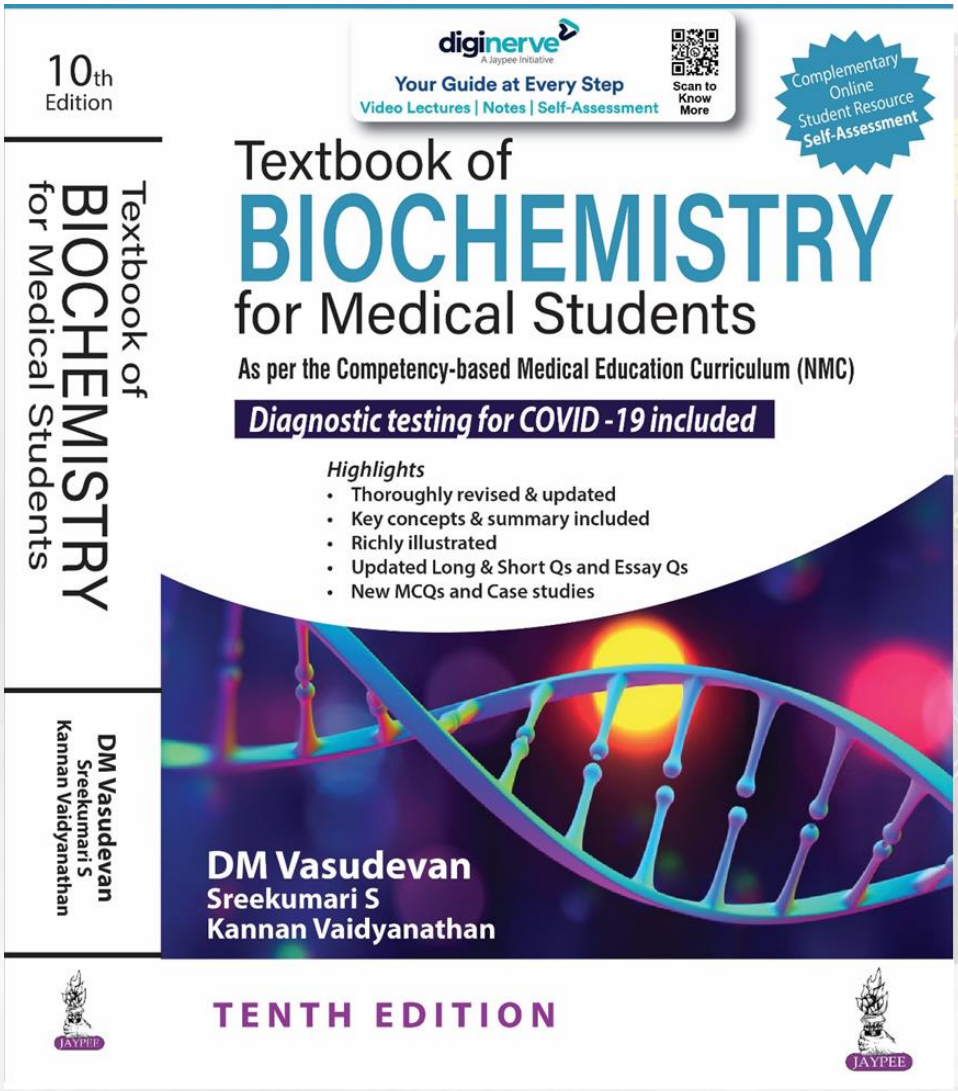


Chapter 17:

Metabolism of Aromatic Amino Acids (Phe, Tyr, Trp, His, Pro)

Textbook of
BIOCHEMISTRY
for Medical Students

By DM Vasudevan, *et al.*

TENTH EDITION

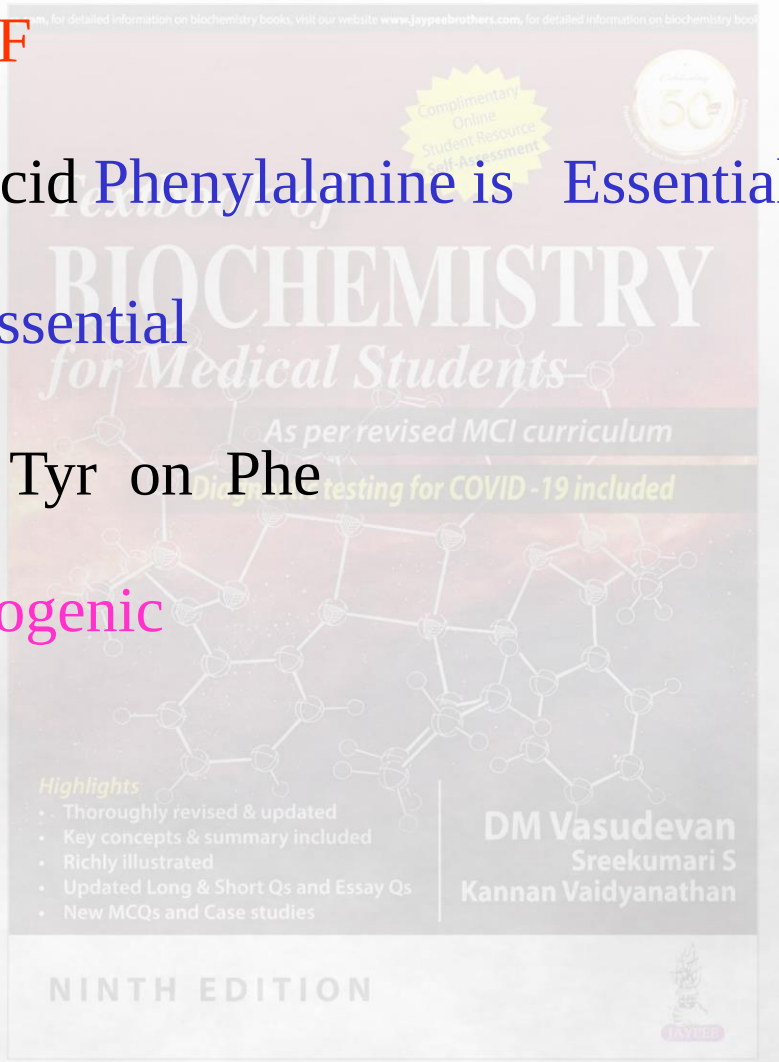
Phenylalanine Phe F

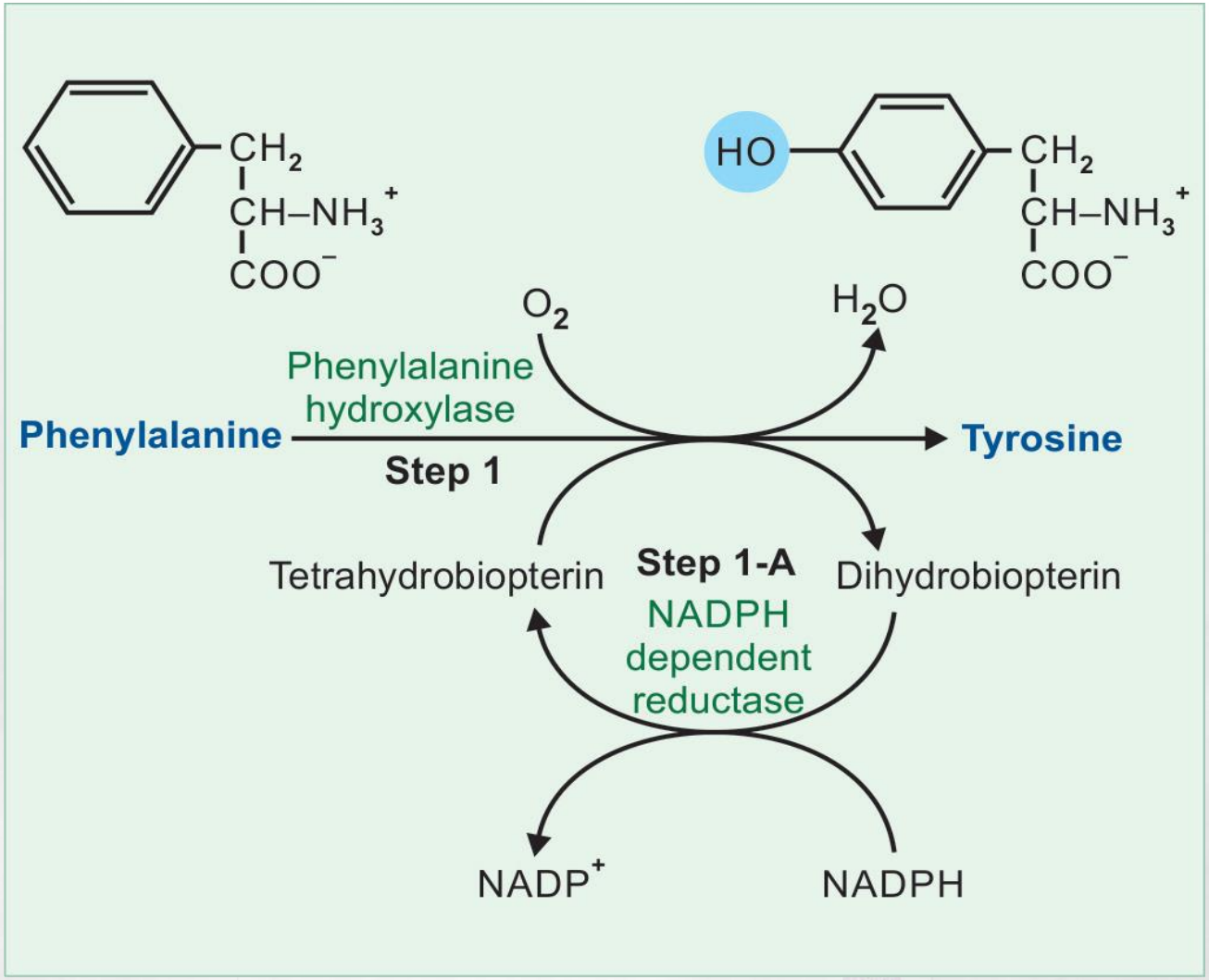
Aromatic amino acid Phenylalanine is Essential

Tyrosine is Non-essential

Sparing action of Tyr on Phe

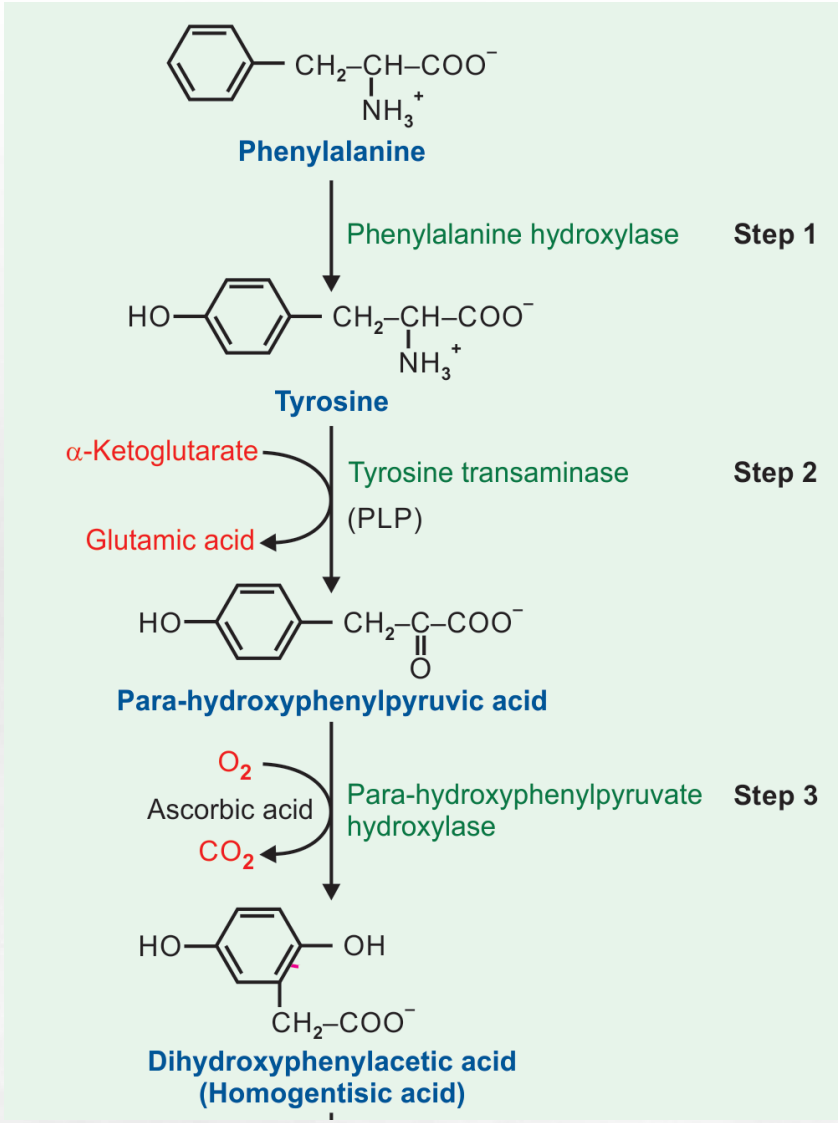
Glucogenic + Ketogenic

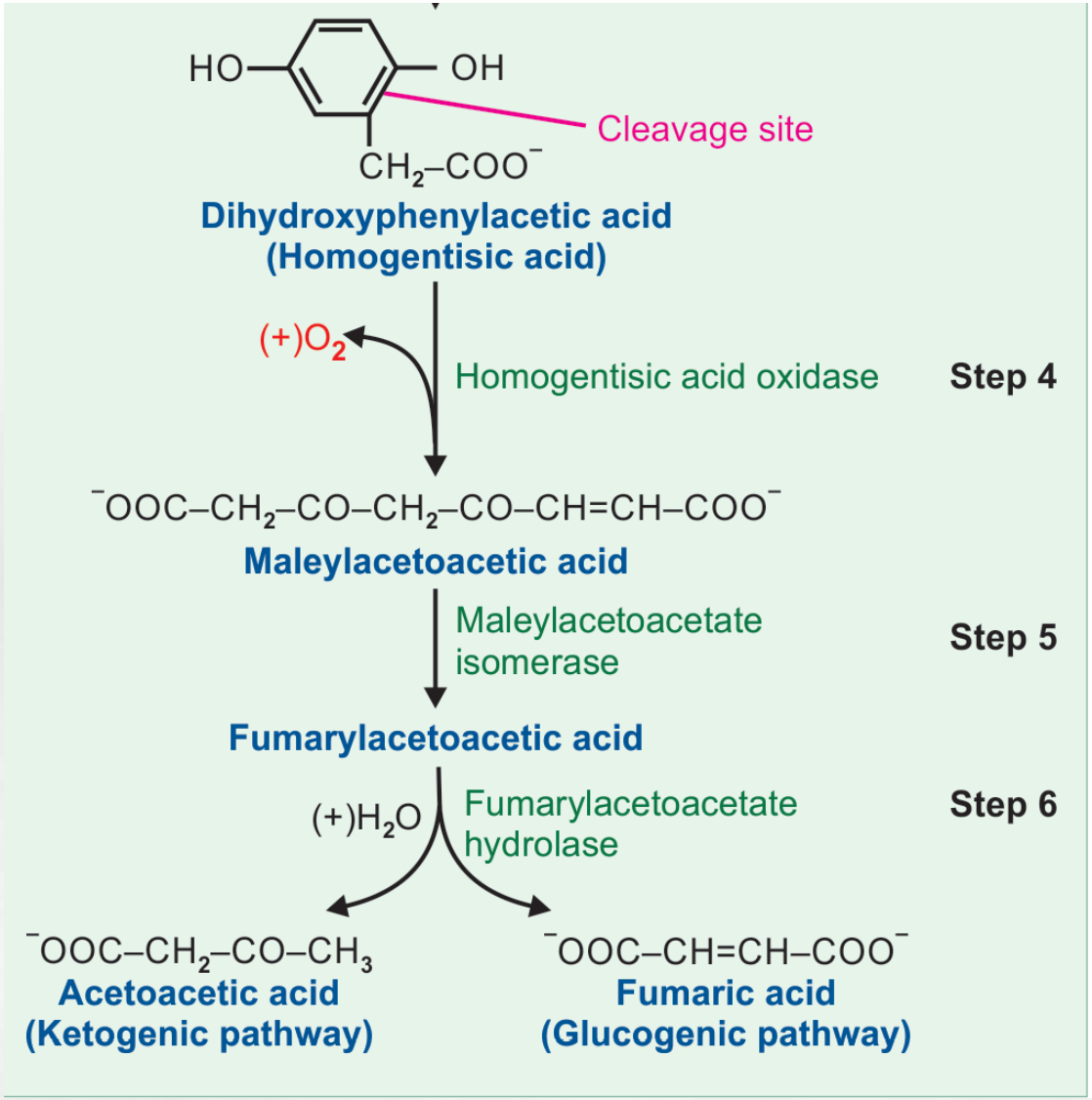




Phenylalanine Catabolism

Catabolism of tyrosine



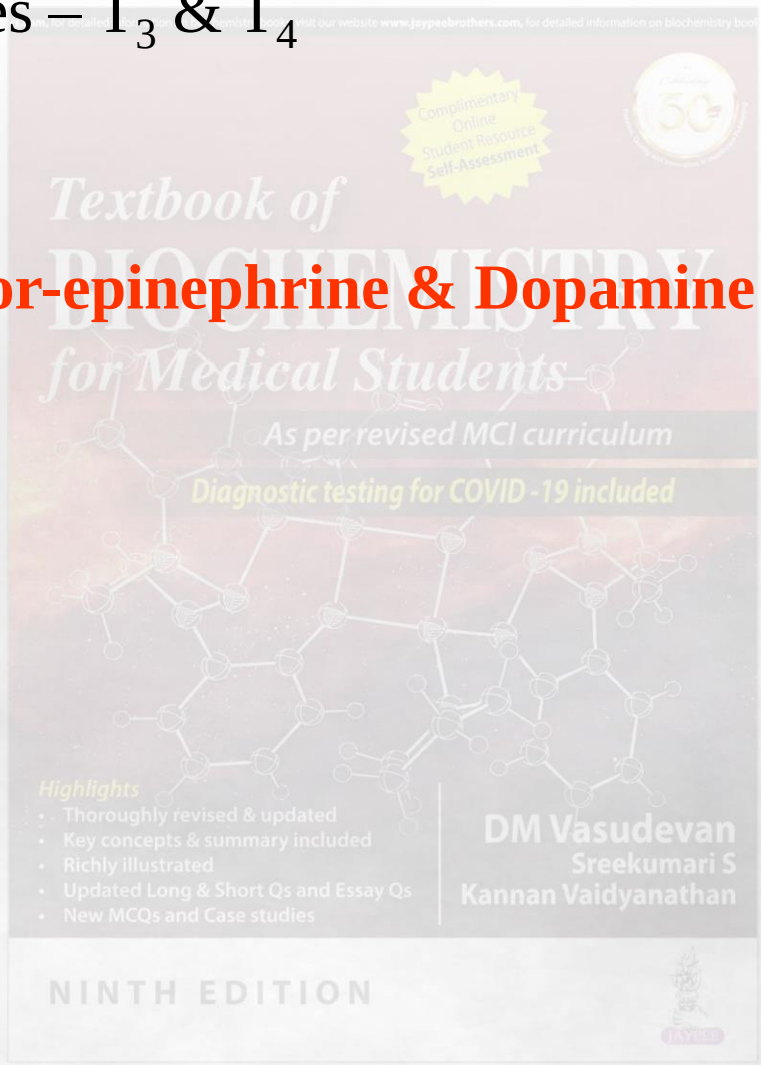


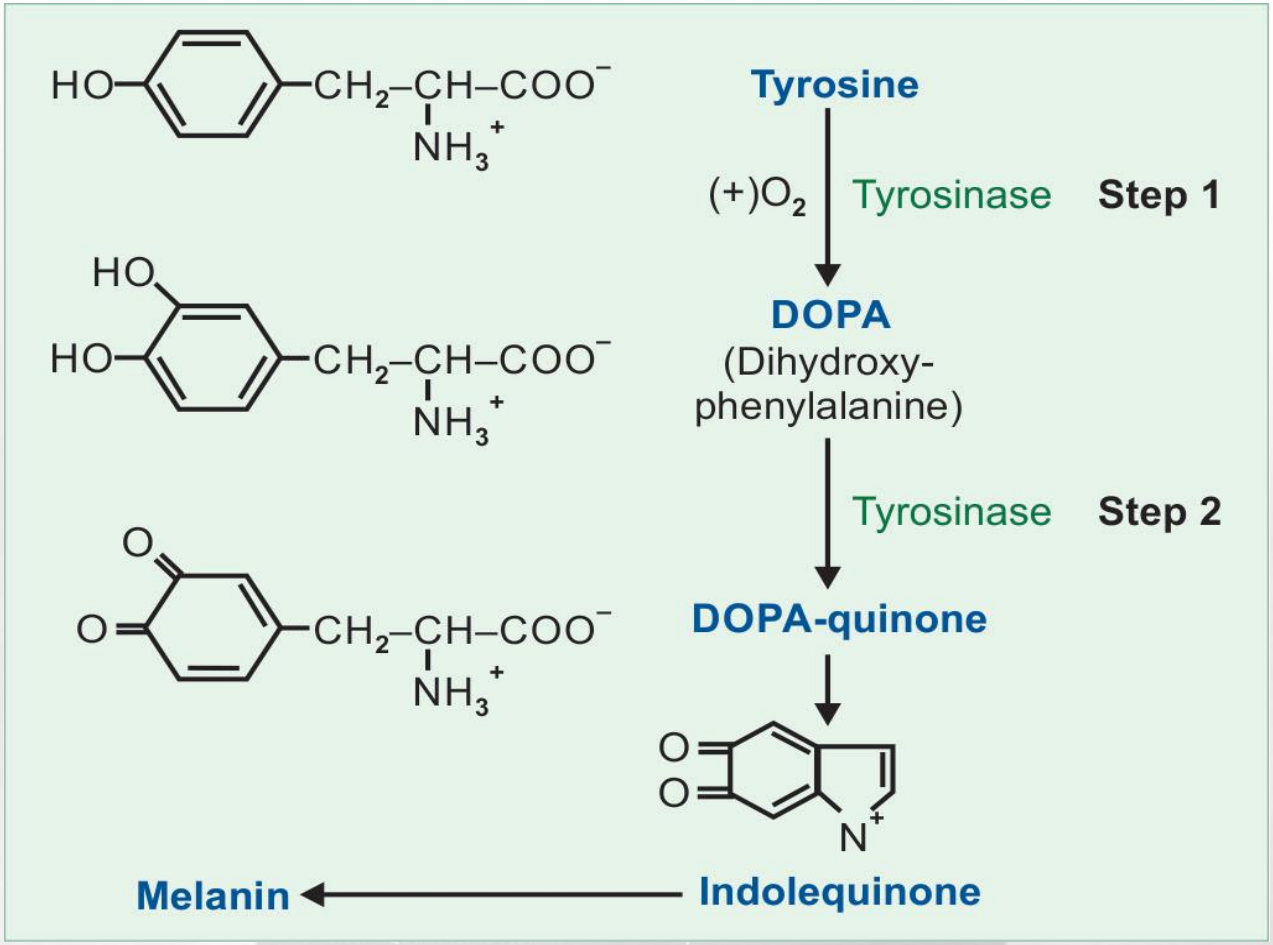
Catabolism of tyrosine

Important Substances Derived from Tyrosine

- Thyroid hormones – T_3 & T_4
- Melanin
- Catecholamines

  Epinephrine, Nor-epinephrine & Dopamine





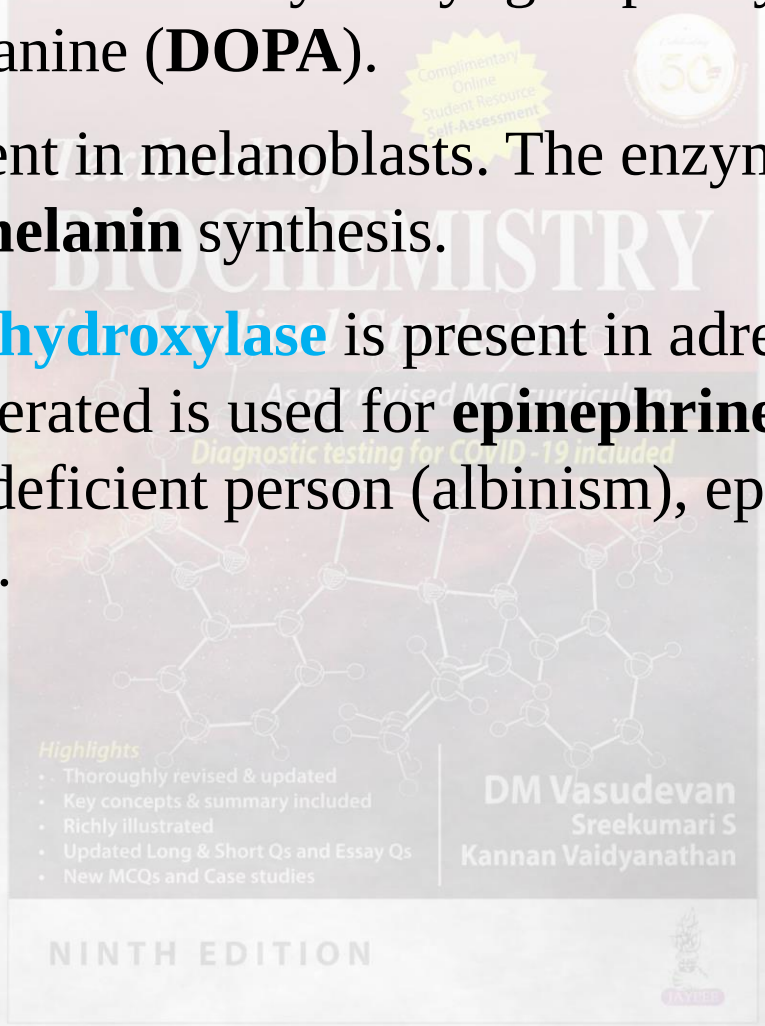
Melanin synthesis pathway; Step 1 and 2 have the same enzyme, tyrosinase.

Tyrosinase and Tyrosine Hydroxylase are Different

Both these enzymes will add hydroxyl group to tyrosine to produce dihydroxyphenylalanine (**DOPA**).

Tyrosinase is present in melanoblasts. The enzyme produces DOPA, which is used for **melanin** synthesis.

Whereas **Tyrosine hydroxylase** is present in adrenal medulla and the DOPA thus generated is used for **epinephrine** synthesis. Thus, even in tyrosinase deficient person (albinism), epinephrine synthesis is normal.



Clinical Applications of Melanin

1. **Copper deficiency:** Since tyrosinase is a copper-containing enzyme, there may be disturbances in pigmentation during copper deficiency. Hair synthesized at the time of deficiency may be depigmented. If copper deficiency is intermittent, alternate black and white regions may be seen in the hair (flagtype of hair).
2. **Malignant melanoma:** Melanoblasts, especially in junctional nevi, may multiply to give rise to malignant melanoma.

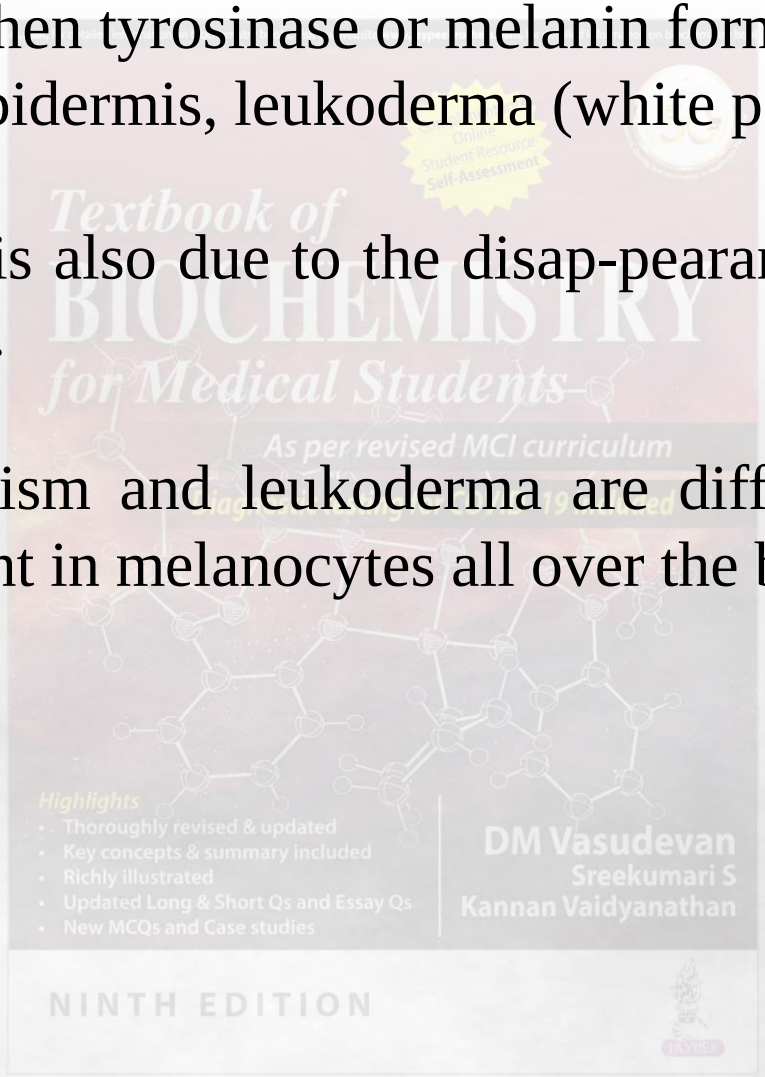
Melanogen may be excreted through urine in such conditions.

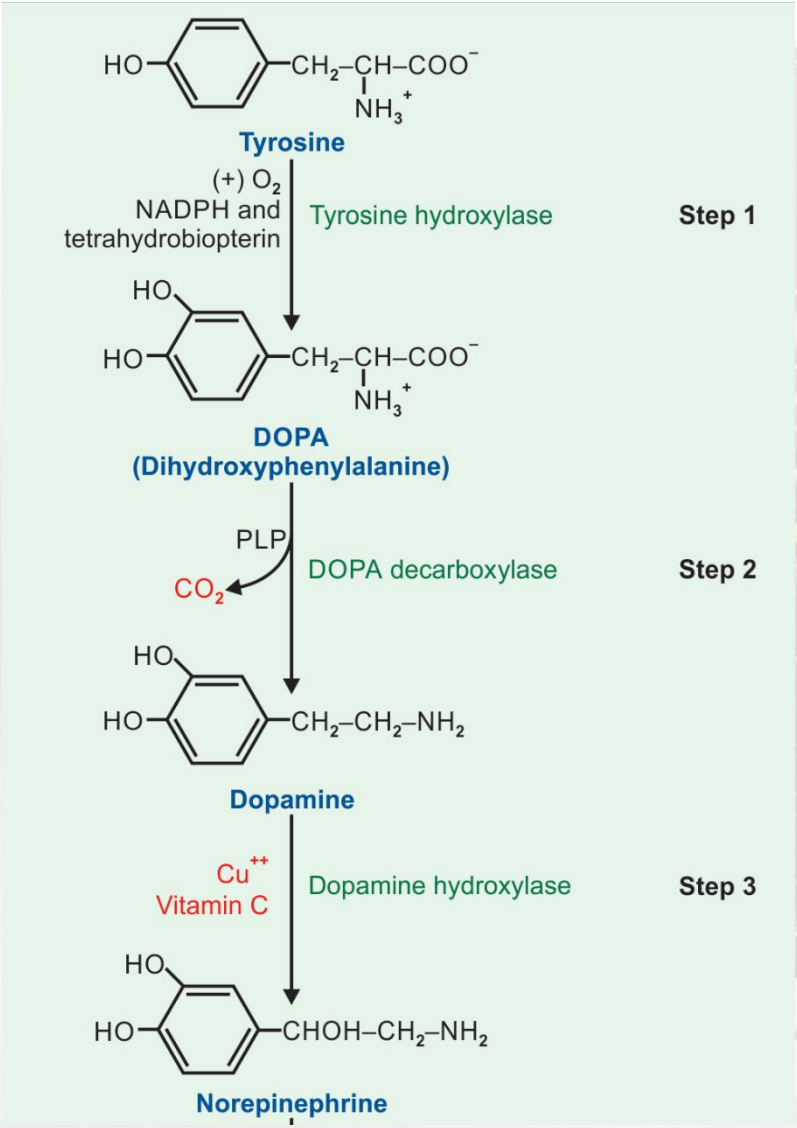
Clinical Applications of Melanin, Continued

3. **Leukoderma:** When tyrosinase or melanin forming cells or both are absent from epidermis, leukoderma (white patches) results.

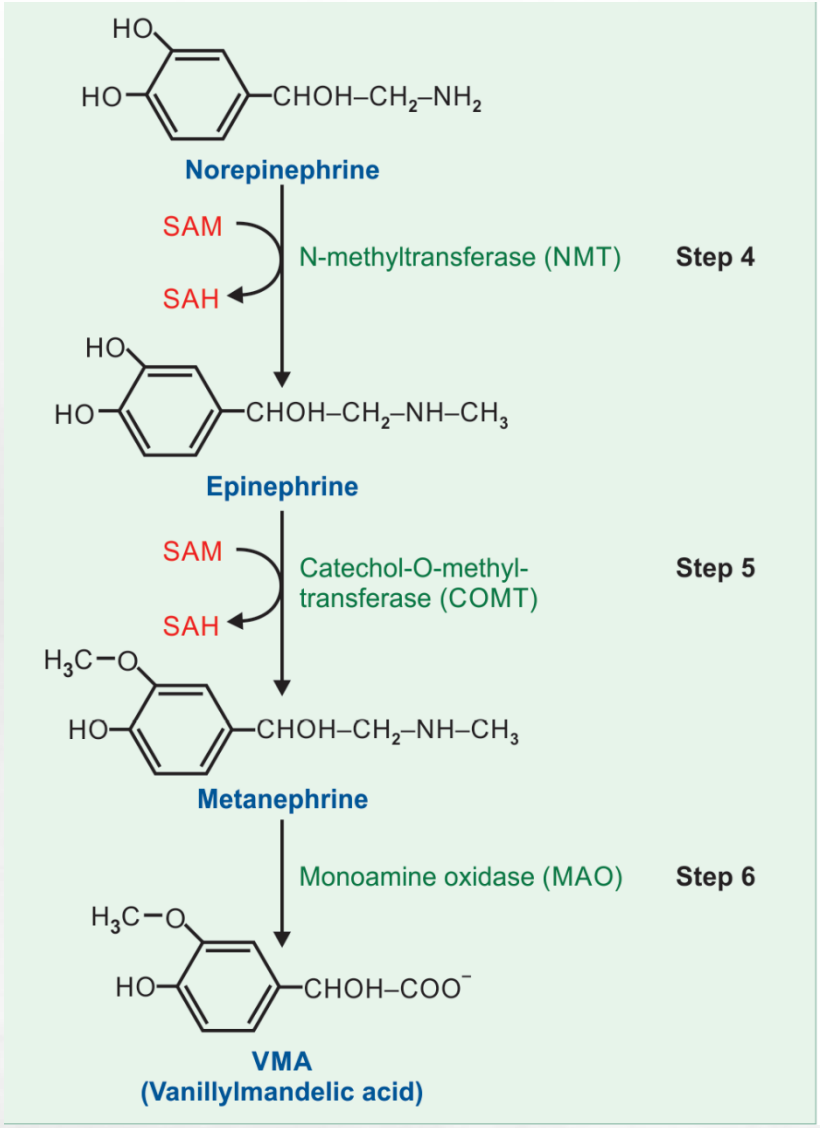
4. **Graying** of hair is also due to the disap-pearance of melanocytes from the hair root.

5. **Albinism:** Albinism and leukoderma are different. In albinism, tyrosinase is absent in melanocytes all over the body.

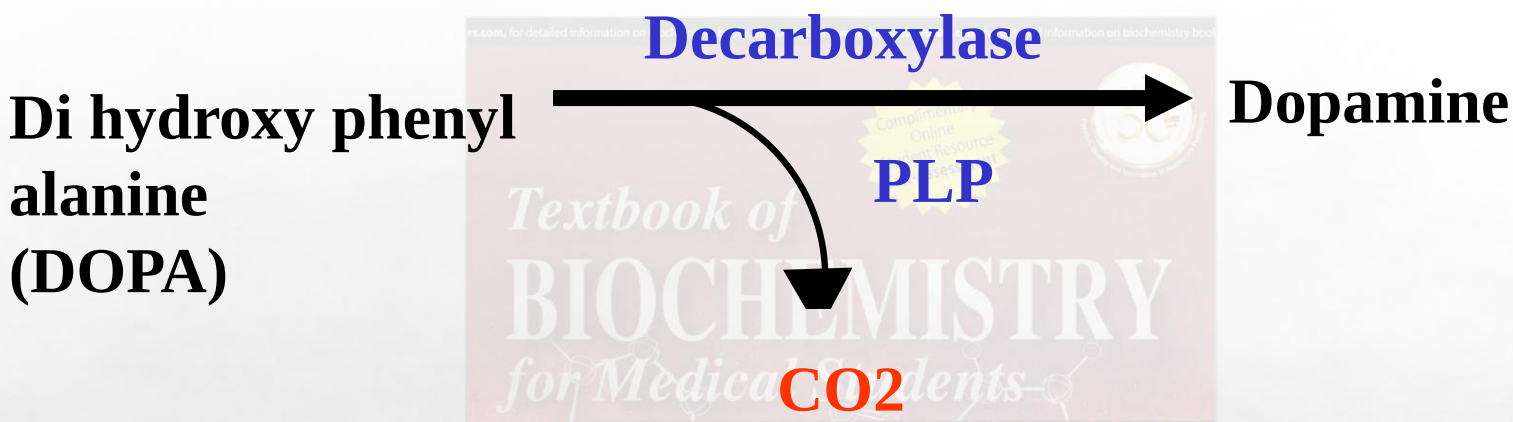




Metabolism of catecholamines



Metabolism of catecholamines



First catecholamine
Inhibitor of Prolactin

Parkinsonism, dopamine is reduced **L-Dopa** is the treatment

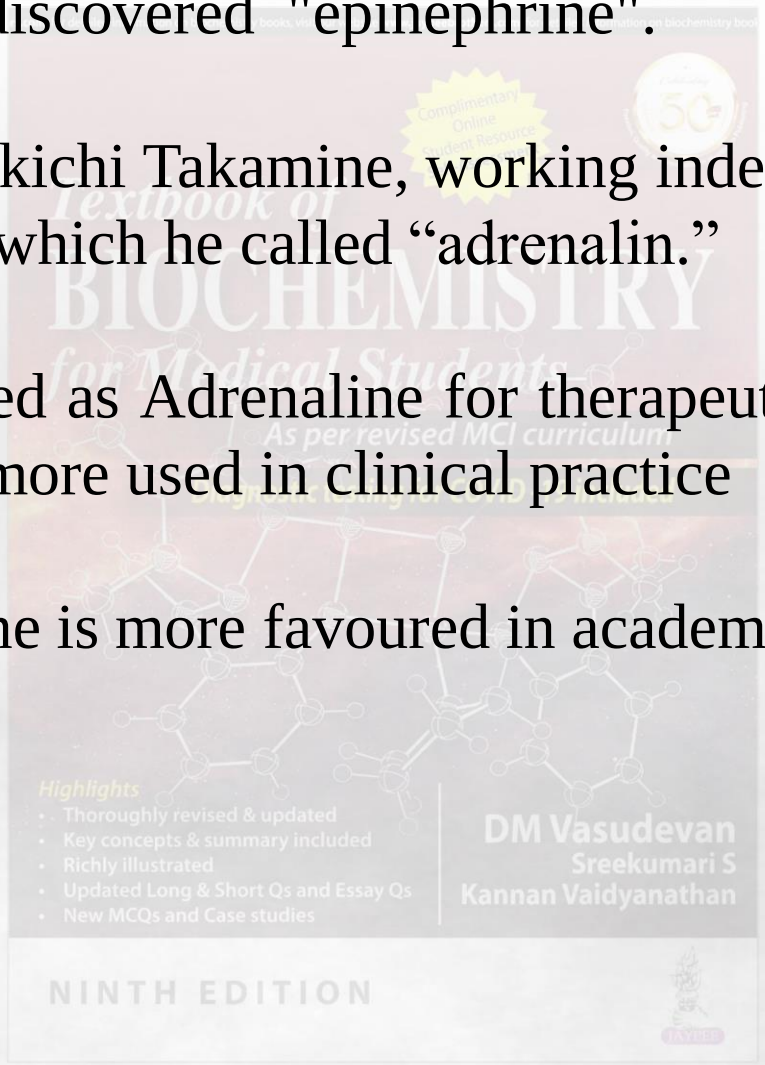
Alpha methyl Dopa inhibits enzyme Prevents production of epinephrine Methyl dopa is antihypertensive

In 1901 John Abel discovered "epinephrine".

In the same year, Jokichi Takamine, working independently, isolated the same hormone, which he called “adrenalin.”

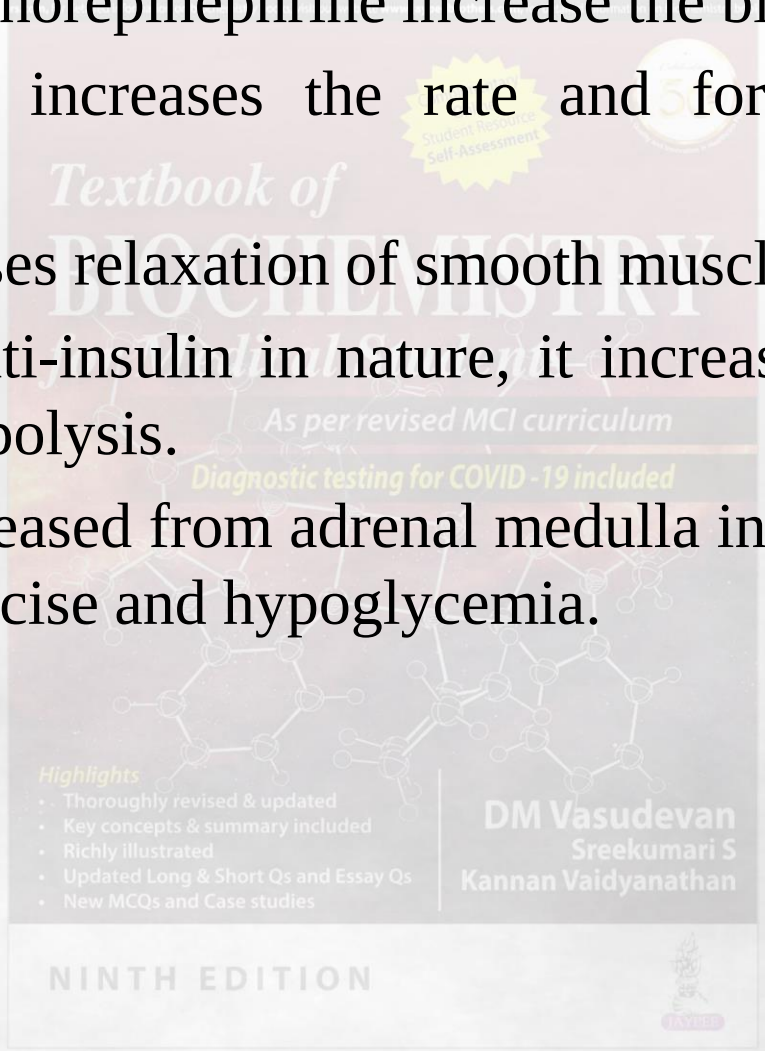
It was first marketted as Adrenaline for therapeutic use. Hence the word adrenaline is more used in clinical practice

The term epinephrine is more favoured in academic circles.



Actions of Epinephrine

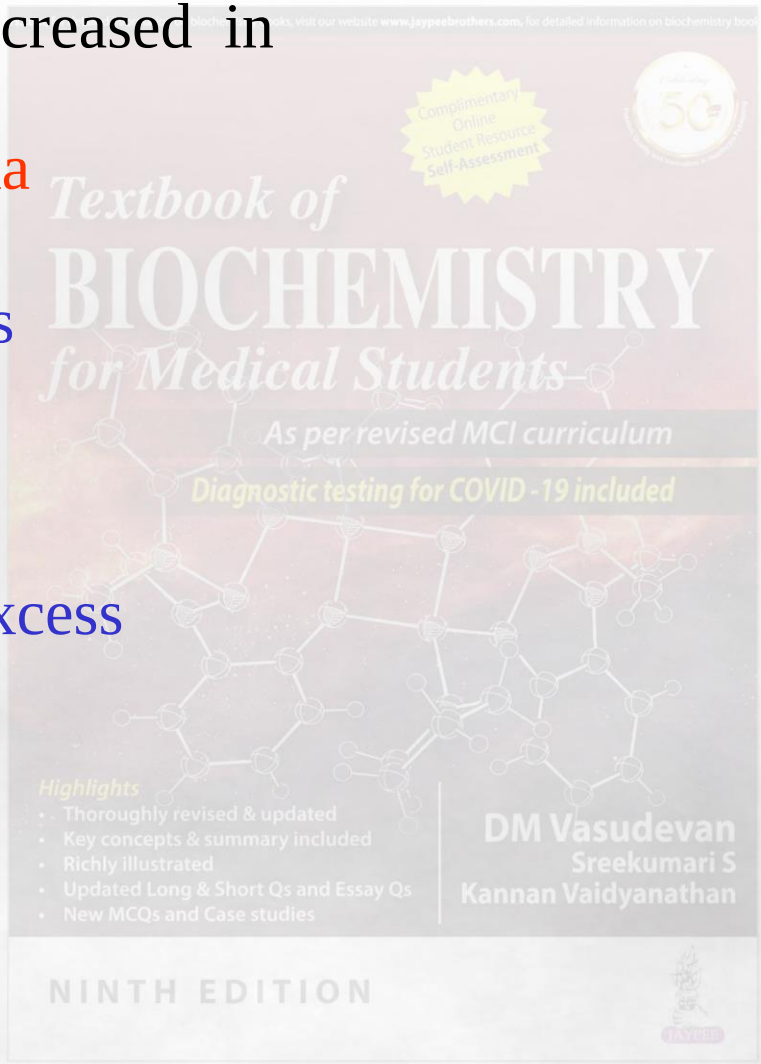
- Epinephrine and norepinephrine increase the blood pressure.
- Adrenaline also increases the rate and force of myocardial contraction.
- Epinephrine causes relaxation of smooth muscles of bronchi.
- Adrenaline is anti-insulin in nature, it increases glycogenolysis and stimulates lipolysis.
- Adrenaline is released from adrenal medulla in response to flight, fight, fright, exercise and hypoglycemia.

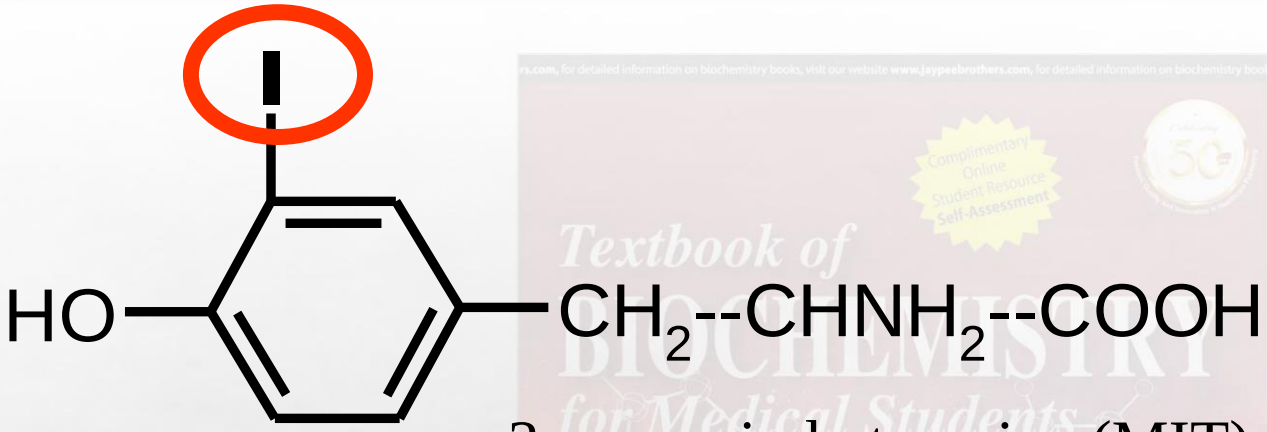


VMA excretion increased in

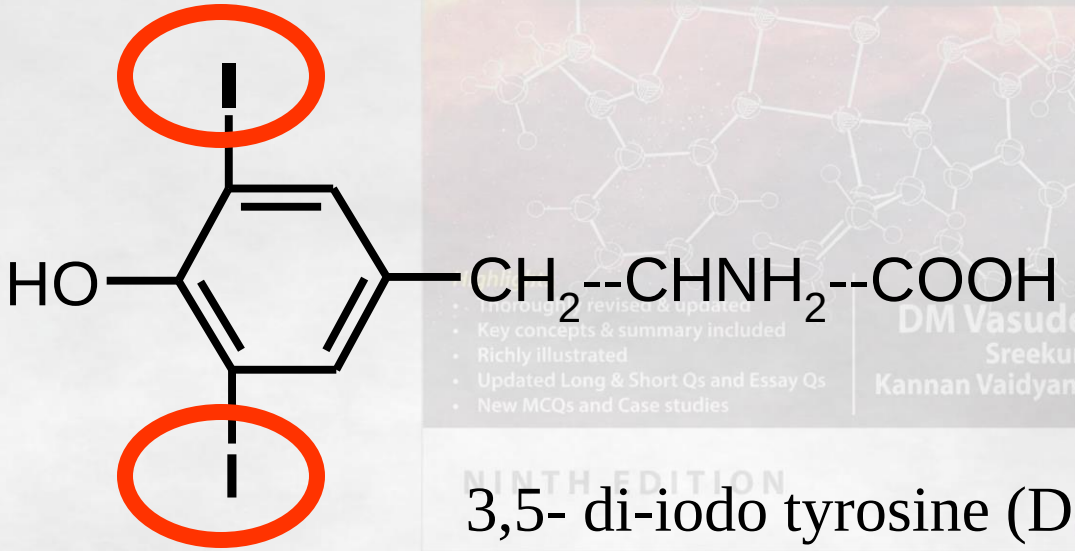
Pheochromocytoma
Supra renal gland
Epinephrine excess

Neuroblastoma
Nerve cells
Nor-epinephrine excess

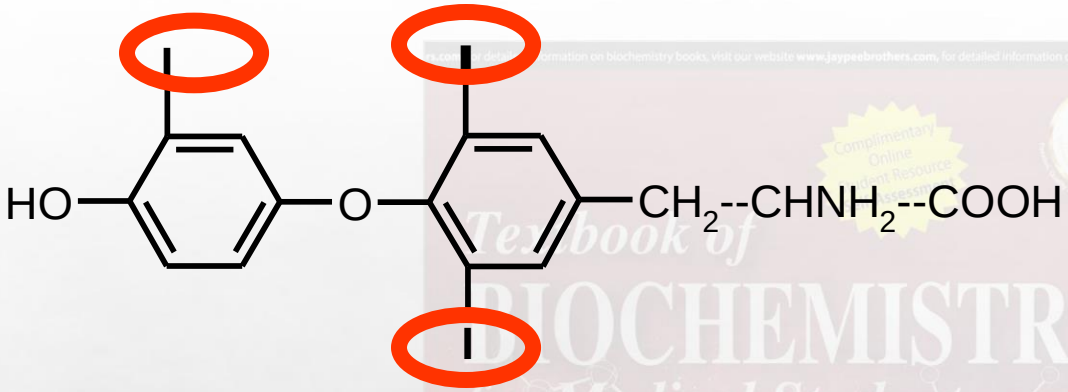




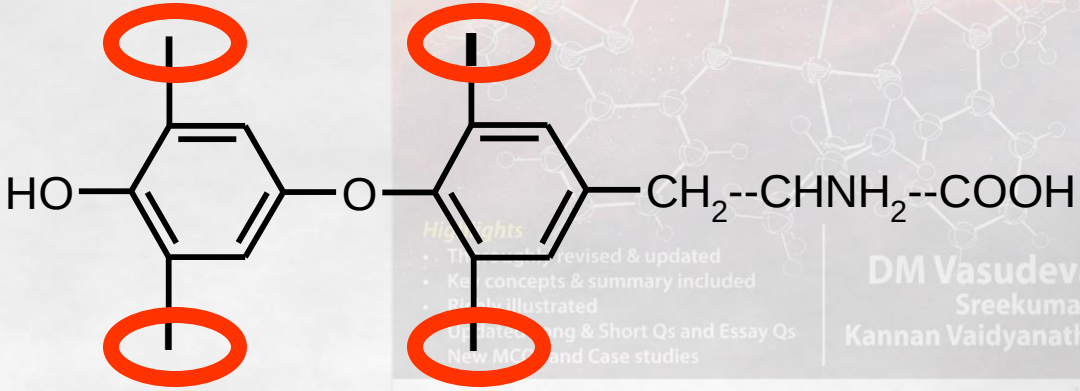
3- mono iodo tyrosine (MIT)



3,5- di-iodo tyrosine (DIT)



3,5,3’- tri-iodo thyronine (T3)

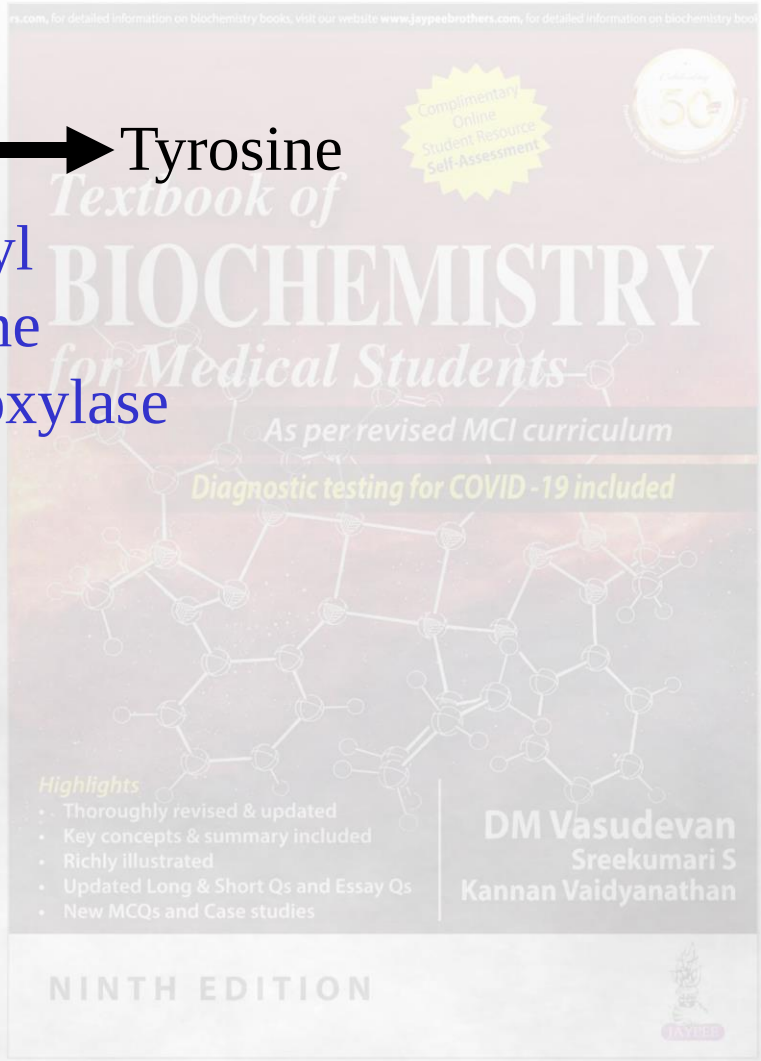


3,5,3’,5’-tetra iodo thyronine (T4)

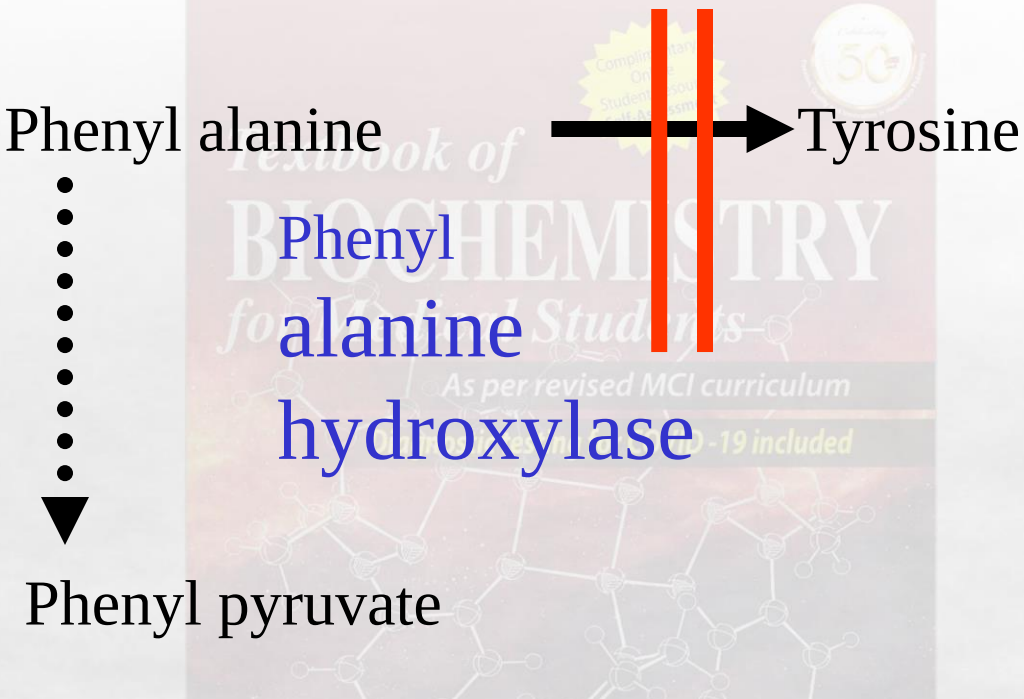
Phenyl Ketonuria

Phenyl alanine → Tyrosine

Phenyl alanine hydroxylase



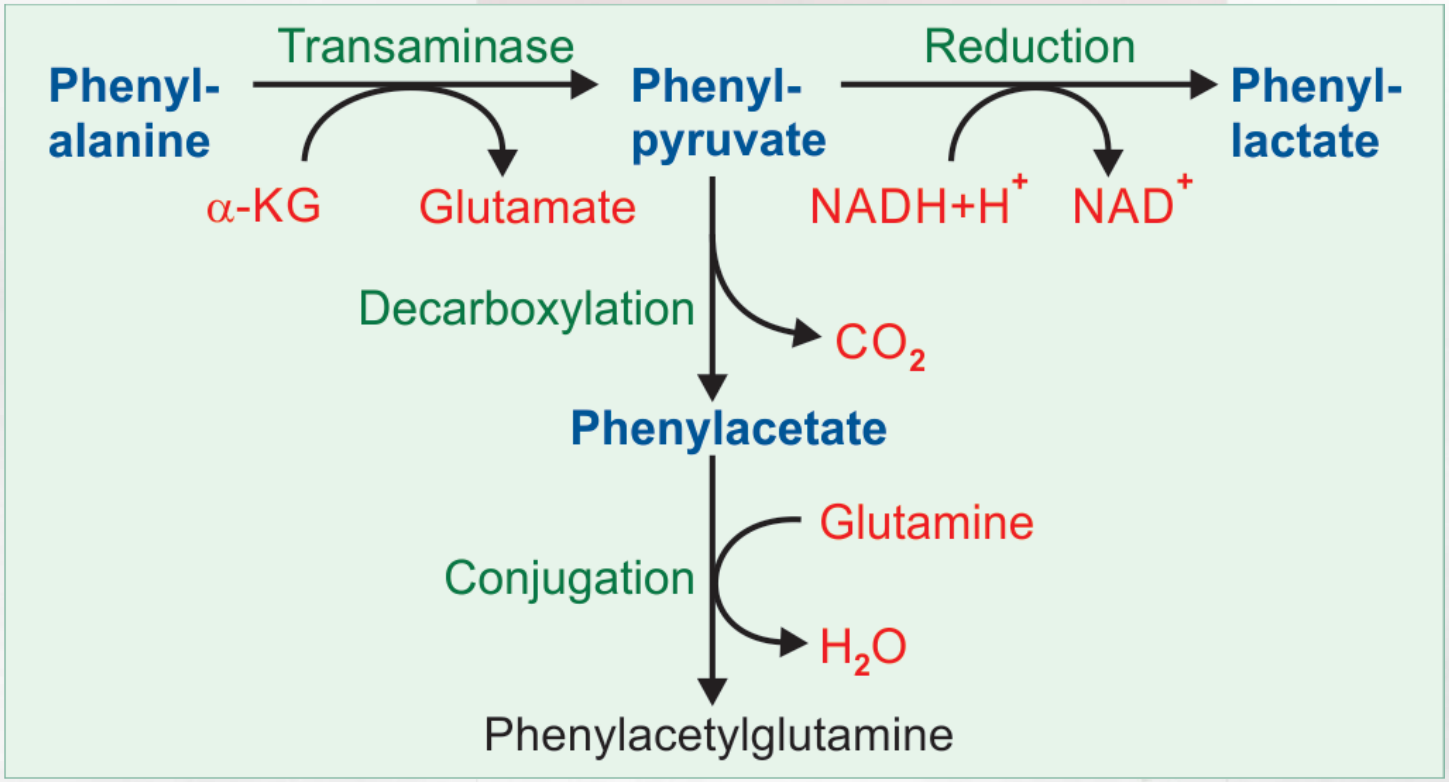
Phenyl Ketonuria



Phenyl Ketonuria

Phenyl alanine → Tyrosine

Phenyl alanine hydroxylase



Phenyl Ketonuria (PKU)

Autosomal recessive 1 in 10,000 to 25,000 births

Clinical Manifestations in PKU

- The classical PKU child is **mentally retarded** with an IQ of 50.
- Agitation, hyperactivity, tremors and **convulsions** are often manifested.
- The child often has **hypopigmentation**, explained by the decreased availability of tyrosine.
- Phenyl acetic acid in sweat may lead to mousy **body odor**.

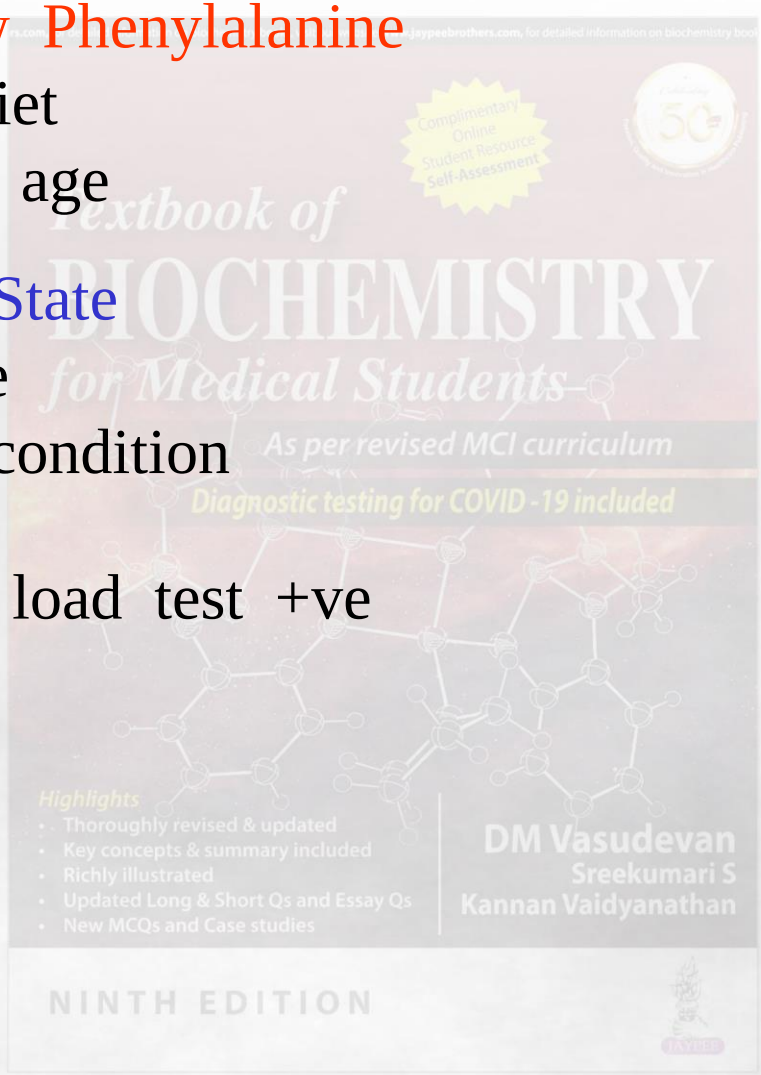
Laboratory Diagnosis of PKU

- **Blood phenylalanine:** Normal level is 1 mg/dL. In PKU, the level is >20 mg/dL. This may be demonstrated by chromatography.
- **Tandem mass spectroscopy** is the most reliable test; but is costly.
- **Guthrie test** is a rapid screening test "bacterial inhibition assay"
- **DNA probes** are now available to diagnose the phenylalanine hydroxylase deficiency.
- **Ferric chloride test:** Urine of the patient contains phenylketones. Add a drop of ferric chloride to the urine. A transient blue-green color is a positive test.

Treatment: Low Phenylalanine
Tapioca based diet
Till 5 years of age

PKU Carrier State
Recessive gene
Heterozygous condition

Phenyl alanine load test +ve



Alkaptonuria

Autosomal recessive 1 in 250,000 births Inborn error of metabolism Deficiency of homogentisic acid oxidase

Homogentisic acid in blood Excretion in urine

Fairly normal life

Blackening of urine on standing

Ferric chloride test + ve

Benedict's test +++

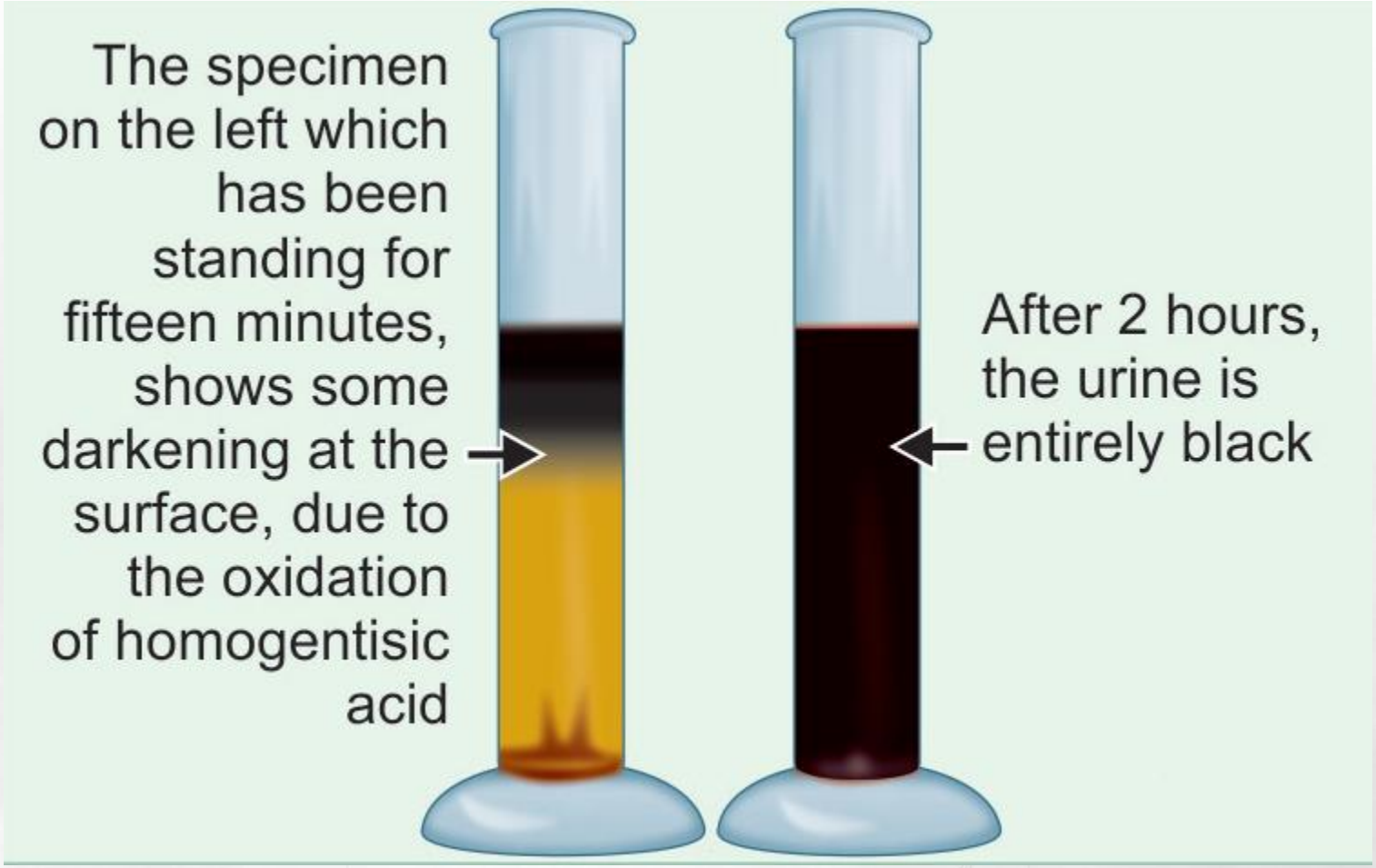
Ochronosis

3rd or 4th decades of life Polymerisation

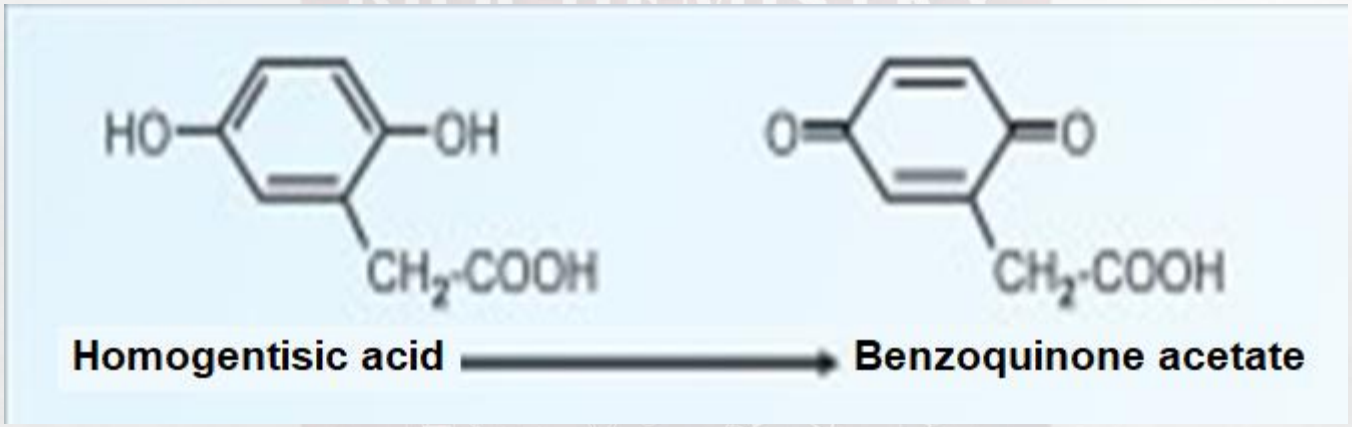
Black Deposits in

Intervertebral discs; Cartilages

Joint cavities



Urine in alkaptonuria



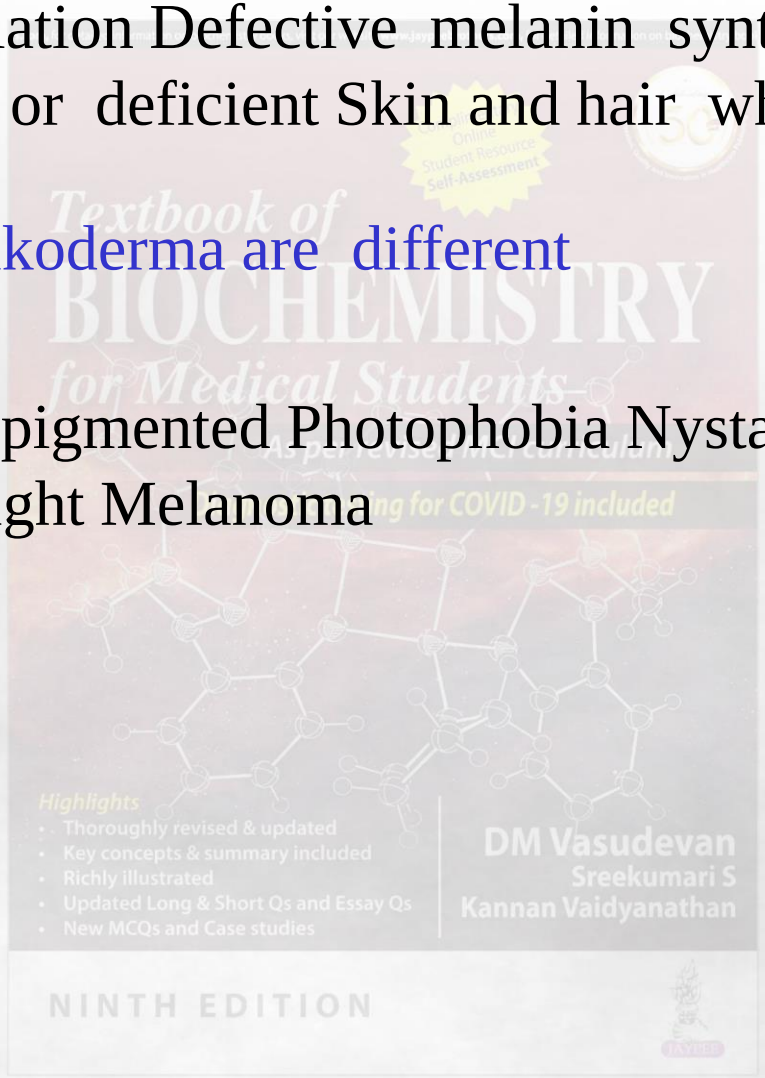
Oxidation of homogentisic acid.

Albinism

1 in 20,000 population Defective melanin synthesis Tyrosinase absent or deficient Skin and hair white

Albinism and Leukoderma are different

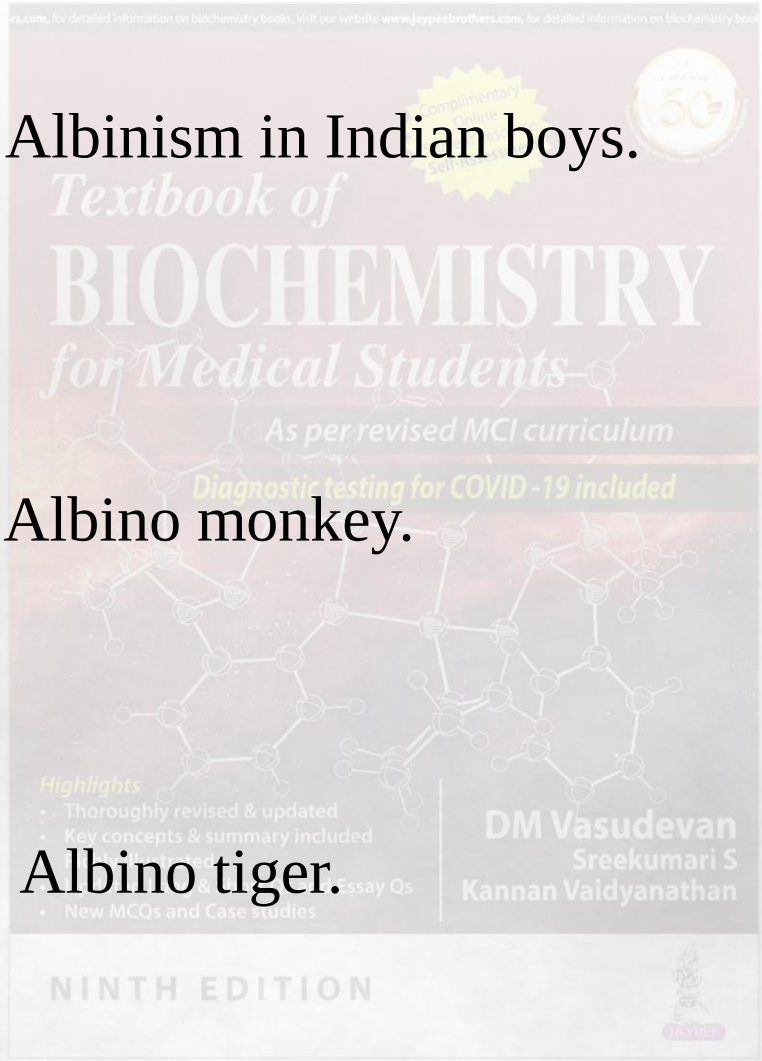
Fundus, iris – hypopigmented Photophobia Nystagmus Skin sensitive to UV light Melanoma



Albinism in Indian boys.

Albino monkey.

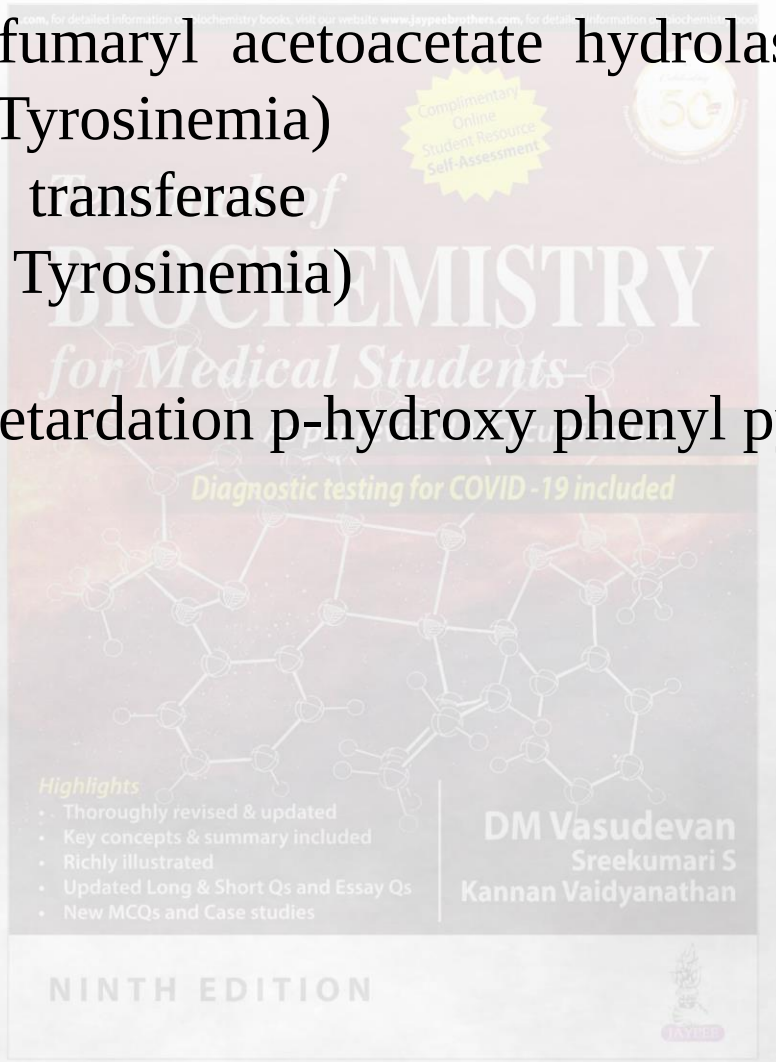
Albino tiger.

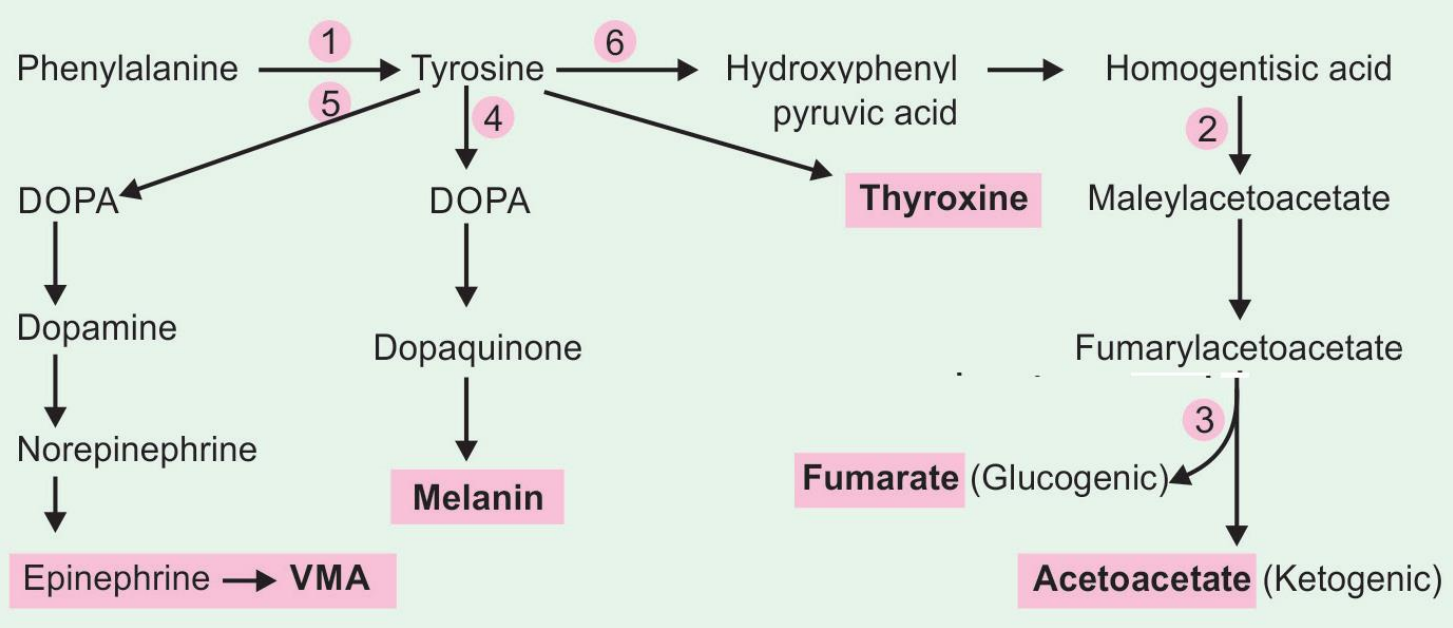


Tyrosinemia

Deficiency of fumaryl acetoacetate hydrolase
(Type I Tyrosinemia)
tyrosine amino transferase
(Type II Tyrosinemia)

Mild mental retardation p-hydroxy phenyl pyruvate in urine
Cirrhosis
Nephropathy
Hypoglycemia
Death

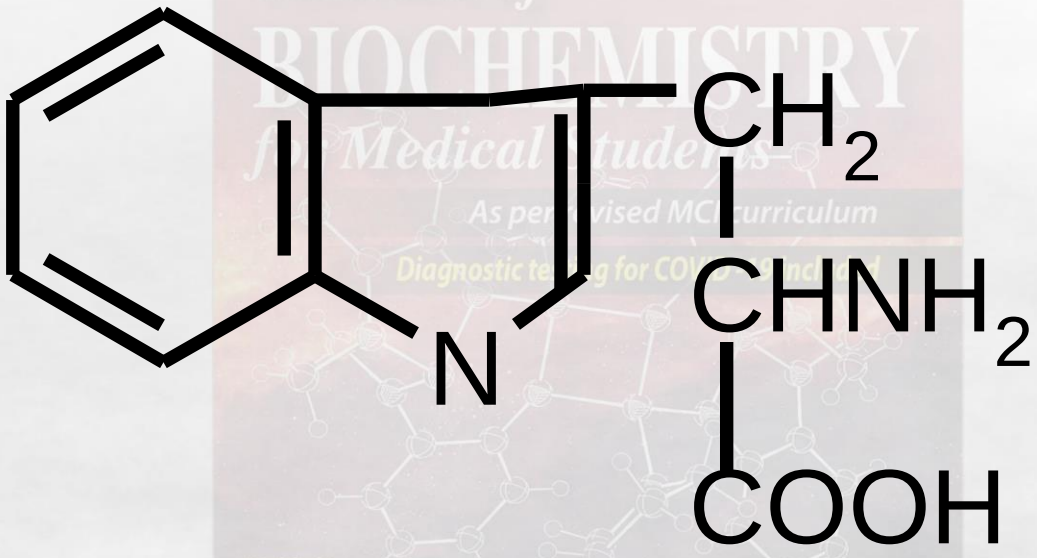




Summary of tyrosine metabolism. 1 = phenyl ketonuria, absence of phenylalanine hydroxylase. 2 = alkaptonuria, absence of homogentisic acid oxidase. 3 = hypertyrosinemia (tyrosinemia type I), absence of fumaryl acetoacetate hydroxylase. 4 = albinism, absence of tyrosinase. 5 = tyrosine hydroxylase, key enzyme of epinephrine synthesis. 6 = tyrosinemia type II, absence of tyrosine transaminase.

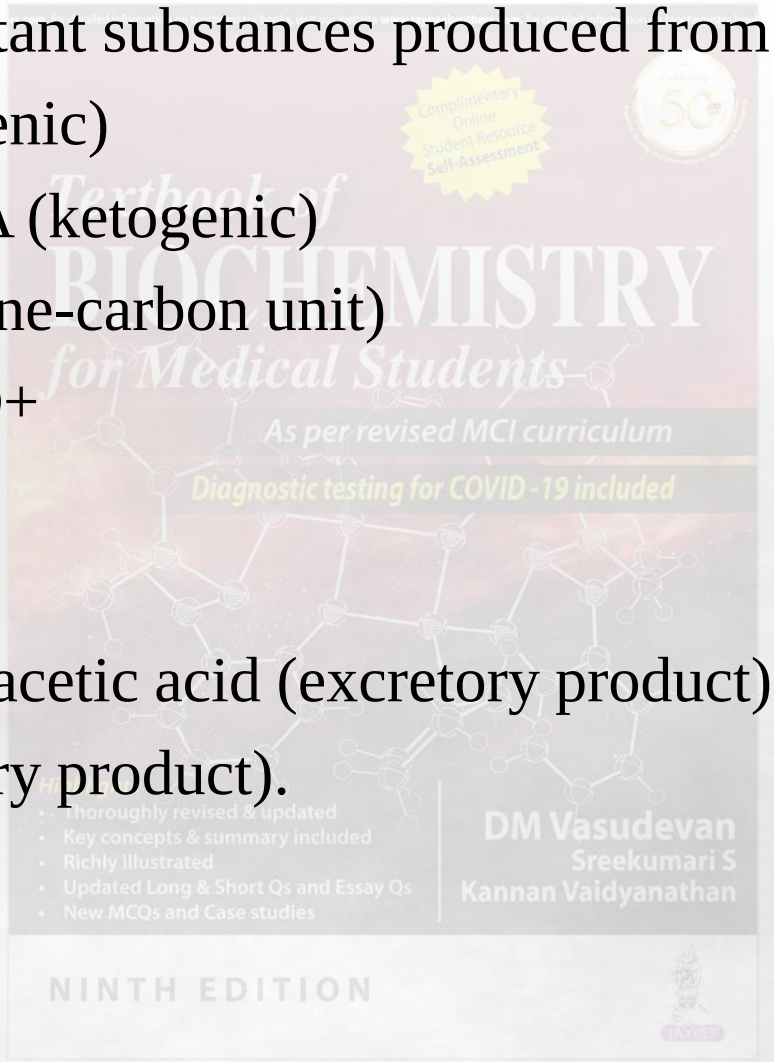
Tryptophan TRP W

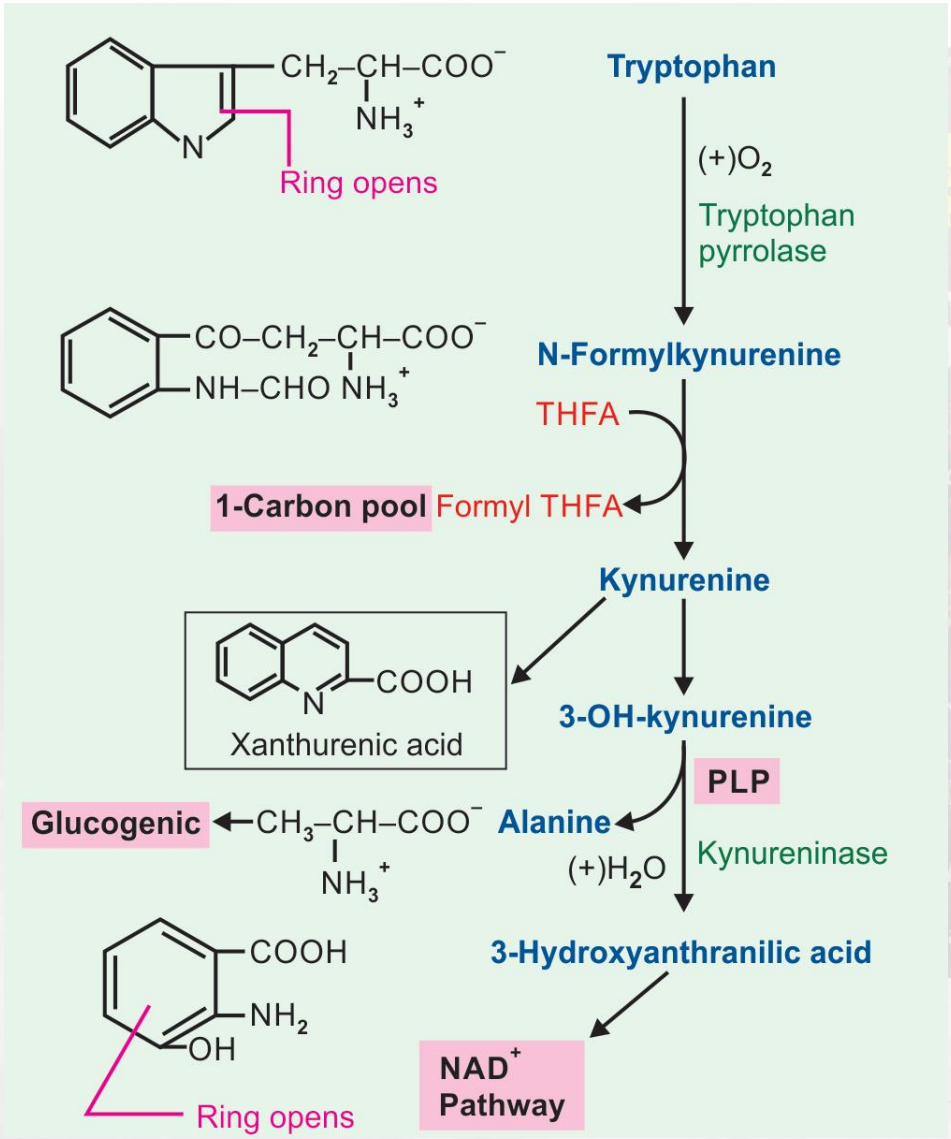
Essential Aromatic amino acid with Indole ring



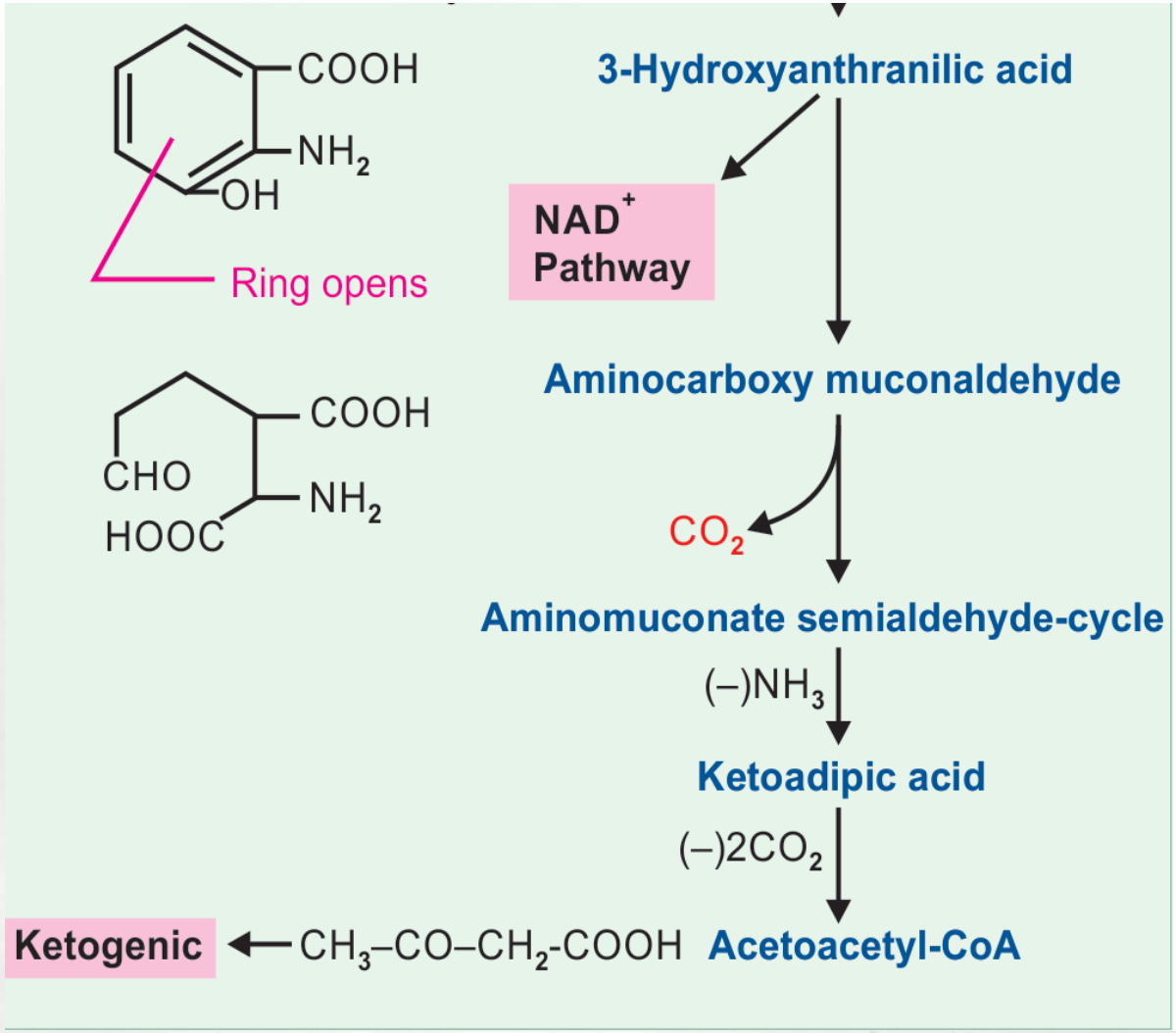
Biologically important substances produced from tryptophan are:

1. Alanine (glucogenic)
2. Acetoacetyl-CoA (ketogenic)
3. Formyl group (one-carbon unit)
4. Niacin and NAD+
5. Serotonin
6. Melatonin
7. Hydroxy indole acetic acid (excretory product)
8. Indican (excretory product).





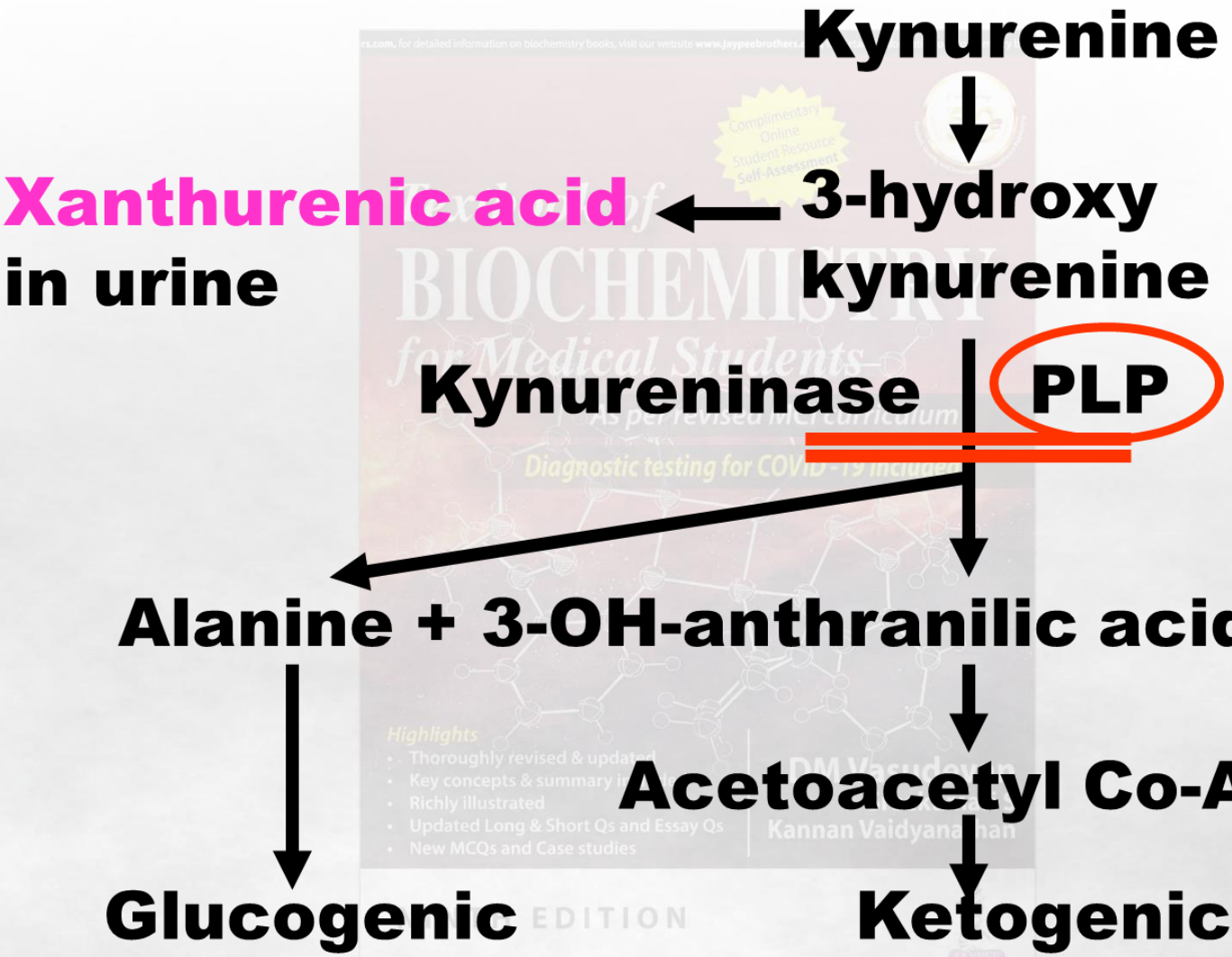
Metabolism of tryptophan.

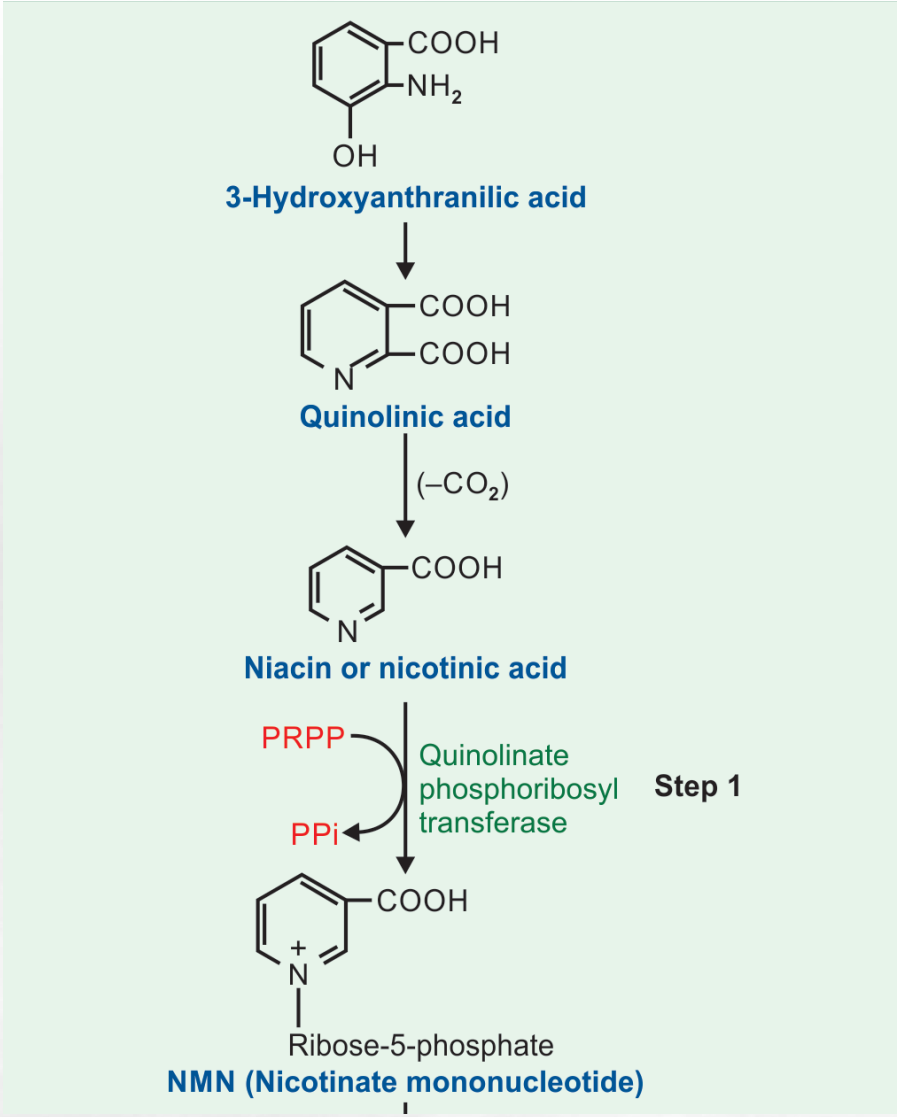


Metabolism of tryptophan.

Tryptophan pyrrolase
Tryptophan di oxygenase

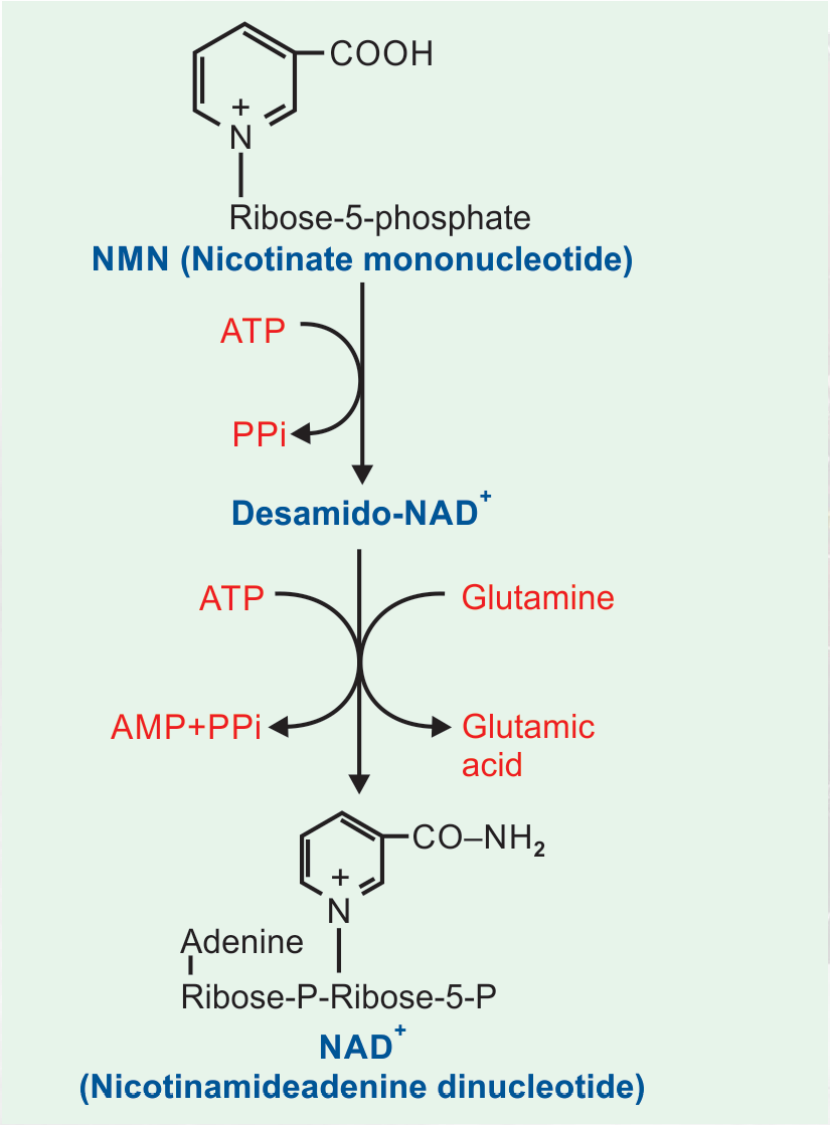
Hemoprotein
Induced by corticosteroids
Induced by dietary Tryptophan


Kynurenine
3-hydroxy kynurenine
Xanthurenic acid in urine
Kynureninase
PLP
Alanine + 3-OH-anthranilic acid
Acetoacetyl Co-A
Glucogenic
Ketogenic



Synthesis of niacin from tryptophan.

(PRPP: phosphoribosyl pyrophosphate).



Synthesis of niacin from tryptophan.

Kynurenine

↓

3-hydroxy kynurenine

↓

Kynureninase | PLP

↓

3-OH-anthranilic acid

↓

(Quinolinic acid)

↓

Nicotinic Acid

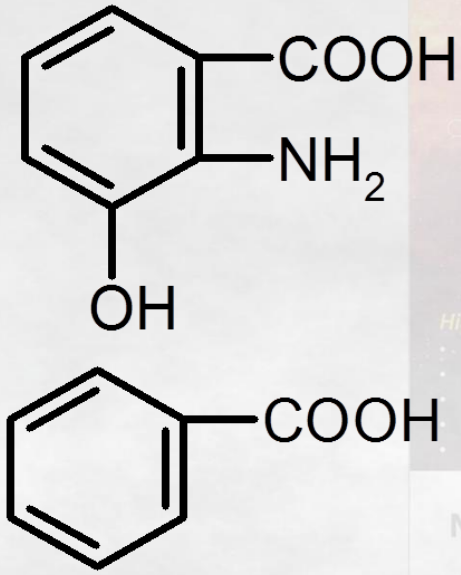
Niacin

↓

NAD

Xanthurenic acid in urine

←



Pyridoxal deficiency

Kynureninase not working

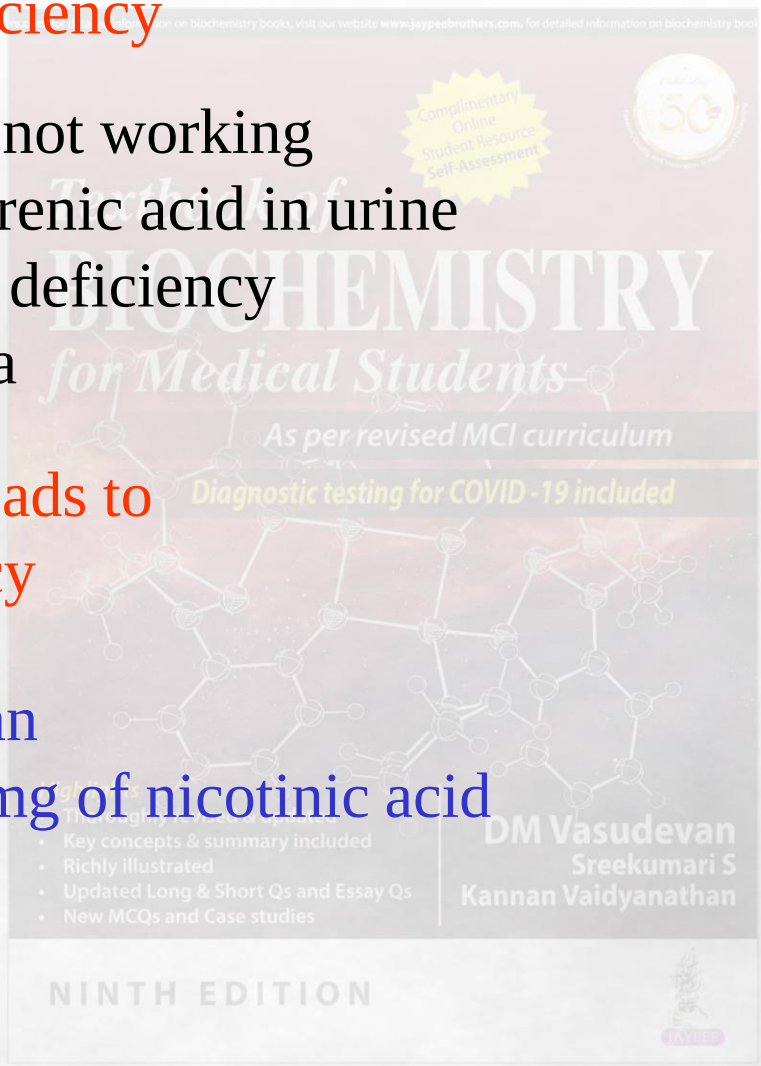
Xanthurenic acid in urine

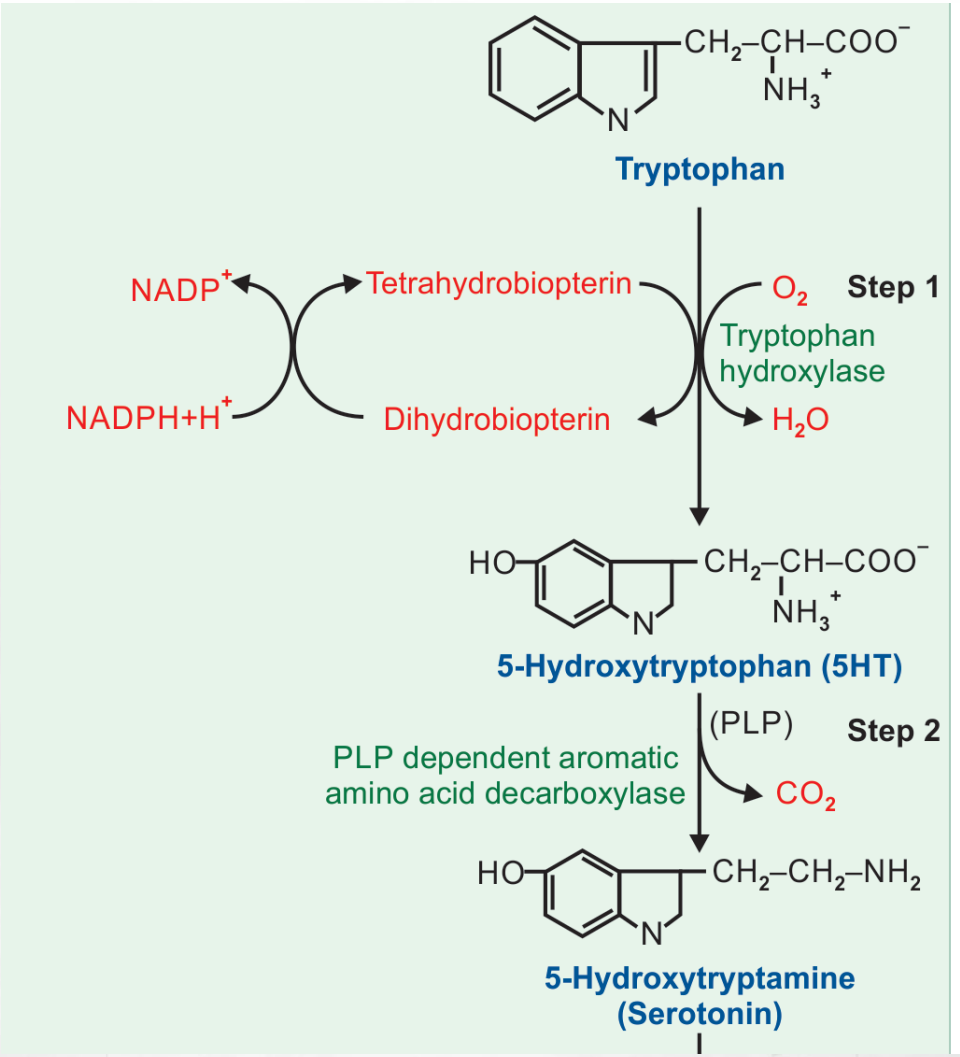
Niacin deficiency

Pellagra

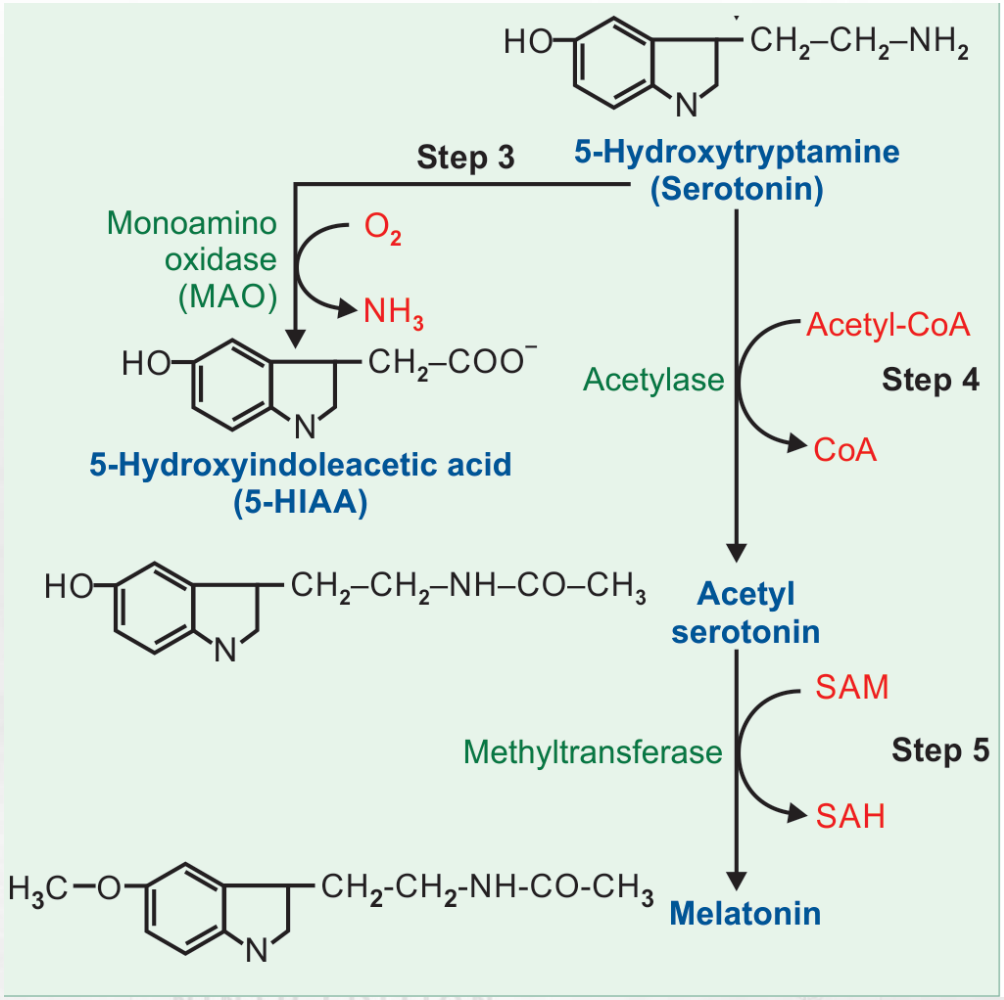
B6 deficiency leads to
Niacin deficiency

60 mg tryptophan
equivalent to 1 mg of nicotinic acid





Synthesis of serotonin



Synthesis of melatonin from serotonin

5-hydroxy tryptamine (Serotonin)

Mono amine; Neuro transmitter Brain Basophils, Mast cells Platelets G I T mucosa

In brain, bound serotonin Reserpine, decreases serotonin level Calming; depression

Serotonin level is lowered in depressive psychosis

Tryptophan availability Serotonin in brain Induce sleep

Protein rich food

All amino acids plenty in bloodTryptophan could not enter into brain Serotonin less; Alertness

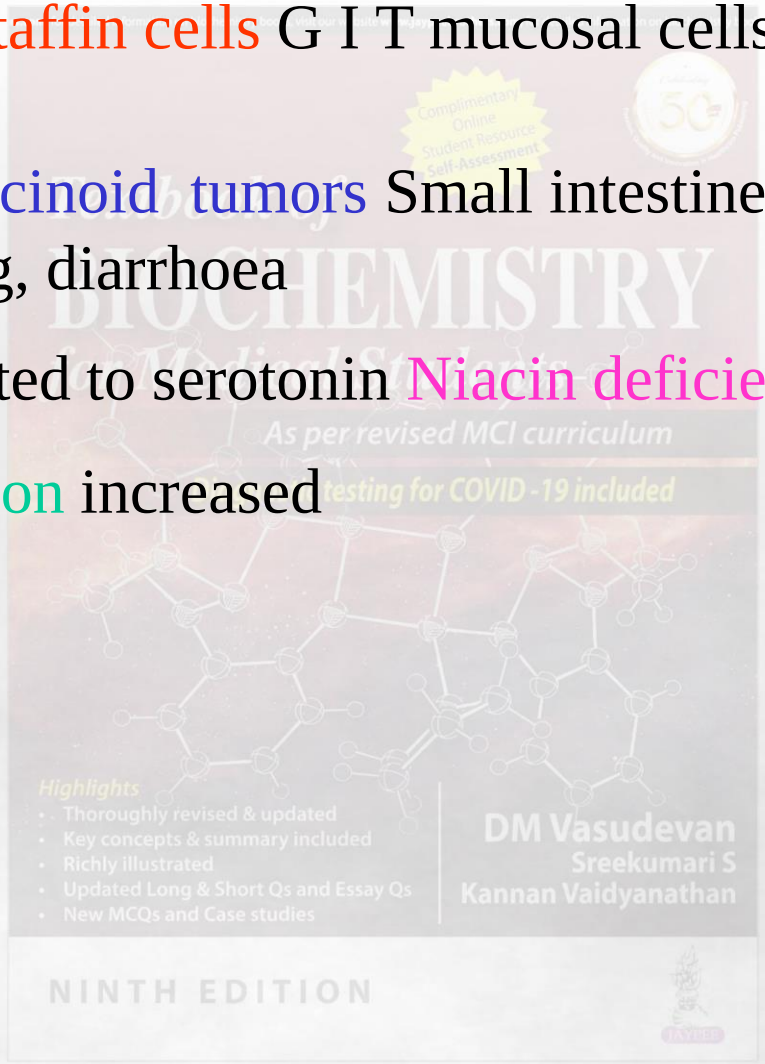
Carbohydrate rich food Insulin secretion Amino acid level in blood lowered Tryptophan could enter into brain More serotonin; Sleep

Serotonin by Argentaffin cells G I T mucosal cells Normal intestinal motility

Agentaffinoma; Carcinoid tumors Small intestine / appendix Intermittent flushing, diarrhoea

Tryptophan is diverted to serotonin Niacin deficiency, Pellagra

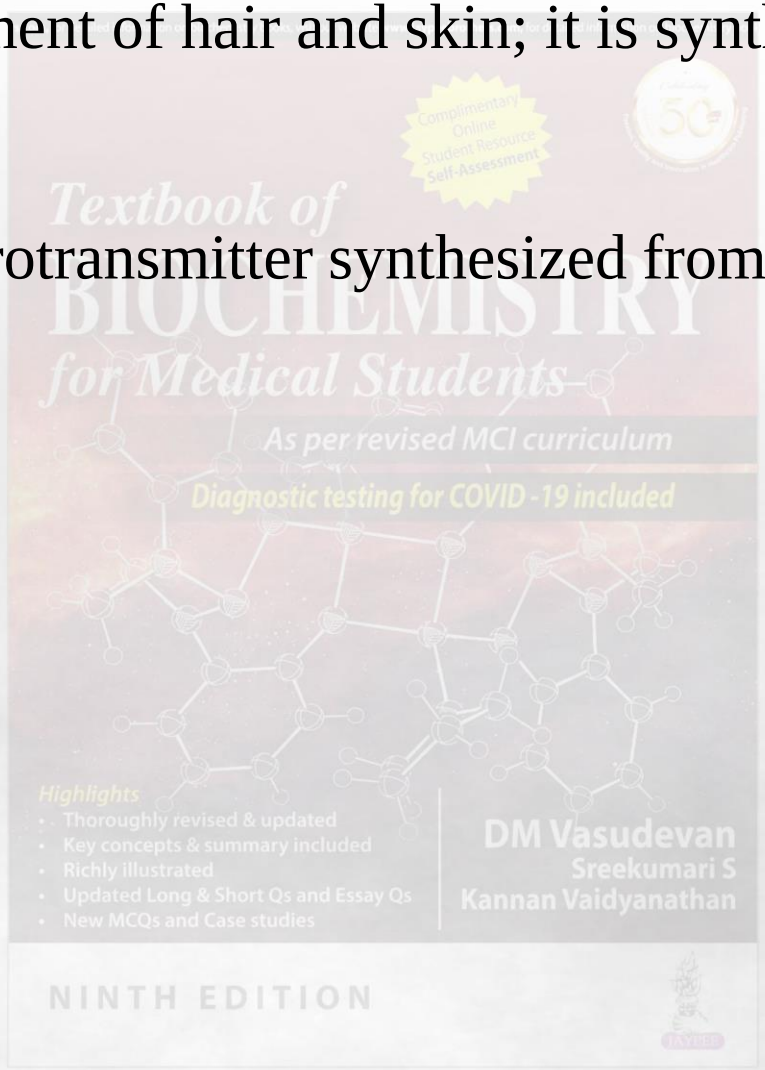
Urine HIAA excretion increased



Melanin and Melatonin are Different

Melanin is the pigment of hair and skin; it is synthesized from tyrosine.

Melatonin is a neurotransmitter synthesized from tryptophan

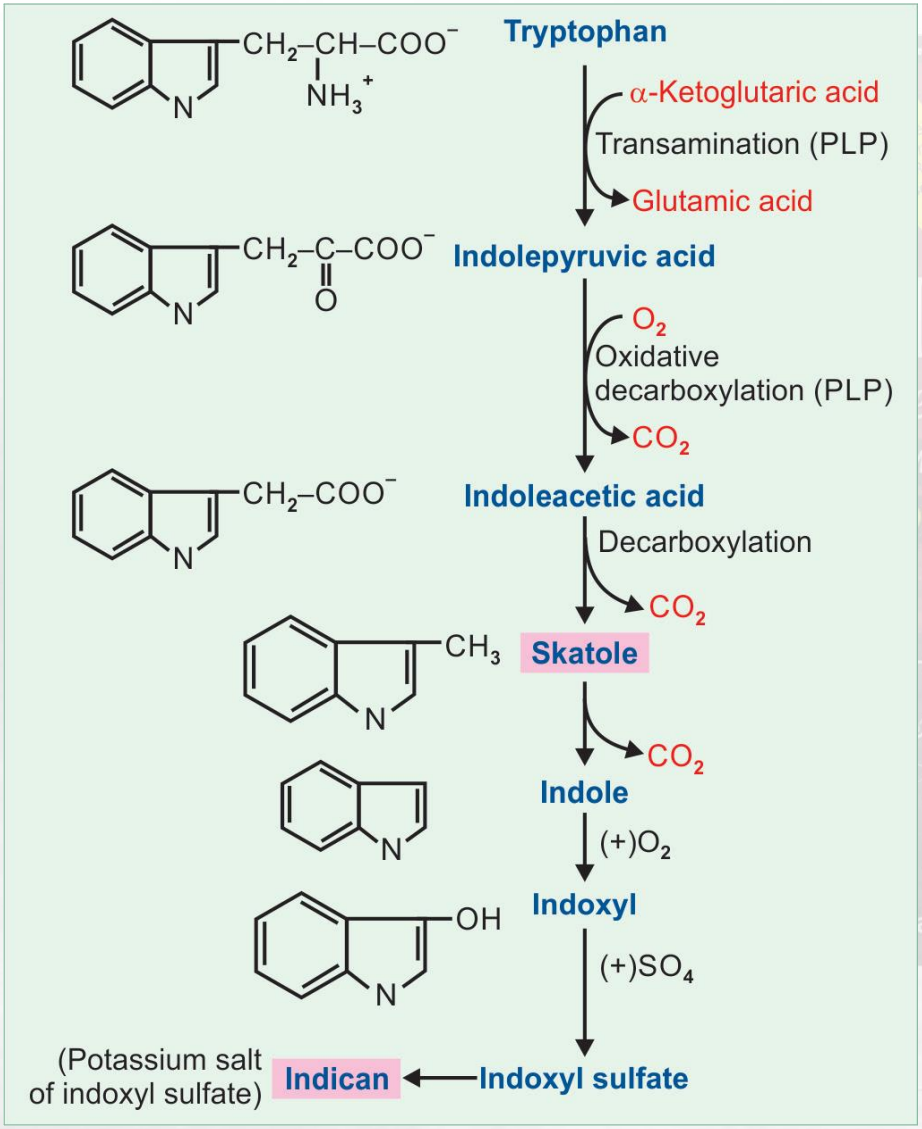


Melatonin

Frrom Pineal gland

Blocks ACTH and MSH secretions

Diurnal variation
Sleep wake cycles
Biological rhythms
Biological clock



Major excretory products of tryptophan.

Hartnup Disease

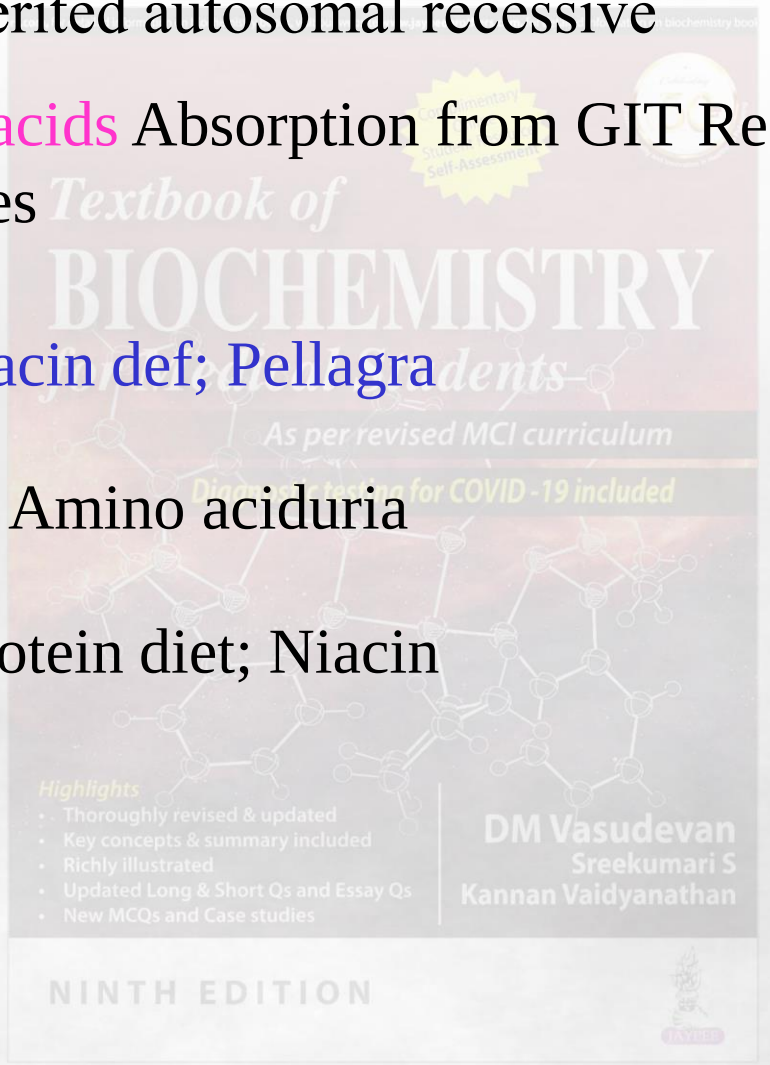
Patient's name Inherited autosomal recessive

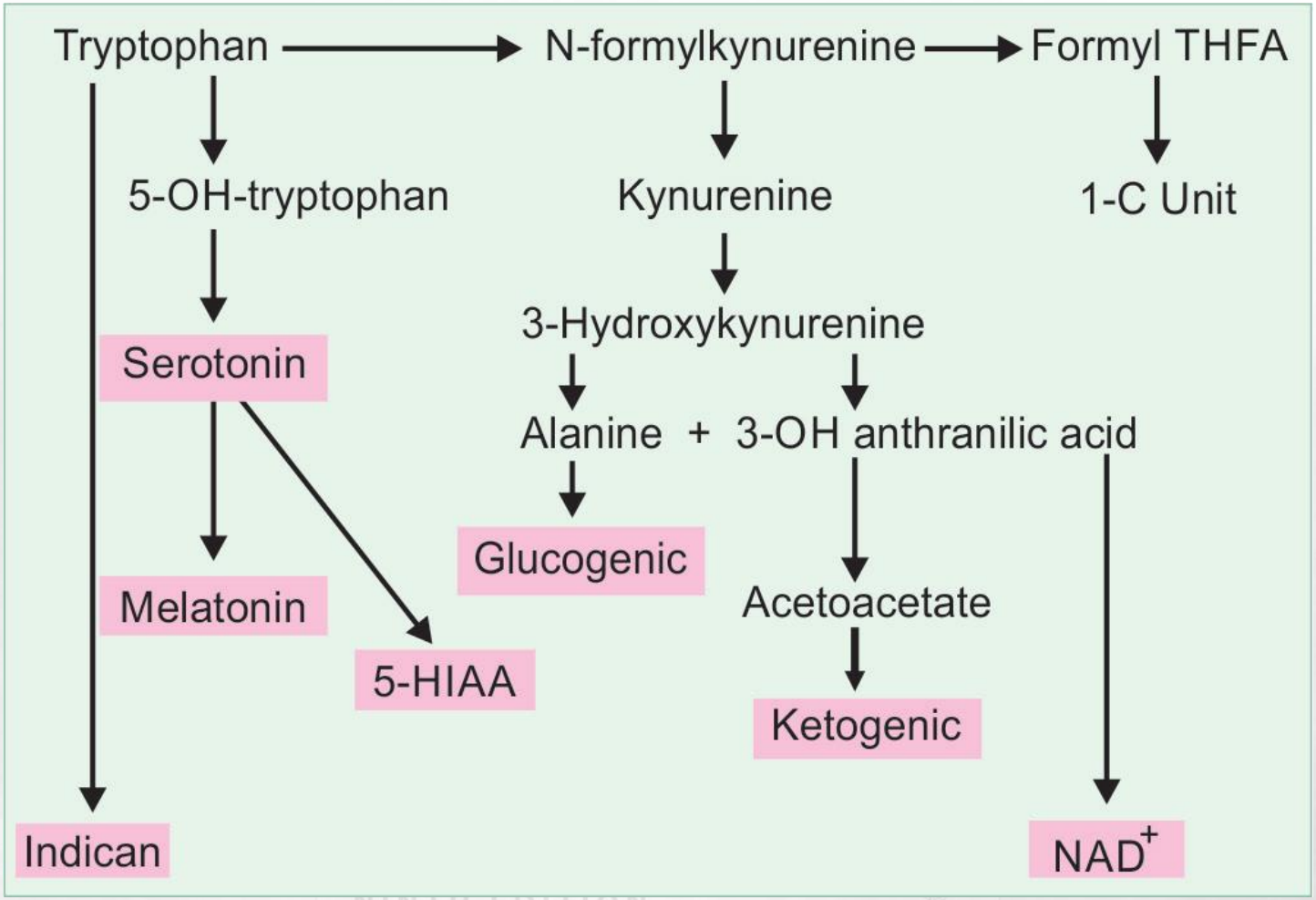
Aromatic amino acids Absorption from GIT Reabsorption from kidney tubules

Trp deficiency; Niacin def; Pellagra

Dermatitis; Ataxia Amino aciduria

Treatment High protein diet; Niacin





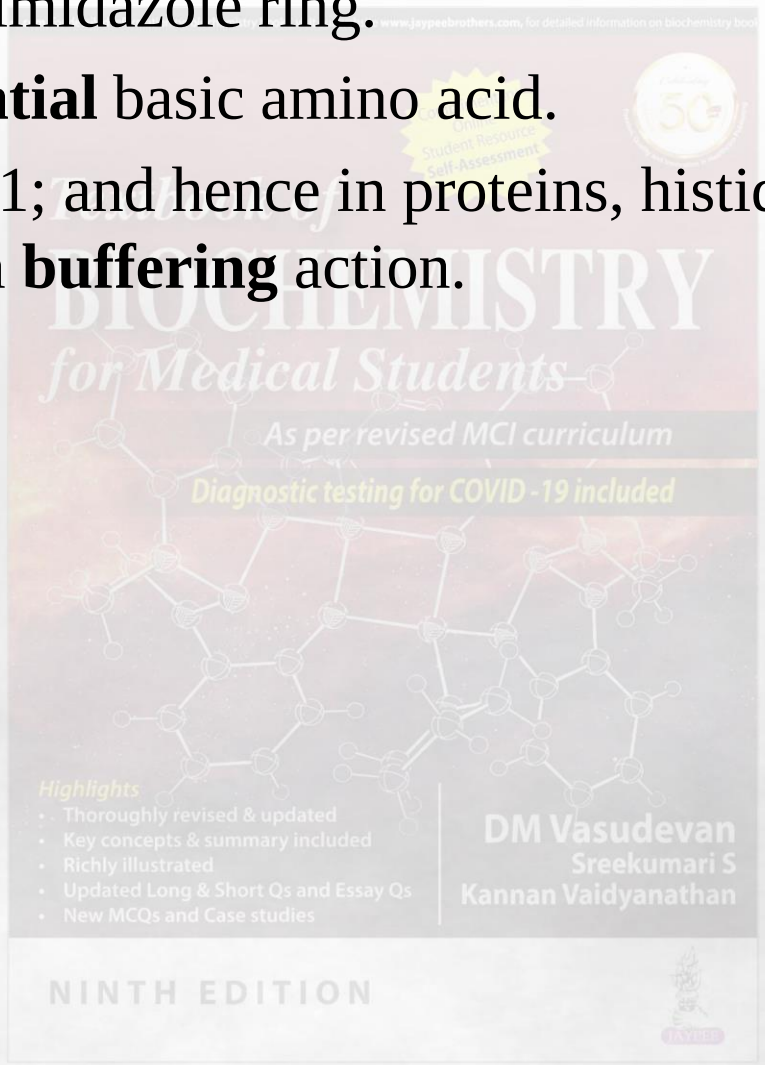
Summary of tryptophan metabolism.

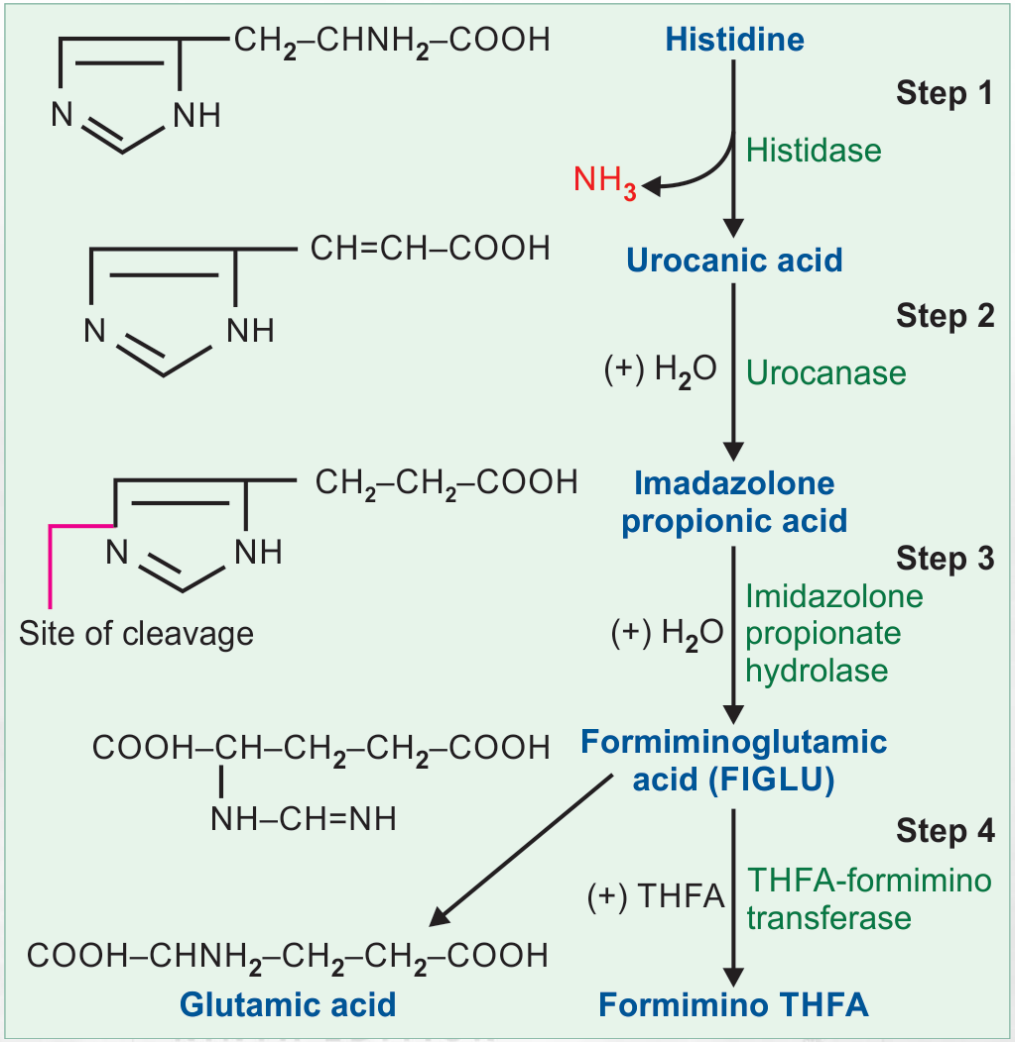
Drugs targetting the enzymes involved in the metabolism of aromatic amino acids

Enzyme	Action	Indication
DOPA decarboxylase	Inhibition of peripheral decarboxylation of L-DOPA. (Dopamine cannot cross blood brain barrier)	Parkinsonism. Keeps dopamine levels high in brain
Monoamine oxidase (MAO)	MAO inhibitors to maintain the levels of neurotransmitter amines	Antidepressants. Keeps dopamine levels high in brain.
Catechol-O-methyl transferase	Inhibitors to keep the level of dopamine high	Parkinsonism. Keeps dopamine levels high in brain.
Selective serotonin reuptake	Inhibitors to maintain serotonin levels constant	Mood disorders. Antidepressants.

Histidine (HIS) (H)

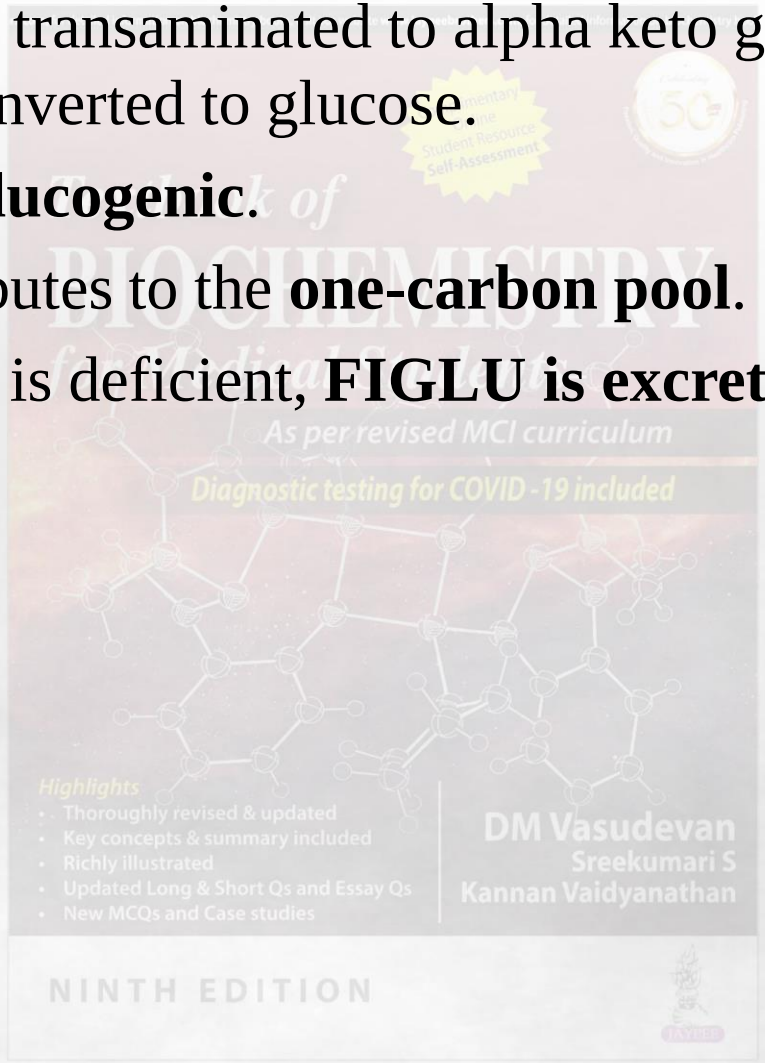
- Histidine has an imidazole ring.
- It is a **semi-essential** basic amino acid.
- Its pK value is 6.1; and hence in proteins, histidine is responsible for the maximum **buffering** action.

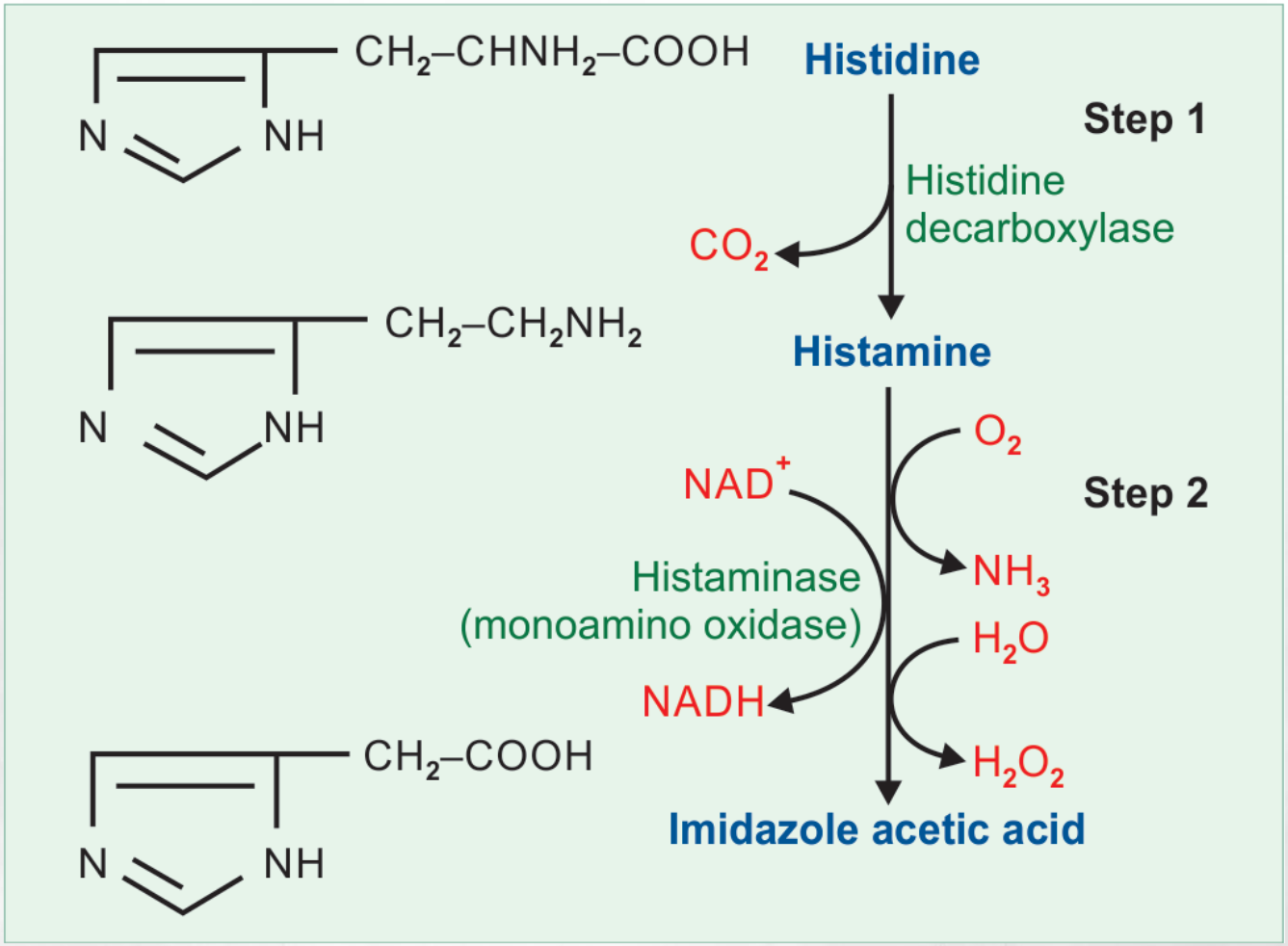




Metabolism of histidine.

- Glutamic acid is transaminated to alpha keto glutarate which can be converted to glucose.
- So histidine is **glucogenic**.
- Histidine contributes to the **one-carbon pool**.
- When **folic acid** is deficient, **FIGLU is excreted** in urine.





Metabolism of histamine.

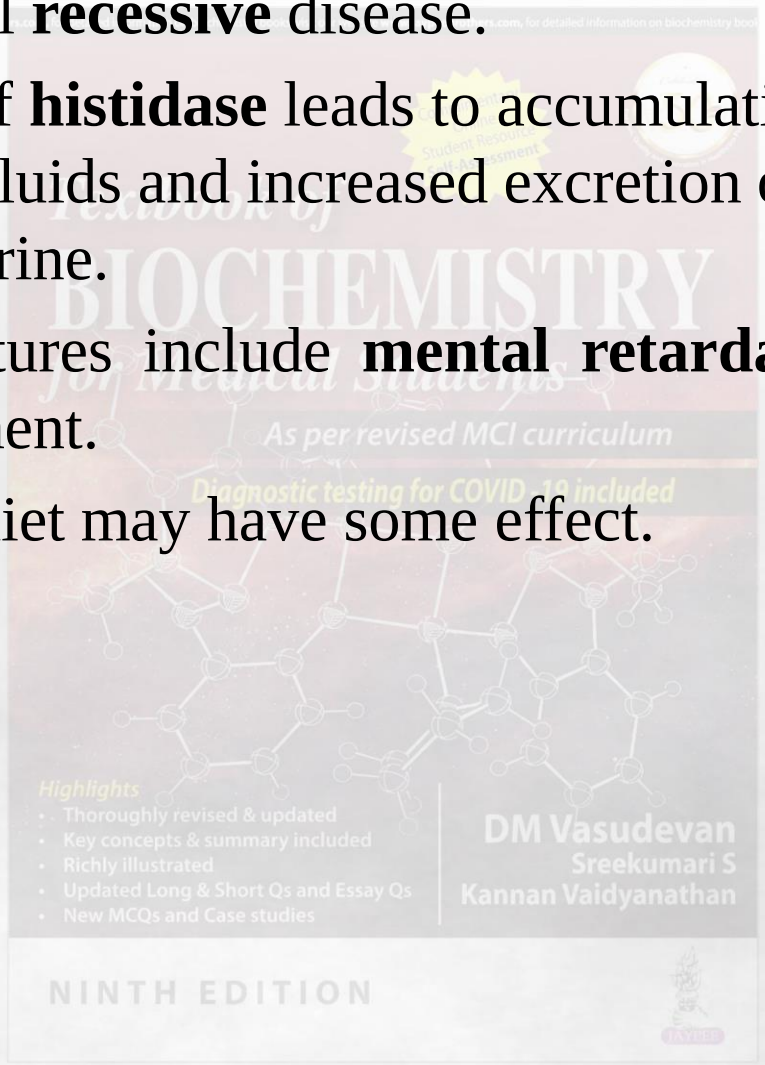
Summary of Action of Histamine

Tissue	Effect
1. Blood vessels	Pulmonary venous dilation; superficial temporal artery dilation (migraine). Large veins, smaller venules and capillaries are dialated
2. Cardiovascular system	Fall in BP; increased capillary permeability
3. Heart	Chronotropic and ionotropic effect on heart, coronary artery flow is increased
4.Smooth muscles	Direct stimulant; contraction of bronchial muscles; bronchospasm
5.Exocrine glands	Stimulates gastric acid secretion

- Certain antigens, such as penicillin will elicit IgE antibodies that are fixed on the mast cells.
- When the next dose of penicillin is injected, it reacts with the antibodies; and degranulation of mast cells takes place.
- Histamine and slow reacting substance (SRS) are released.
- This leads to peripheral vasodilatation, fall in blood pressure and **anaphylaxis**.
- **Antihistamines** are drugs which block histamine receptors.
- They are used to control allergic and anaphylactic reactions.
- The stimulant effect of histamine on gastric acid secretion is by acting on H2 receptors.
- Hence, H2 receptor antagonists are used in the treatment of acid peptic ulcers of stomach.

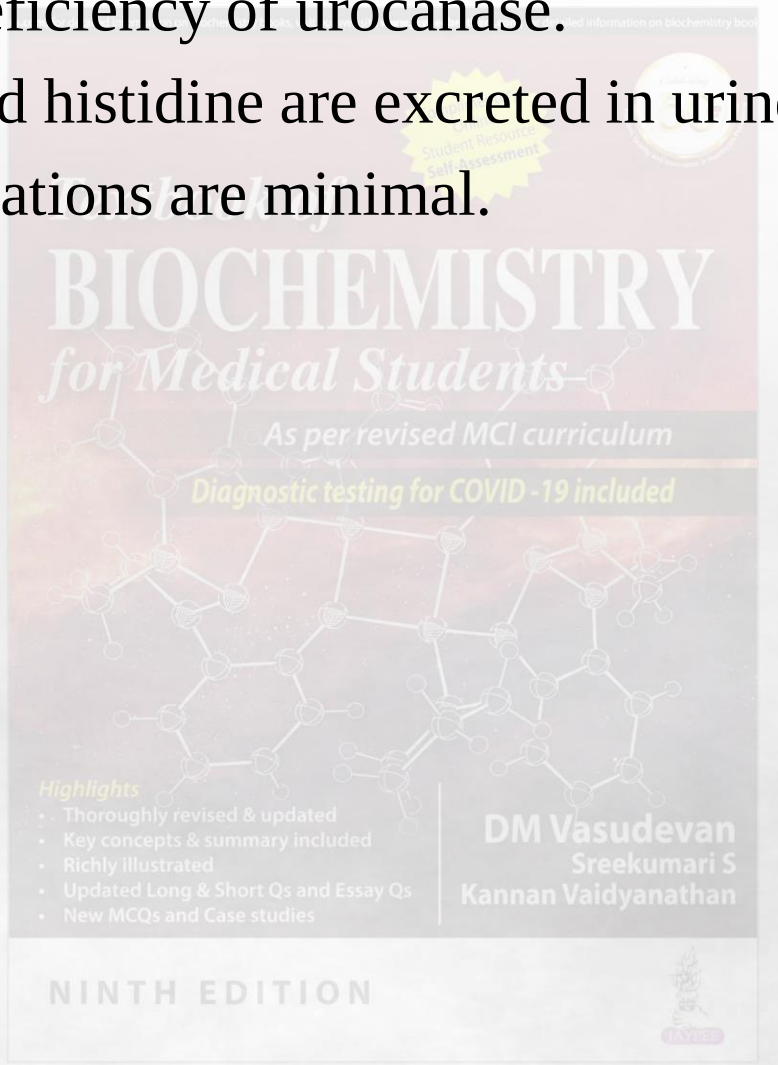
Histidinemia

- It is an autosomal **recessive** disease.
- The deficiency of **histidase** leads to accumulation of histidine in blood and body fluids and increased excretion of imidazole pyruvic acid in urine.
- The clinical features include **mental retardation** and delayed speech development.
- A low histidine diet may have some effect.



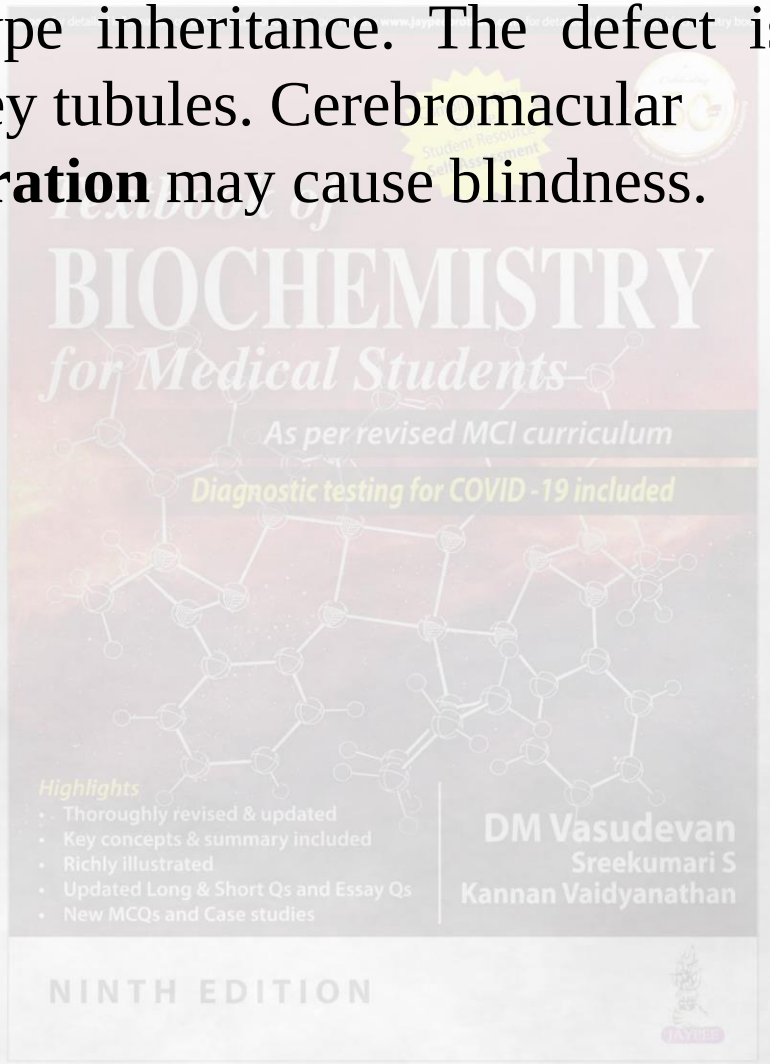
Urocanic Aciduria

- It is due to the deficiency of urocanase.
- Urocanic acid and histidine are excreted in urine.
- Clinical manifestations are minimal.



Imidazole Aminoaciduria

It has dominant type inheritance. The defect is in the transport mechanism in kidney tubules. Cerebromacular and **retinal degeneration** may cause blindness.

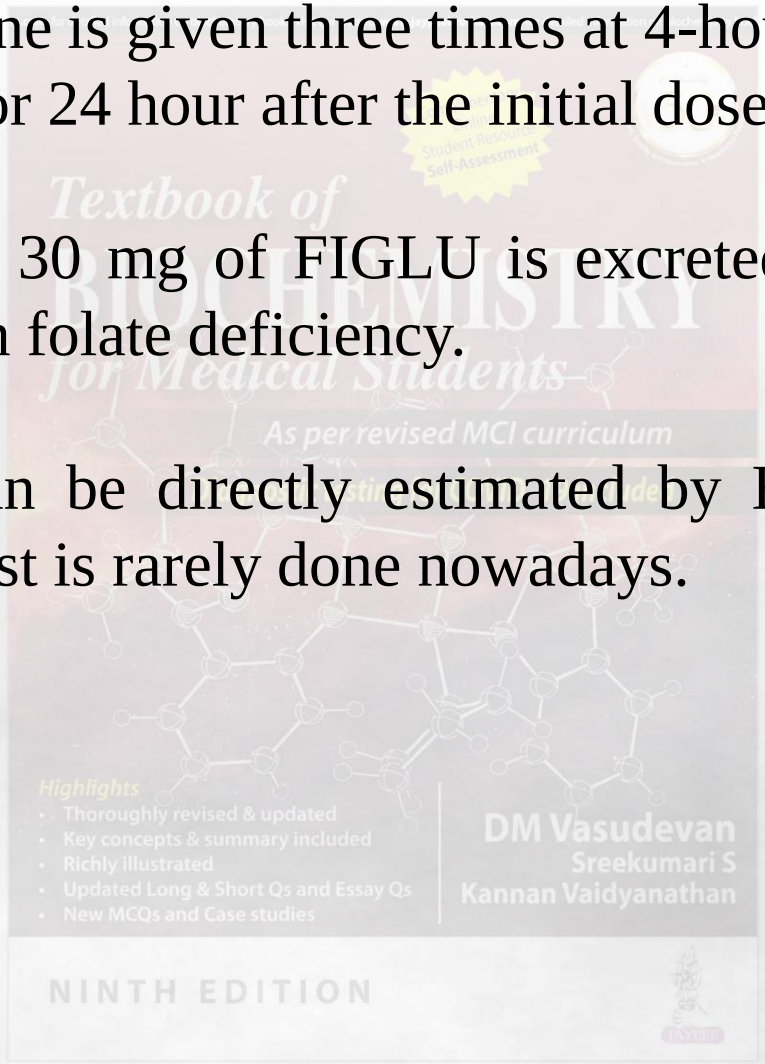


FIGLU Excretion Test

About 5 g of histidine is given three times at 4-hourly intervals. Urine is collected for 24 hour after the initial dose.

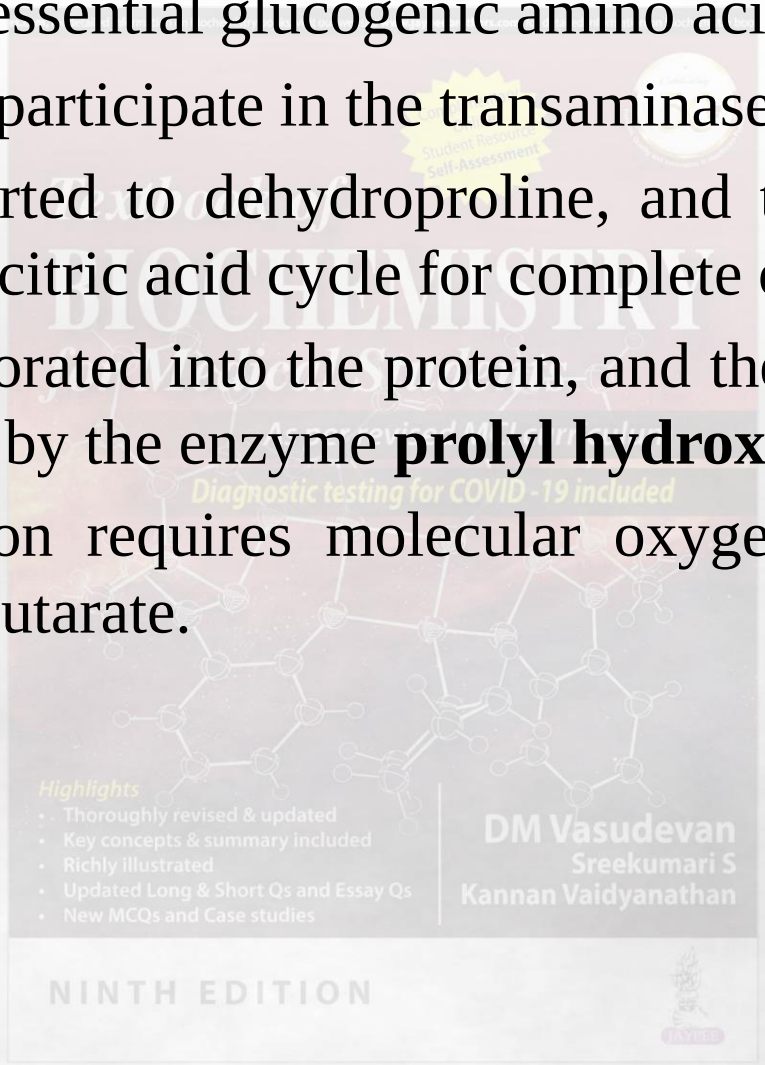
Normally less than 30 mg of FIGLU is excreted within 1 day; the value is increased in folate deficiency.

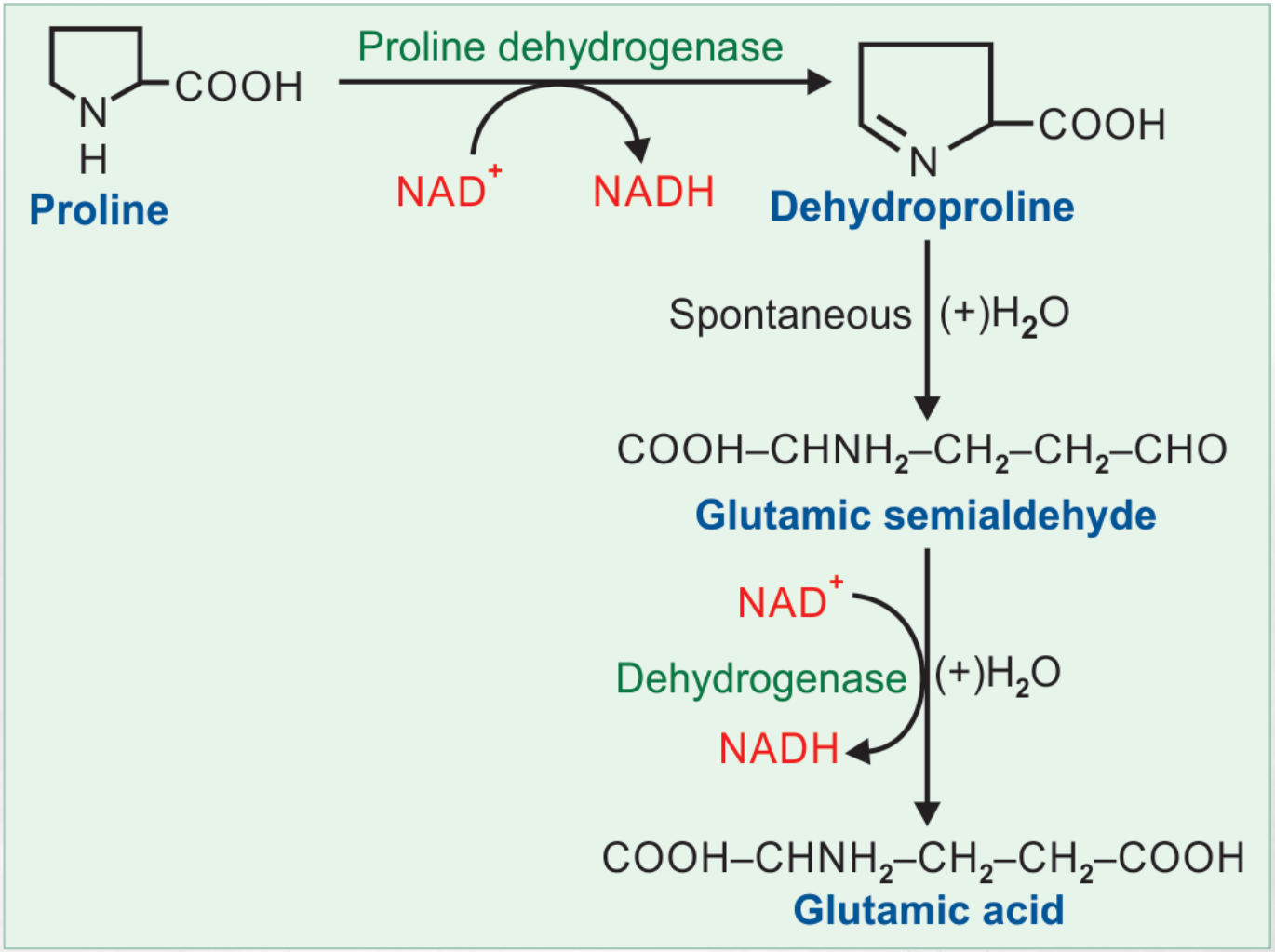
Since folic acid can be directly estimated by ELISA method, the FIGLU excretion test is rarely done nowadays.



Proline (PRO) (P) and Hydroxyproline

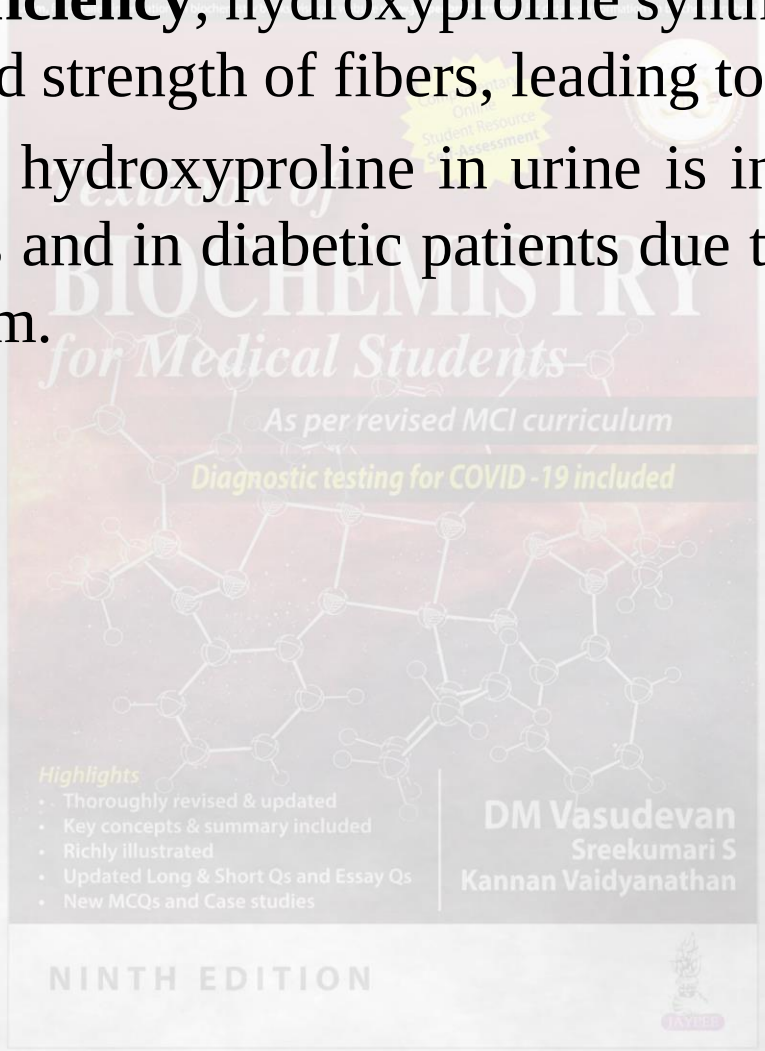
- Proline is a non-essential glucogenic amino acid.
- Proline does not participate in the transaminase reaction.
- Proline is converted to dehydroproline, and then to glutamate, which enters the citric acid cycle for complete oxidation.
- Proline is incorporated into the protein, and then hydroxylated to hydroxy proline, by the enzyme **prolyl hydroxylase**.
- The hydroxylation requires molecular oxygen, ascorbate, iron and alpha keto glutarate.

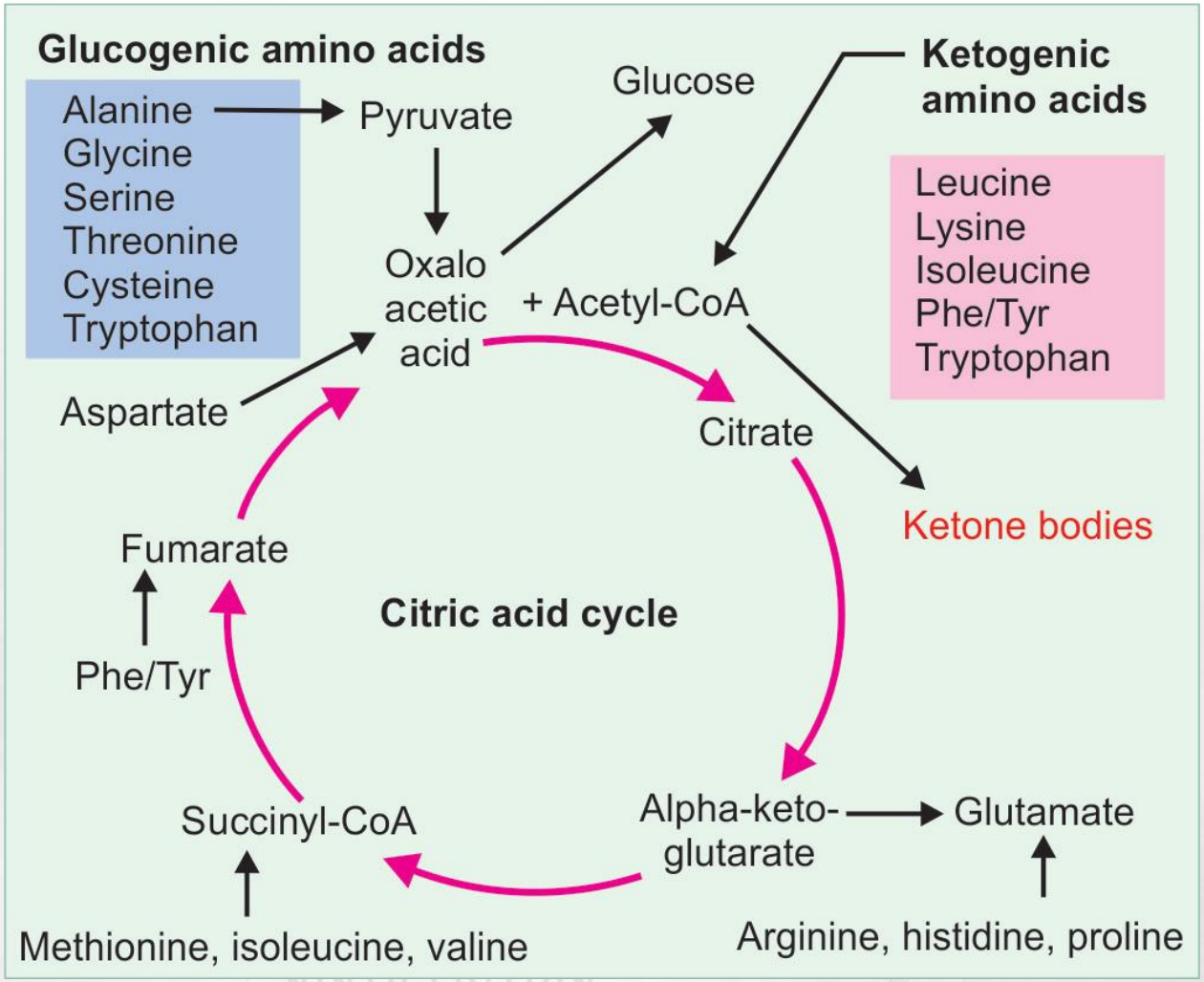




Degradation of proline.

- In **vitamin C deficiency**, hydroxyproline synthesis is reduced, causing decreased strength of fibers, leading to scurvy.
- The excretion of hydroxyproline in urine is increased in tumors infiltrating bones and in diabetic patients due to enhanced rate of protein catabolism.





Glucogenic and ketogenic amino acids.

Amino Acidurias

Disorder	Abnormality or absence of	Clinical manifestation	Substance in urine	Treatment
Phenyl ketonuria (type I)	Phenylalanine hydroxylase	MR, hypertonia, seizure	Phenyl pyruvate	Dietary restriction of Phe
Hyper- tyrosinemia (type I)	Fumaryl acetoacetate hydrolase	MR; hepatorenal damage	Tyrosine, PHPPA	Restrict Phe and Tyr
Alkaptonuria	Homogentisic acid oxidase	Arthritis, cartilage	Homogentisic acid	Nil
Homocystin-uria (type 1)	Cystathionine beta synthase	MR, Ectopia lentis	Homo-cystine	Cysteine ↑ Methionine ↓
Homocystinuria (type 2)	Methyl transferase	MR	Homocystine	Folate
Homocystinuria (type 3)	Methylene THFA reductase	MR	Homocystine	Folate
Histidinemia	Histidase	Mild MR; speech defect	Imidazole pyruvic acid	Restrict Histidine

Disorder	Abnormality or absence of	Clinical manifestation	Substance in urine	Treatment
Maple syrup urine disease	Branched chain keto acid decarboxylase	MR; Maple syrup odor; acidosis	Val; Leu; lle; keto acids	Restrict Val; Leu; IIe
Methyl malonic aciduria	Methyl malonyl CoA mutase	MR; ketosis; hypotonia	Methyl maIonic acid; ketonebodies	Vitamin B12
Cystathioninuria	Cystathionase	Benign	Cystathionine	None required
Hyper prolinemia II	Proline dehydrogenase	Seizures	Proline; OH-proline	
Citrullinemia	Arginino-succinate synthetase	MR;vomiting seizure;	Citrulline	Low protein; high Arg

Amino acidurias

Disorder	Abnormality or absence of	Clinical manifestation	Substance in urine	Treatment
Argininemia	Arginase	Spastic diplegia	Arginine, ornithine	Low protein diet
Hyper ornithinemia	Ornithine decarboxylase	Vomiting; lethargy	Ornithine	do
OTC deficiency	Ornithine transcarbamoylase	Lethargy; convulsion	Orotic acid; uracil;gln	do
CPS I deficiency	Carbamoyl phosphate synthetase I	Vomiting; lethargy	Glutamine	do
Arginino succinic aciduria	Arginino succinate lyase	Vomiting; trichorrhexis nodosa	Arginino succinate; citrulline	Arginine ↑ Protein ↓