiency
- Carnitine palmitoyl transferase deficiency type I & II
- Short chain acyl-CoA dehydrogenase deficiency
- Medium chain acyl-CoA dehydrogenase deficiency
- Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency
- Very long chain acyl-CoA dehydrogenase deficiency
- Multiple acyl-CoA dehydrogenase deficiency

Characteristic metabolic disturbances



Disorders of fatty acid breakdown

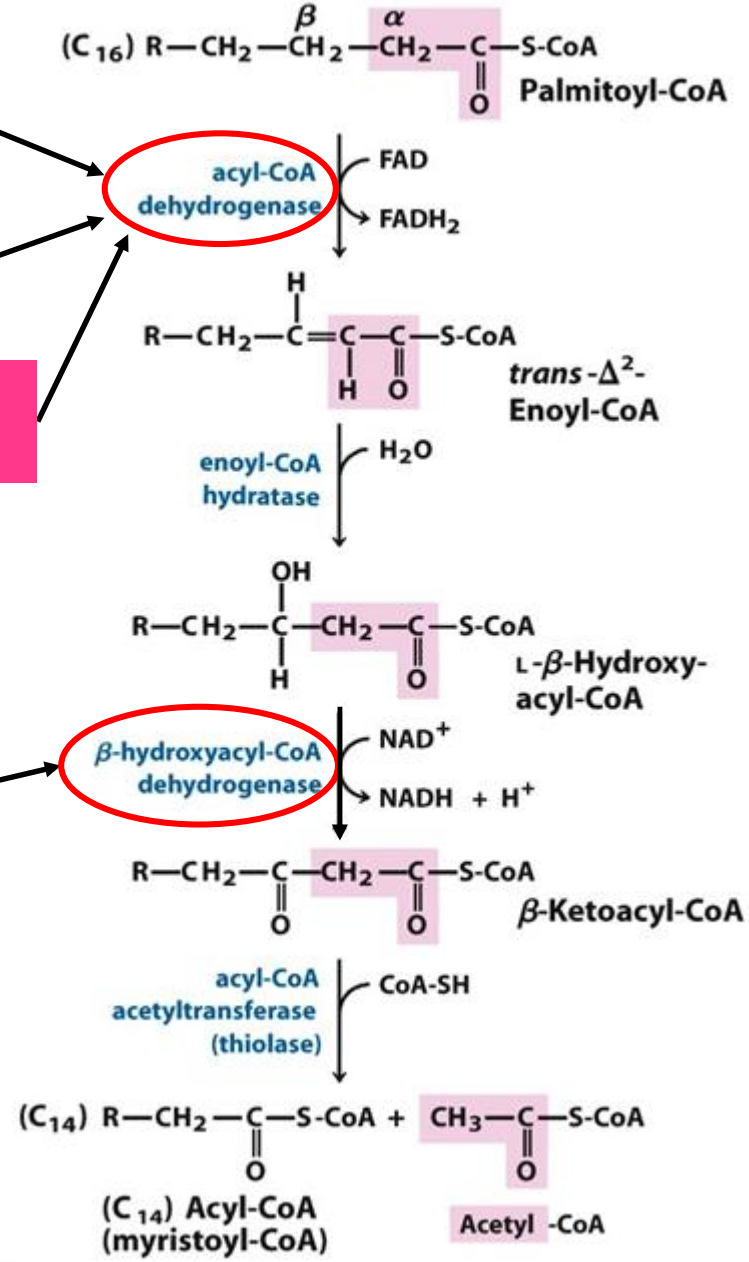


Short chain (4-6 C)

Medium chain (6-12 C)

Very long chain (14-20 C)

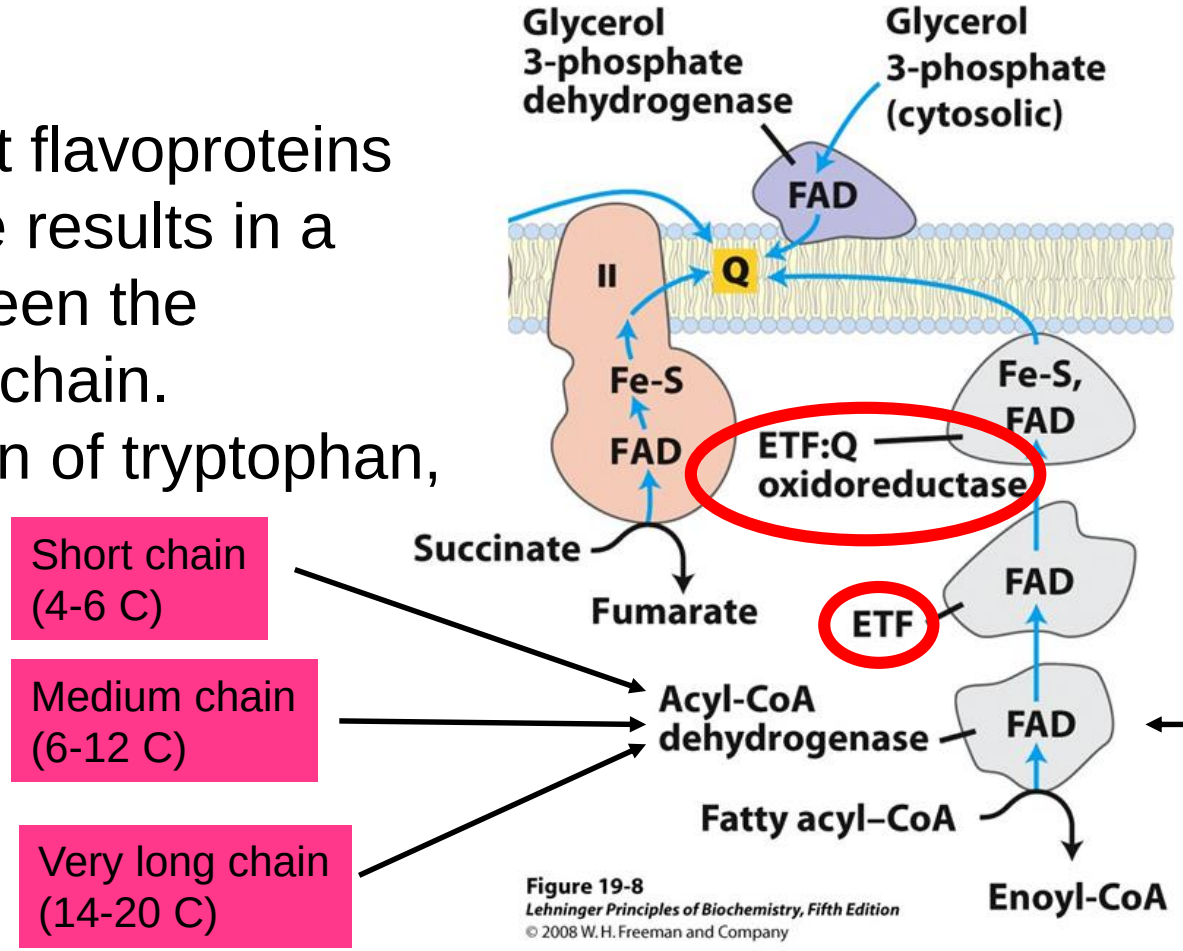
Long chain (12-18 C)



Multiple acyl-CoA dehydrogenase deficiency

Incidence: 1:1 000 000

Deficiency of electron transport flavoproteins (ETF) or ETF:Q oxidoreductase results in a blocked electrontransport between the ß-oxidation and the respiratory chain.
The block affects the breakdown of tryptophan, lysine and hydroxylysine too.



Tryptophan
Lysine
Hydroxylysine

Treatment:-dietary riboflavin and carnitin supplementation
-low fat/protein and high carbohydrate diet

Organic acid disorders

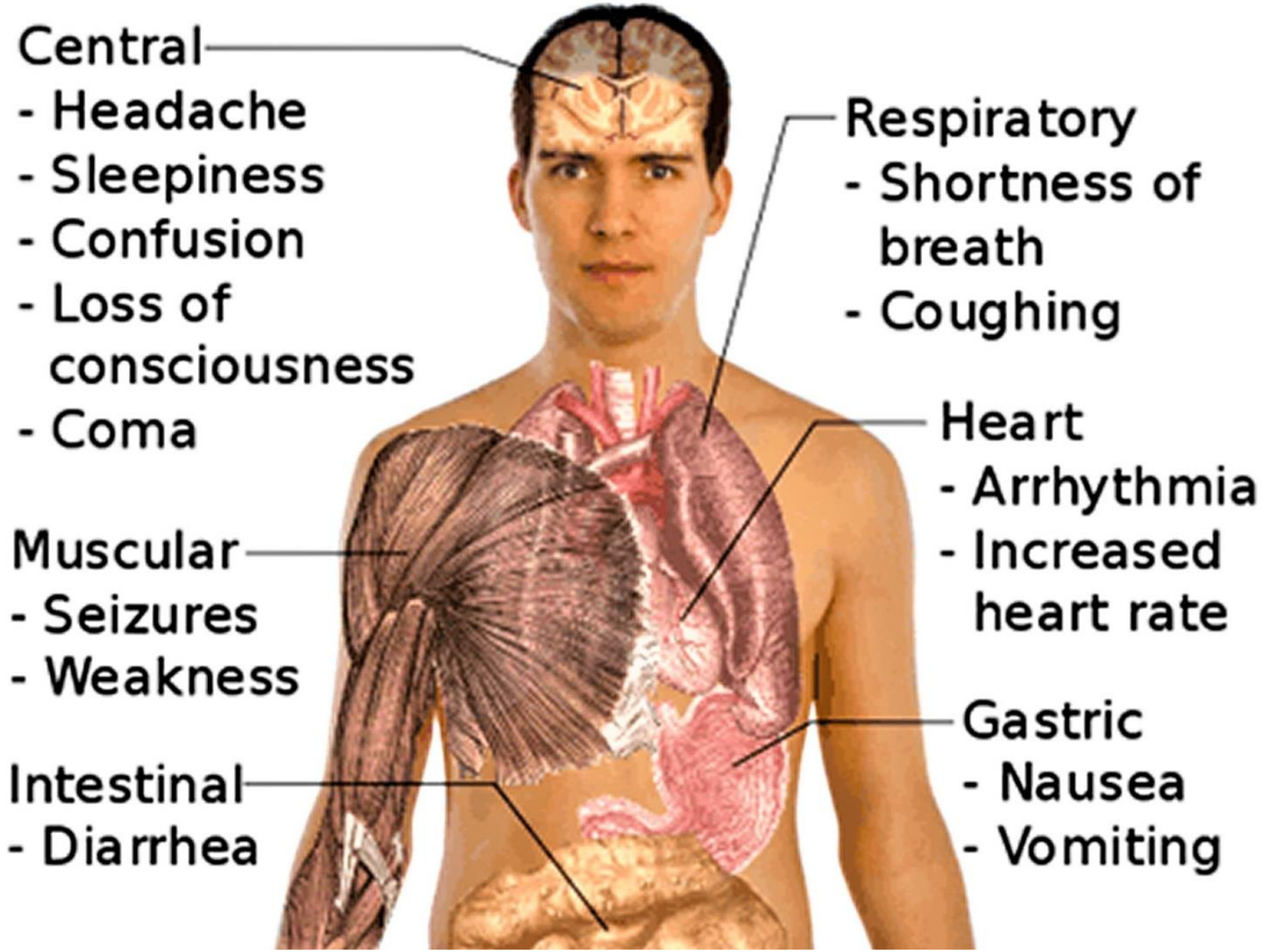
Disorders of the breakdown of certain amino acids and odd chain fatty acids

Nomenclature: based on the type of accumulated organic acids/deficient enzymes

Characteristic findings:

- Attacks of **metabolic acidosis** and its symptoms as a response to increased protein administration usually with **ketosis, secunder carnitine deficiency and hyperammonemia**
- Between the crises symptomsless or progressive neurological disorders
- Growth failure due to protein lack
- **Elevated** plasma and urine **organic acids and organic acid-carnitine conjugates**

The symptoms of metabolic acidosis

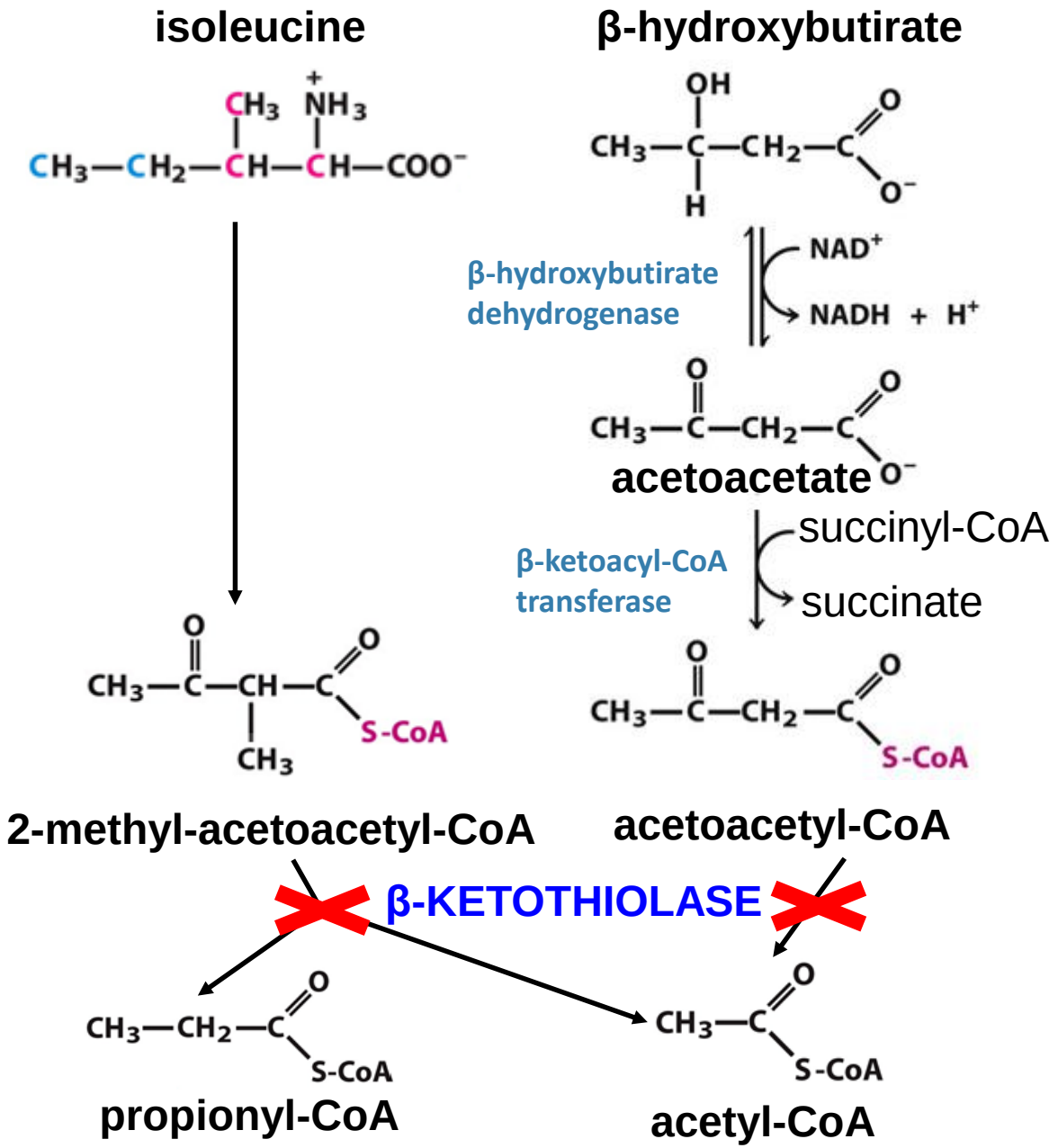


β-ketothiolase deficiency

Incidence: 1:100.000

Deficiency of mitochondrial acetoacetyl-CoA thiolase.

Mainly the breakdown of isoleucine and ketone bodies is affected. The synthesis of the ketone bodies is usually not affected.



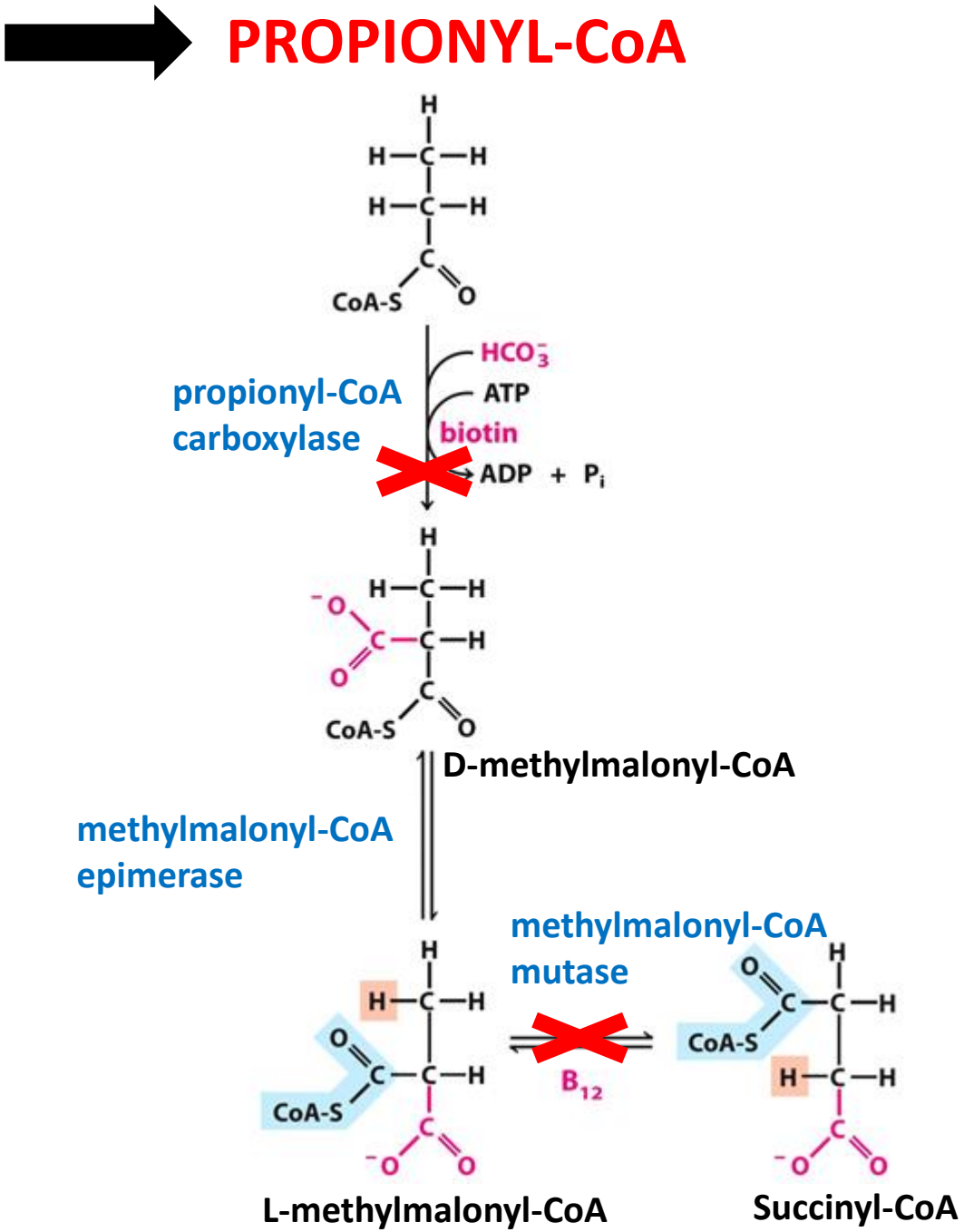
Aminoacids: Valin, Methionine, Isoleucine, Threonine (50%)
Odd chain fatty acids (30%)
Propionate (gut flora derived) (20%)

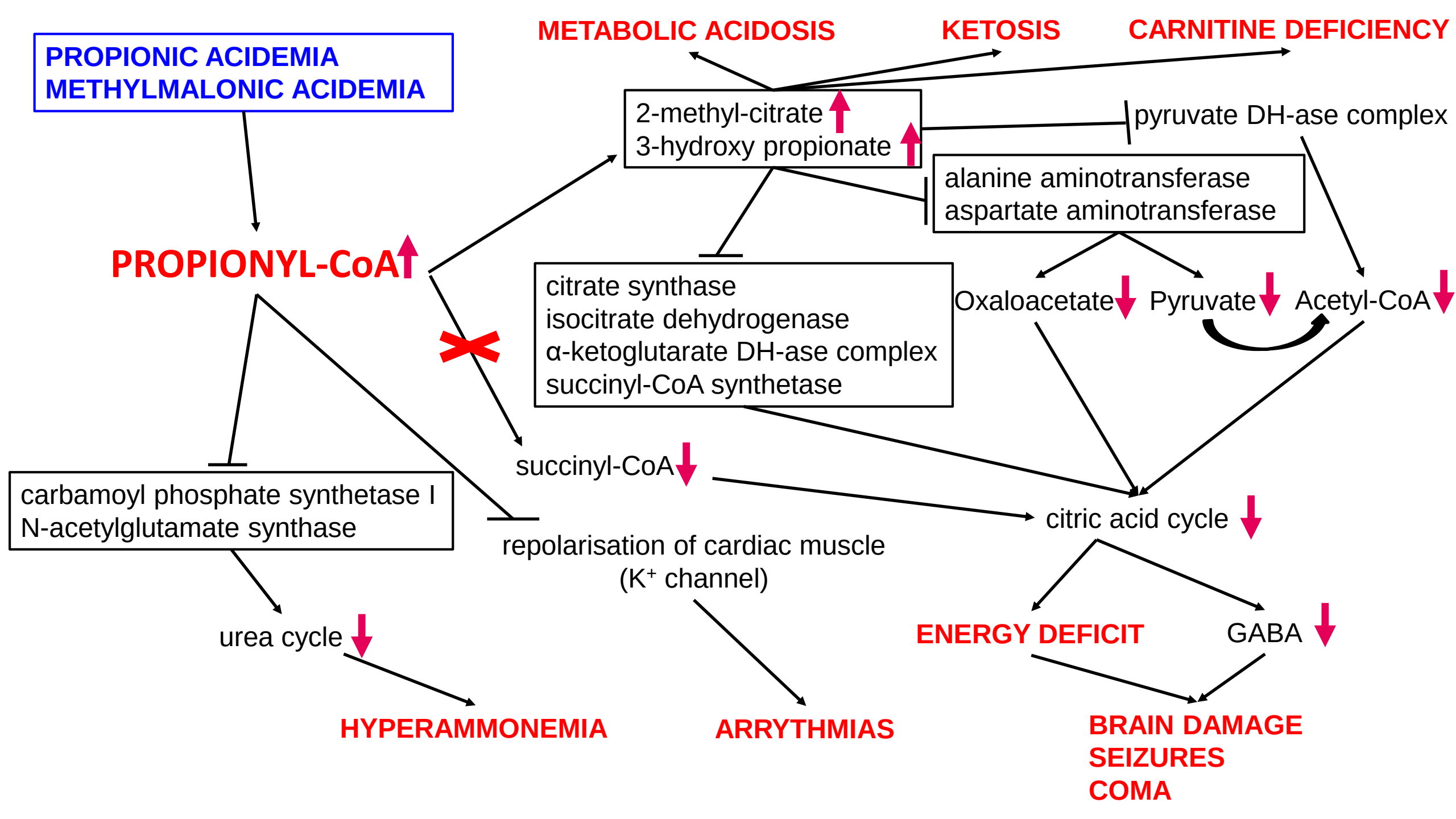
Propionic acidemia

Incidence: 1:75000
Deficiency of propionyl-CoA carboxylase.

Methylmalonic acidemia

Incidence: 1:75000
Deficiency of methylmalonyl-CoA mutase or methylmalonyl-CoA epimerase or the disorder of B12 synthesis/transport.




PROPIONIC ACIDEMIA
METHYLMALONIC ACIDEMIA
METABOLIC ACIDOSIS
KETOSIS
CARNITINE DEFICIENCY
2-methyl-citrate
3-hydroxy propionate
pyruvate DH-ase complex
alanine aminotransferase
aspartate aminotransferase
PROPIONYL-CoA
citrate synthase
isocitrate dehydrogenase
α-ketoglutarate DH-ase complex
succinyl-CoA synthetase
Oxaloacetate
Pyruvate
Acetyl-CoA
carbamoyl phosphate synthetase I
N-acetylglutamate synthase
succinyl-CoA
citric acid cycle
repolarisation of cardiac muscle
(K+ channel)
urea cycle
ENERGY DEFICIT
GABA
HYPERAMMONEMIA
ARRYTHMIAS
BRAIN DAMAGE
SEIZURES
COMA

Amino acid disorders

- Phenylketonuria
- Tyrosinemia type I and II
- Albinism
- Alkaptonuria
- Urea cycle disorders:

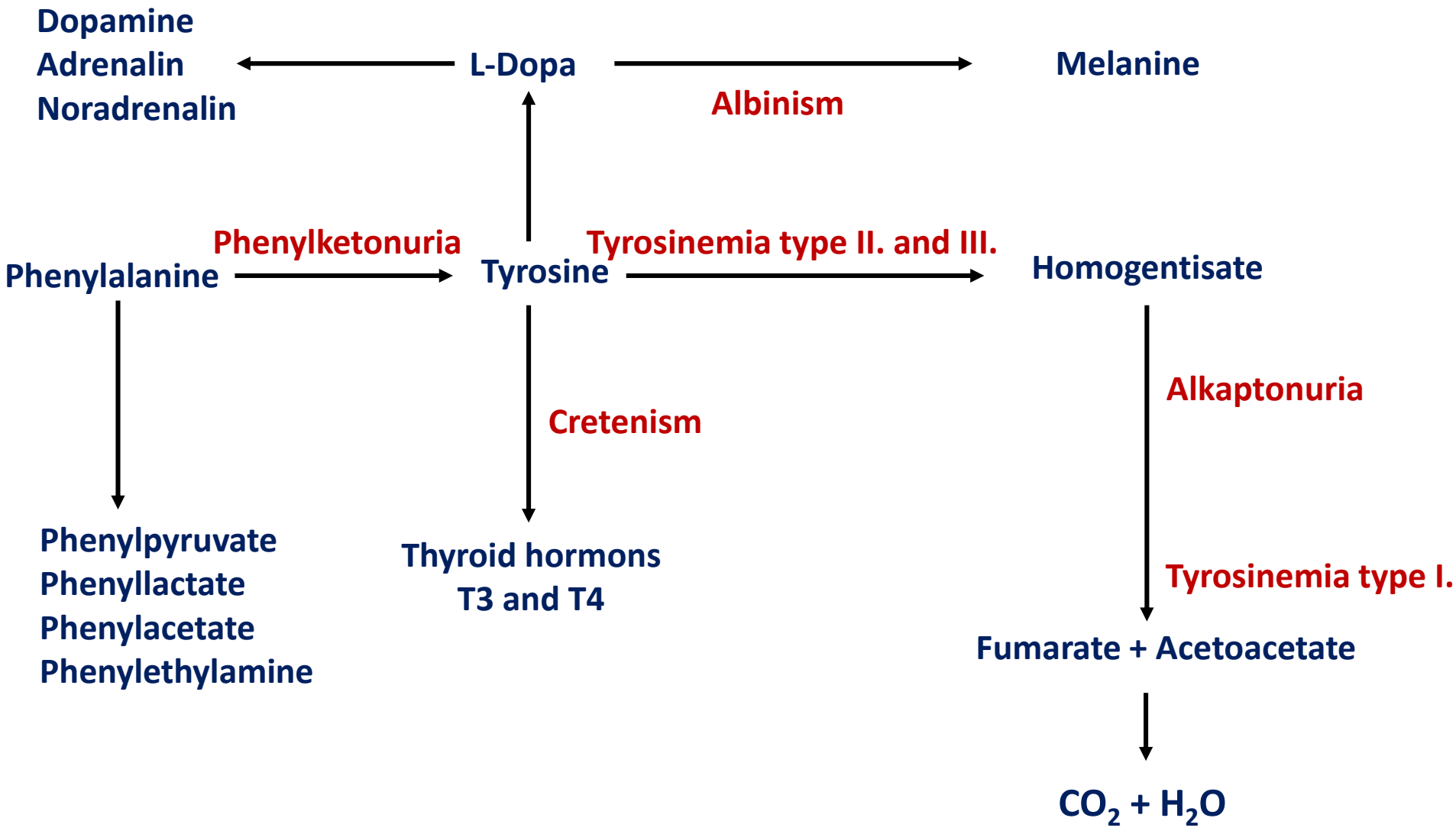
  Argininosuccinate synthetase deficiency

  Argininosuccinyl lyase deficiency

  Argininemia
- Homocystinuria
- Mapple syrup urine disease

Except albinism the rest of the aminoacid disorders are presented in "The enzymopathies of amino acid metabolism" lecture of the III. semester.

Metabolism of phenylalanine



Breakdown of phenylalanine

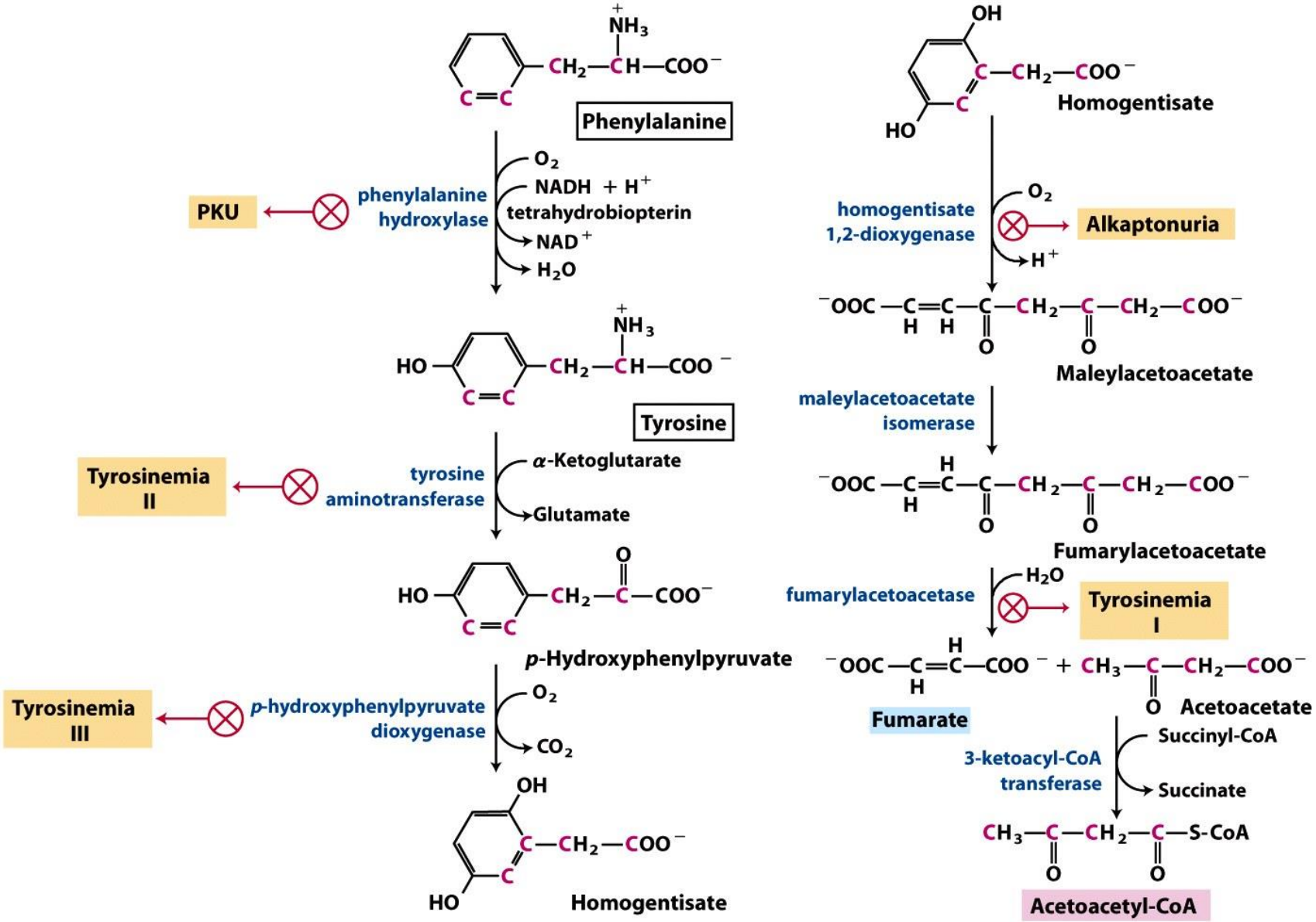


Figure 18-23
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Albinism

Incidence: 1:20000

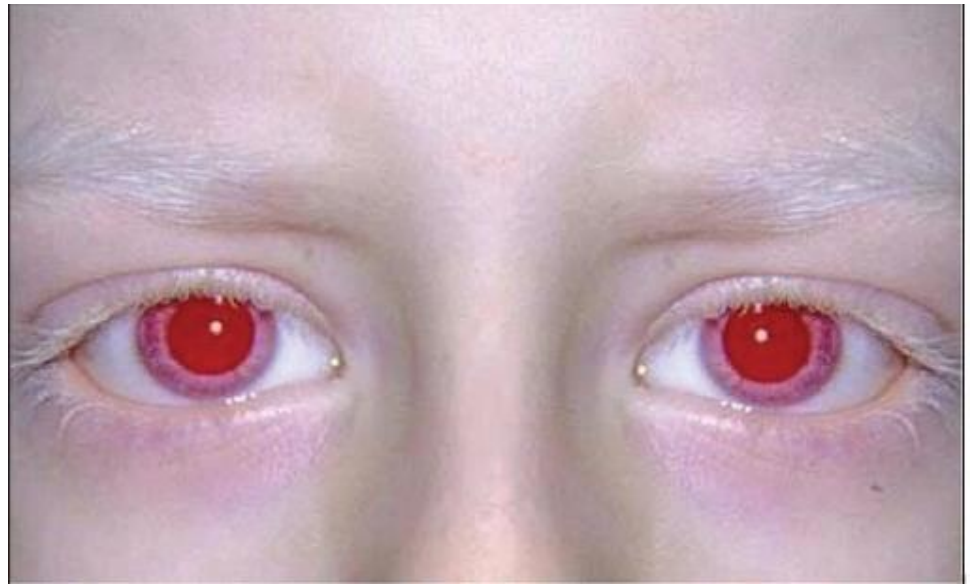
- General term for a number of defects in melanin synthesis or distribution
- Complete or partial absence of pigment in the skin, hair and eyes due to tyrosinase enzyme deficiency

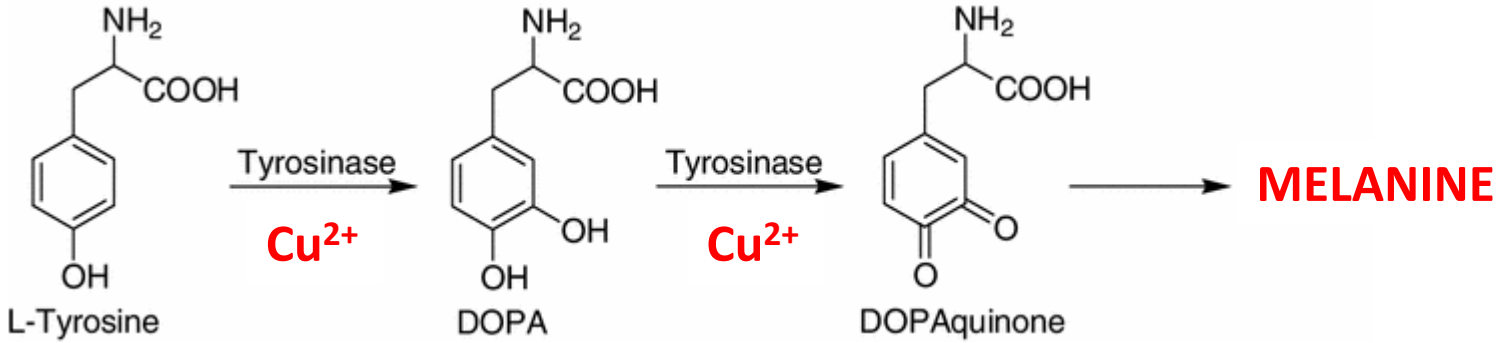
Symptoms:

- Lighter than normal skin and hair
- Increased light sensitivity, risk of skin cancer development
- Physical and mental development unaffected

Treatment

- No specific medical treatment to correct the metabolic disorder. Medical aids: tinted contact lenses, sunscreen





Hereditary disorders of nucleotide metabolism

Purine metabolism disorders

- Myoadenylate deaminase deficiency
- Adenosine deaminase deficiency
- Purine nucleoside phosphorylase deficiency
- Xanthine oxidase deficiency
- Phosphoribosylpyrophosphate synthetase superactivity
- Adenylosuccinase deficiency
- Adenine phosphoribosyltransferase deficiency
- Lesch-Nyhan Syndrome

Pirimidine metabolism disorders

- Uridine monophosphate synthase deficiency
  (Hereditary orotic aciduria)

Lesch-Nyhan syndrome

Hypoxanthine-guanine phosphoribosyltransferase deficiency

Incidence: 1:380 000

Pathophysiology:

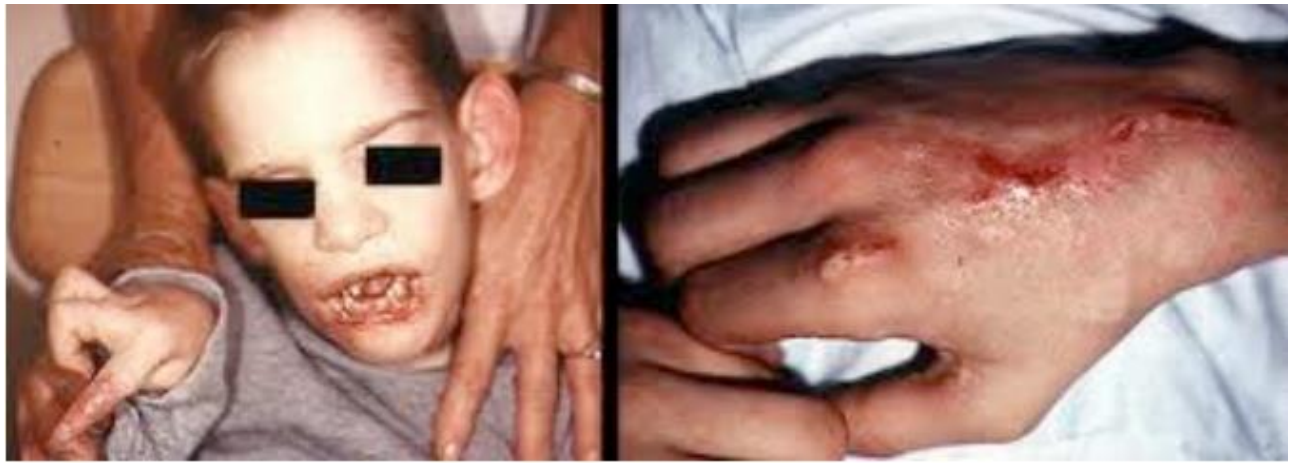
- Brain highly depends on salvage pathways
- Without salvage pathway, PRPP levels rise, purines overproduced
- High levels of uric acid
- Brain damage

$$\text{Hypoxanthine} + \text{PRPP} \longrightarrow \text{IMP} + PP_i$$

$$\text{Guanine} + \text{PRPP} \longrightarrow \text{GMP} + PP_i$$

Symptoms:

- Poorly coordinated
- Mentally retarded
- Extremely hostile
- Self destructive tendencies – biting off fingers, toes, lips ect.



Adenosine deaminase deficiency

Incidence: 1:200 000-1:1 000 000

Pathophysiology:
- increased concentrations of dATP and ADP have toxic effects on the lymphocytes (T-, B- and NK-cells)

Symptoms:
- neurological disorders
- severe combined immunodeficiency (SCID)

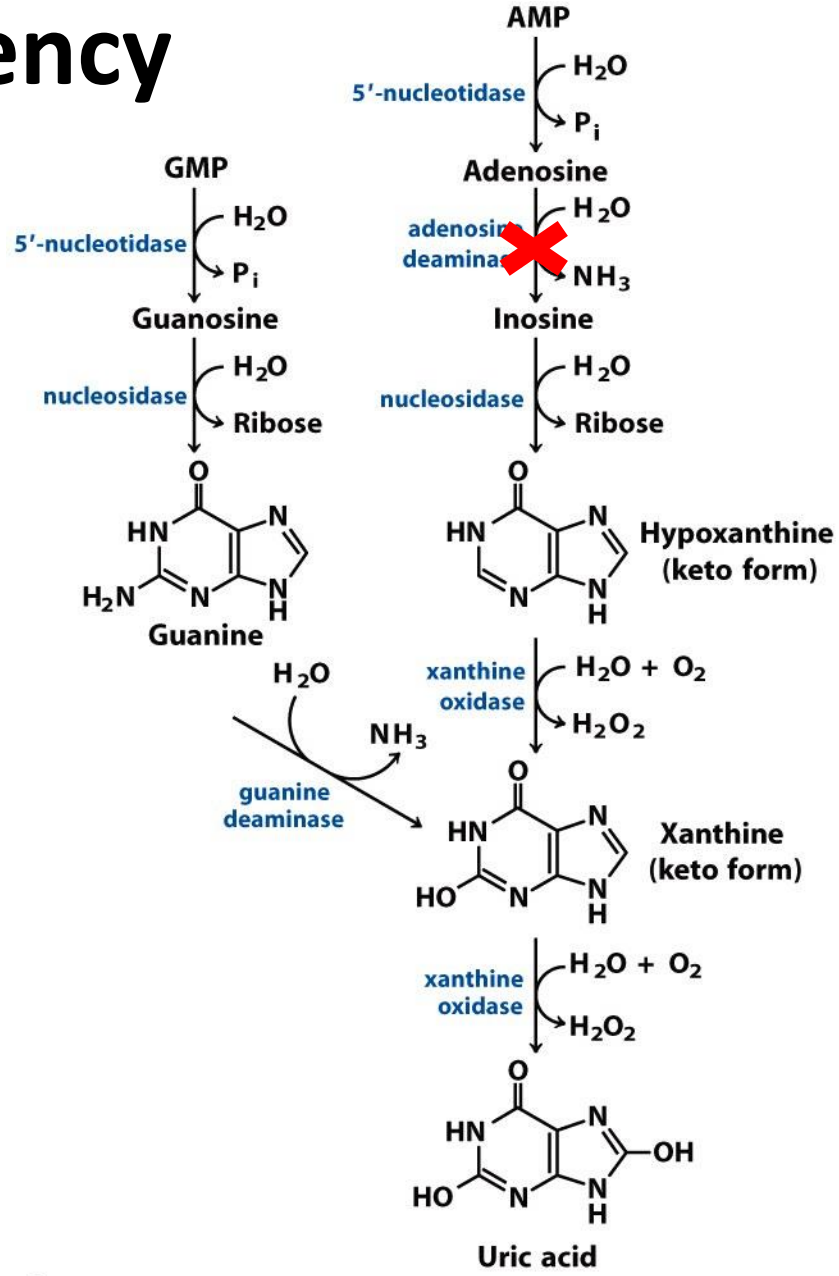


Figure 22-45 part 1
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