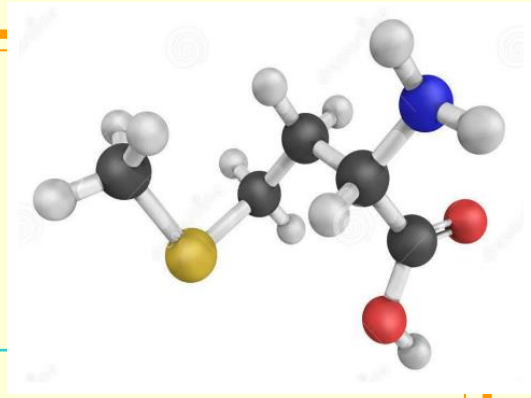
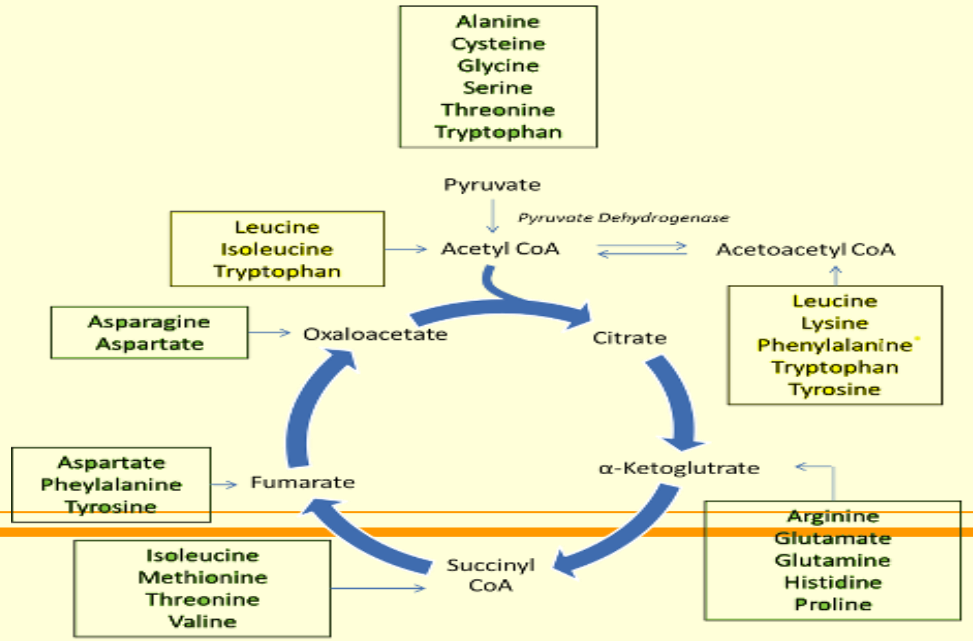
Metabolism of certain amino acids





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QUESTIONS

1. Catabolism of amino acids in the organism. Glucogenic and ketogenic amino acids.

2. Metabolism of methionine: formation of S-adenosylmethionine, its role in transmethylation reactions. Synthesis of creatine. Lipotropic effect of methionine.

3. Metabolism of phenylalanine and tyrosine. Disorders of phenylalanine and tyrosine metabolism (phenylketonuria, alkaptonuria, albinism).

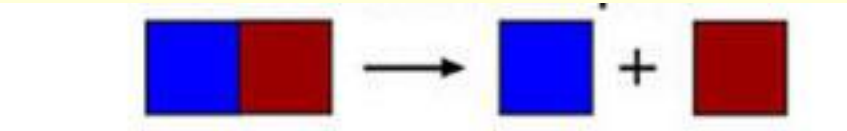
Catabolism of amino acids in the body

- Amino acids are obtained from dietary sources, as well as from cellular proteins.
- They are used for:
  - Anabolic purposes: synthesis of proteins, peptides, neurotransmitters, purine and pyrimidine nucleotides, etc.
  - Catabolic purposes: degradation of amino acids to form waste products (CO_2, H_2O, NH_3, urea, indican, etc) and energy in form of ATP.

CATABOLISM

breaking down of complex molecules to simpler compounds with release of energy

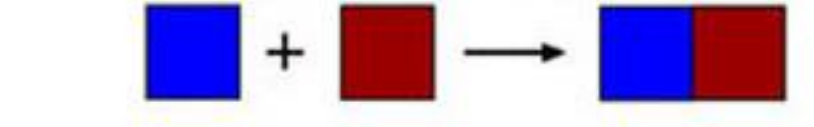
EX: degradation of complex compounds to the simple ones



ANABOLISM

synthesis of complex molecules from simpler components with use of energy.

EX: linking amino acids to form proteins



1. After removal of NH_2-groups from amino acids their carbon skeletons are catabolized to intermediate substances for carbohydrate and lipid metabolism.

2. Therefore 20 amino acids can be divided into following groups:

I. **Glucogenic amino acids**

II. **Ketogenic amino acids**

III. **Mixed group**

Glucogenic amino acids (only)

- Their carbon skeletons are converted to the intermediates used in the synthesis of glucose (carbohydrates). **(14 AMINO ACIDS)**

  - **Alanine, Glycine, Cysteine, Serine,**
  - **Threonine, Aspartate, Asparagine,**
  - **Glutamate, Glutamine, Histidine,**
  - **Arginine, Proline, Valine, Methionine**

Ketogenic amino acid (only)

- Its carbon skeleton can be converted both to acetoacetyl CoA and acetyl CoA (substances used in the synthesis of ketone bodies (lipids)) (1 AMINO ACID)

Leucine

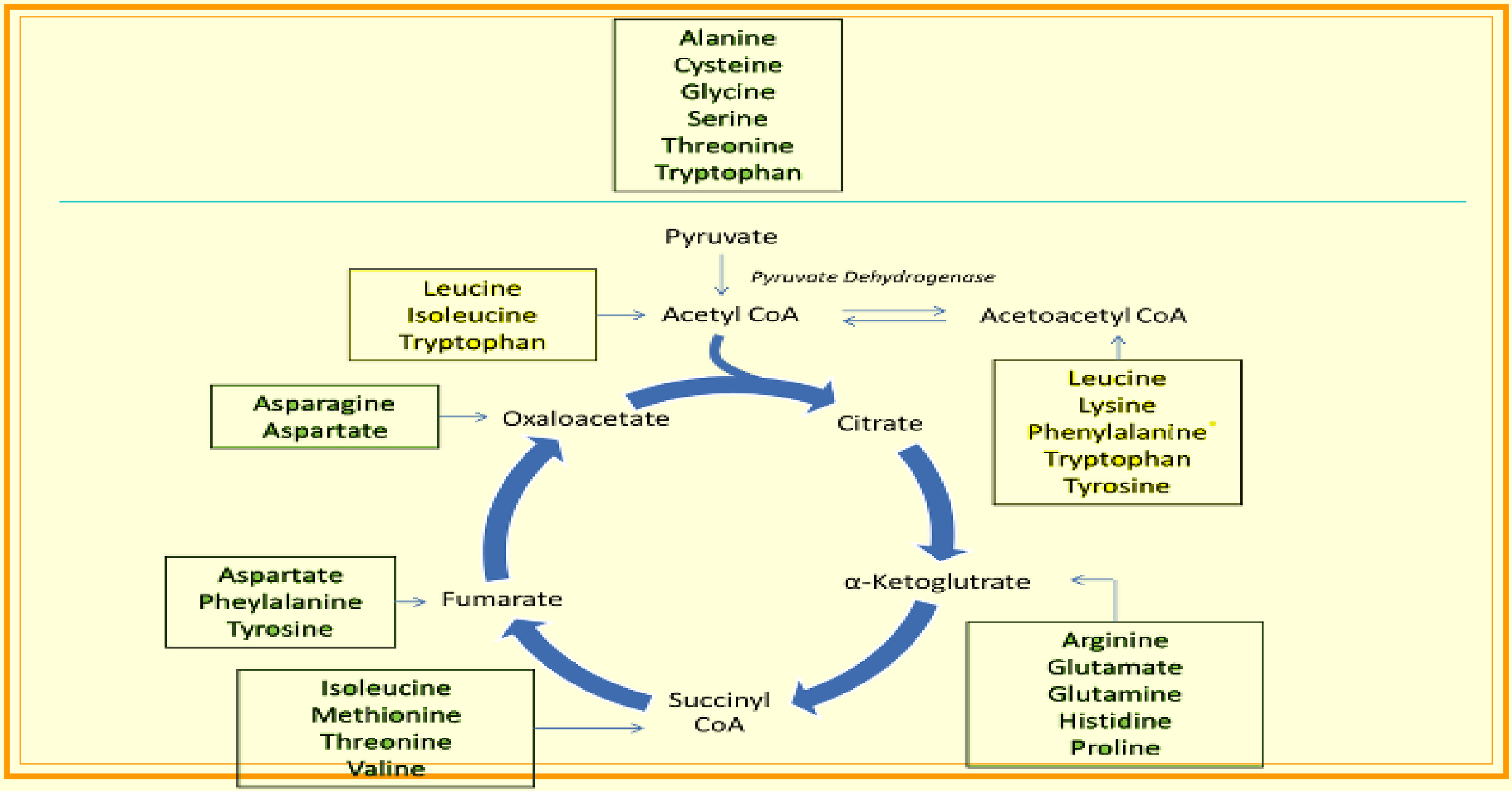
Mixed group (ketogenic and glucogenic amino acids)

- Their carbon skeletons can be converted either to the acetyl CoA and acetoacetyl CoA, or to carbohydrates (5 AMINO ACIDS)

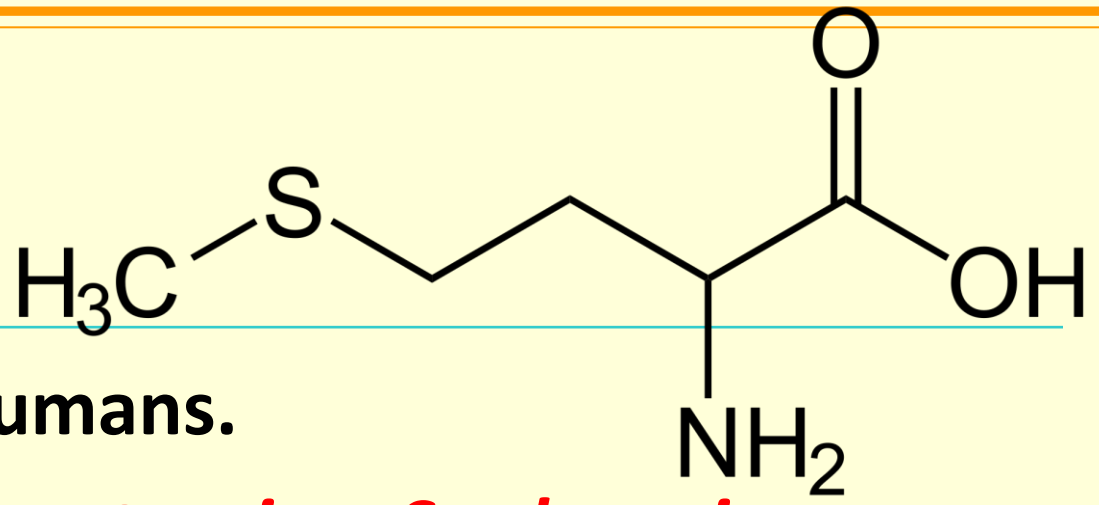
Tryptophan, Tyrosine, Isoleucine, Phenylalanine, Lysine

- Amino acids converting to intermediate substrates of the tricarboxylic acid cycle (the TCA cycle)

Amino acids	Intermediate
Alanine, glycine, cysteine, serine, threonine	Pyruvate
Aspartate, asparagine	Oxaloacetate
Tyrosine, phenylalanine	Fumarate
Valine, methionine, isoleucine	Succinyl CoA
Glutamate, glutamine, histidine, arginine, proline	α-ketoglutarate


Alanine
Cysteine
Glycine
Serine
Threonine
Tryptophan
Pyruvate
Pyruvate Dehydrogenase
Leucine
Isoleucine
Tryptophan
Acetyl CoA
Acetoacetyl CoA
Leucine
Lysine
Phenylalanine*
Tryptophan
Tyrosine
Asparagine
Aspartate
Oxaloacetate
Citrate
α-Ketoglutrate
Arginine
Glutamate
Glutamine
Histidine
Proline
Aspartate
Pheylalanine
Tyrosine
Fumarate
Isoleucine
Methionine
Threonine
Valine
Succinyl
CoA

Methionine

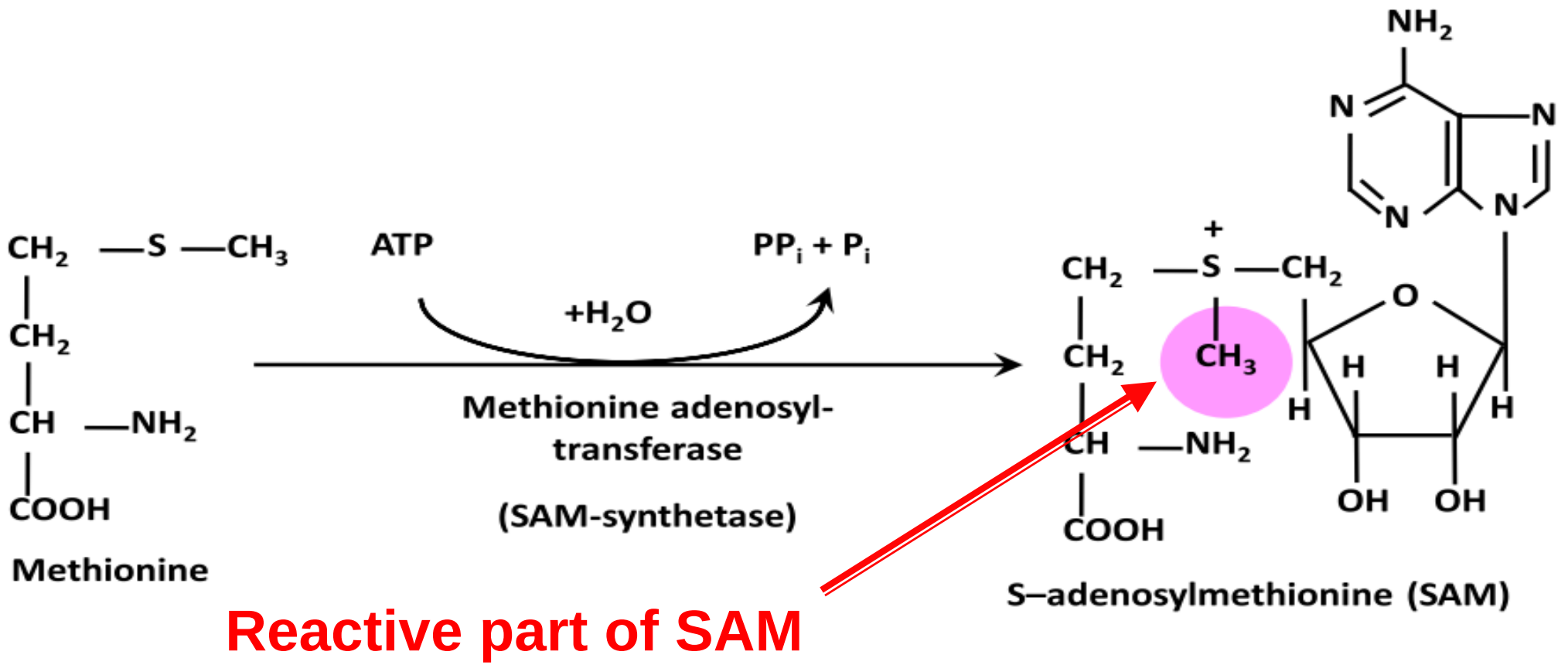


- Is an essential amino acid for humans.
- Precursor in synthesis of *cysteine, taurine*, *S-adenosine methionine (SAM), phospholipids*, etc.
- Methionine plays an important role in the growth of new blood vessels, in healthy functioning of the liver.
- The main dietary sources are meat, and dairy products.
- Fatty liver disease is the disorder associated with the deficiency of lipotropic substances (methionine, etc).

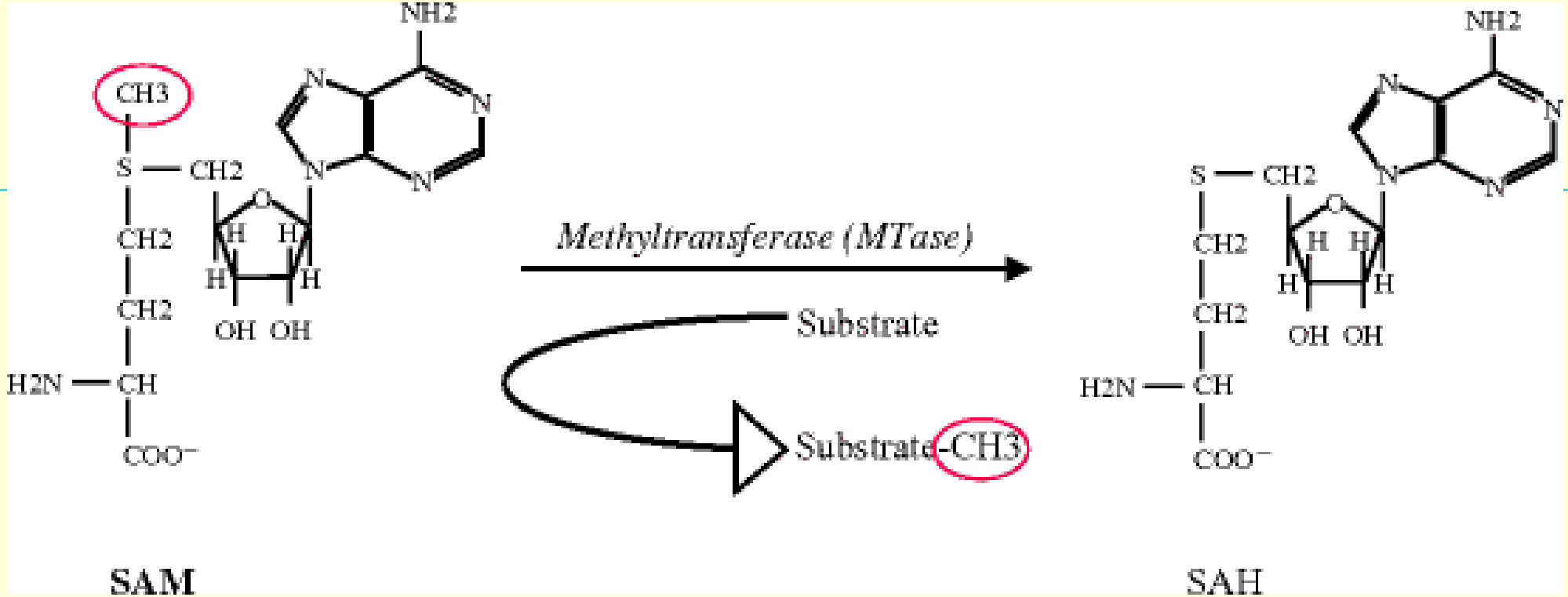
S-adenosine methionine (SAM)

- Is derivative of Met, called "active methionine",
- Serves as the principle donor of methyl groups (CH_3-) in the reactions, followed by addition of CH_3- to a molecule (transmethylation).
- Synthesis of SAM from Met is catalyzed by the enzyme L-Methionine adenosyltransferase.

Synthesis of SAM

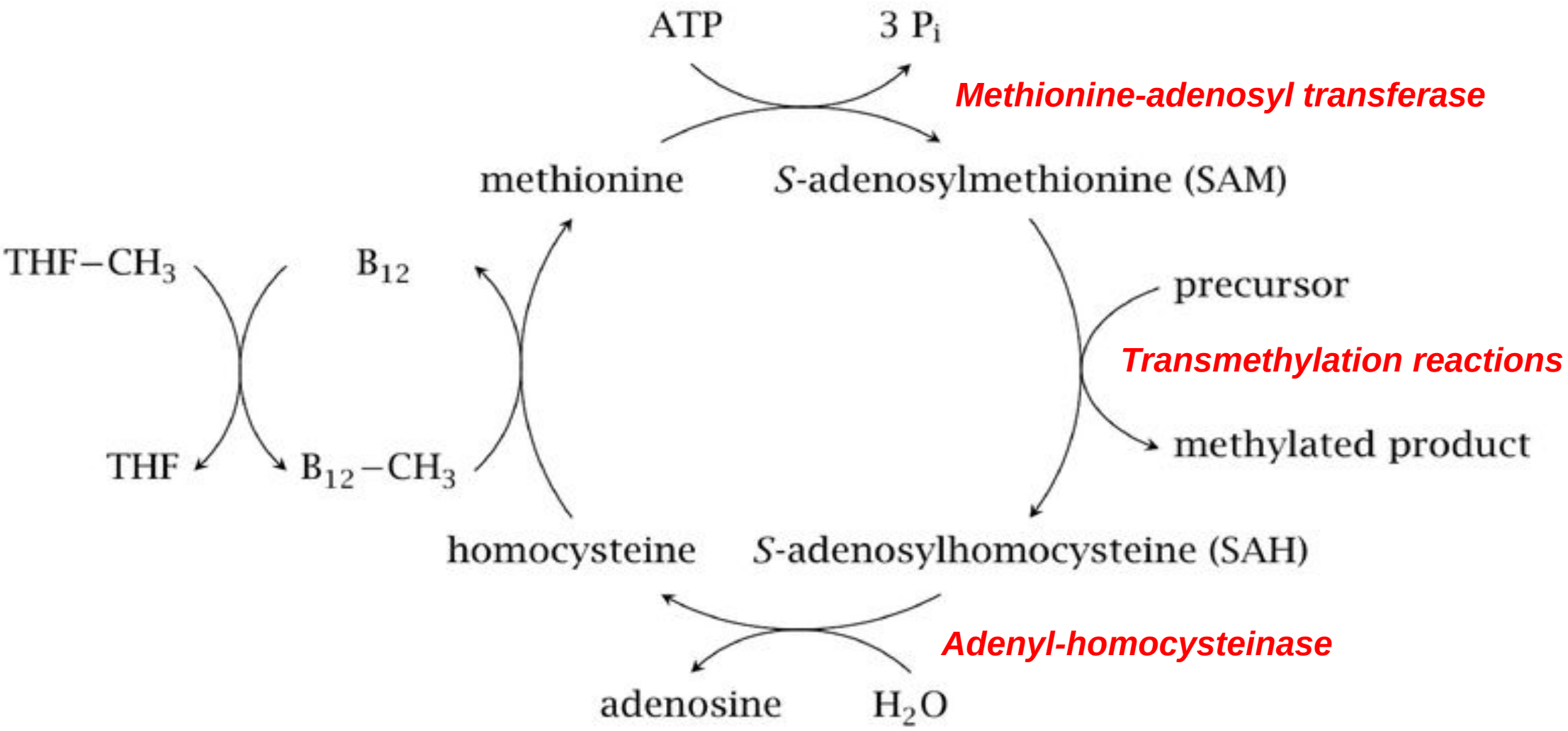


Reactive part of SAM



The principal role of SAM is participation in the reactions, where the methyl group is transferred to a substrate. In the reactions, catalyzed by methyltransferases, S-adenosyl methionine looses CH_3- to form S-adenosyl homocysteine (SAH).

SAM is regenerated in the SAM Cycle, that requires essential vitamins: folic acid (coenzyme tetrahydrofolate, THF) and B12.

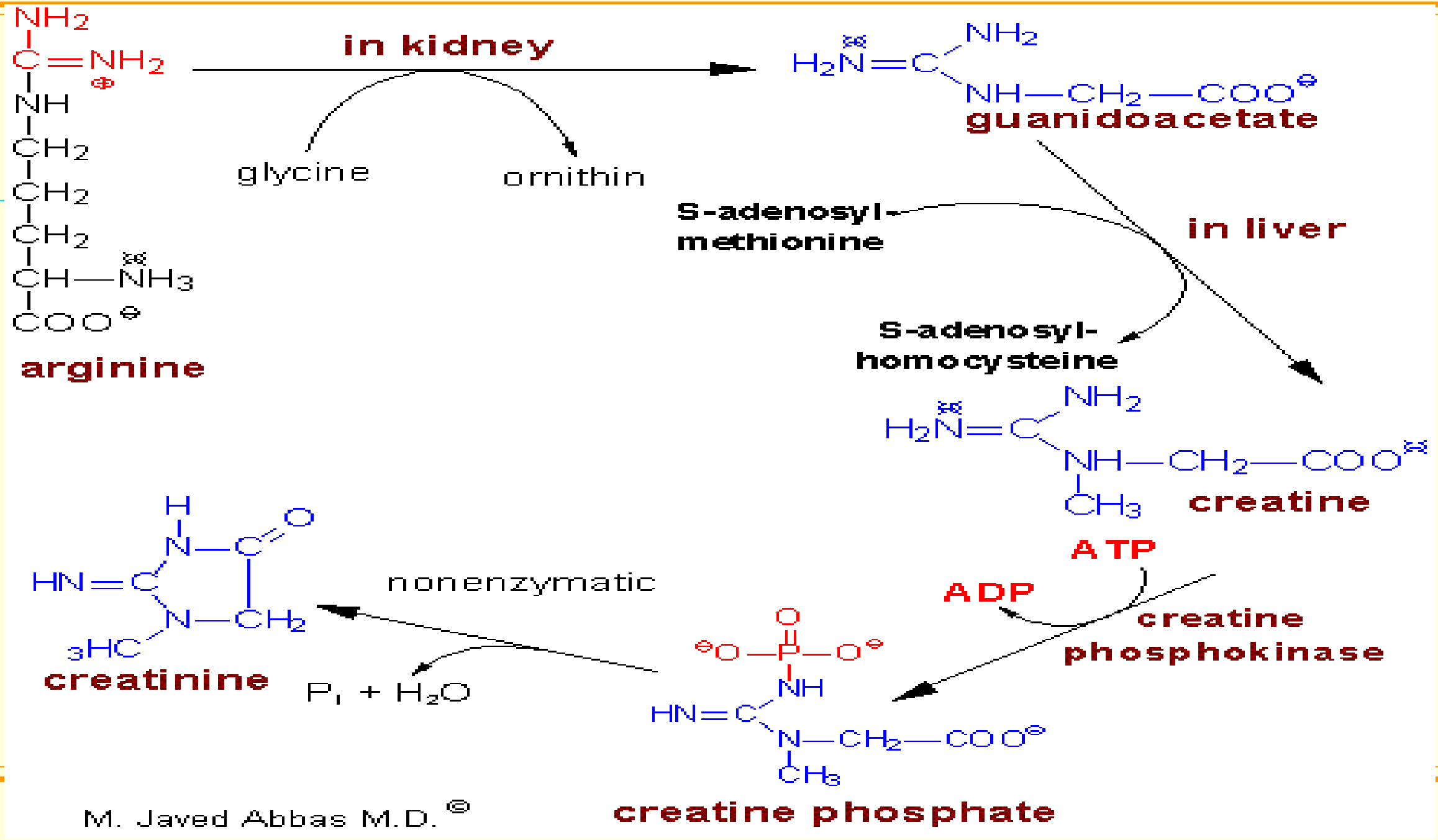


Transmethylation reactions play a role in synthesis of important cellular components

- Guanidinoacetate → creatine
- Norepinephrine (Noradrenaline) → Epinephrine (Adrenaline)
- Phosphatidyl-ethanolamine → Phosphatidyl-choline
- Ethanolamine → Choline
- Acetylserotonin → Melatonin
- Cytosine → 5-Methylcytosine

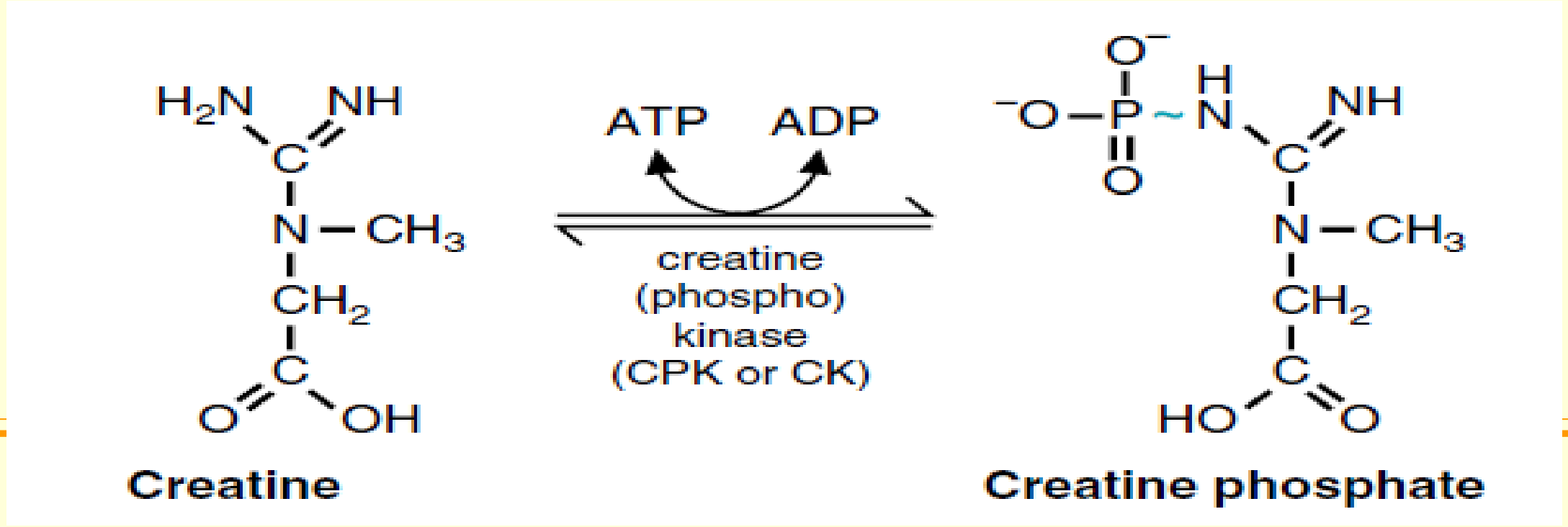
Synthesis of creatine, creatine phosphate, and creatinine

- Creatine is produced in the kidneys and the liver from the arginine, glycine, and SAM as the donor of the methyl group.
- In the skeletal muscles and brain creatine in converted to Creatine Phosphate.
- In the muscles Creatine Phosphate is degraded spontaneously to Creatinine, which is excreted by the kidneys.


in kidney
glycine
ornithin
arginine
guanidoacetate
S-adenosyl-
methionine
in liver
S-adenosyl-
homocysteine
creatine
ATP
ADP
creatine
phosphokinase
nonenzymatic
creatinine
creatine phosphate
M. Javed Abbas M.D. ©

Creatine Phosphate

- is a substance that provides a quick source of energy for muscle fibers to contract, when they need an initial burst of energy. In the brain CP provides energy for neurons.

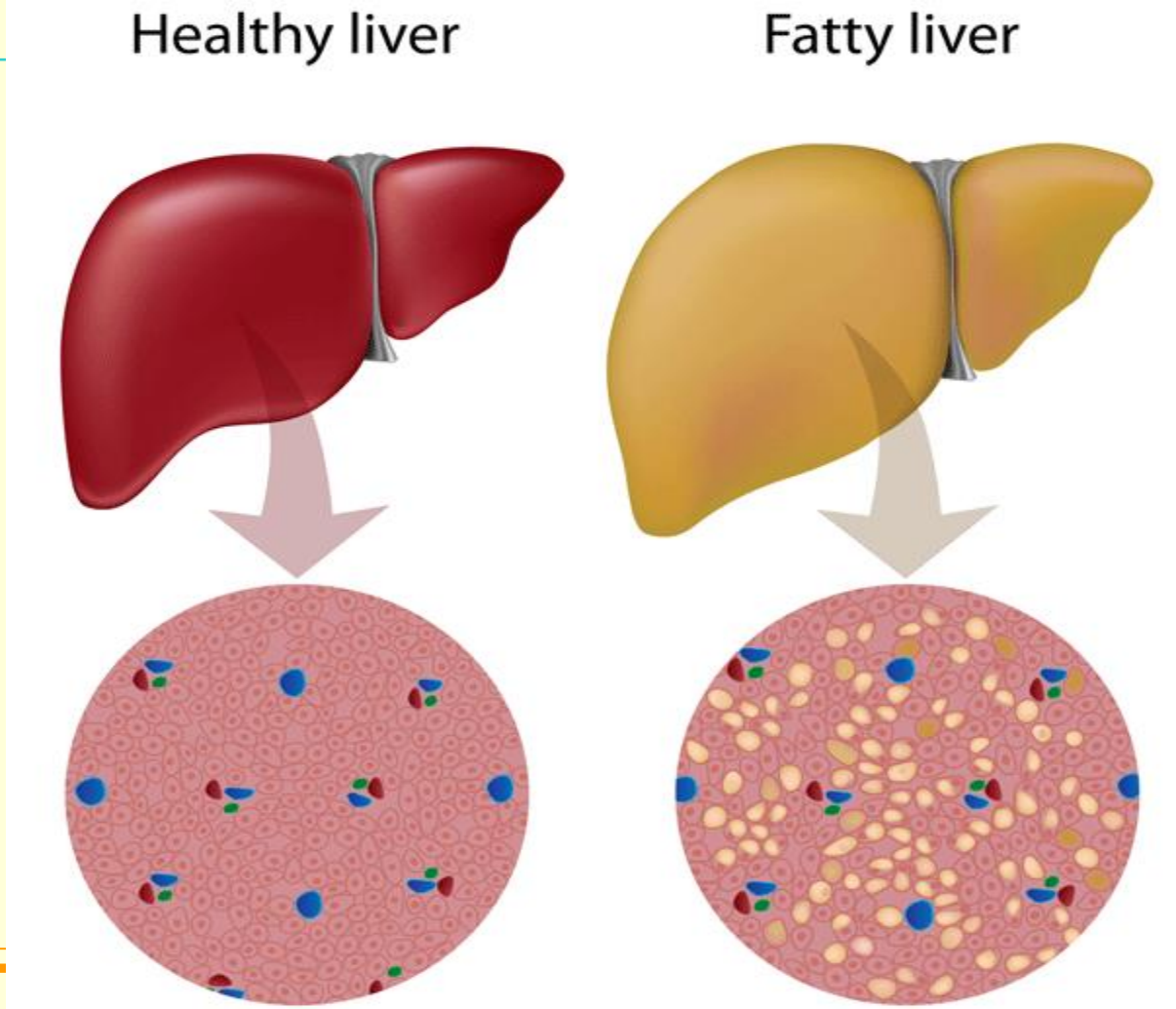


Clinical significance of Creatine and Creatinine

- In adults creatine is fully converted to CP and creatinine, and is not detected in biological fluids. Creatinuria (creatine in the urine) can be detected only in children.
- Creatinine is produced in the muscles and brain as the waste product of amino acid metabolism, and removed from the body by the kidneys. Elevated serum and urine creatinine is the most commonly used indicator of **impaired renal function**.

Lipotropic effect of Met.
Fatty liver disease

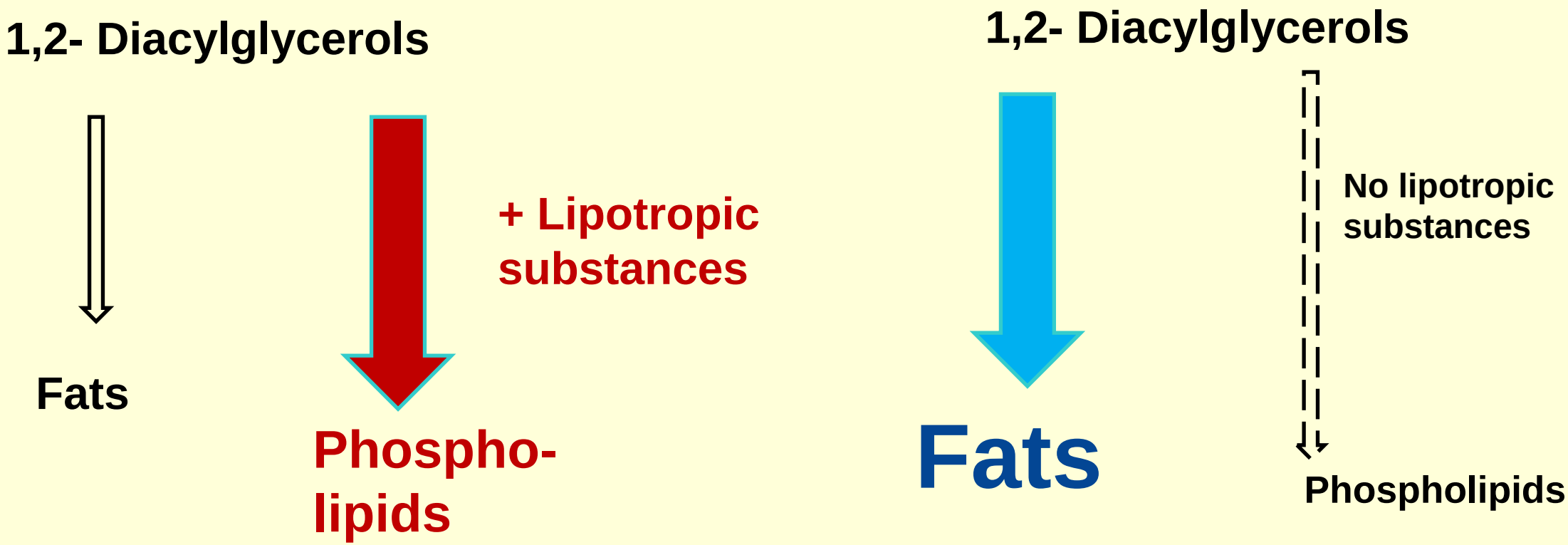
- Fatty liver is an reversible condition wherein large vacuoles of fats (triacylglycerols) accumulate in cells that leads to the enlargement of the liver.
- FLD may occur in those who abuse alcohol, or suffer of obesity.



Fatty liver disease

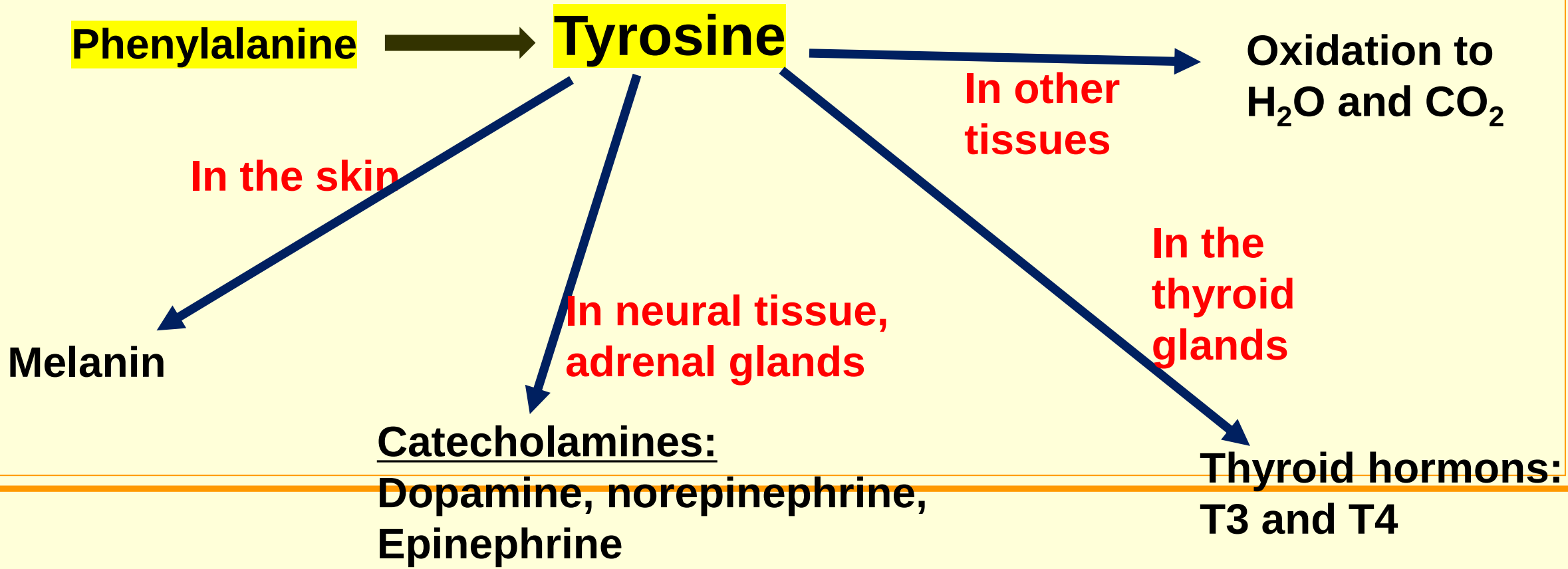
- Reason: In the normal liver synthesis of fats is remarkedly lower compared to the synthesis of phospholipids, which are necessary constituents of cell membranes.
- The synthesis of phospholipids requires essential lipotropic substances, such as methionine (SAM), choline, vitamin B15, which are not synthesized in the body.
- Patients with the FLD usually suffer of malnutrition and impaired intestinal absorption of vitamins and amino acids.
- Diet containing lipotropic substances can be used for the treatment of the FLD on early stages of the disease.

Metabolism of lipids in the healthy and fatty liver

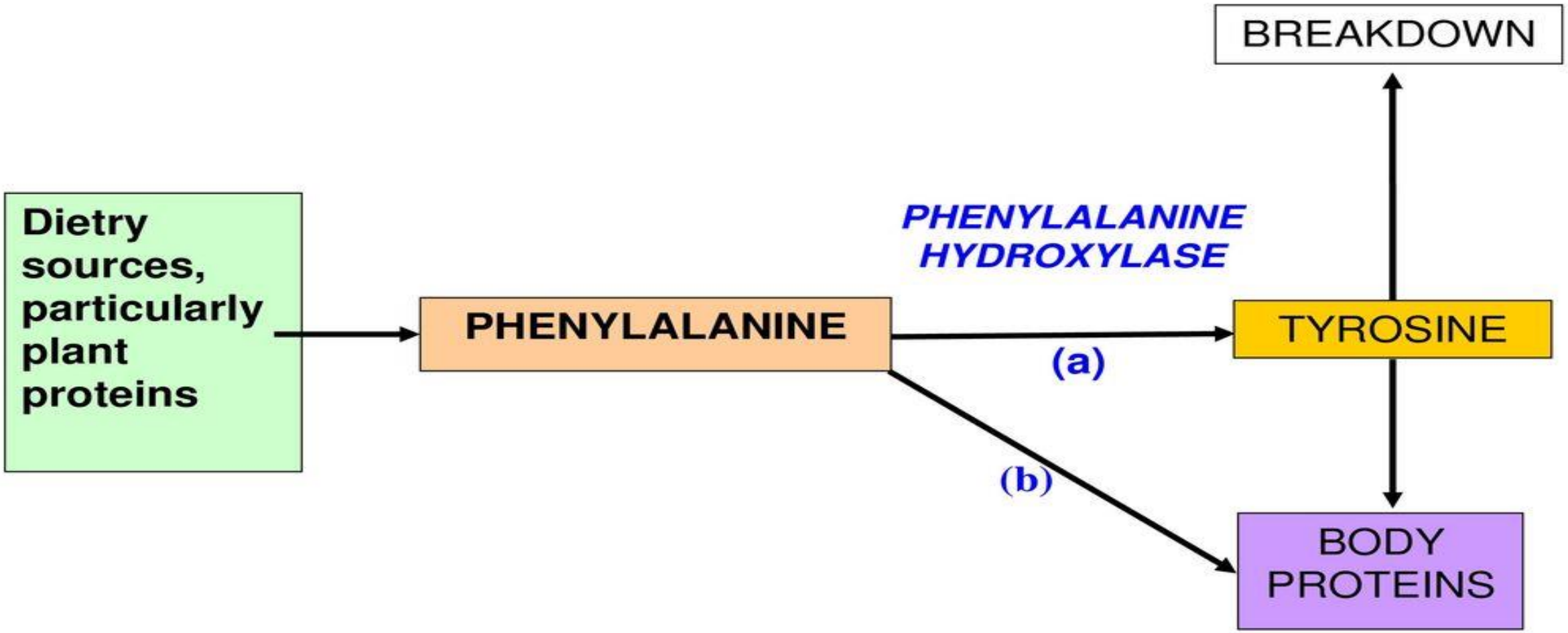


Metabolism of phenylalanine and tyrosine

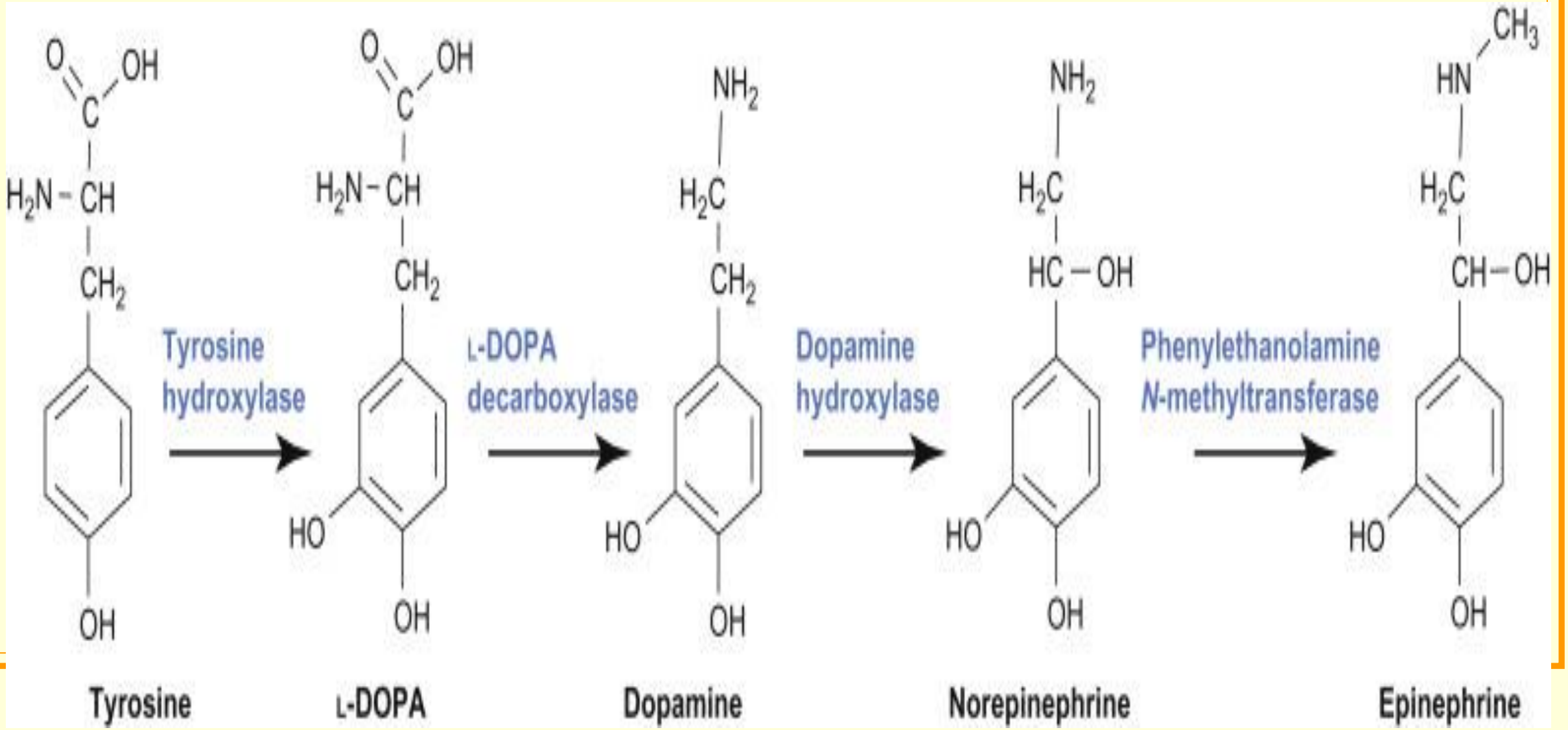
- Phenylalanine is an essential amino acid, that serves as a precursor for tyrosine. Tyrosine is than used for the synthesis of catecholamines, thyroid hormones, melanin, depending on a tissue.



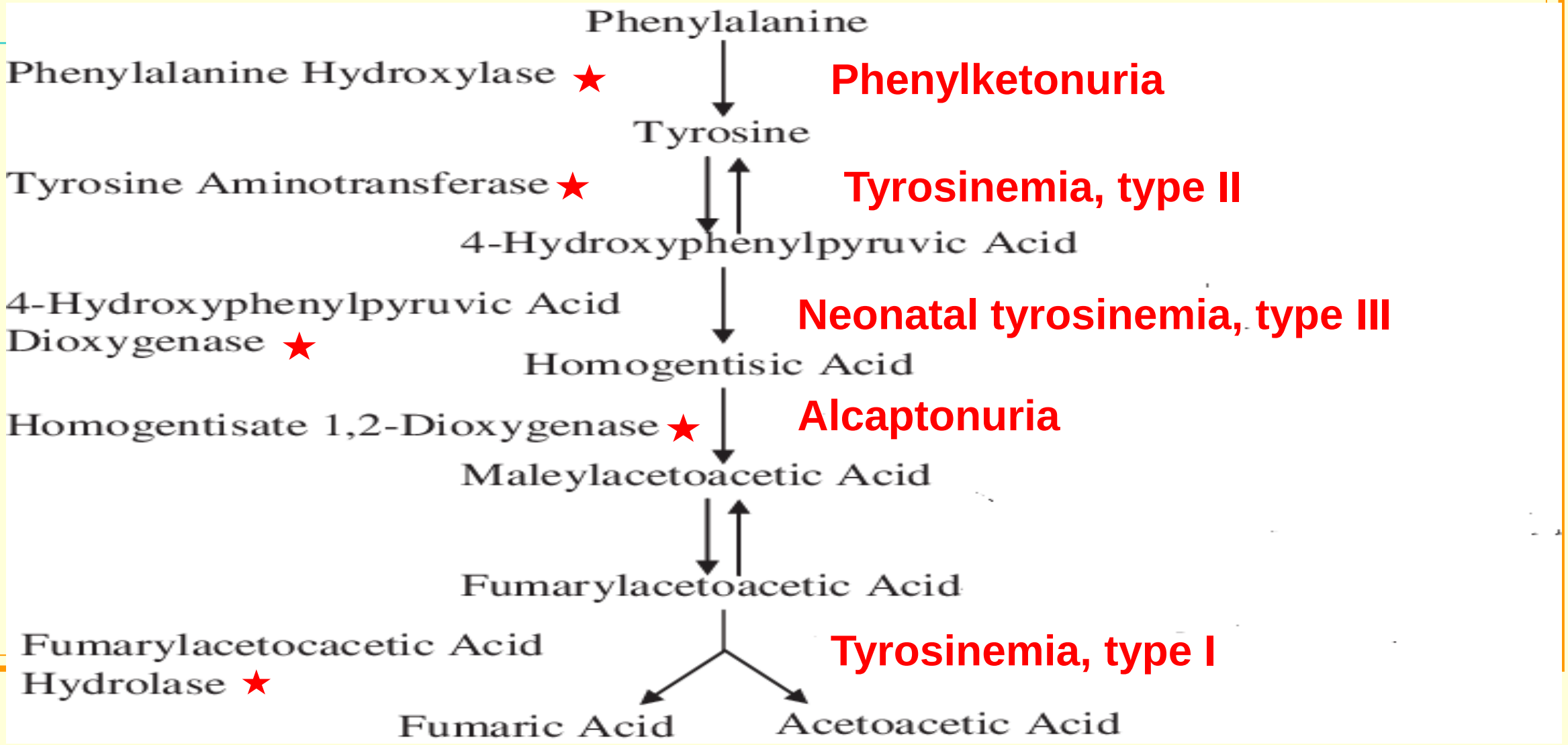
THE NORMAL METABOLISM OF PHENYLALANINE (pathways **a** and **b**)

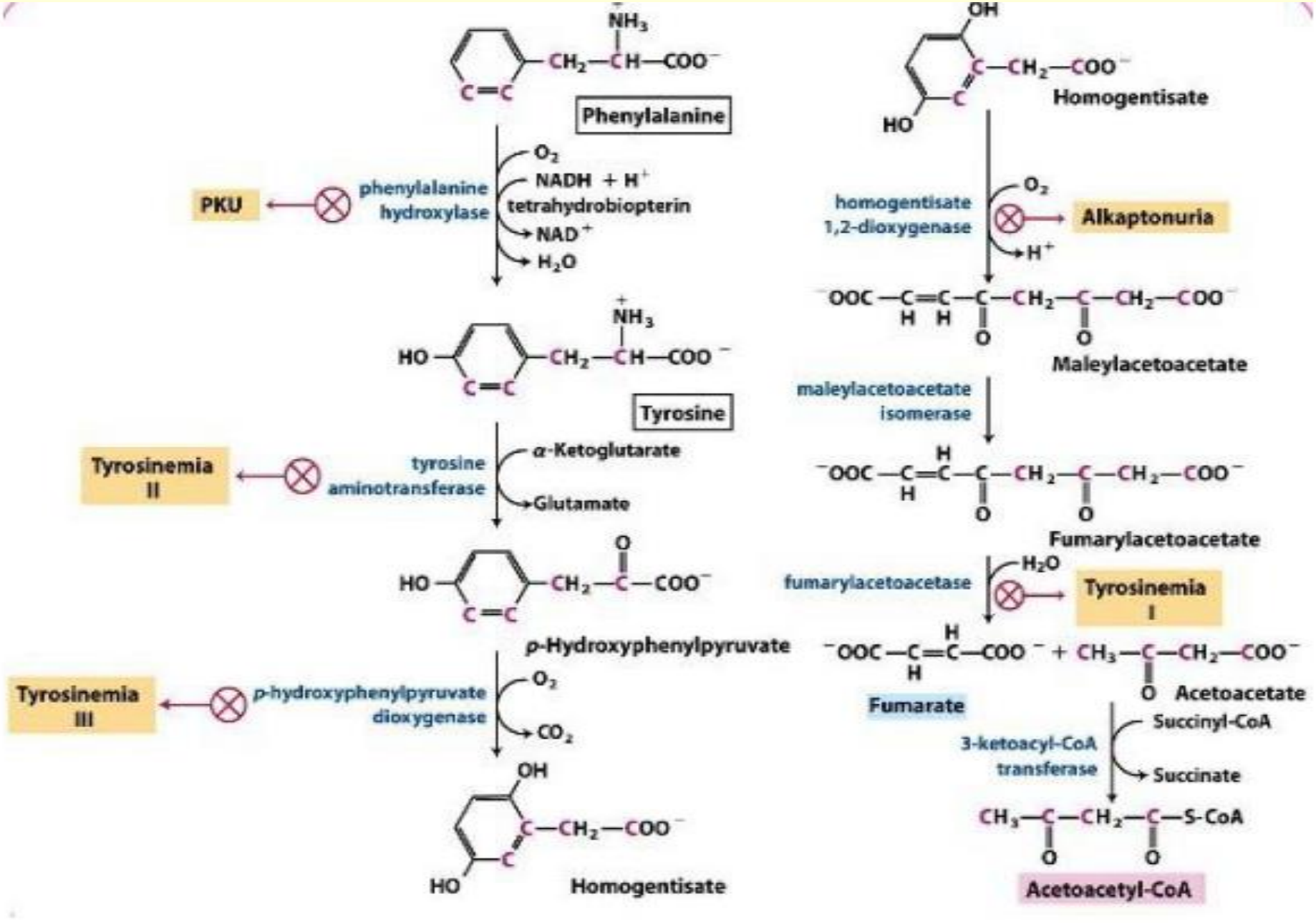


Fate of tyrosine in the brain, sympathetic neurons, adrenal glands



Catabolism of phenylalanine and tyrosine in many tissues and associated enzyme deficiencies

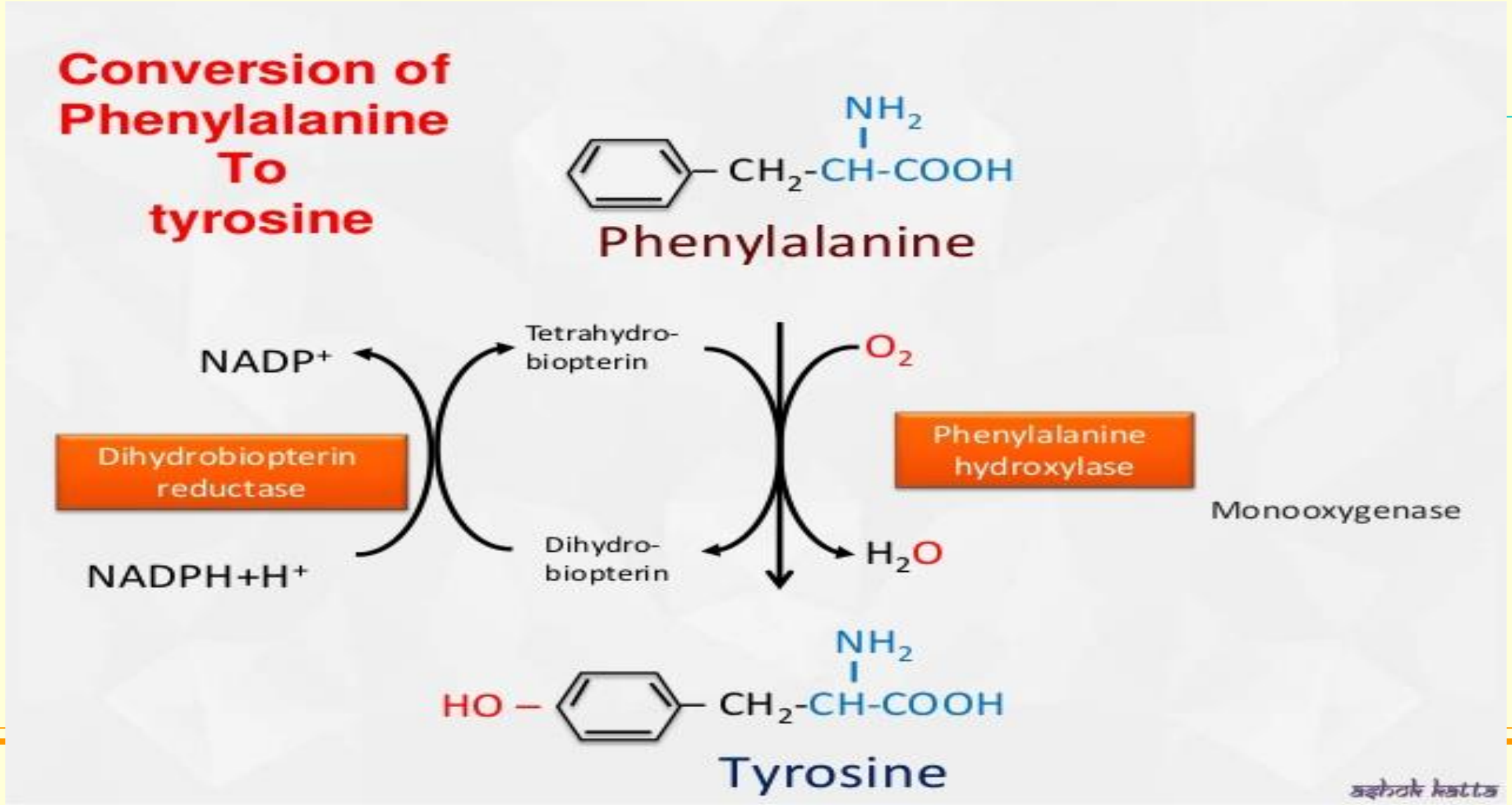



Phenylalanine
phenylalanine hydroxylase
O2
NADH + H+
tetrahydrobiopterin
NAD+
H2O
PKU
Tyrosine
tyrosine aminotransferase
α-Ketoglutarate
Glutamate
Tyrosinemia II
p-Hydroxyphenylpyruvate
p-hydroxyphenylpyruvate dioxygenase
O2
CO2
Tyrosinemia III
Homogentisate
Homogentisate
homogentisate 1,2-dioxygenase
O2
H+
Alkaptonuria
Maleylacetoacetate
maleylacetoacetate isomerase
Fumarylacetoacetate
fumarylacetoacetase
H2O
Tyrosinemia I
Fumarate
Acetoacetate
3-ketoacyl-CoA transferase
Succinyl-CoA
Succinate
Acetoacetyl-CoA

Phenylketonuria

- Genetic disorder with inherited defect in conversion of Phe to Tyr.
- Failure of phenylalanine hydroxylase leads to metabolic blockage of tyrosine metabolism.
- Phenylalanine is elevated in the blood and excreted though the urine.
- Besides, excess of Phe is converted to toxic phenylpyruvate and phenyllactate (phenylketones).

Normal oxidation of Phe to Tyr

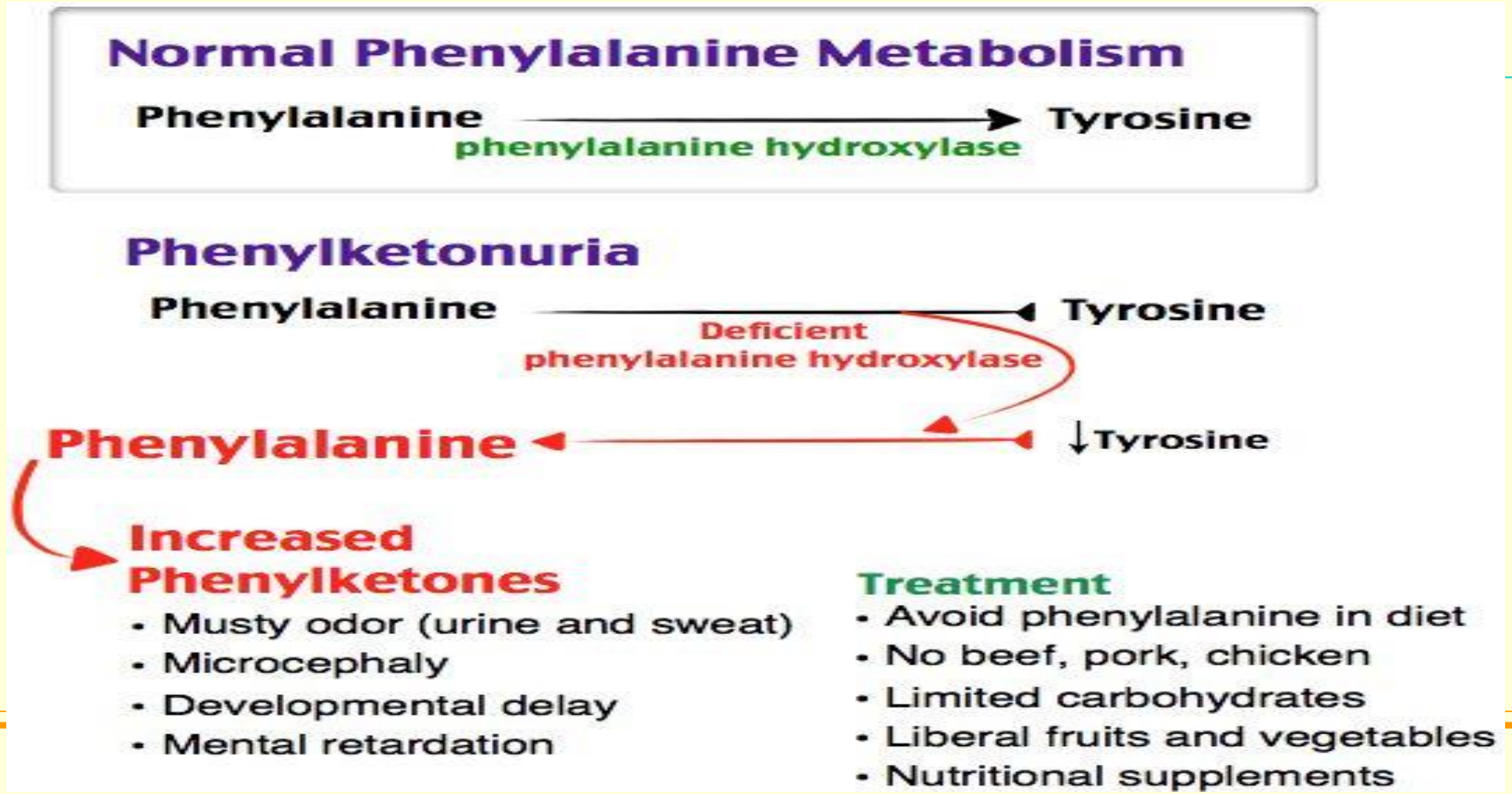


- PKU, Type I – classic, defective Phe-hydroxylase;

- PKU, Type II and III – deficiency in dihydrobiopterin reductase;

- PKU, Type IV and V – deficiency in the synthesis of dihydrobiopterin.

Phenylketonuria



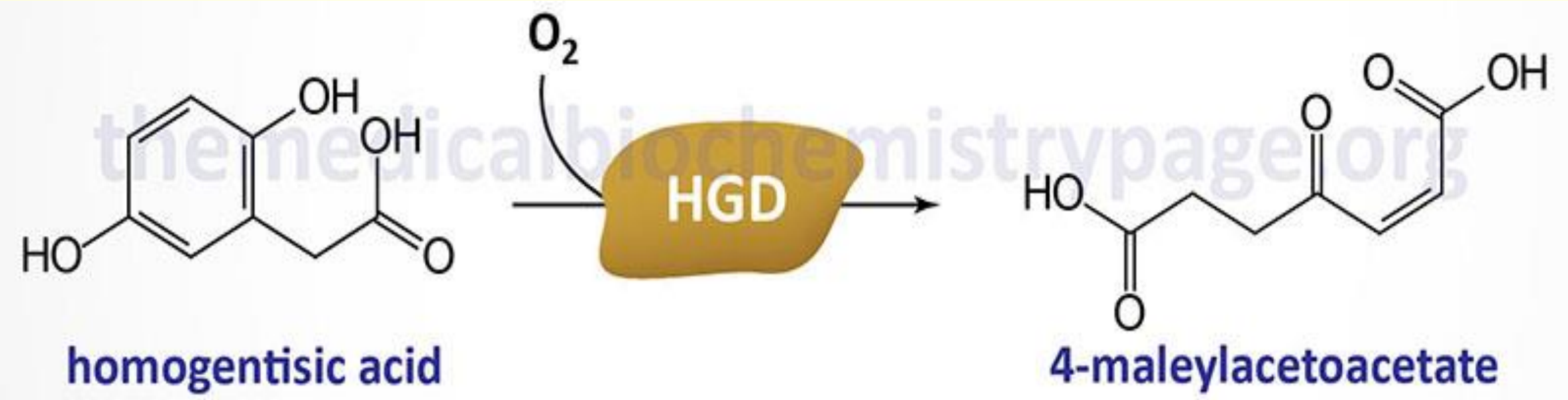
Boy with untreated PKU

Because a child with PKU lacks the normally functioning enzyme necessary to break down phenylalanine (PHE), it accumulates in the blood and body tissues.

This excess PHE can prevent normal brain development and result in mental retardation.

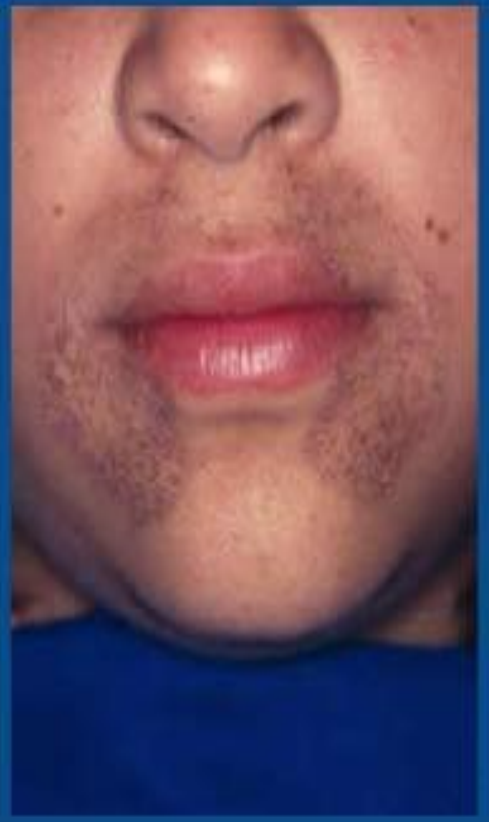
Alcaptonuria (or Black urine disease)

- is a rare inherited genetic disorder caused by a mutation in the *gene* for the enzyme homogentisate 1,2-dioxygenase.
- The body cannot process phenylalanine and tyrosine and accumulates homogentisic acid in the blood and tissues.
- The oxidized form of homogentisic acid (*alkapton*) is excreted in the urine, giving it an unusually dark color.



Symptoms & Signs of Alkaptonuria

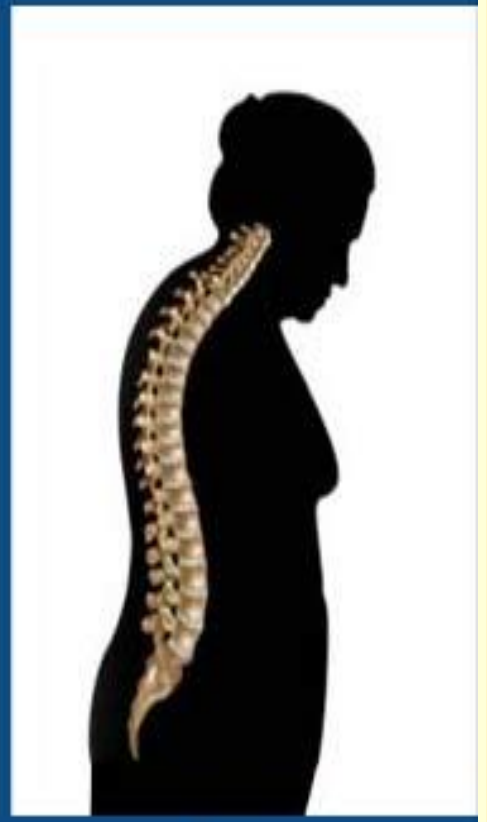
Black colored urine



Ochronosis

Tendinitis

Kidney & prostate stones



Kyphosis or hunchback

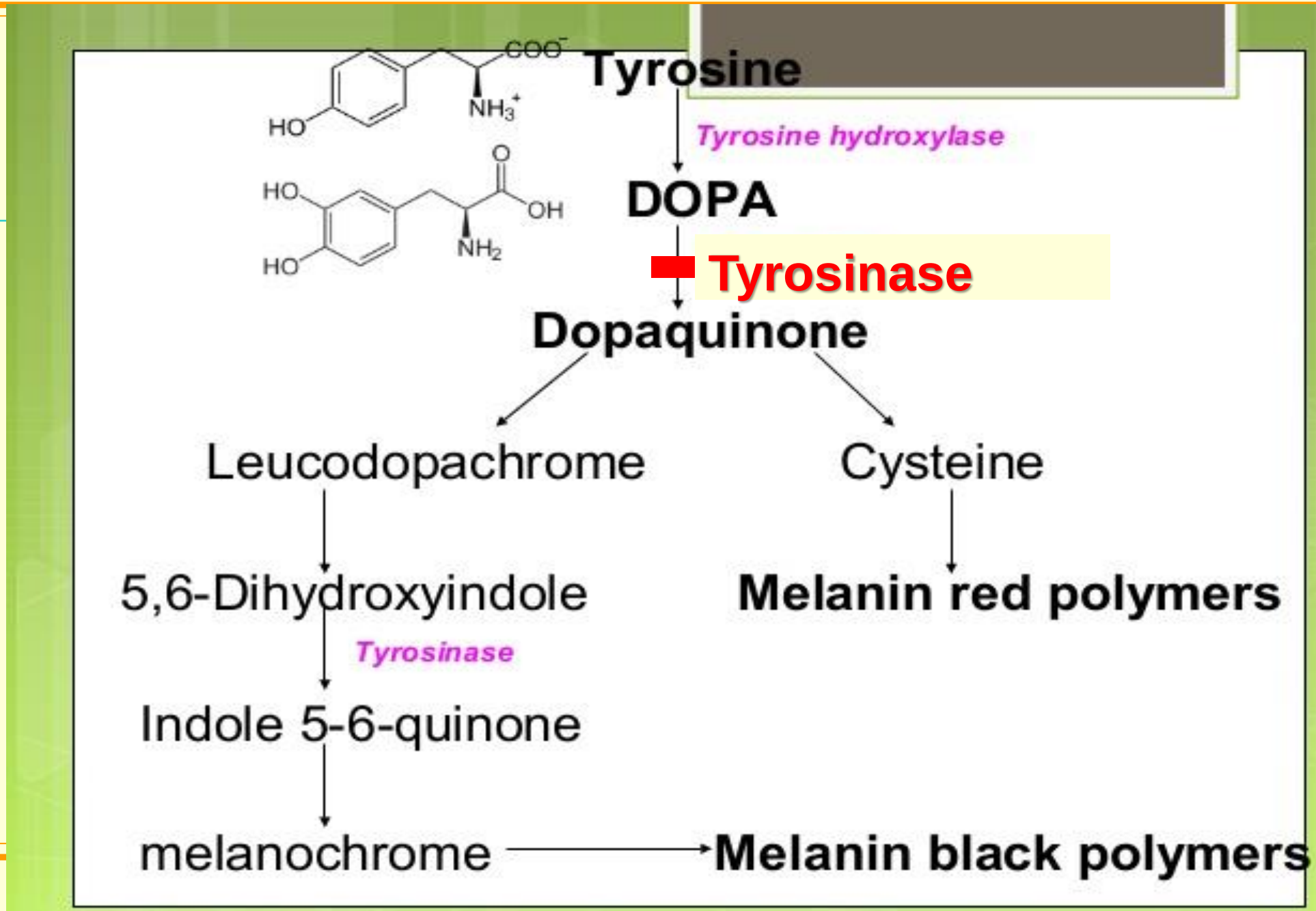
source : wikipedia.org

Complications of alcaptonuria

- Excessive homogentisate causes:
  - Damage to cartilage, osteoarthritis,
  - Formation of insoluble precipitates in the kidneys (kidney stones).
  - Pigmented sclera of the eyes,
  - Accumulation of dark pigment in the skin.

Albinism

- Is congenital disorder characterized by complete or partial absence of pigment in the skin, hair, and eyes due to absence or defect in TYROSINASE, a copper containing enzyme, involved in the production of melanin.


Tyrosine
Tyrosine hydroxylase
DOPA
Tyrosinase
Dopaquinone
Leucodopachrome
Cysteine
5,6-Dihydroxyindole
Melanin red polymers
Tyrosinase
Indole 5-6-quinone
melanochrome
Melanin black polymers

Albinism

- Affect people of all ethnic backgrounds;
- Frequency worldwide is appr. 1 in 17.000;
- The highest rate is met in people of Sub-Saharian African countries.
- Albinic people are mentally healthy, but have some problems in vision, photosensitivity.
- They are prone of skin cancer development (melanoma)