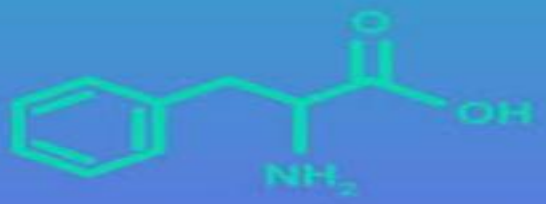

بسم الله الرحمن الرحيم

Aromatic Amino Acids

tryptophan (Trp)



phenylalanine (Phe)

tyrosine (Tyr)

FIZZA HABIB

* LEARNING OBJECTIVES

- Biosynthetic reactions involving amino acids and tetra biopterin
- Phenyl ketonuria
- Catabolism of Tyrosine
- Inherited disorders of phenyl alanine and tyrosine metabolism

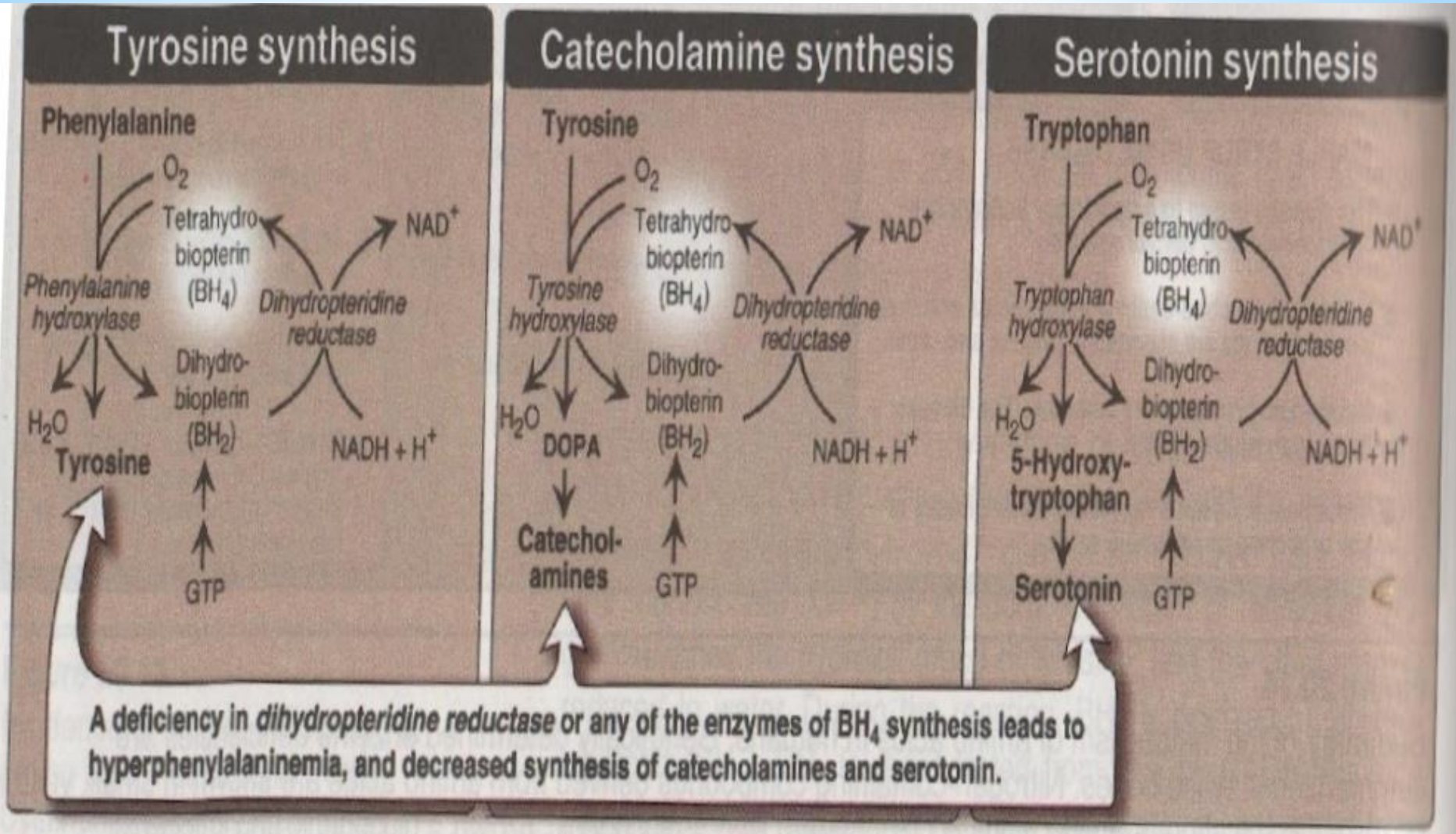


Figure 20.16
Biosynthetic reactions involving amino acids and tetrahydrobiopterin.

*PHENYL KETONURIA

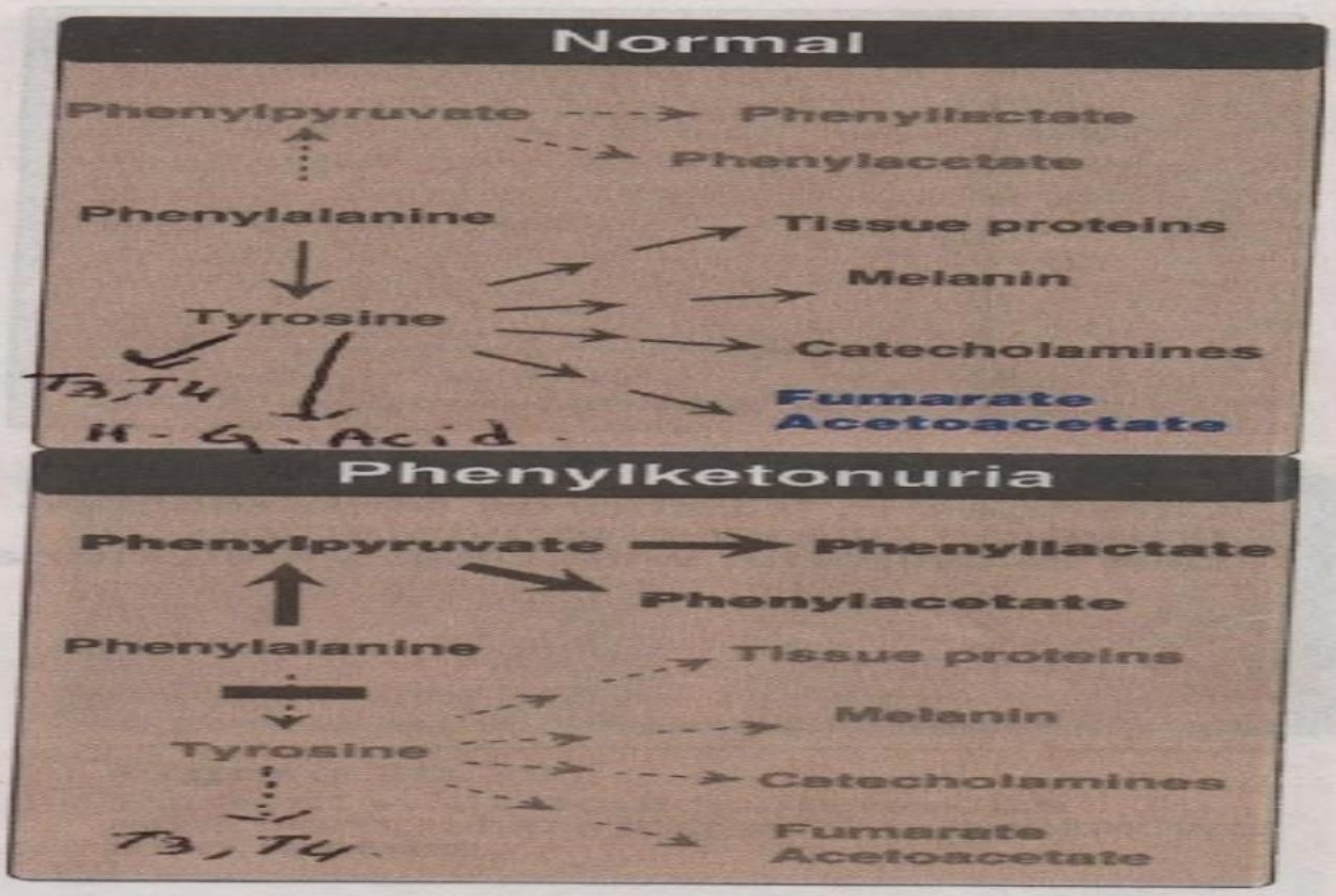
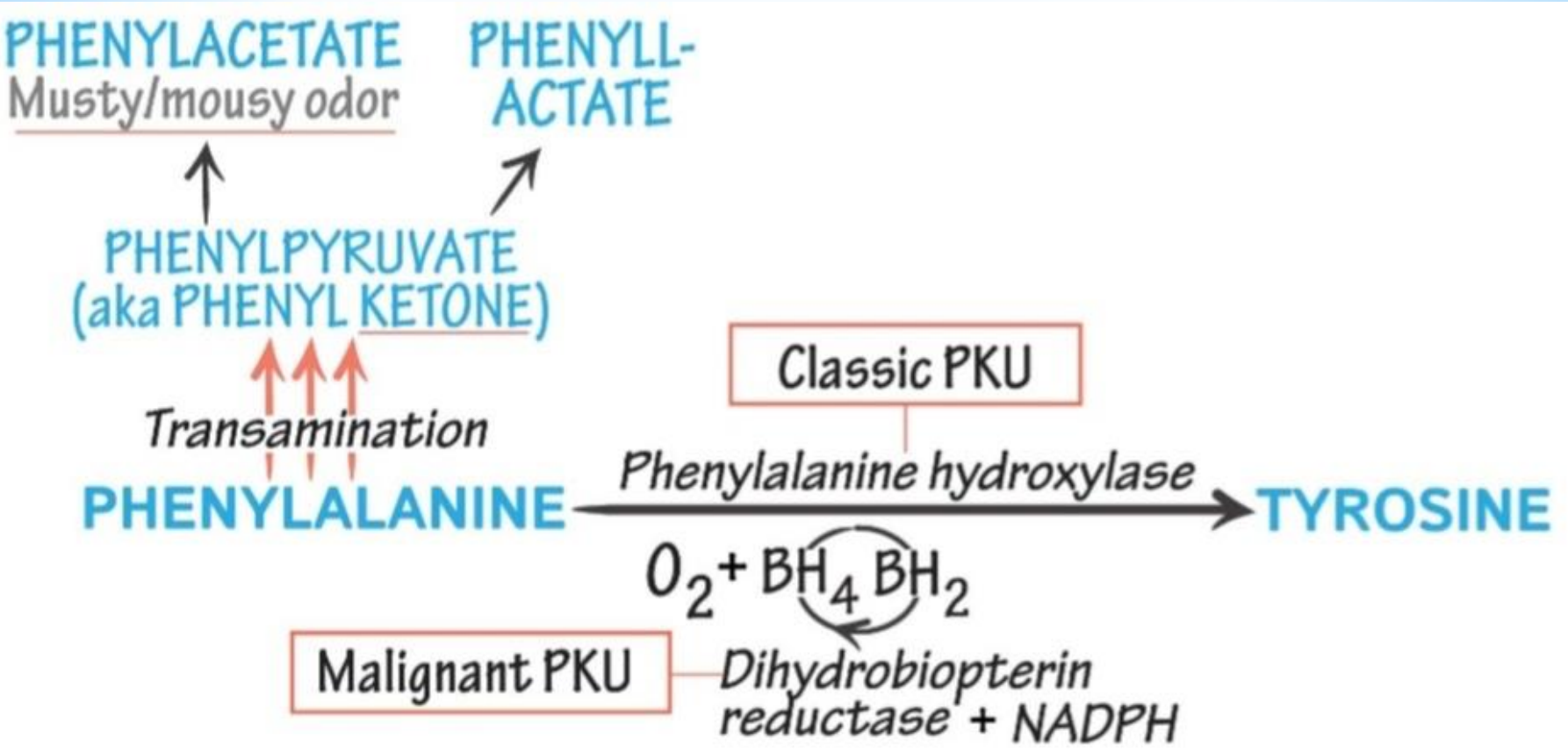


Figure 20.17
Pathways of phenylalanine metabolism in normal individuals and in patients with phenylketonuria.


PHENYLACETATE
Musty/mousy odor
PHENYLL-
ACTATE
PHENYLPYRUVATE
(aka PHENYL KETONE)
Transamination
PHENYLALANINE
Classic PKU
Phenylalanine hydroxylase
TYROSINE
$O_2 + BH_4$ BH_2
Malignant PKU
Dihydrobiopterin
reductase + NADPH

Clinical Presentation

Hypopigmentation (skin + iris)

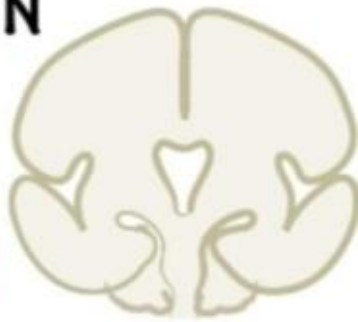
Melanin Deficiency

↓ Tyrosine

Skin

Tremor/Psychosis/Seizures/ Cognitive Dysfunction

↑↑↑ Phenylalanine & Toxic Metabolites

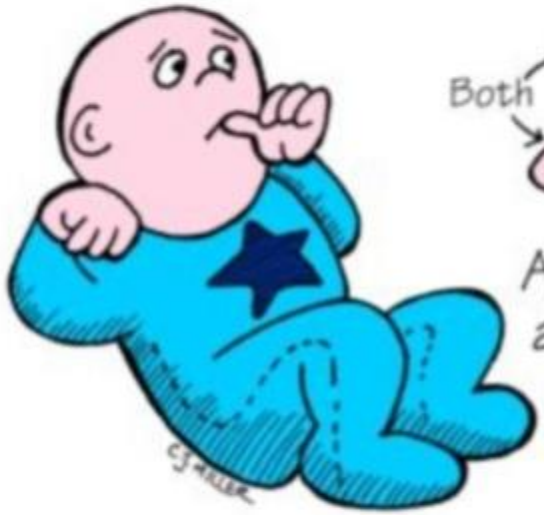


PHENYLKETONURIA (PKU) - Inherited Error In Metabolism

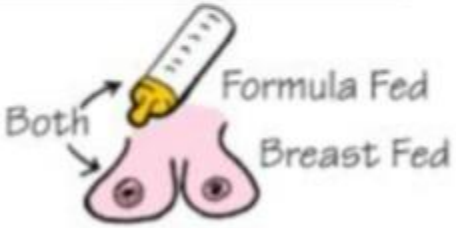
[Toxic levels of Phenylalanine (common protein amino acid) due to inability of body to convert]

Can Cause...

- Mental Retardation
- Convulsions
- Behavior Problems
- Skin Rash
- Musty Body Odor



Babies Are Tested...



A minimum of 24 hrs after beginning milk.

Retest in 7-10 days to catch earlier false negatives.

NO

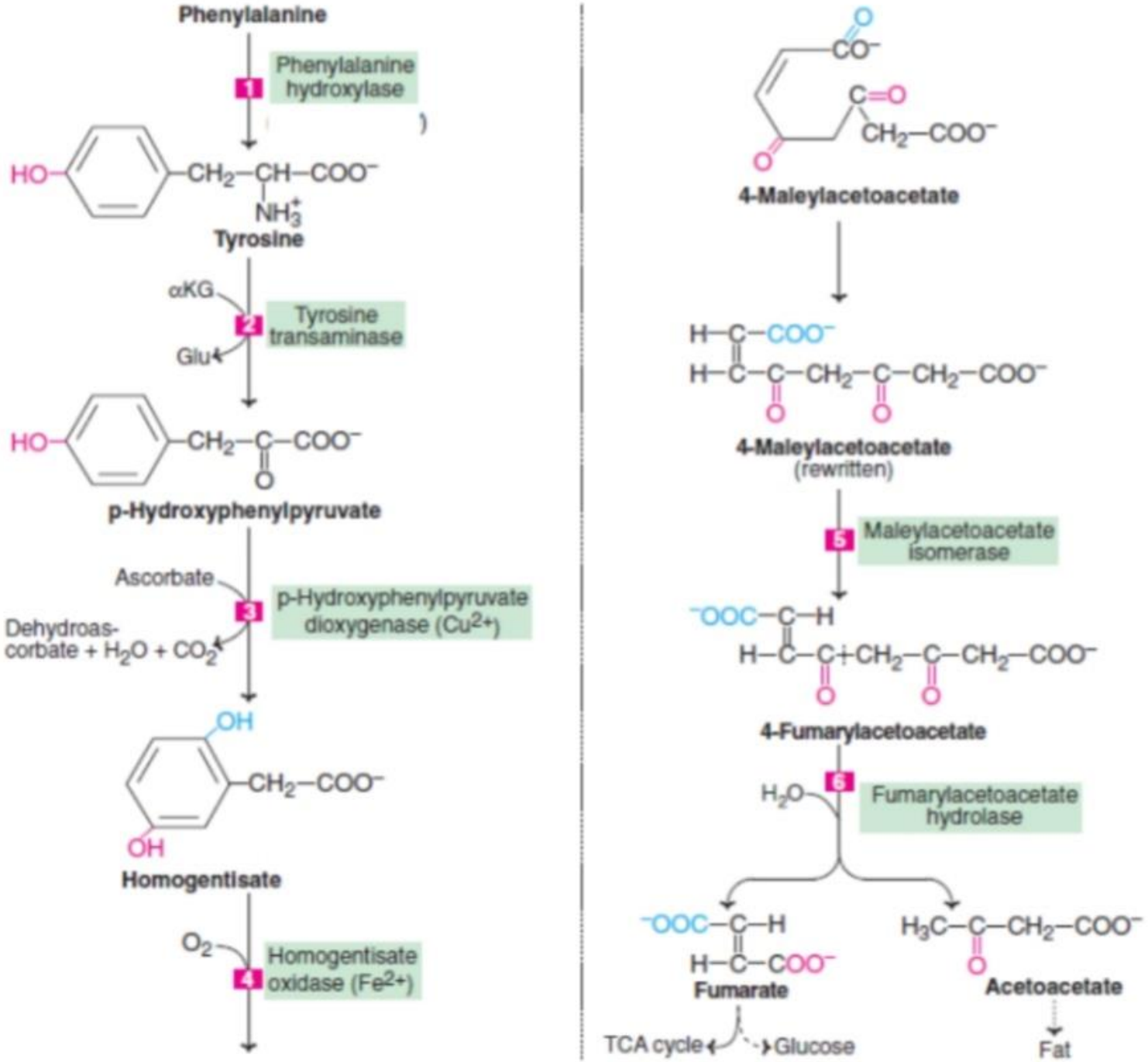
- Meat
- Dairy Products
- Dry Beans
- Nuts
- Eggs

* Cereals, Fruits & Vegetables in Moderation *

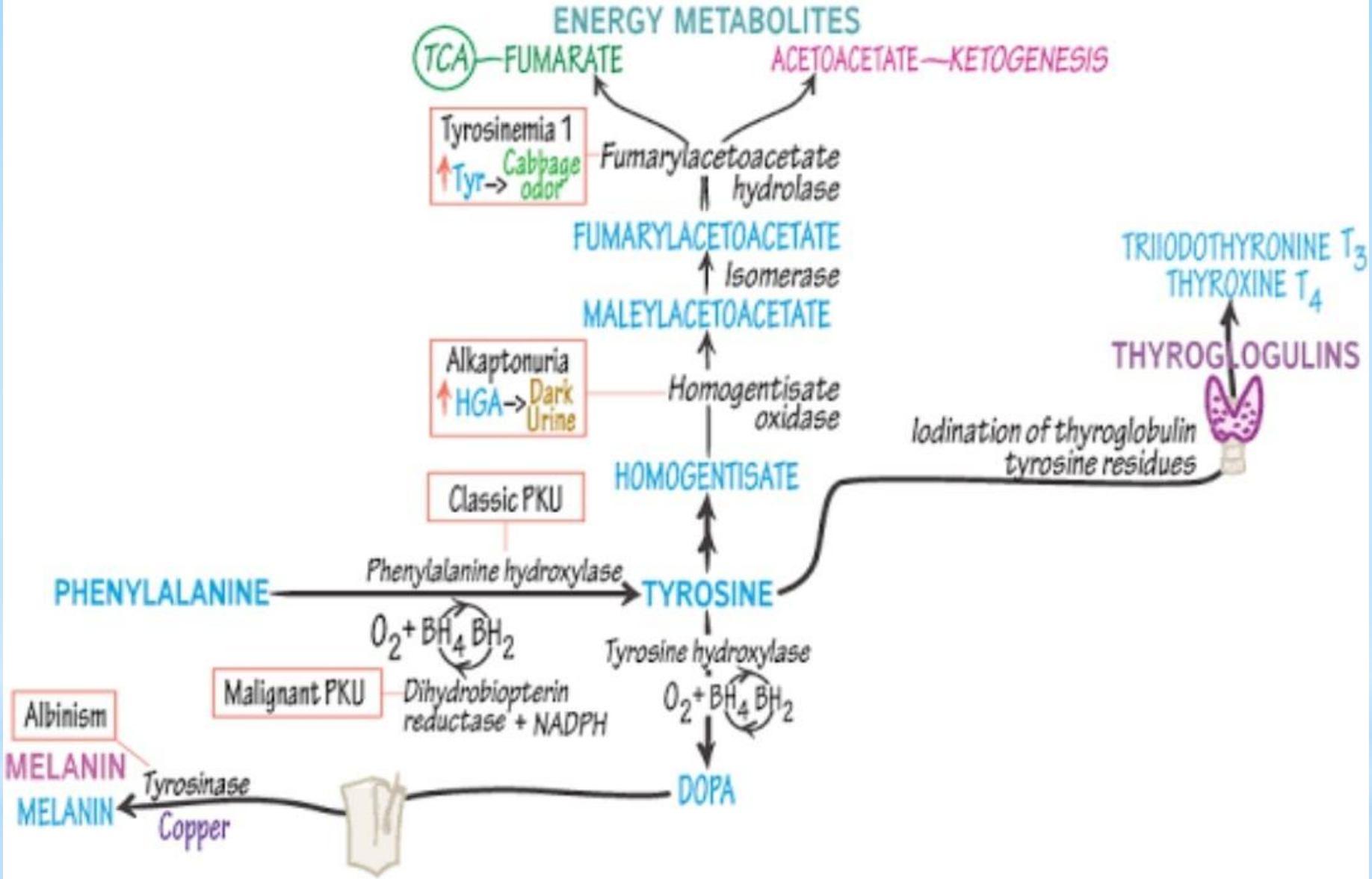
TABLE 27.2: HYPERPHENYLALANINAEMIAS

Type	Condition	Probable enzyme defect	Treatment
I.	Classical type of phenyl ketonuria (PKU)	Phenyl alanine hydroxylase enzyme absent	Low phenyl alanine diet
II.	Persistent hyperphenylalaninaemia	Decreased Phenyl alanine hydroxylase enzyme	None but temporary dietary therapy
III.	Transient mild hyperphenylalaninaemia	Maturational delay of phenyl alanine hydroxylase enzyme	Same as Type II
IV.	Dihydropteridine reductase deficiency	Deficient or absent *dihydropteridine reductase*	Dopa, 5-OH tryptophan, carbi Dopa
V.	Abnormal dihydrobiopterin function	Dihydrobiopterin synthesis defect	Same as Type IV

*TYROSINE CATABOLISM


Phenylalanine
1
Phenylalanine hydroxylase
Tyrosine
αKG
Glu
2
Tyrosine transaminase
p-Hydroxyphenylpyruvate
Ascorbate
Dehydroascorbate + H2O + CO2
3
p-Hydroxyphenylpyruvate dioxygenase (Cu2+)
Homogentisate
O2
4
Homogentisate oxidase (Fe2+)
4-Maleylacetoacetate
4-Maleylacetoacetate (rewritten)
5
Maleylacetoacetate isomerase
4-Fumarylacetoacetate
H2O
6
Fumarylacetoacetate hydrolase
Fumarate
Acetoacetate
TCA cycle
Glucose
Fat

*DISORDERS ASSOCIATED WITH PHENYL ALANINE AND TYROSINE CATABOLISM


ENERGY METABOLITES
TCA
FUMARATE
ACETOACETATE—KETOGENESIS
Tyrosinemia 1
↑Tyr-> Cabbage odor
Fumarylacetoacetate hydrolase
FUMARYLACETOACETATE
Isomerase
MALEYLACETOACETATE
TRIIODOTHYRONINE T_3
THYROXINE T_4
THYROGLOGULINS
Alkaptonuria
↑HGA-> Dark Urine
Homogentisate oxidase
Iodination of thyroglobulin tyrosine residues
HOMOGENTISATE
Classic PKU
Phenylalanine hydroxylase
PHENYLALANINE
TYROSINE
$O_2 + BH_4\ BH_2$
Tyrosine hydroxylase
Malignant PKU
Dihydrobiopterin reductase + NADPH
$O_2 + BH_4\ BH_2$
Albinism
MELANIN
Tyrosinase
Copper
MELANIN
DOPA

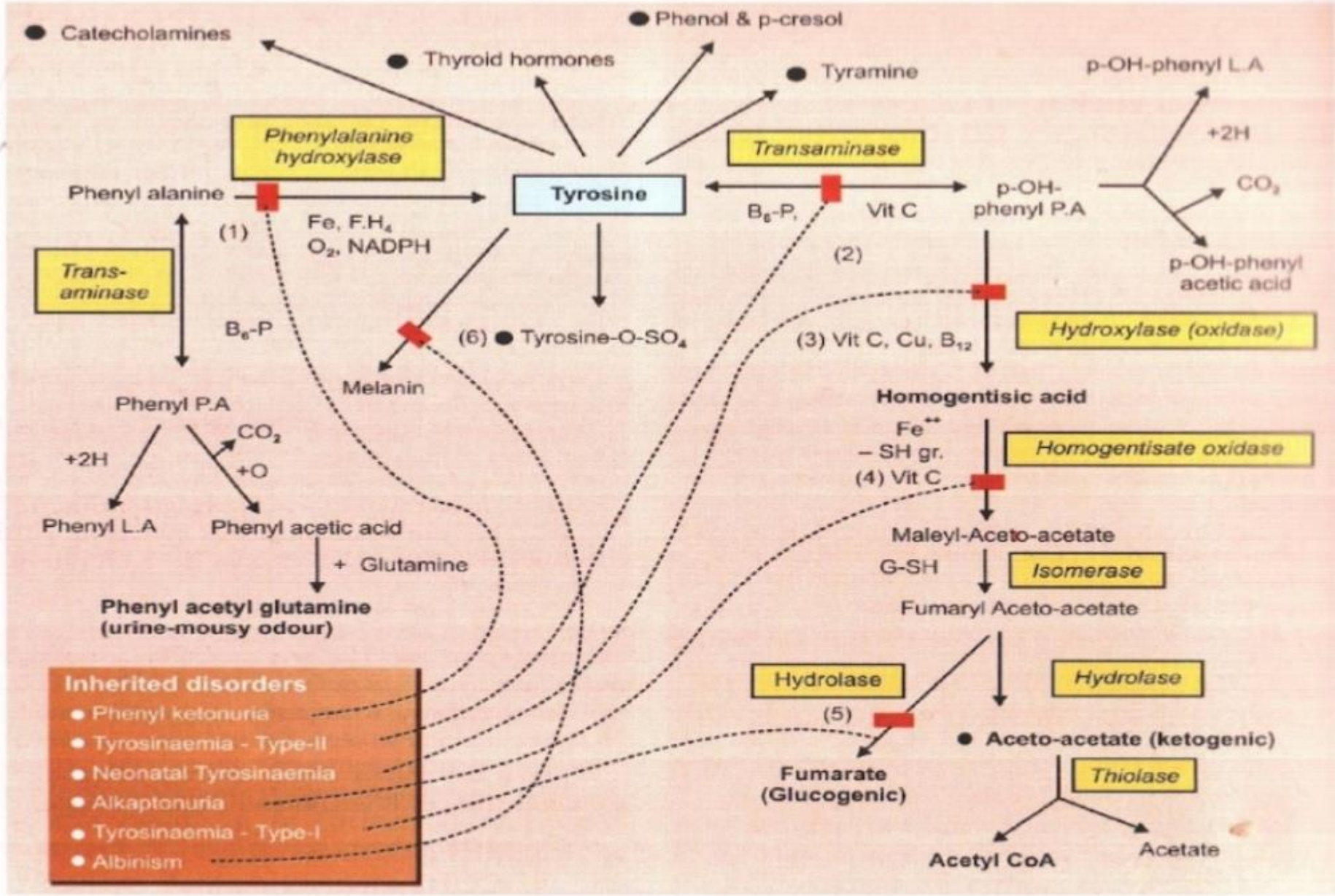
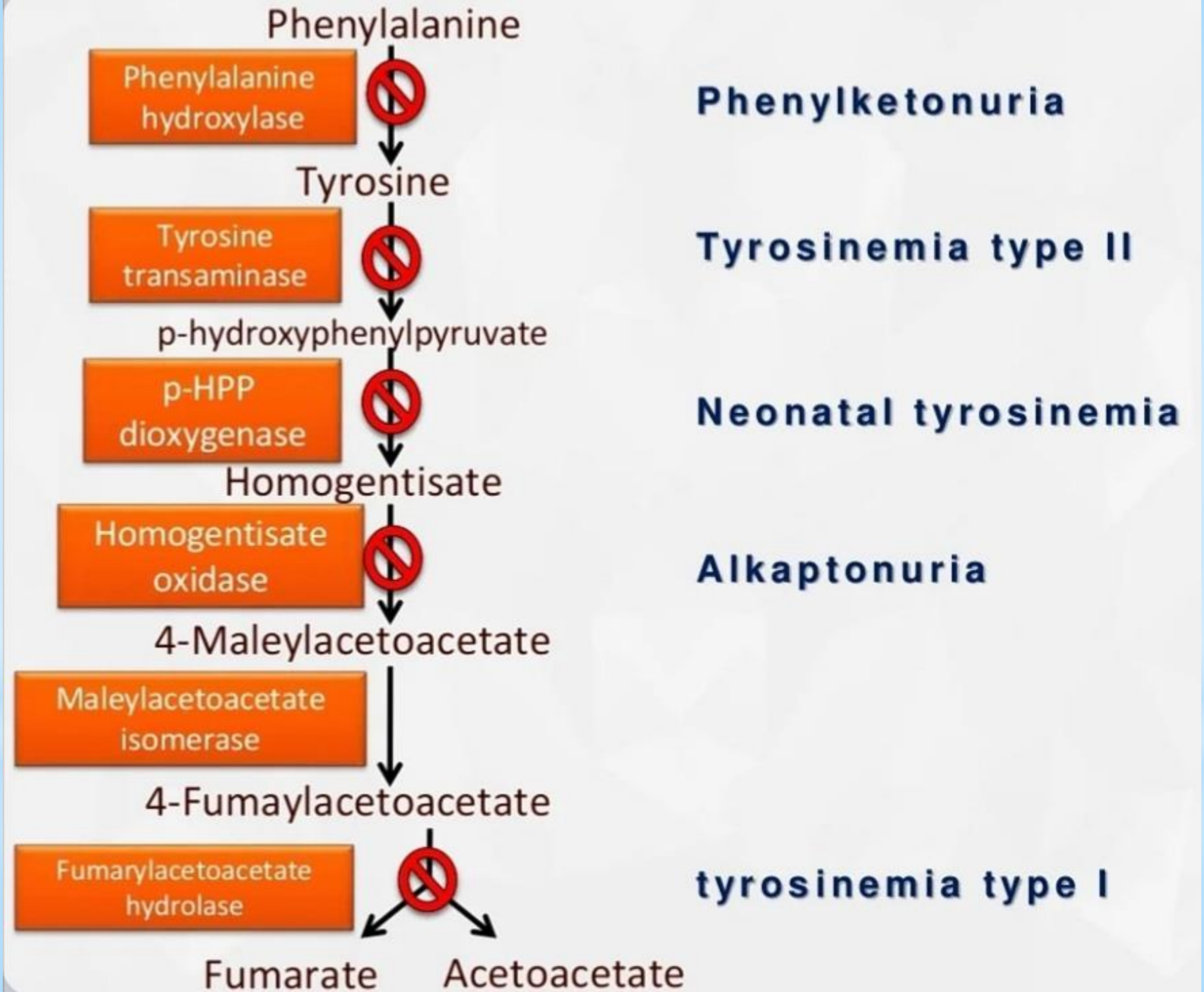
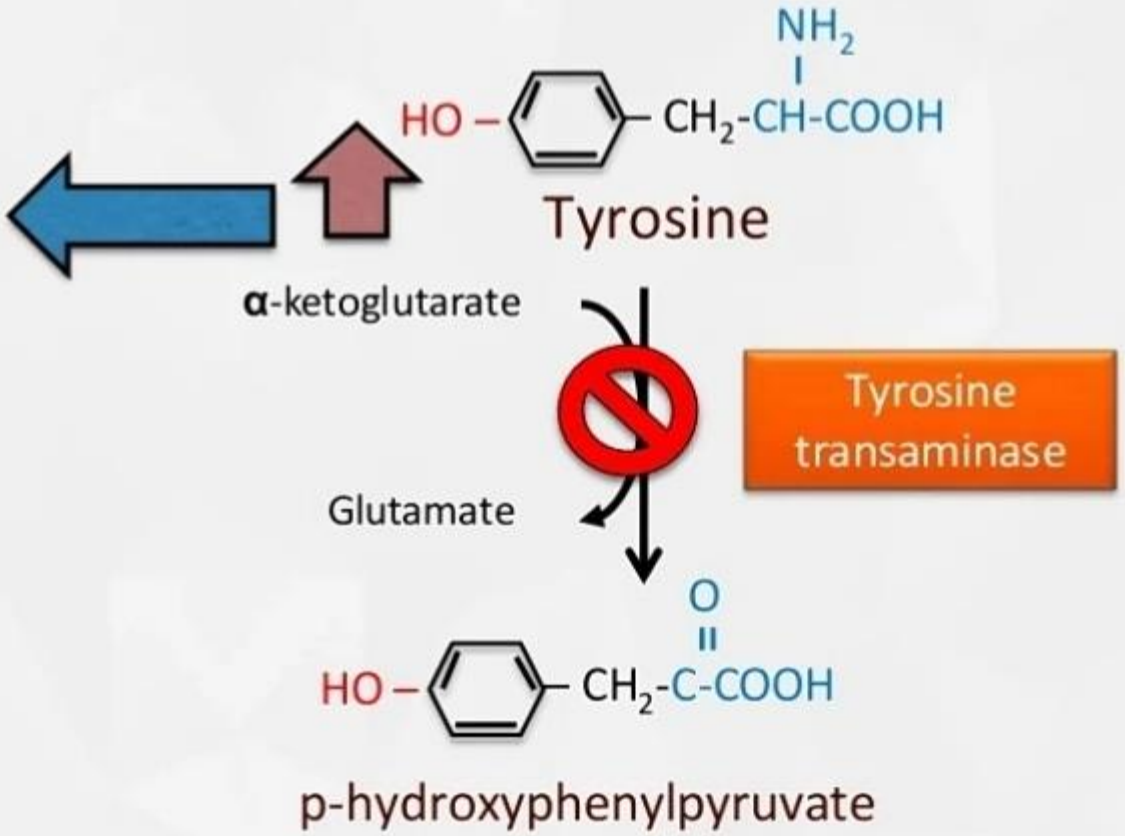


FIG. 27.9: FLOW CHART OF METABOLIC FATE AND METABOLIC ROLE OF PHENYLALANINE AND TYROSINE


Phenylalanine
Phenylalanine hydroxylase
Phenylketonuria
Tyrosine
Tyrosine transaminase
Tyrosinemia type II
p-hydroxyphenylpyruvate
p-HPP dioxygenase
Neonatal tyrosinemia
Homogentisate
Homogentisate oxidase
Alkaptonuria
4-Maleylacetoacetate
Maleylacetoacetate isomerase
4-Fumaylacetoacetate
Fumarylacetoacetate hydrolase
tyrosinemia type I
Fumarate
Acetoacetate

Tyrosinemia type II

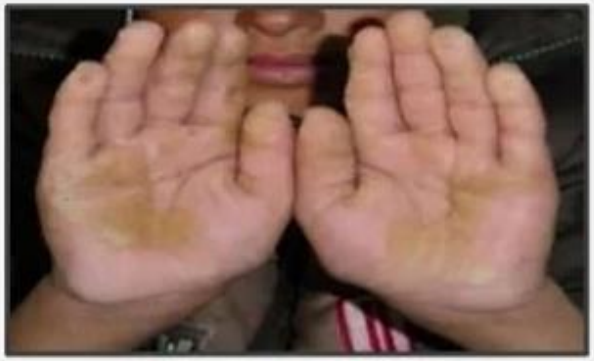
p-hydroxyphenylpyruvate,
p-hydroxyphenyllactate,
phydroxyphenylacetate,
N-acetyltyrosine,
tyramine

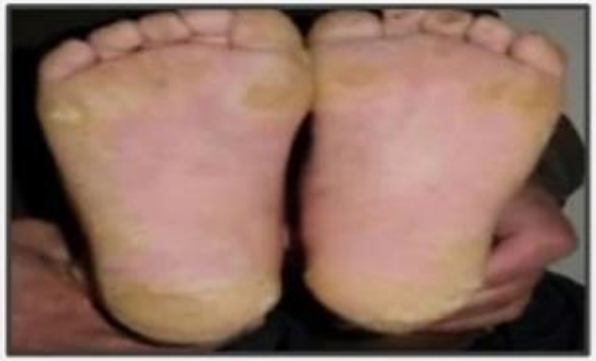


Clinical features of Tyrosinemia type II

Distinctive clinical features of Tyrosinemia type II due to intracellular crystallization of tyrosine include...

Skin lesions



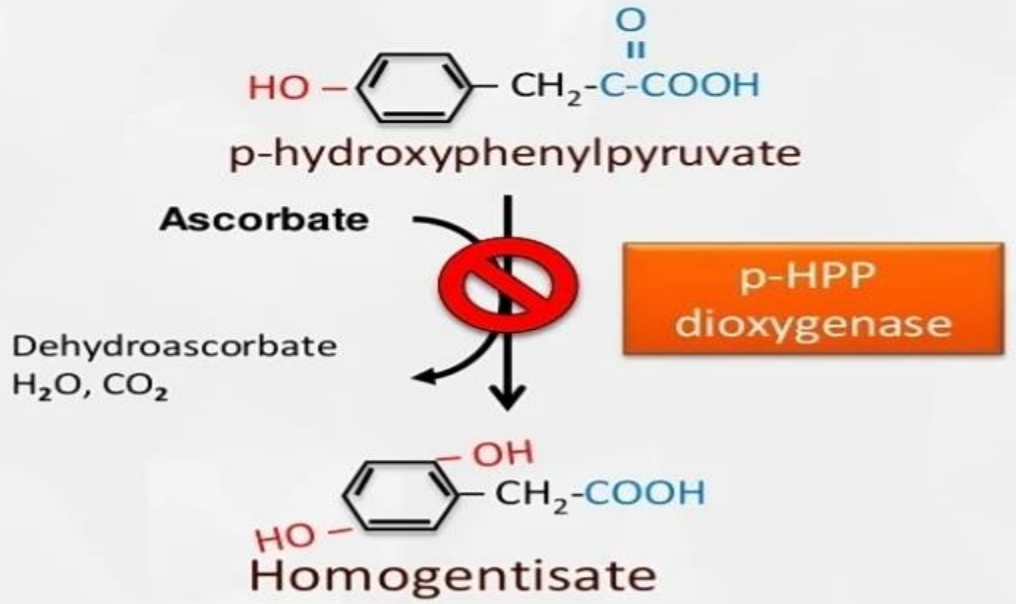


Eye lesions

rarely, Mental retardation.

Neonatal tyrosinemia

Degradation of
Phenylalanine To tyrosine



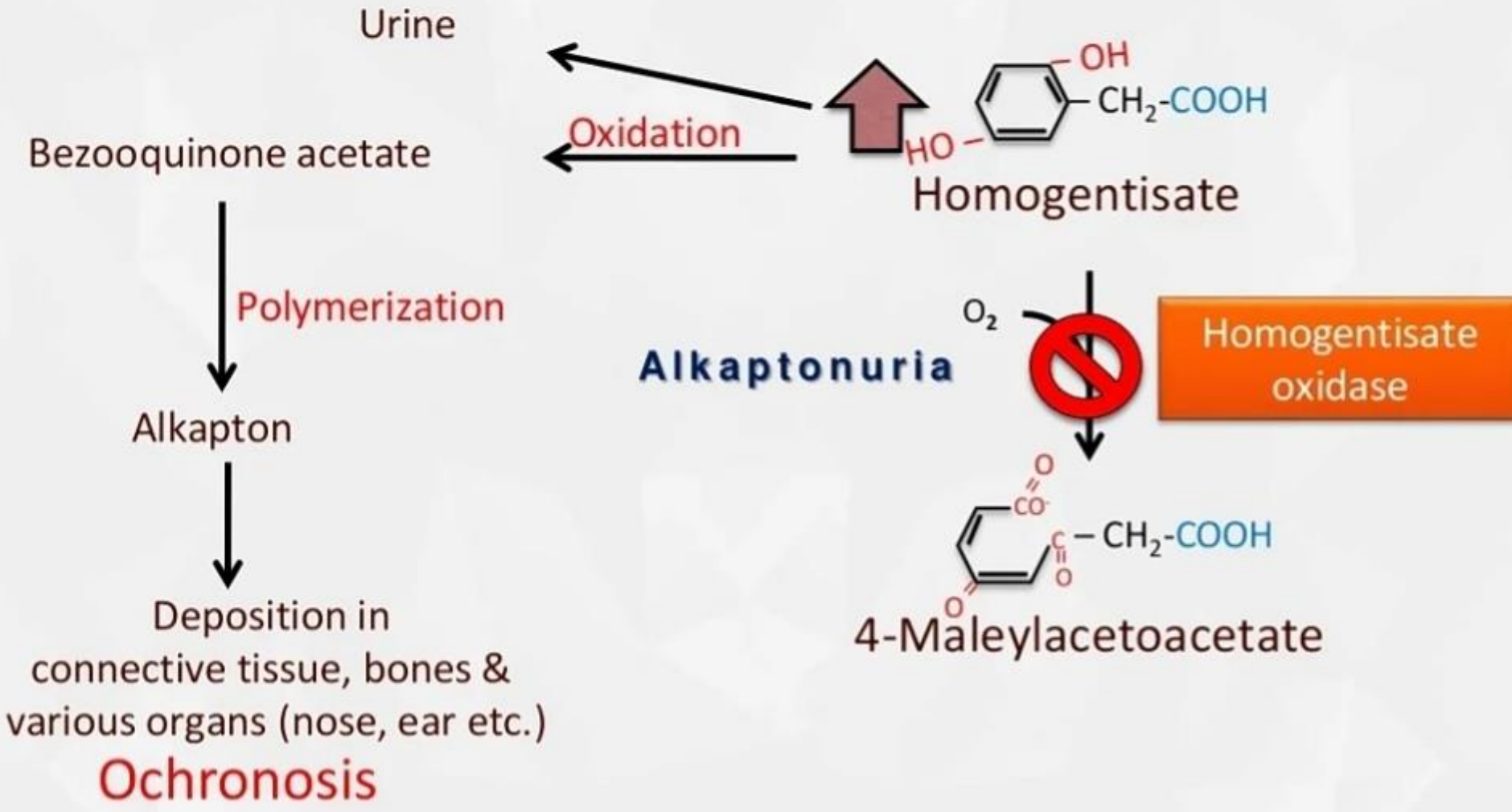
This is mostly a temporary condition and usually responds to ascorbic acid.

Alkaptonuria

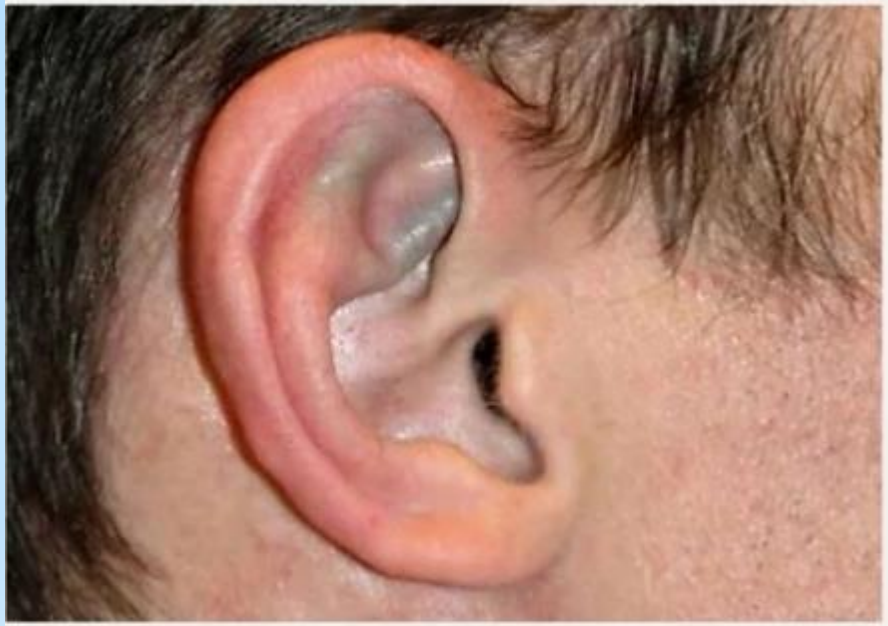
- **Other name**: Black urine disease
- **Genetic**: An autosomal recessive defect.
- **Incidence** : 1 in 25,000.
- **Enzyme defect**: **homogentisate oxidase**,
- **The net outcome**: Homogentisate accumulates in tissues and blood, and is excreted into urine.

Alkaptonuria has great historical importance.
Garrod conceived the idea of inborn errors of metabolism from his observation on **alkaptonuria**.

Clinical features Alkaptonuria



Clinical features Alkaptonuria



tyrosinemia type I

- **Other name**: Tyrosinosis
- **Genetic**: An autosomal recessive rare but serious disorder.
- **Incidence** : 1 in 1,00,000.
- **Enzyme defect**: **fumarylacetoacetate hydroxylase**,
- **The net outcome**: It causes liver failure, rickets, renal tubular dysfunction and polyneuropathy.
- Tyrosine, its metabolites and many other amino acids are excreted in urine..

tyrosinemia type I

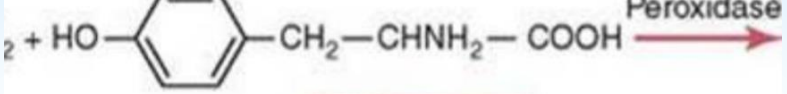
- In acute tyrosinosis, the infant exhibits diarrhea, vomiting, and 'cabbage-like' odor.
- Death may even occur due to liver failure within one year.
- For the treatment, diets low in tyrosine, phenylalanine and methionine are recommended.

Albinism

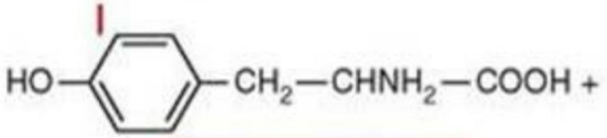
- **Other name**: Tyrosinosis
- **Genetic**: An autosomal recessive defect.
- **Incidence** : 1 in 20,000.
- **Enzyme defect**: **Tyrosinase**
- **The net outcome**: lack of synthesis of the pigment melanin.

Clinical features of albinism

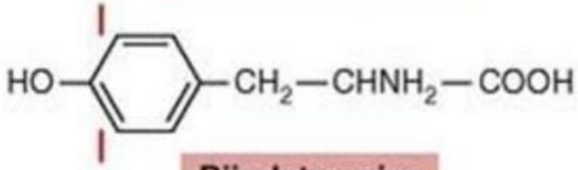
- Lack of melanin in albinos makes them sensitive to sunlight.
- Increased susceptibility to skin cancer (carcinoma).
- Photophobia (intolerance to light) is associated with lack of pigment in the eyes.
- However, there is no impairment in the eyesight of albinos.
- Their entire body, including their hair, is characteristically white.



Tyrosine

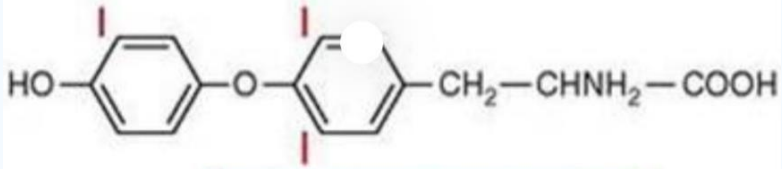


Monoiodotyrosine



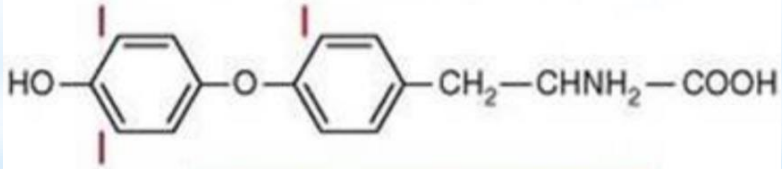
Diiodotyrosine

Monoiodotyrosine + Diiodotyrosine →



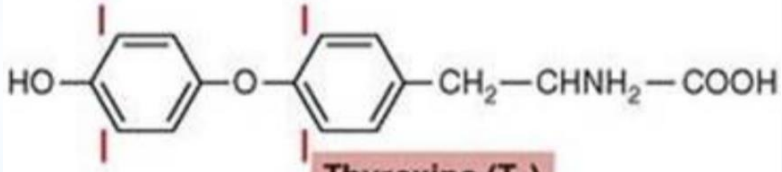
3,5,3'-Triiodothyronine (T_3)

Diiodotyrosine + Diiodotyrosine →



3,3',5-Triiodothyronine (RT_3)

Diiodotyrosine + Diiodotyrosine →



Thyroxine (T_4)


THANK YOU

Any Questions?