Amino acid Catabolism -Diseases

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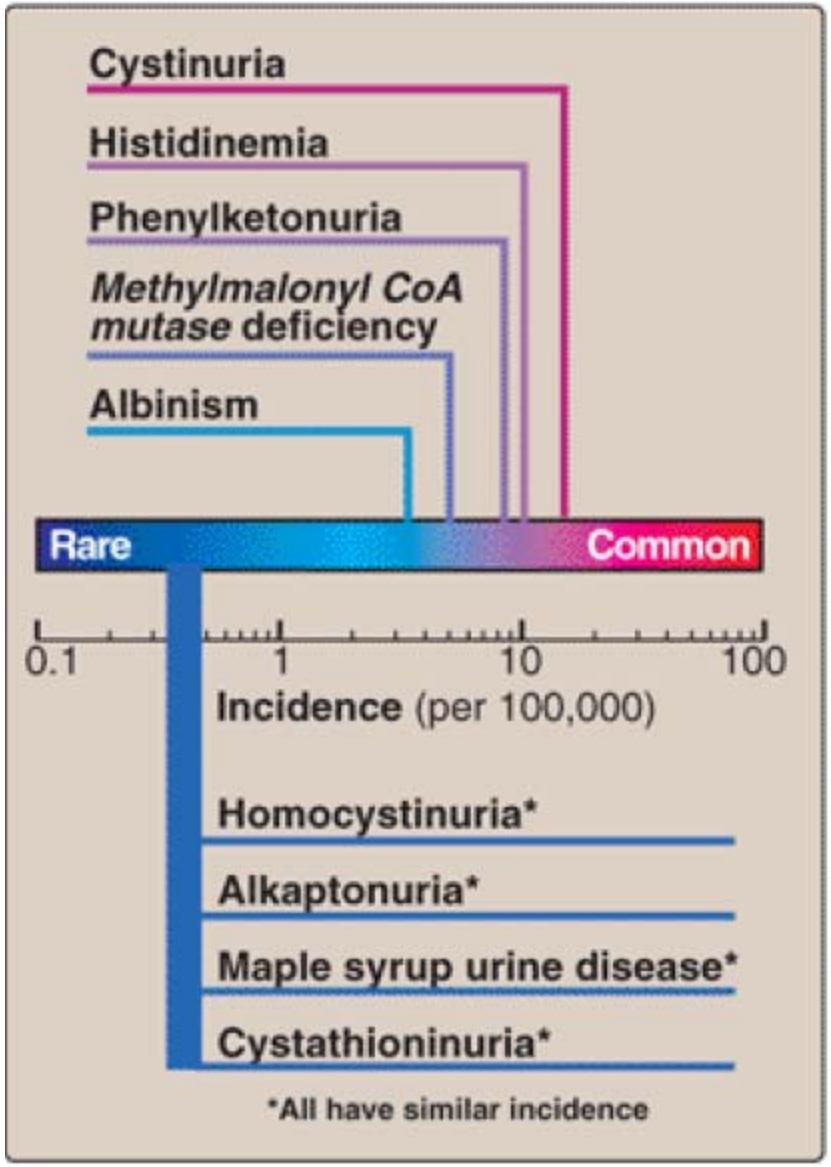
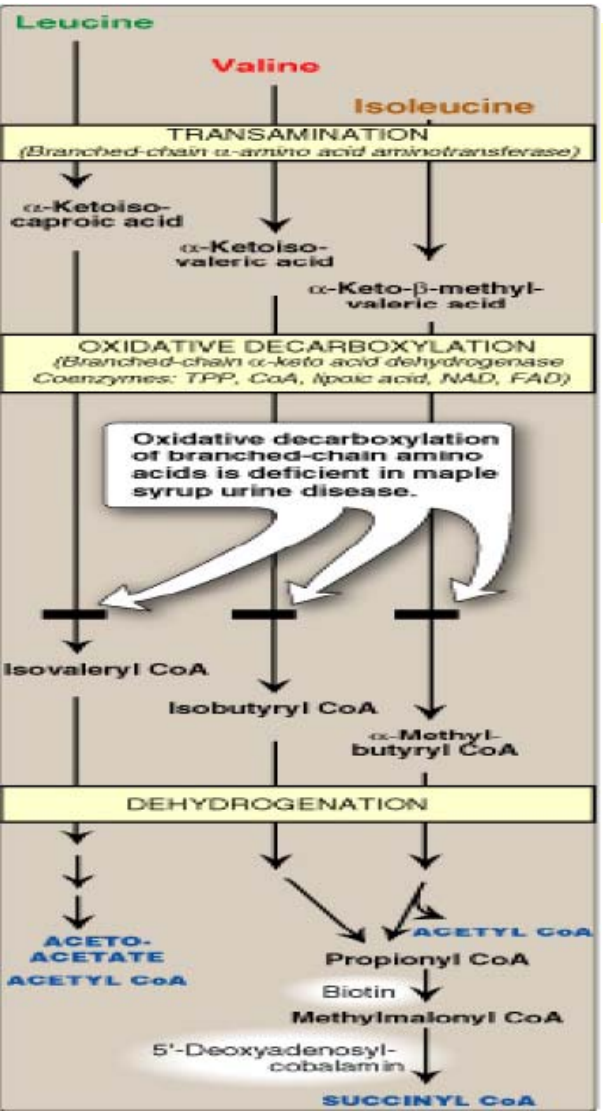
Diseases caused by Enzyme defects in amino acid catabolism

Metabolic defects in Amino acid metabolism



Maple syrup urine disease (MSUD) (rare, prevalence of 1:185,000)

Autosomal recessive disease in which there is a partial or complete deficiency of Branched chain α-keto acid dehydrogenase, an enzyme that decarboxylates leucine, Isoleucine, and Valine.



Disease leads to accumulation of these amino aids and branched chain α-keto acid substrates causing abnormalities in brain functions.

Characteristics of MSUD

Patients show feeding problems, vomiting, dehydration, severe metabolic acidosis and Classic maple syrup odor to the urine.

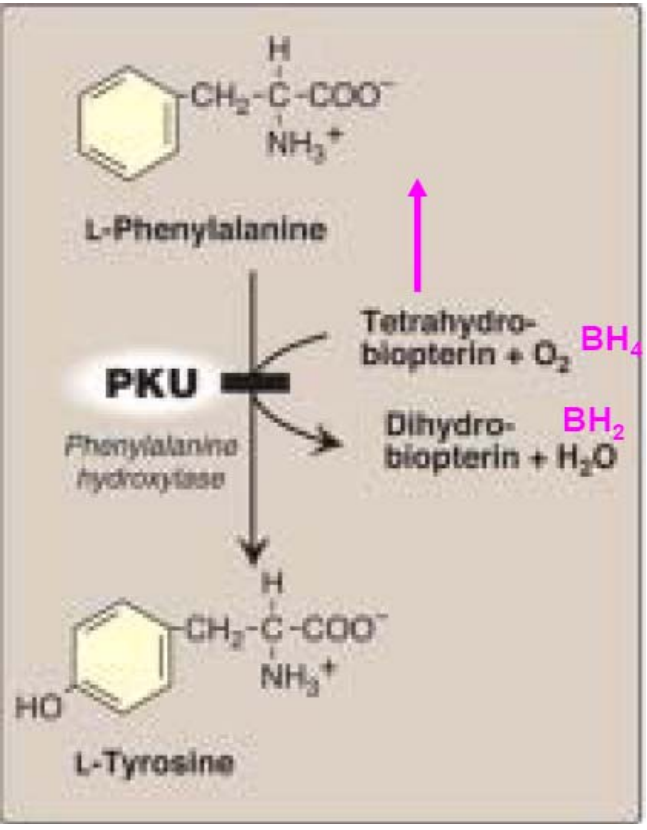
Treatments:

Giving a synthetic formula that contains limited amount of leucine, Isoleucine, and Valine.

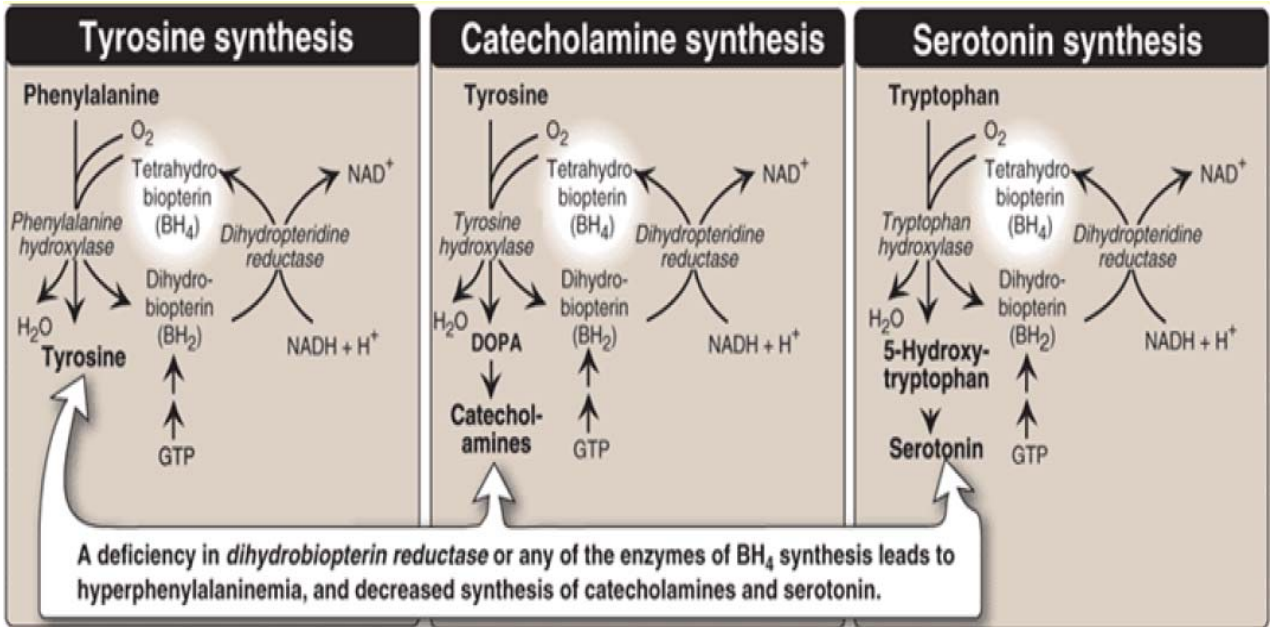
Phenylketonuria (PKU): (Prevalence of 1:15,000)

A deficiency in phenylalanine hydroxylase results in the disease phenylketonuria (PKU).

More than 400 mutations in gene that code for PKU has been identified and the disease is often heterozygous.



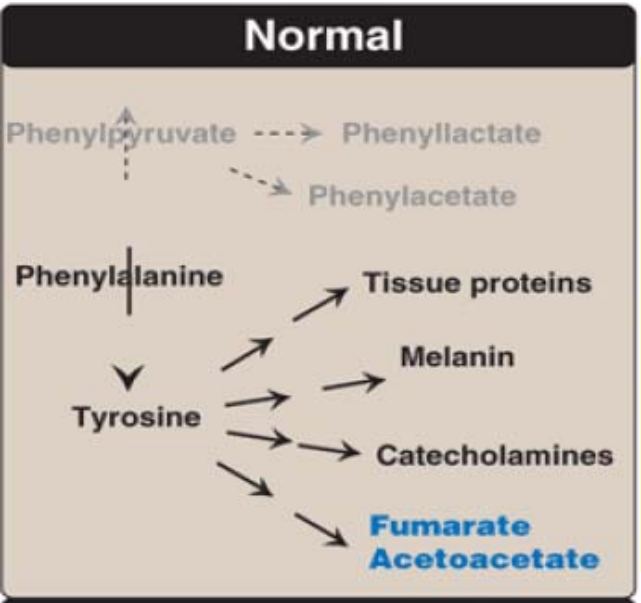
Deficiency of enzymes required for the synthesis of BH4 and dihydropterine (BH2) Reductase which regenerates BH4 from BH2 also leads to hyperphenylalaninemia.

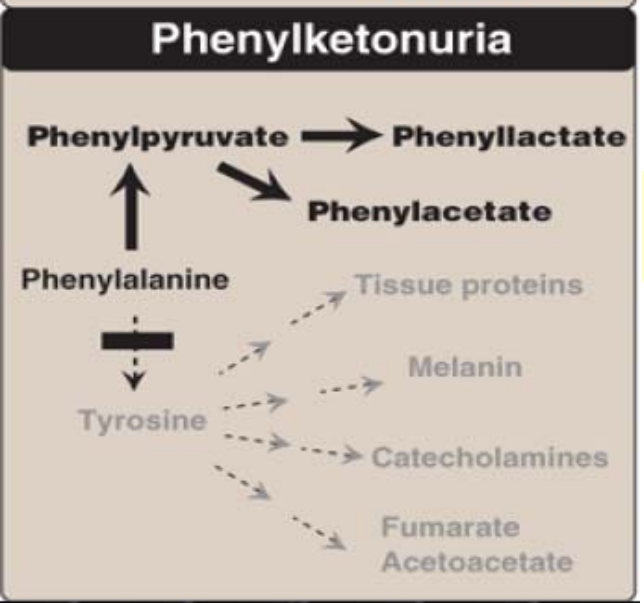


BH4 is also required for tyrosine hydroxylase and tryptophan hydroxylase

Treatment: replacement therapy with BH4 or generated products

Pathways of phenylalanine metabolism in normal and in patients with phenylketonuria





Characteristics of classic PKU:

1) Elevated phenylalanine, phenylpyruvate, phenyllactate and phenylacetate in tissues, plasma and urine.
2) CNS symptoms: Mental retardation, failure to walk or talk, seizures, hyperctivity, tremor etc.
3) Hypopigmentation: deficiency in the formation of Melanin lead to the deficiency of pigmentation (fair hair, light skin, color, and blue eyes.

Treatments: Synthetic nutrient with low phenylalanine content supplemented with tyrosine

Phenylketonuria (PKU): CONT'D

•Also called Hyperphenylalaninemia - complete deficiency of phenylalanine hydroxylase (plasma level of Phe raises from normal 0.5 to 2mg/dL to more than 20 mg/dL).

•The mental retardation is caused by the accumulation of phenylalanine (and its toxic metabolities phenylpyruvic acid, phenyllactic acid and phenylacetic acid), which becomes a major donor of amino groups in aminotransferase activity and depletes neural tissue of α-ketoglutarate.

•Absence of α-ketoglutarate in the brain shuts down the TCA cycle and the associated production of aerobic energy, which is essential to normal brain development.

•Newborns are routinelly tested for blood concentration of Phe.

•This inborn disease may also be due to deficiency of reductase enzyme or biopterin substrate itself.

Phenylketonuria (PKU): CONT'D

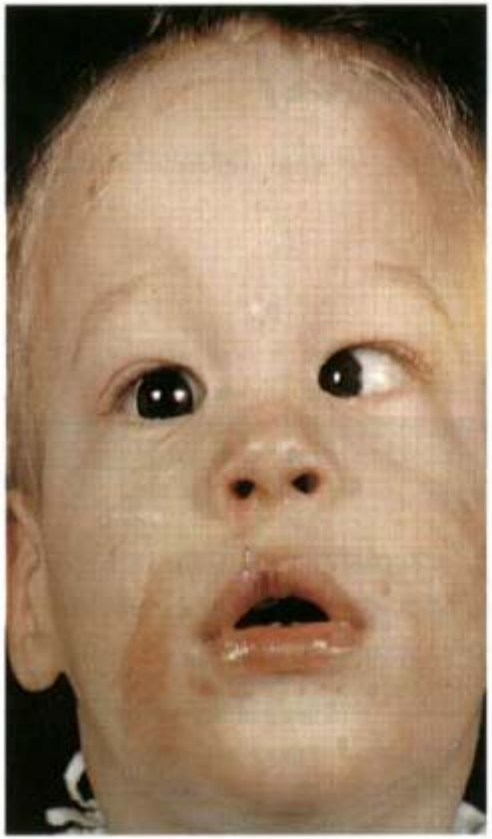


Fig. 19.3 The face of this patient with PKU illustrates the rather subtle eczematoid rash. The brown eyes remind us that not all patients with this disease have blue eyes. In addition, he had epicanthal folds and a left internal strabismus.

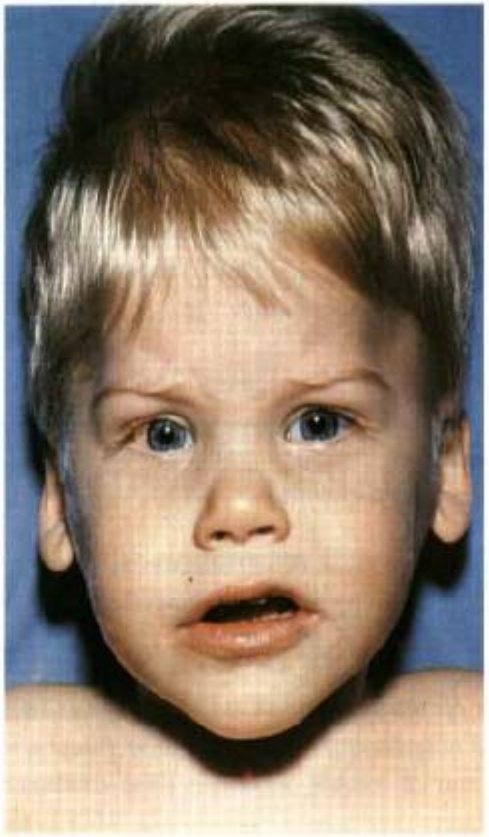


Fig. 19.4 L.S. This patient was diagnosed as having PKU at 10 months of age. The eyes were blue, the skin fair and the hair blond.

TYROSINEMIA

- **Hereditary tyrosinemia is a genetic inborn error of metabolism associated with severe liver disease in infancy.**

- **The disease is inherited in an autosomal recessive fashion which means that in order to have the disease, a child must inherit two defective genes, one from each parent.**

- **In families where both parents are carriers of the gene for the disease, there is a one in four risk that a child will have tyrosinemia.**

- **About 1 person in 100,000 is affected with tyrosinemia globally**

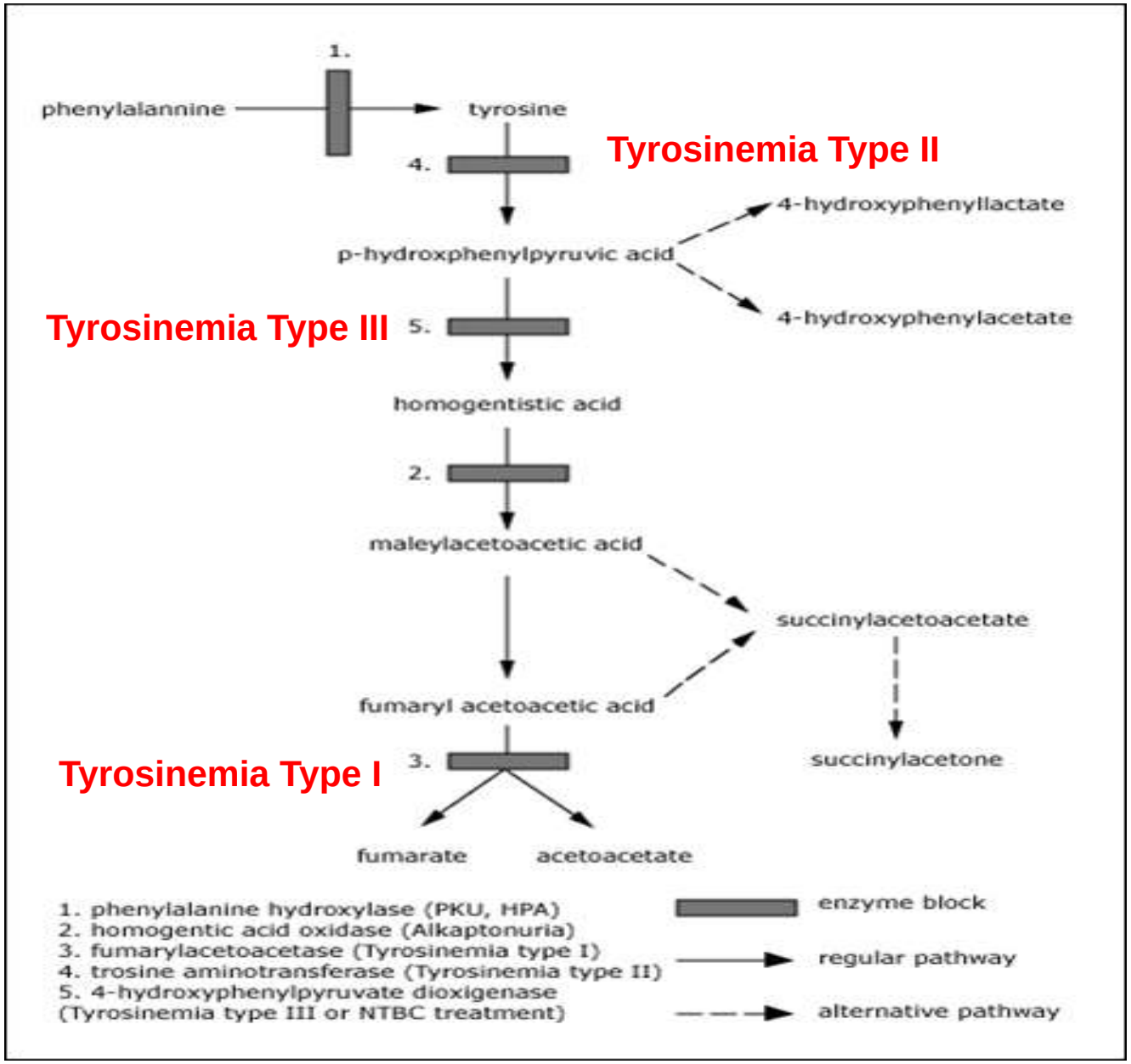
•*TYROSINEMIA-Causes*

•The metabolism of tyrosine in humans takes place primarily in the liver.

•Tyrosinemia is caused by an absence of the enzyme fumarylacetoacetate hydrolase (FAH, also called fumarylacetoactase) which is essential in the metabolism of tyrosine.

•The absence of FAH leads to an accumulation of toxic metabolic products in various body tissues, which in turn results in progressive damage to the liver and kidneys.

•Three types of tyrosinemia I, II, III


1.
phenylalannine
tyrosine
Tyrosinemia Type II
4.
4-hydroxyphenyllactate
p-hydroxphenylpyruvic acid
4-hydroxyphenylacetate
Tyrosinemia Type III
5.
homogentistic acid
2.
maleylacetoacetic acid
succinylacetoacetate
fumaryl acetoacetic acid
succinylacetone
Tyrosinemia Type I
3.
fumarate
acetoacetate
1. phenylalanine hydroxylase (PKU, HPA)
2. homogentic acid oxidase (Alkaptonuria)
3. fumarylacetoacetase (Tyrosinemia type I)
4. trosine aminotransferase (Tyrosinemia type II)
5. 4-hydroxyphenylpyruvate dioxigenase
(Tyrosinemia type III or NTBC treatment)
enzyme block
regular pathway
alternative pathway

Albinism

•Tyrosine is also the precursor to pigment molecules called melanins that are produced from dopaquinone.

•The two primary melanins are eumelanins, which are dark pigments having a brown or black color, and pheomelanins that have red or yellow color.

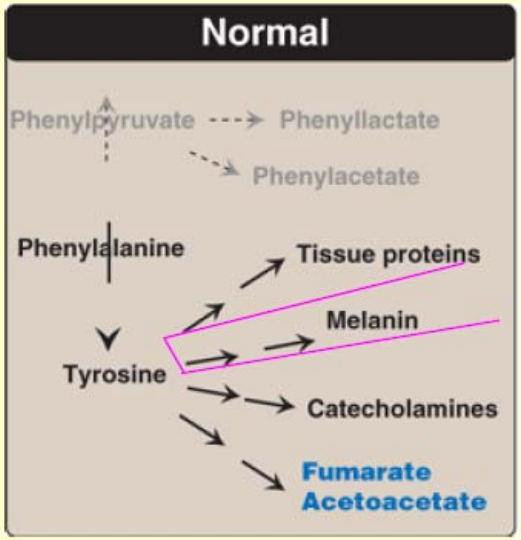
•The yellow color of pheomelanin pigments comes from the sulfur in cysteine that is combined with dopaquinone.

•Melanocytes are cells that produce melanins, and depending on the ratio of eumelanin and pheomelanin pigments, one can have either dark hair or light hair depending in the distribution of melanin-filled granules along the hair shaft.

•Natural loss of hair color occurs as a result of aging when melanin production in human melanocytes located near the base of hair follicles shuts down and these defective cells are not replaced as they normally are in younger individuals.

•Gray hair can be colored by treating it with a mixture of hydrogen peroxide and an ammonia based solution containing artificial pigments.

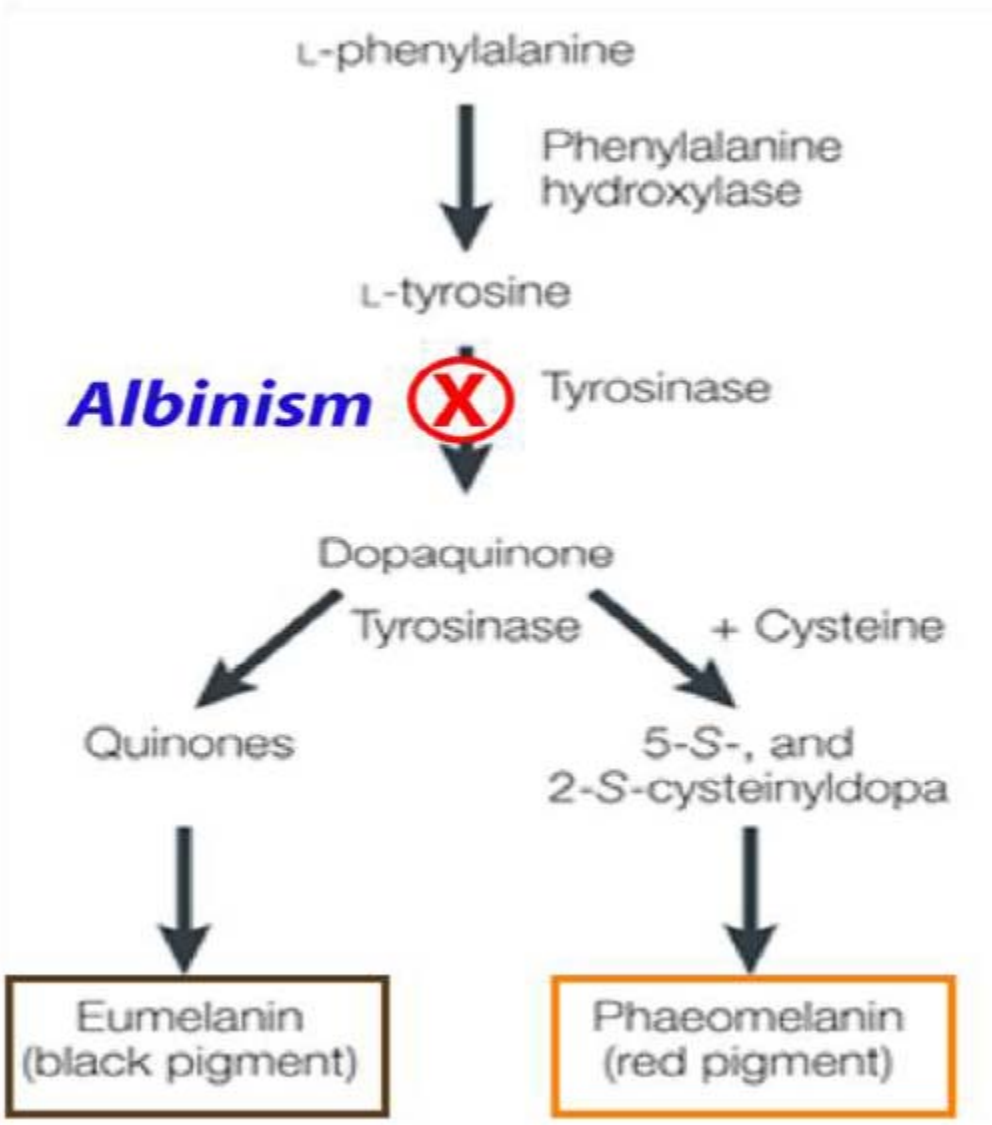
Albinism



Condition in which defect in tyrosine metabolism results in deficiency in the production of melanin.

Characteristics: hypopigmentation caused due to the deficiency in the formation of melanine results in partial or full absence of pigment from the skin, hair, and eyes.

Albinism


L-phenylalanine
Phenylalanine hydroxylase
L-tyrosine
Albinism
X
Tyrosinase
Dopaquinone
Tyrosinase
+ Cysteine
Quinones
5-S-, and 2-S-cysteinyldopa
Eumelanin (black pigment)
Phaeomelanin (red pigment)

Albinism

- **Absence of melanin pigment Type 1 albinism is an autosomal recessive genetic mutation in the tyrosinase gene**

- **A deficiency in tyrosinase will result in loss of hair and skin pigments which explains the albino phenotype.**

- **Interestingly, individuals with phenylketonuria can have light skin and hair at birth because of low levels of tyrosine.**

- **However, *phenylketonuriacs are not albinos because they obtain sufficient* amounts of tyrosine in their diets to support melanin biosynthesis.**

Alkaptonuria

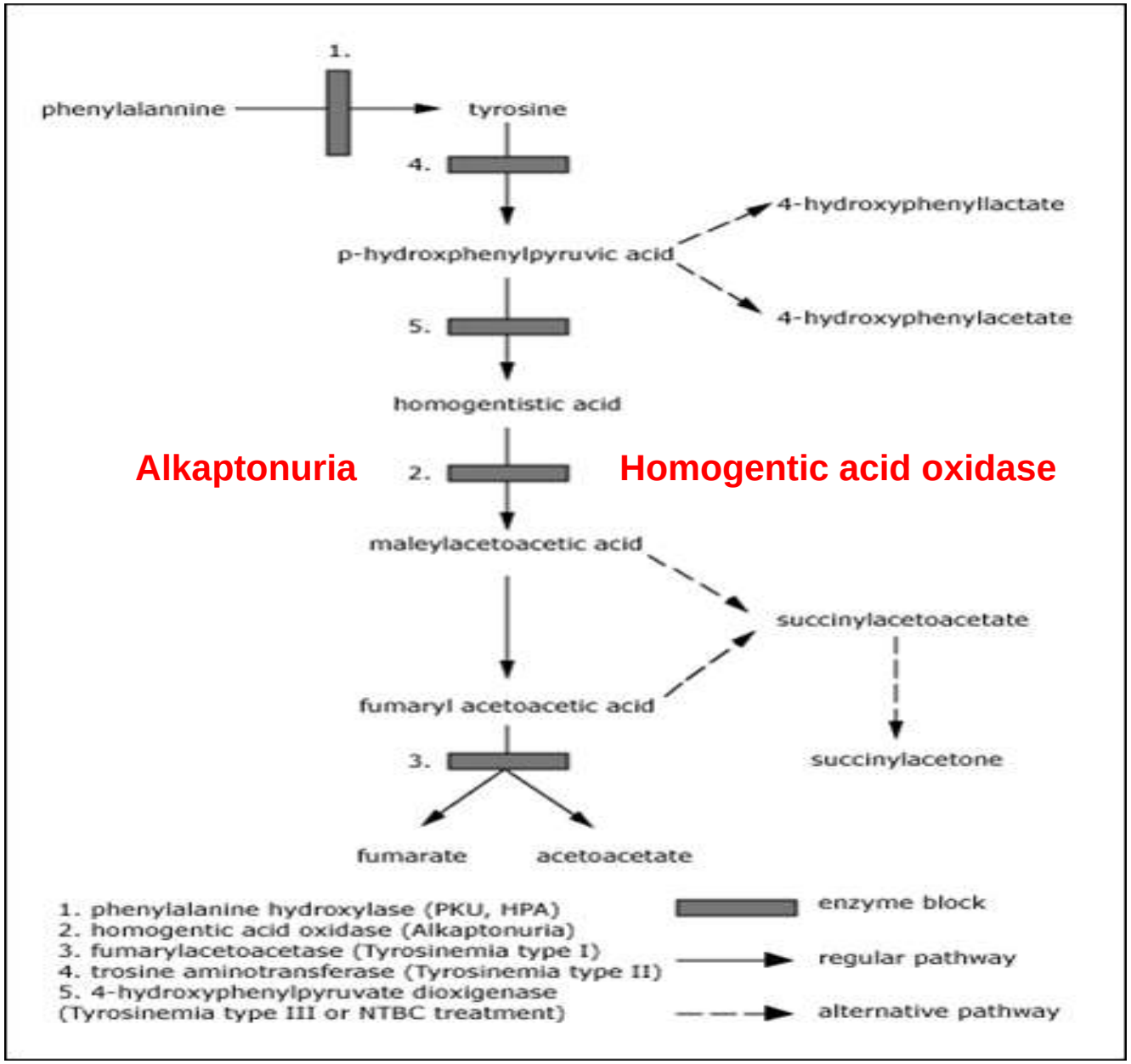
•Autosomal recessive Homogentisic acid oxidase deficiency resulting in:
-Homogentisic acid (HGA) accumulation causes blackening and destruction of cartilage and connective tissue; Spine, hips, knees, shoulders, aortic valve.

•The patient's urine contains large amounts of HGA which is oxidized to
•a dark pigment on standing(dark urine appearance).

•Its occurrence usually beyond the 40 year of age, but sometimes
•dark staining of diapers may indicates the disease in
•infants.

•Although Alkaptonuria is not life-threatening, the
•associated arthritis may be severely crippling.

•The three characteristics of this disorder are: joint arthritis,
•pigmentation and dark urine.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Alkaptonuria
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Homogentic acid oxidase
maleylacetoacetic acid
succinylacetoacetate
fumaryl acetoacetic acid
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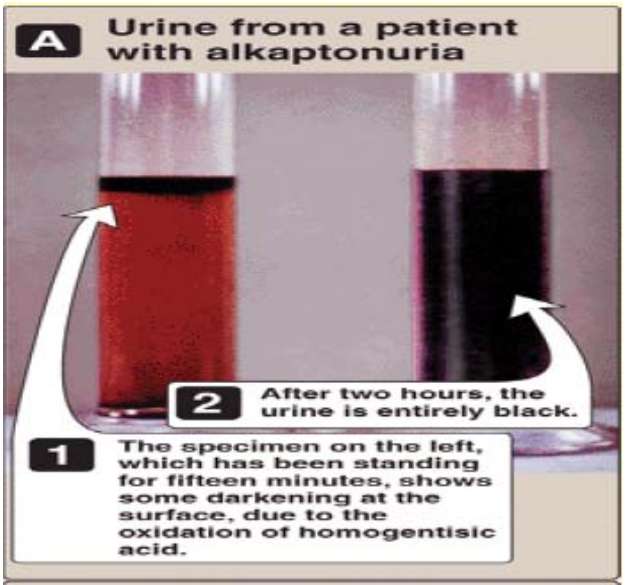
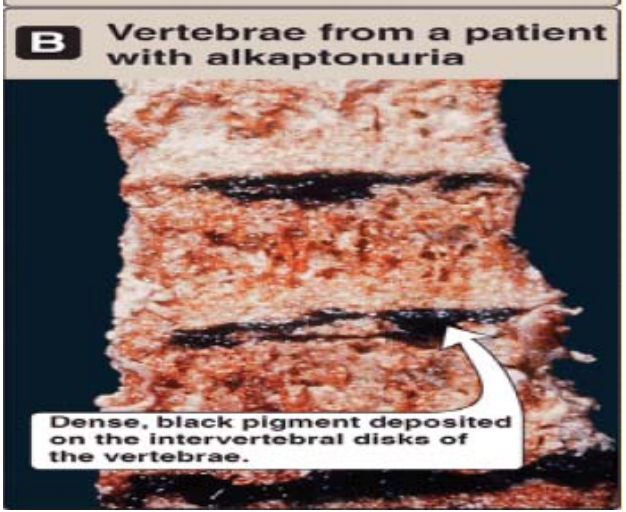
enzyme block
regular pathway
alternative pathway

Alkaptonuria

Rare disease involving deficiency in homogentisic acid oxidase, enzyme in tyrosine degradation pathway.



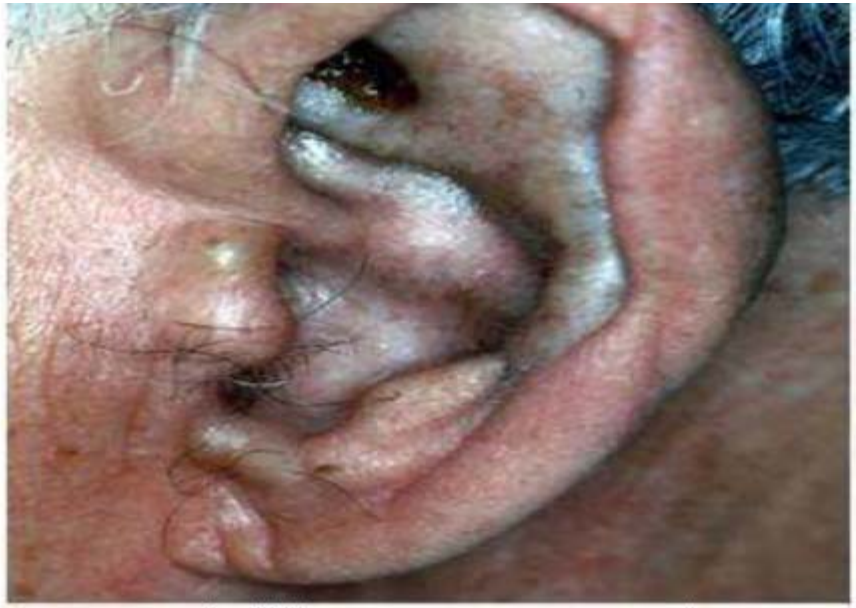


Characteristics:

1) Results in accumulation of homogentisic acidurea.
2) Large joint arthritis
3) Dense, black pigments deposited on the intravetebral disks of the vertebrae.

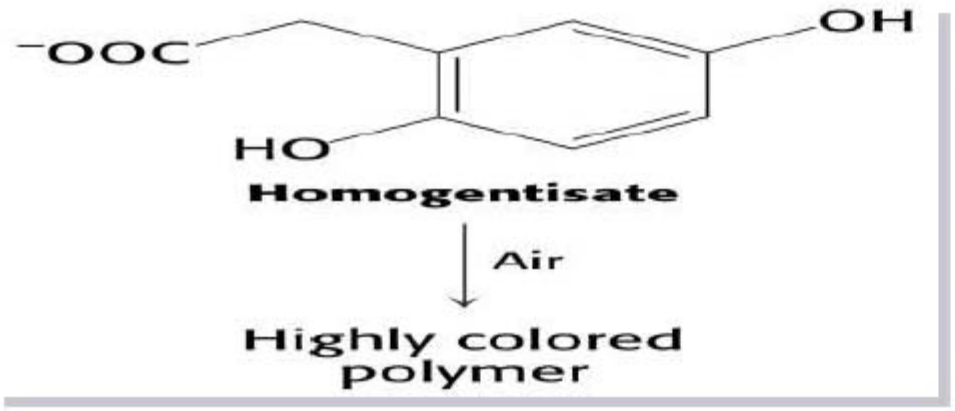
Treatment:

Low protein (low in phenylalanine and tyrosine) diet
Help reduce the levels of homogenistic acid.

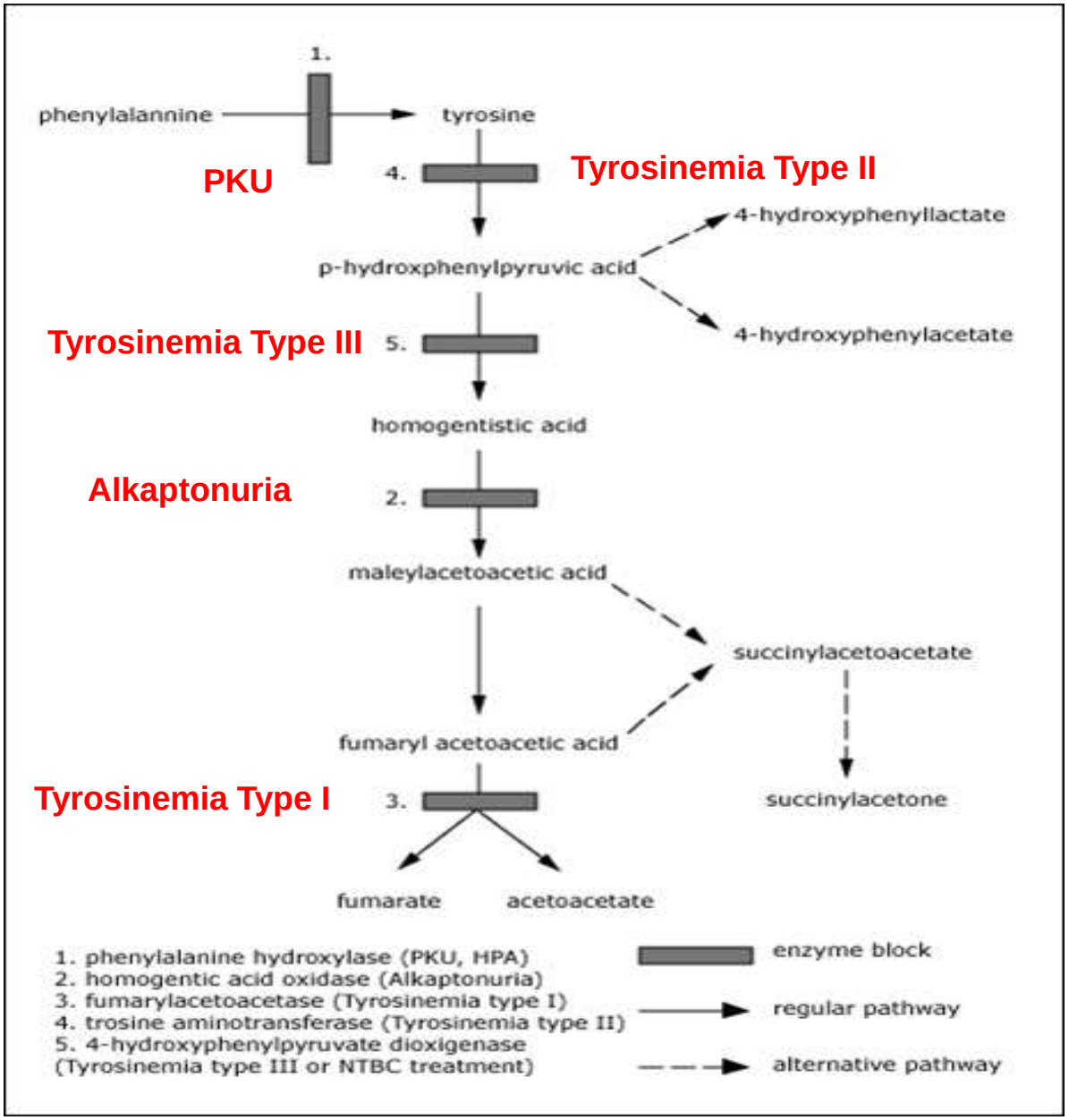


Alkaptonuria

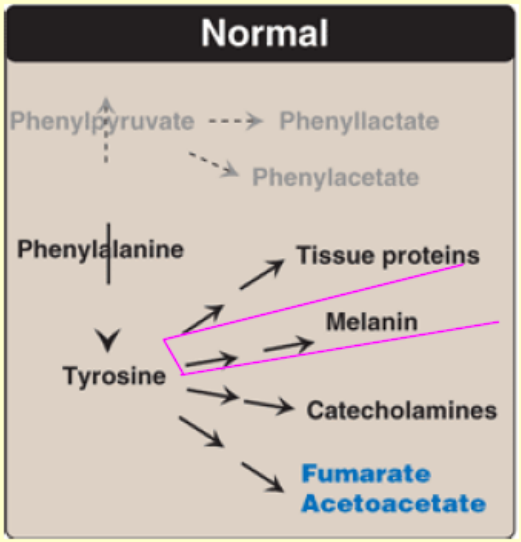
Absence of homogentisate oxidase activity;



Summary



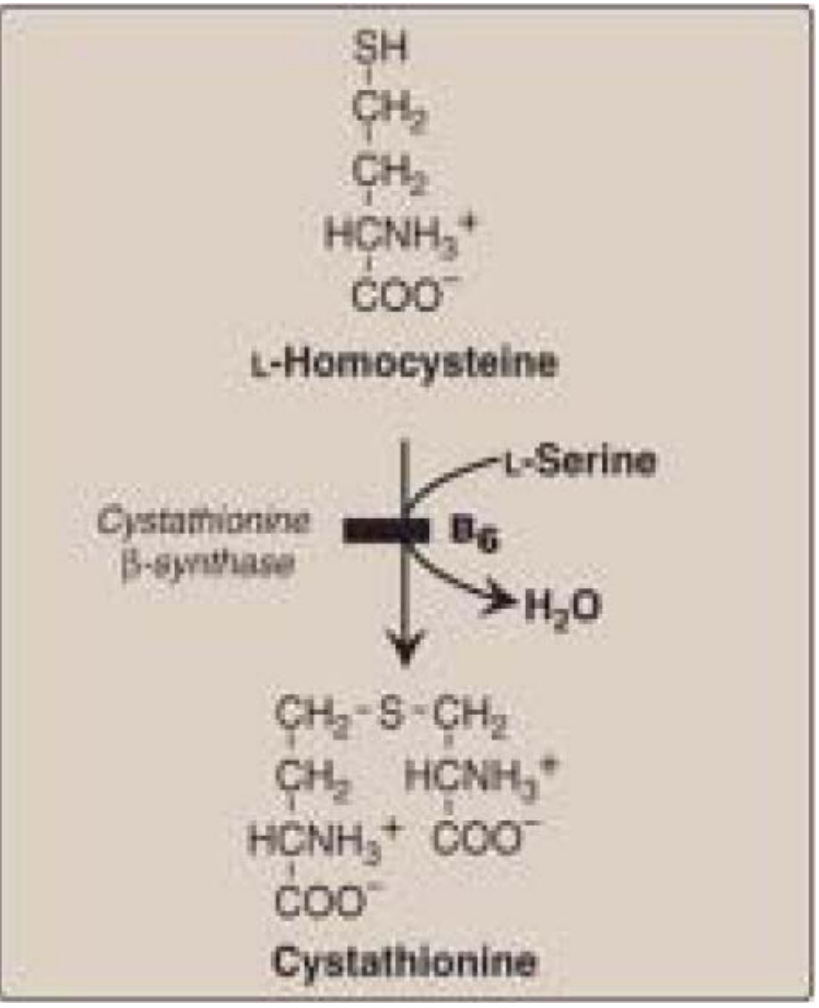
Albinism



Homocystinuria

Caused due to the defect in the metabolism of homocysteine. Most common cause is A defect in the enzyme cystathionine β-synthatase.

Results in elevation of homocysteine, methionine, and low levels of cysteine in plasma



Charactristics:

1) High levels of homocysteine and methionine in plasma and urine.
2) Patients exhibit ectopia (displacement of the lens of the eye)
3) Skeletal abnormalities
4) Premature arterial disease
5) Osteoporosis
6) Mental retardation

Treatment:

Restriction of methionine intake and supplementation with Vit B6, B12, and folate.

MAJOR PHENOTYPIC EXPRESSION

Ectopia lentis, vascular occlusive disease, malar flush, osteoporosis, accumulation of homocystine and methionine and defective activity of cystathionine synthase.

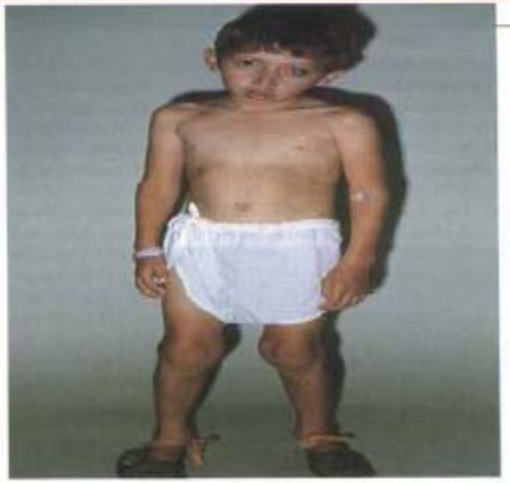


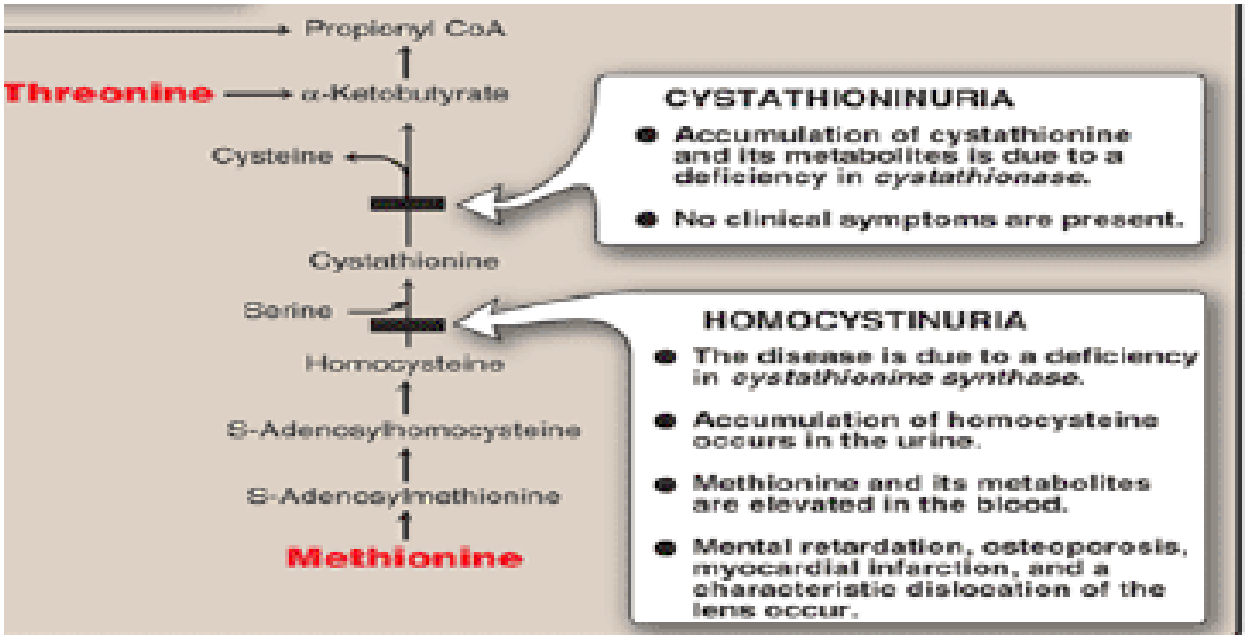
Fig. 21.2 M.G., a 6-year-old boy with homocystinuria. He had short stature and genu valgum.

Fig. 21.3 Closer view illustrates M.G.'s eyes. Subluxed lenses had previously been removed bilaterally, after which he developed glaucoma in the left eye. He had fair skin and hair and a pronounced malar flush.

Fig. 21.4 The dislocated lens in homocystinuria is usually downward, while in Marfan syndrome it is upward.

Cystathioninuria

- High levels of Cystathionine
- Deficiency of Cystathionase



Cystinuria

- Cystinuria is an inherited autosomal
- recessive disease.

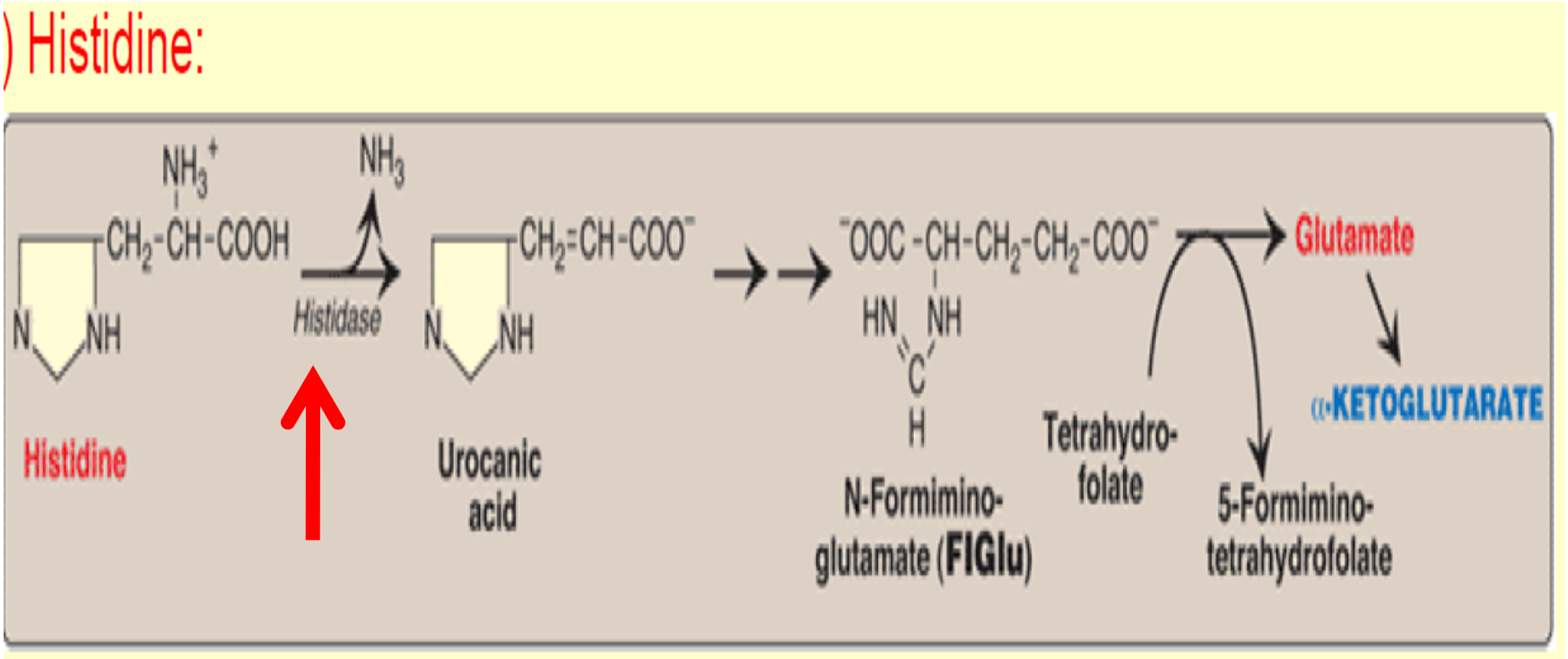
- Its characterized by the formation of cystine (cysteine-S-S cysteine) stones in the kidneys, ureter, and bladder.

- Cystinuria is a cause of persistent kidney stones.

- It is a disease involving the defective transepithelial transport of cystine and dibasic amino acids in the kidney and intestine, and is one of many causes of kidney stones.

HISTIDINEMIA

- **Deficiency of Histidase**
- **Elevated level of Histidine in blood and urine**



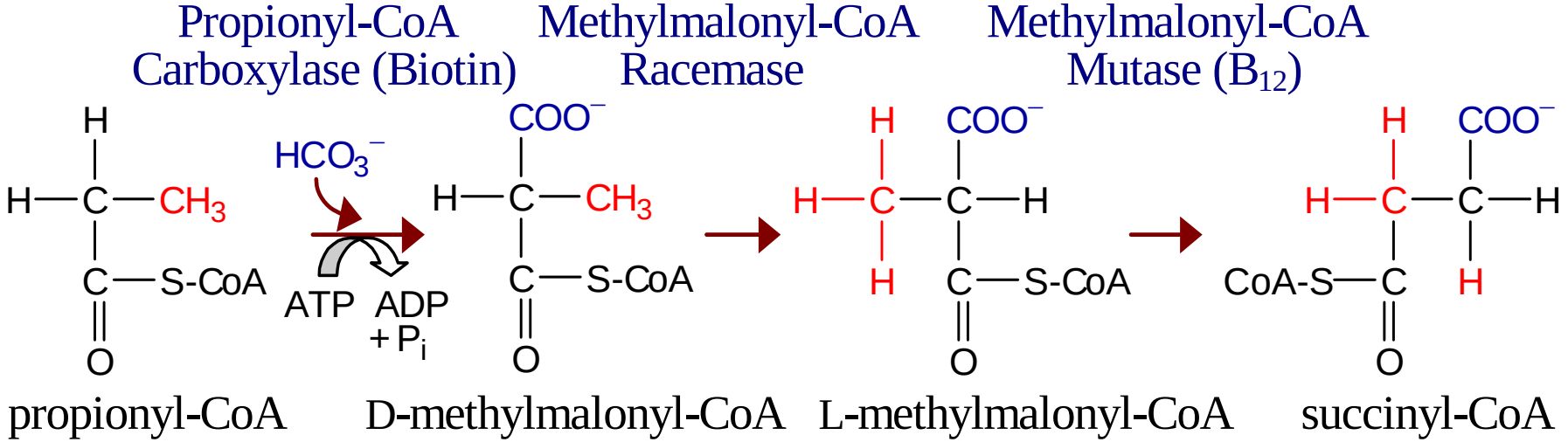
Methylmalonyl-CoA mutase deficiency (MUT)

- **Methylmalonyl-CoA mutase deficiency ("MUT") is an inborn error of organic acid metabolism.**

- **Symptoms include: failure to thrive, vomiting, dehydration, developmental delay, and seizures.**

- **An accumulation opropionyl CoA, a substrate for a TCA cycle enzyme, and of citrate synthase, leading to an accumulation of methyl citrate (a TCA toxin) accompanies the lack of ethylmalonyl CoA mutase.**

- **It is a form of methylmalonic acidemia**



Summary of the metabolism of amino acids