Biochemistry
UNit-III

Lipid Metabolism :-

A lipid is a chemically defined as a Substance that insoluble in water and soluble in alcohol, ether and Chloroform.

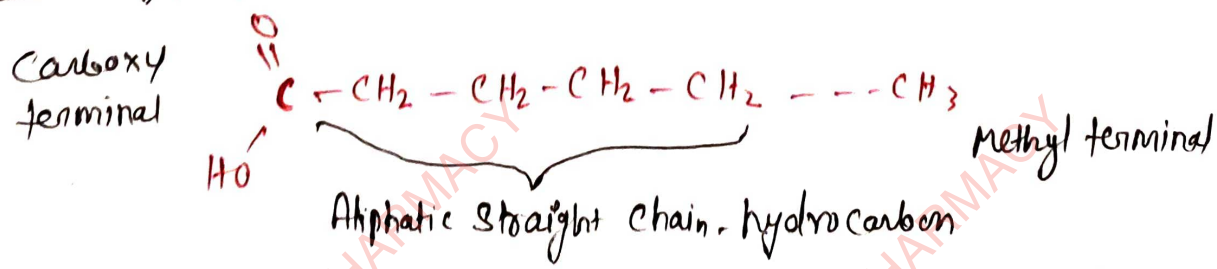
- Formation and break down of lipids is called lipid Metabolism which involves Lipogenesis (synthesis of lipid) and oxidation of fatty acid to produce energy.

- Fatty acids are Synthesised from Carbohydrates and proteins. Carbohydrate and lipid metabolism are closely related to each other.
- In mitochondria, fatty acids are oxidised to Acetyl CoA, utilising the fatty acid spiral.
- Finally, Citric Cycle along with electron transport chain Contributes in Conversion of acetyl CoA into ATP, CO_2 and H_2O.

Fatty acids :-

- Chemically, fatty acids are monocarboxylic acids with aliphatic Carbon chain.
- They are obtained in esterified form from animal or vegetable fat and oil.

Structure of fatty acid :-



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Type of fatty acid:-

Based on the no. of hydrogens present on the fatty acid structure, fatty acids are classified into 2 types.

(i) Saturated fatty acids
(ii) Unsaturated fatty acid.

① Saturated fatty acids:-

Fatty acids which Contain only Single 'H' bond in its structure is known as Saturated fatty acid.

② Unsaturated fatty acids:-

Fatty acids which Contain one or more than one 'H' bond in its structure is known as Unsaturated fatty acid.

☆ Oxidation of Saturated fatty acid (palmitic acid):-

By β-oxidation, fatty acids are broken down to Smaller units of acyl-CoA Molecule in mitochondria and peroxisomes to produce acetyl-CoA (The Starting Molecule of the Citric acid cycle).

- The β-oxidation of fatty acids occurs in three stages.

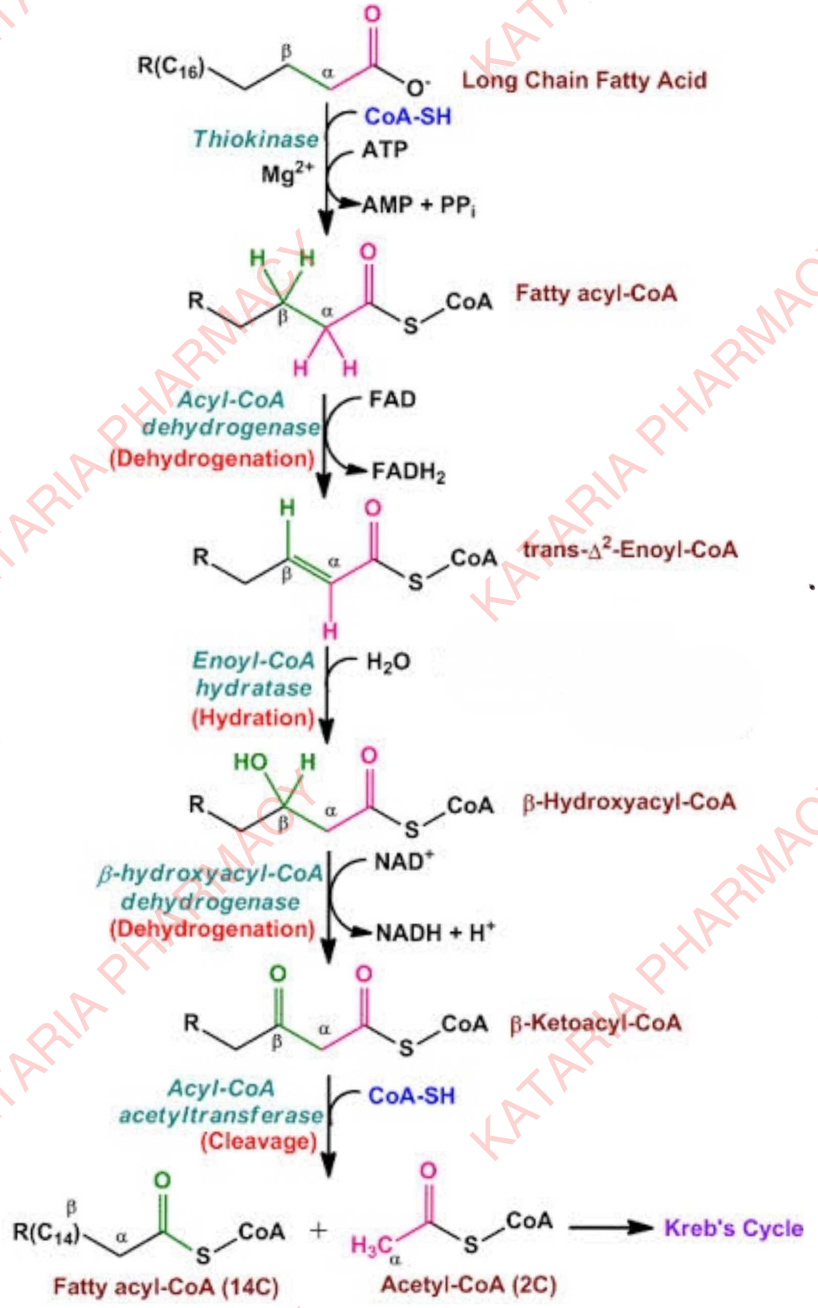
1. Activation of fatty acids in the Cytosol
2. Transport of activated fatty acid into the Mitochondria.
3. β-oxidation in the Mitochondrial Matrix.

① Activation of fatty acid in the Cytosol:-

In the presence of enzyme thiokinase or acyl CoA Synthetase, the fatty acids are activated to acyl CoA.

- This is a two-step reaction that required ATP, Coenzyme-A and Mg^{+2} ions:

1. Fatty acid and ATP reacts to form acyladenylate.
2. Acyladeylate combines with Coenzyme-A yielding acyl CoA.



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(2) Transport of activated fatty acids into the Mitochondria :-

The Membrane of Mitochondria is impermeable to fatty acids. therefore required Specialised Carnitine Carrier System to transport active fatty acids from Cytosol to the Mitochondrial Matrix.

(3) β-oxidation proper :-

Every β-oxidation Cycle gives one Molecule of two Carbon Compound acetyl CoA.

- The β-oxidation Comprises of following four reaction.

(i) oxidation :-
Dehydrogenation of acyl CoA occurs by the FAD-dependent flavoenzyme, acyl CoA dehydrogenase. In this reaction double bond is formed b/w α and β Carbon.

(ii) Hydration :-
Enoyl CoA hydratase Causes hydration of the double bond producing β-hydroxyacyl CoA.

(iii) oxidation :-
In the second oxidation, β-ketoacyl CoA is formed and NADH is generated. The reaction is Catalysed by β-hydroxy acyl CoA dehydrogenase.

(iv) Cleavage :-
In the ~~step~~ of last Step of β-oxidation, two Carbon atoms are removed from acetyl CoA to form acyl CoA. This reaction is referred as thiolytic Cleavage and is Catalyses by β-ketoacyl CoA thiolase.

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☆ De Novo Synthesis of fatty acid (palmitic acid) :-

De novo Synthesis of fatty acids or Biosynthesis of fatty acids occurs in liver, kidney, adipose tissue and Lactating mammary gland.

- Acetyl CoA is the Source of Carbon atoms while NADPH provides the reducing equivalents and ATP Supplies energy for fatty acid formation.

- The fatty acid Synthesis occurs in 3 Stages.

1. Production of acetyl CoA and NADPH
2. Conversion of acetyl CoA to Malonyl CoA
3. Reaction of fatty acids Synthase Complex.

① production of acetyl CoA and NADPH :-

Acetyl CoA is produced in the Mitochondria by the oxidation of pyruvate and fatty acids, degradation of Carbon Skeleton of amino acid and form ketone bodies.

→ Transport of acetyl CoA from Mitochondria to Cytosol.

→ Degradation of citrate in Cytosol.

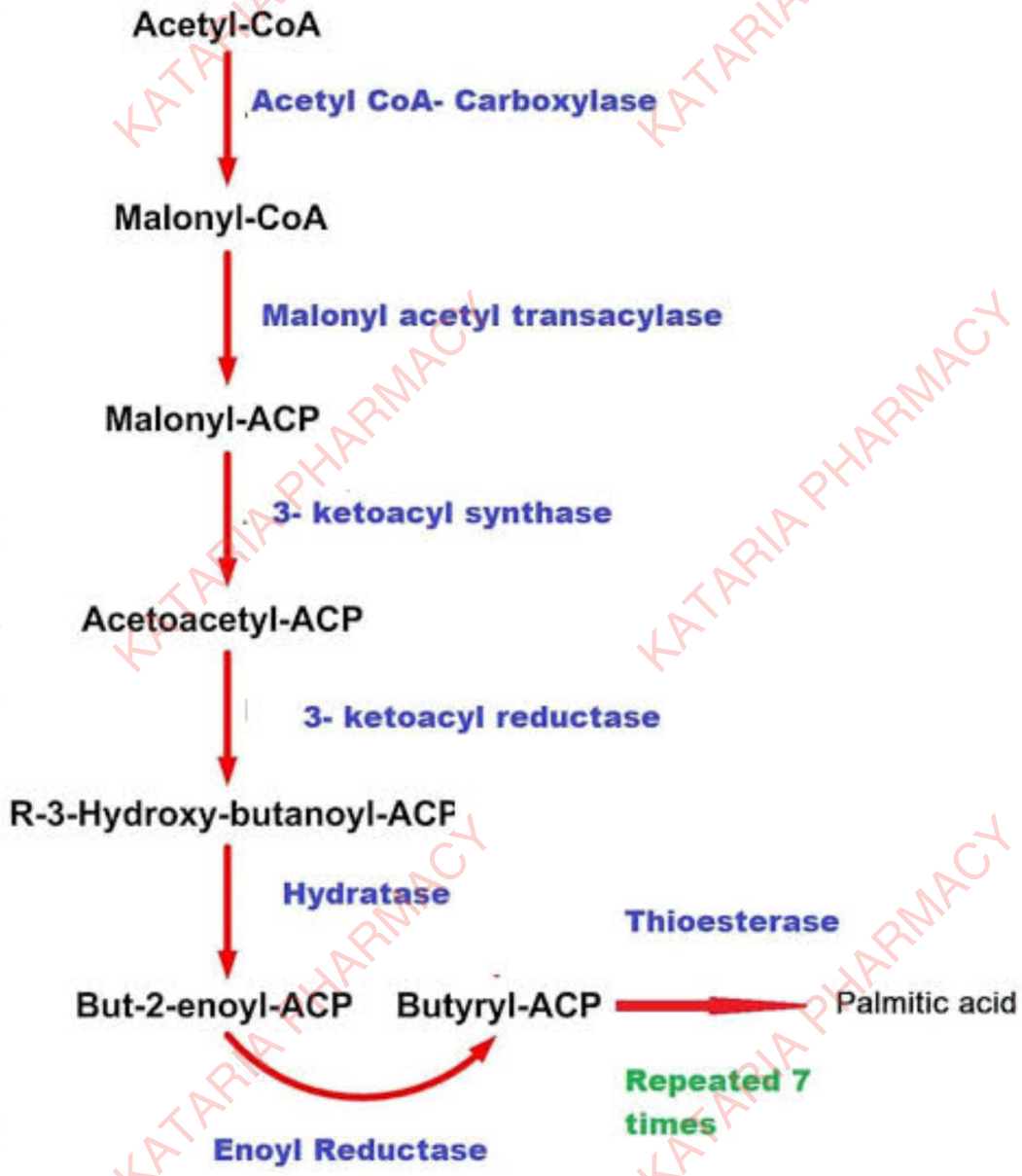
② Conversion of acetyl coA to Malonyl CoA :-

Acetyl CoA is Carboxylated to malonyl CoA with the help of enzyme. acetyl CoA Carboxylase.

→ Reaction with fatty acid ~~Biotin~~ Synthase Complex enzyme.

(3) Reaction with fatty acid Synthase Complex enzyme :- (44)

Fatty acid Synthase in multiple enzyme complexes acts as dimer dimer with two similar units. As Malonyl CoA is Synthesised, the remaining reaction occur with fatty acid Synthase Complex.



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* Formation and Utilization of ketone bodies :-

The ketone bodies or acetone bodies comprises of three substances acetoacetic acid, D(-). β-hydroxy butyric acid, and acetone.

- A condition in which there is an increased level of ketone bodies in the blood (ketonaemia) or urine (ketonuria) is known as ketosis.

Formation of ketone bodies (Ketogenesis) :-

Ketogenesis is the synthesis of ketone bodies. In this the excess acetyl CoA (From oxidation of fatty acid, pyruvate or some amino acid) is transfered into ketone bodies by the liver cells. This takes place in the liver a site for

- Takes ketone bodies production.

- ketogenesis involves the following reaction -

1. Acetoacetyl CoA is formed by condensation of two moles of acetyl CoA.
2. The β-hydroxy-β-methyl glutaryl CoA is produced by combining of acetoacetyl CoA with a molecule of acetyl CoA. The catalysing enzyme for ketone body synthesis is HMG CoA Synthase.
3. HMG CoA Lyase cleaves HMG CoA giving aceto-acetate and acetyl CoA

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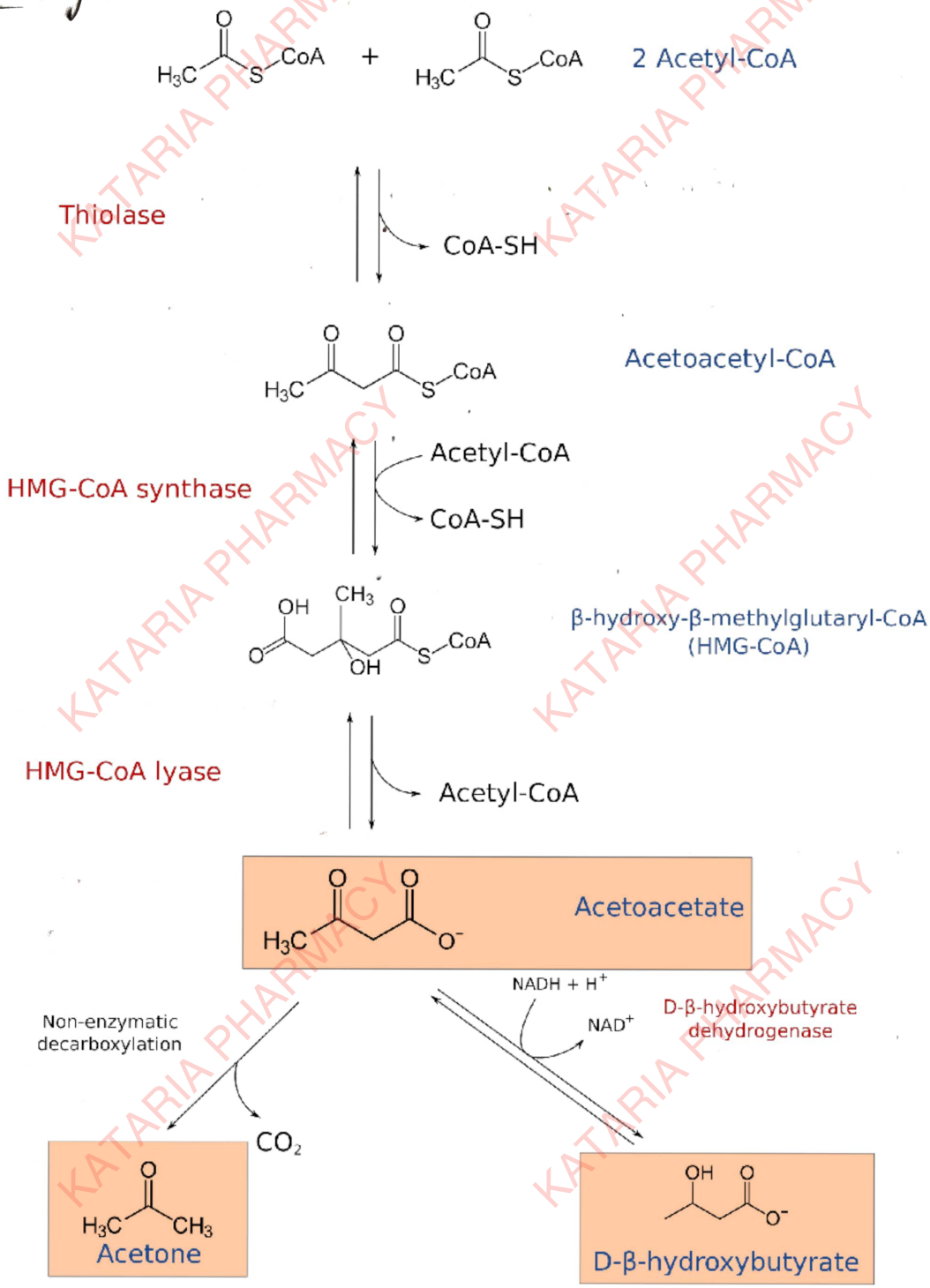
4. Spontaneously, acetoacetate decarboxylases to produce acetone
5. Dehydrogenase reduces acetoacetate yielding β-hydroxy-butyrate.

Pathway -



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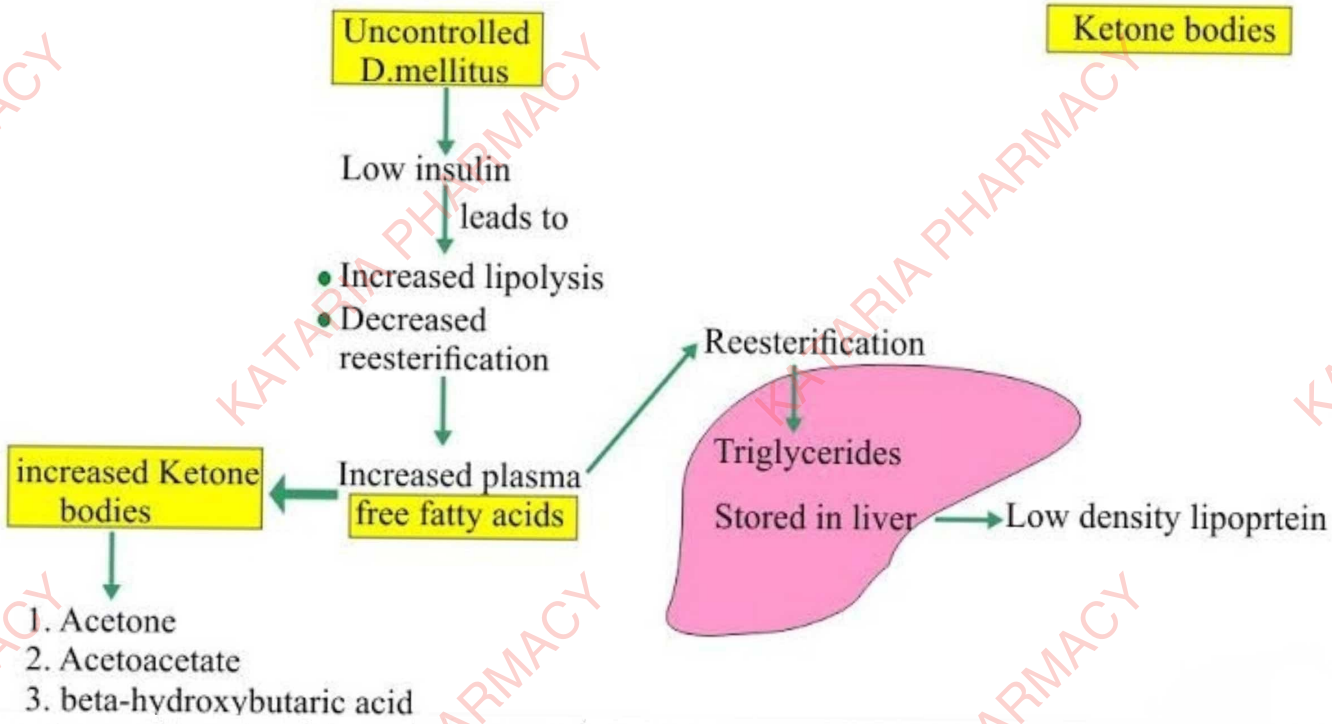
Utilisation of ketone bodies :-

Ketone bodies produced in the liver circulates in the blood and are taken up to be utilised by peripheral tissues such as Muscle.

- During a prolonged fasting condition, the brain cells start utilising the ketone bodies.
- The reaction forms acetoacetyl CoA and Succinate.

Pathway



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- The Succinate can be further metabolised by the Citric acid cycle. and the acetoacetyl CoA is acted upon by thiolase to yield two molecules of acetyl CoA.

Ketoacidosis :-

ketone bodies are produced when body burns fat for energy. If insulin level is decrease in body, ketone bodies will begin to build-up in bloodstream will result in a life-threatening condition known as ketoacidosis.

Types :- Along with general ketoacidosis, there are some specific type like.

1. Alcoholic ketoacidosis, Caused by excessive alcohol consumption.
2. Diabetic ketoacidosis, occuring due to type I diabetes.
3. Starvation ketoacidosis. Commonly seen in pregnant women. in the trimester, and experiencing excessive vomiting.

Symptoms :-

(i) Alcoholic ketoacidosis :-

- pain in abdomen
- confusion and agitation
- fatigue
- slowed movement
- loss of apetite
- Dehydration.

(ii) Diabetic ketoacidosis :-

- Abdominal pain
- Confusion.
- Deep and rapid breathing
- Fatigue
- Increased blood glucose level
- Nausea and vomiting

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Diagnosis :-

(i) Alcoholic ketoacetosis :-

- Amylase and lipase test.
- Arterial blood Gas test.
- Blood alcohol test.
- Blood glucose test.
- Urine test.

(ii) Diabetic ketoacetosis

- Blood test
- Urine test.

Treatment :-

(i) Alcoholic ketoacidosis :-

- Vitamines and following nutrients are given immediately to treat Malnutrition.
  - Thiamine
  - potassium
  - phosphorus
  - magnesium.

(ii) Diabetic ketoacidosis :-

- Resuscitation of fluids
- Acidosis and ketosis Reversal.
- Lowering plasma glucose. Conc. to normal.

Following medication :-

(1) Rapid-acting insulin e.g insulin aspartate
(2) Short-acting Insulin. e.g regular insulin
(3) Electrolyte Supplement e.g potassium chloride
(4) Alkalinising agent e.g. sodium bicarbonate.

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☆ Biological Significance of Cholestrol :-

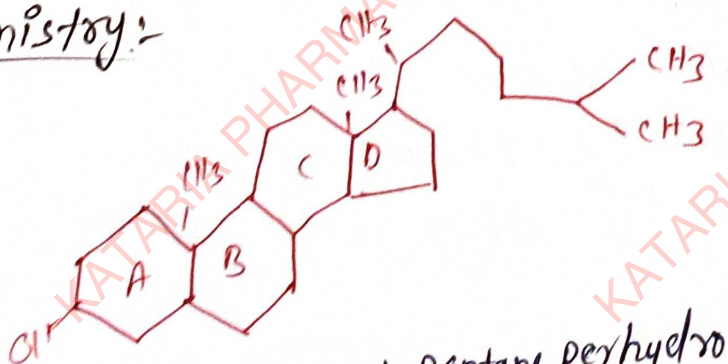
- Cholestrol is a lipid found in the Cell Membrane of all animal tissue.
- The name cholestrol originated from greek word 'chole' meaning 'bile', steros' meaning "solid".
- cholestrol is amphipathic in nature that it structure has both hydrophilic and hydrophobic properties.
- Cholestrol is very important for the mammalian tissue.
- It serves as a precursors for the synthesis of bile, salts, steroids, hormones, vitamine D and neutral steroids.

Source :-

Cholestrol is a major sterol occuring in brain, Spinal cord, nervous tissue, adrenal gland, Gallstone, fish liver oil, and eggs of animals.

- It is found in all animal cells and animal based food ~~it is~~

Chemistry :-



Cyclo pentane perhydro phenthrene.

(S1)

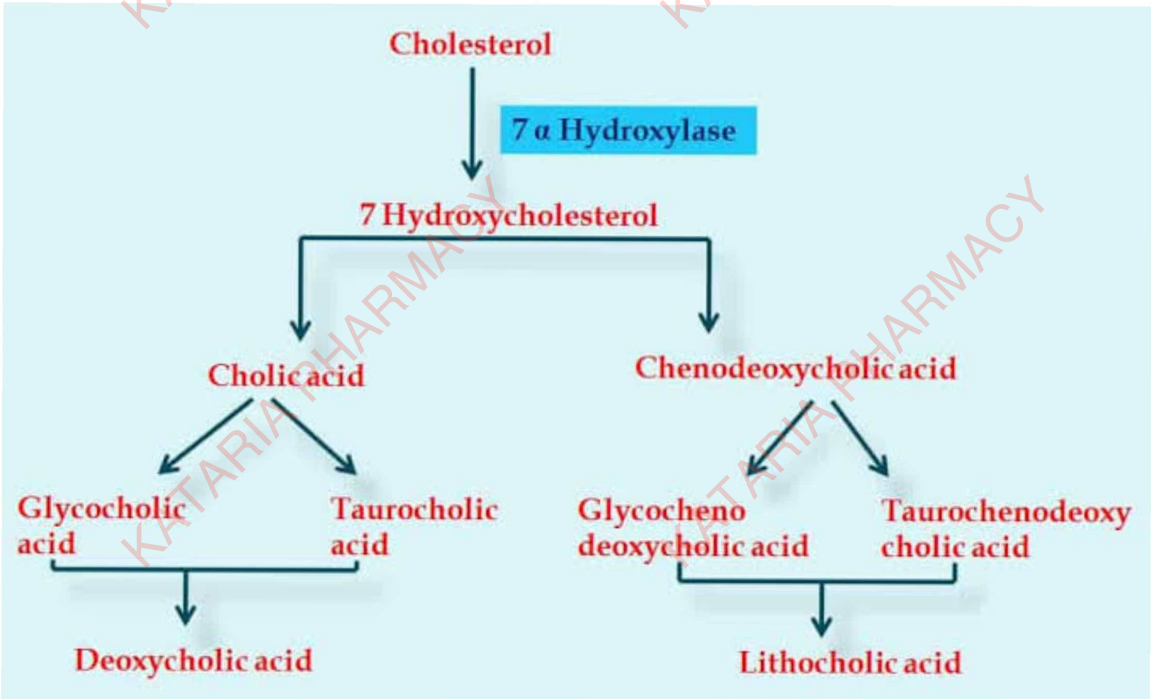
—Cholestrol has a molecular formula $C_{27}H_{46}O$ and consists of steroidal ring with 19 carbon atoms and a side chain comprising of 8 carbon atoms.

Biochemical Role of Cholestrol :-

- Cholestrol serves as a precursors for the synthesis of vit. D
- Cholestrol serve as a precursor for the synthesis of steroidal hormone like.

① Glucocorticoids (eg: Cortisol) in adrenal gland
② Mineralocorticoids (eg Aldosterone) in adrenal gland
③ Androgens (eg Testosterone) in testes
④ Progestins (eg progesterone) in ovaries
⑤ Estrogens (eg estrodiol) in ovaries.

Conversion of cholestrol into bile acids :-

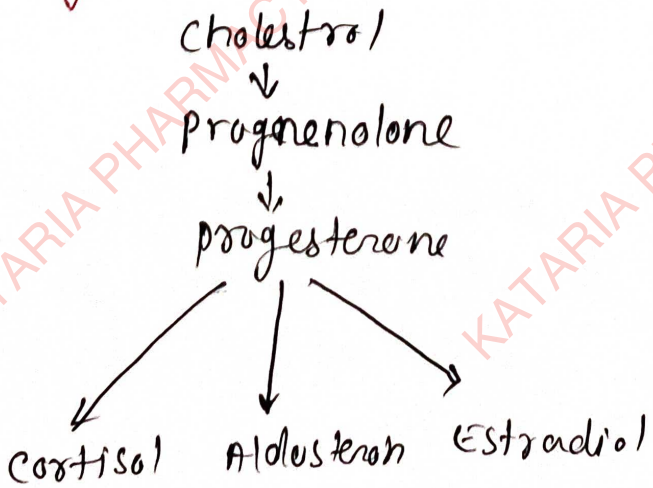


- The Synthesis of primary bile acids takes place in the liver and involves a series of reaction.
- The Step Catalysed by 7-α-hydroxylase reaction.
- Cholic acid and chenodeoxycholic acid are the primary bile acids and the former is found in the largest amount in bile.
- Conjugation with glycine or taurine. Conjugated bile acids (glycocholic acid, taurocholic acid etc) are formed. In the . Conjugated bile acids exist as Sodium and potessium salts which are known as bile salts.
- In intestine, primary bile acids undergoes deconjugation and dehydroxylation to form Secondry bile acid.

(deoxycholic acid and Lithocholic acid).

- These reaction are catalysed by bacterial enzymes in the intestine.

Conversion of Cholestrol to Steroid hormones :-



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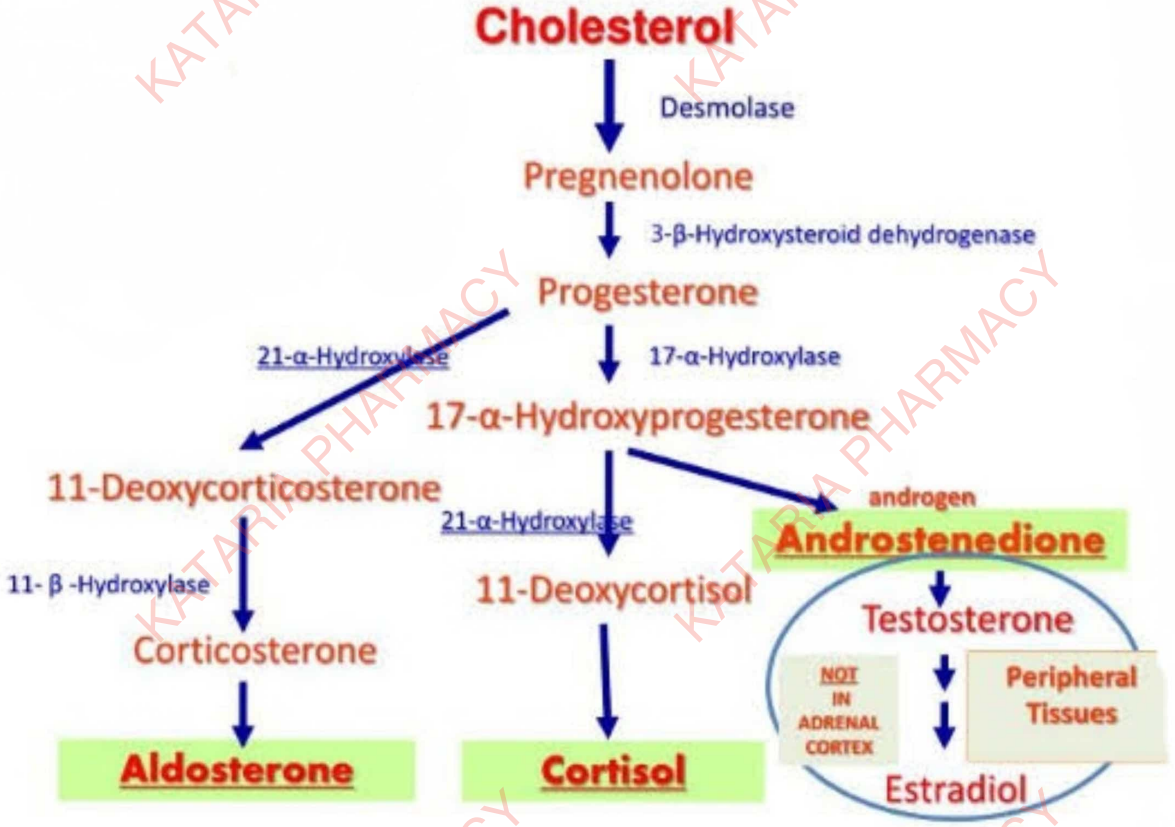

- Cholestrol is the precursor for the Synthesis of all the five Classes of Steroid hormones.

(a) Glucocorticoids Eg Cortisol
(b) Mineralocorticoids E.g aldosterone
(c) Progestine Eg. progesterone
(d) Androgens Eg Testosterone
(e) Estrogens Eg :- estradiol.

Conversion of vitmine D on the Surface of skine :-

7- dehydrocholestrol, an intermediate in the Synthesis of Cholesterol is Converted to Chole Calcitrol (vitamine-D) by Ultraviolet rays in the skin.

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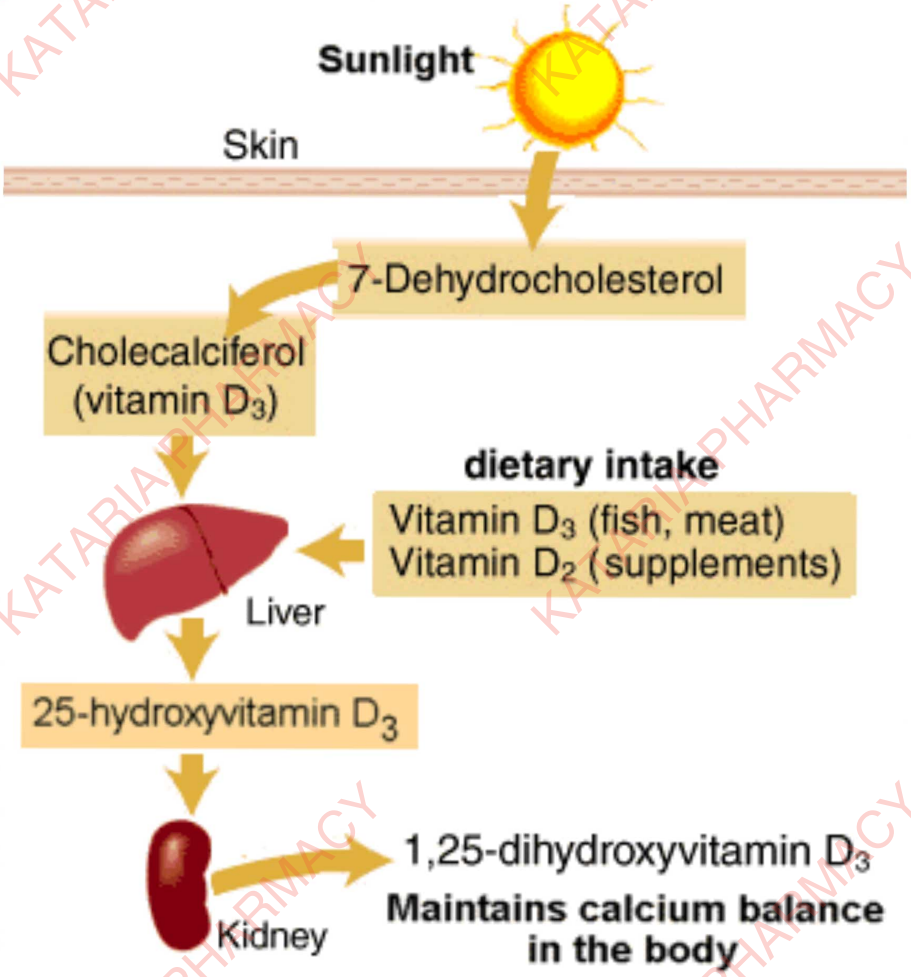
pathway :-



- Vitamin D helps in the regulation of Calcium and phosphorus metabolism.

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✱ Disorder of lipid metabolism :-

→ Lipids (or fat) are important source of energy for the body.

(i) Hypercholesterolemia :-

- Hypercholesterolemia is a condition of high cholesterol levels in the blood.
- Cholesterol, a wax-like, fatty substance is produced in the body as well as obtained from animal-derived foods (e.g. egg yolks, meat, poultry, fish, and dairy products)

(ii) Atherosclerosis :-

Formation of plaque inside the arteries (blood vessels carrying oxygen-rich blood to heart and other body parts) is refered as as state of atherosclerosis.

- Atherosclerosis may lead to further complication like heart attack, stroke even death.

(3) Fatty liver :-

Fatty liver of hepatic steatosis defines excessive fat accumulation in liver accounts for more than 5-10% of liver's weight.

- Fatty liver condition can controlled by making certain changes in lifestyle.
- Alcoholism and heavy drinking are the most common causes of fatty liver.

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(4) Obesity :-

Obesity is a Condition of abnormal increase in body weight due to excessive fat deposition.

- Obese men and women show 20% and 25% of increase in their body weight, respectively due to accumulation of fat in adipose tissue.
- Obesity is the result of over-eating, i.e excessive intake of Calories in diet and lack of physical activity.

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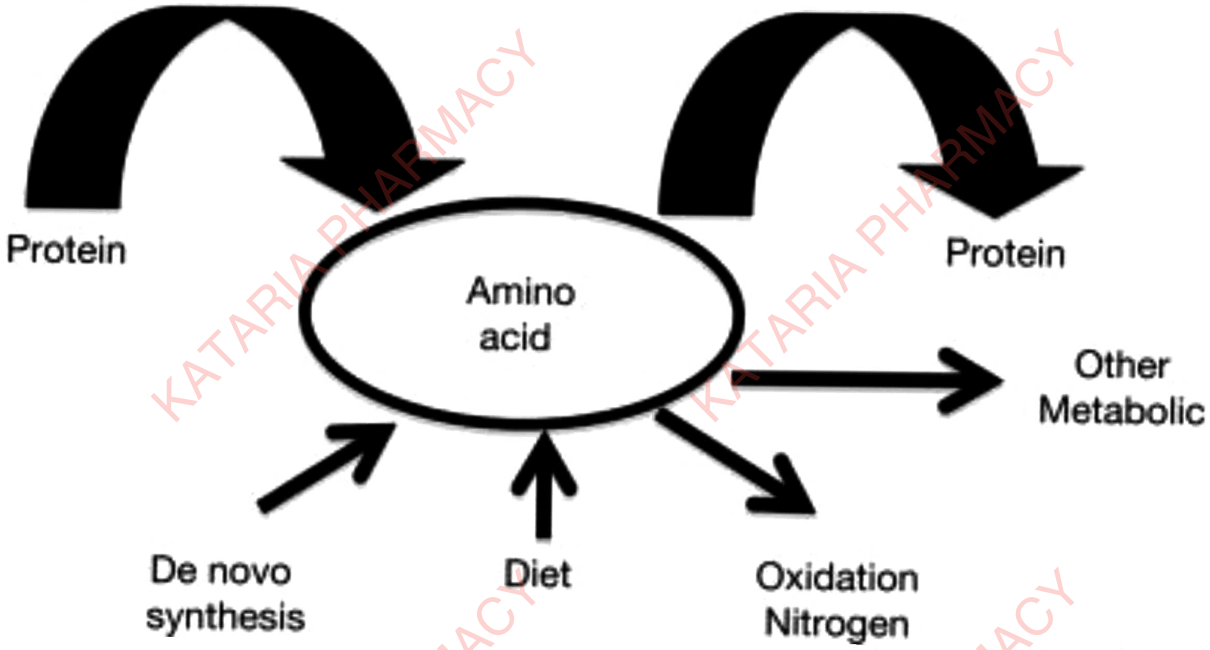
☆ Amino acid Metabolism :-

- Proteins undergo breakdown into Smaller units Called Amino acids.
- The amino acid Molecules are absorbed by liver and other tissues, and participate in the production of protein for tissues, enzymes and hormones.
- Nitrogen obtained from the breakdown of amino acids is utilised in the Synthesis of nitrogeneous Substance like Creatinine and Choline.



Amino acid Metabolism

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✱ General Reactions of Amino acid Metabolism:-

In the metabolism of amino acid following processes are involved -

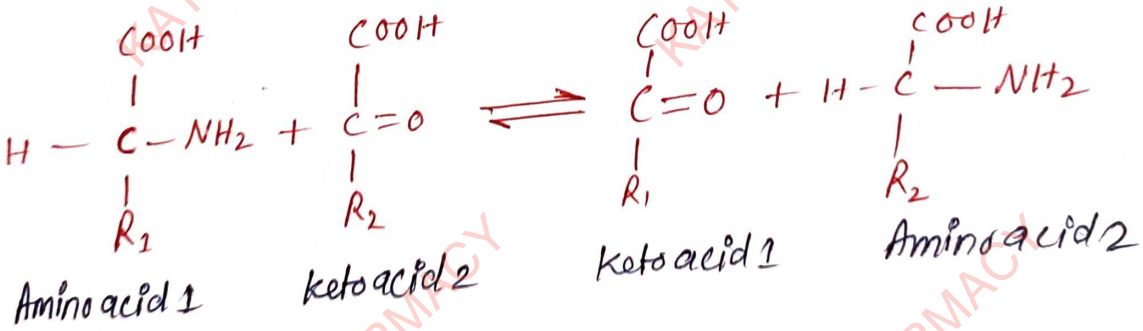
① Transamination
② Deamination
③ Decarboxylation

① Transamination:-

Transamination reaction involved exchange of an amine on an acid with a ketone group on another acid, just like double replacement reaction.

Transamination reaction is defined as transfer of an amine group from one molecule to another in the presence of enzyme of family Transaminases.

The basic reaction of transamination can be written as:



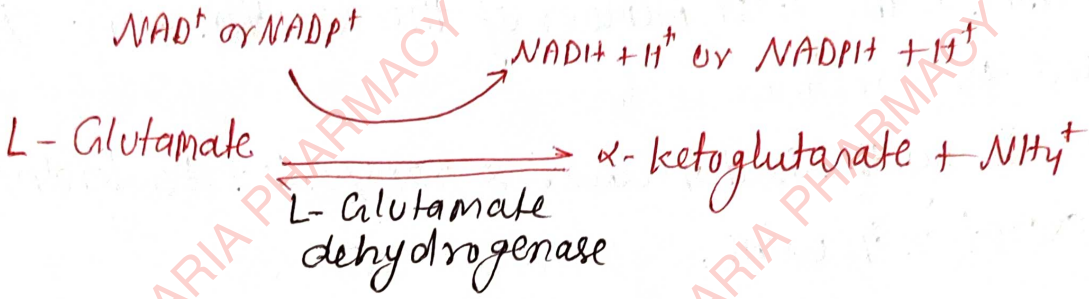
② Deamination:-

- Removal of amino ~~acid~~ group from amino acid as NH_3 is called deamination.
- The ammonia thus produced participates in urea synthesis and the remaining Carbon skeleton of amino acid is Catabolised into keto acid.

- Deamination is of two types - oxidative and Non-oxidative.

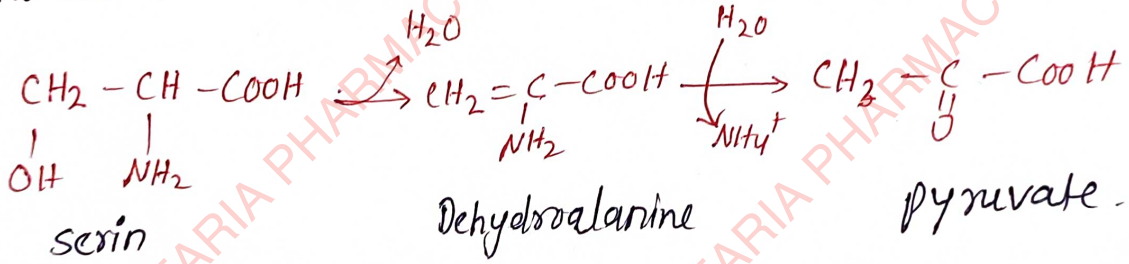
(i) oxidative deamination :-

oxidative deamination by Glutamate dehydrogenase



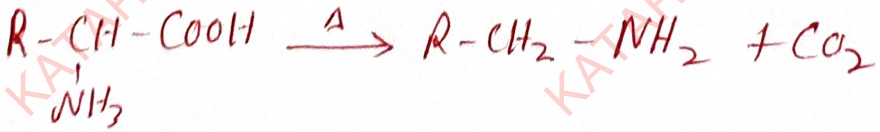
(ii) Non-oxidative deamination :-

Following enzyme Catalyse non-oxidative deamination of amino acids.



(3) Decarboxylation :-

- Amino acid are decarboxylated by dry distillation or by heating with bases such as barium oxide.
- There are some specific enzymes which Catalyse the decarboxylation of specific amino acid.



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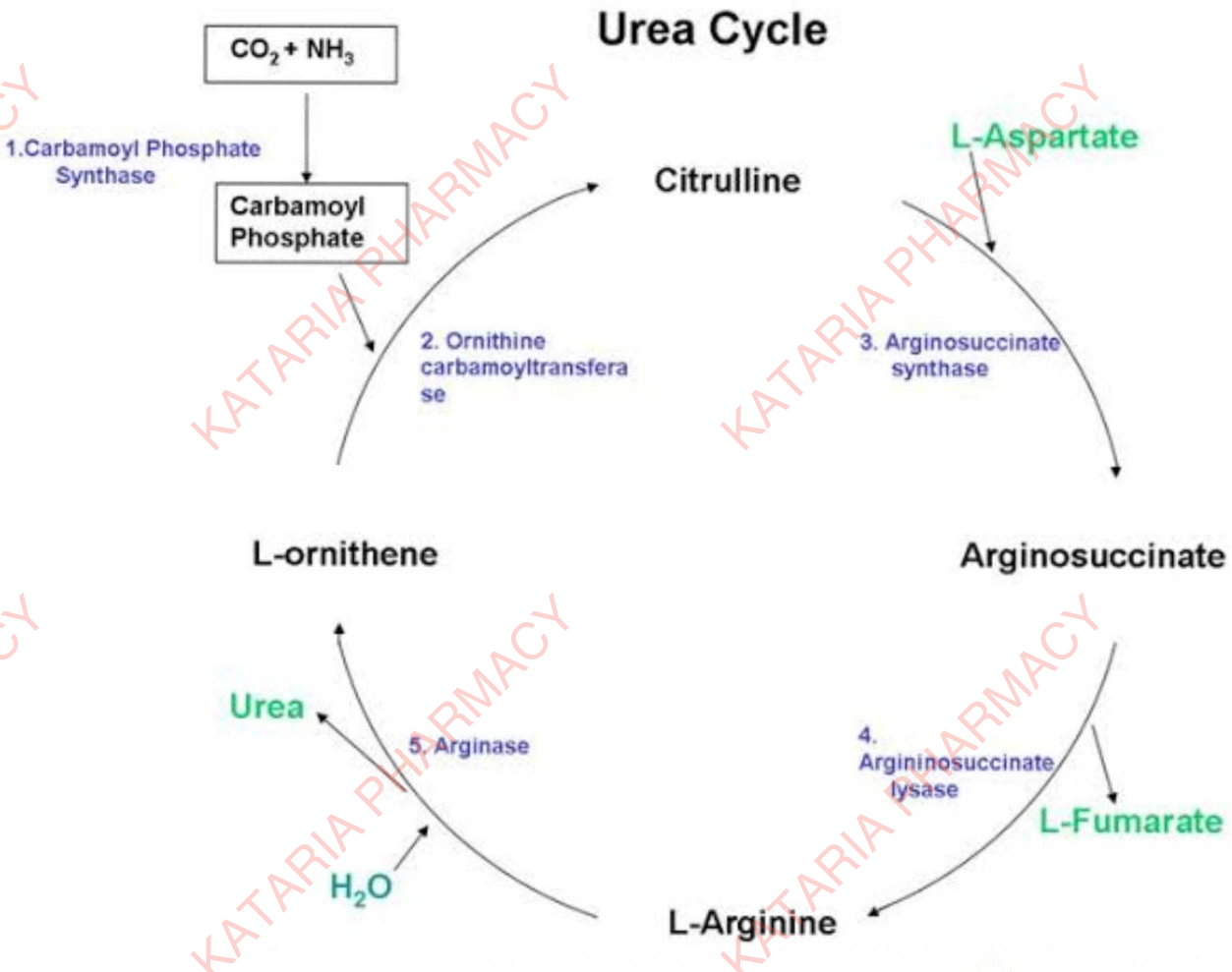
☆ Urea Cycle :-

- The urea cycle is the first metabolic pathway to be elucidated.
- The cycle is known as Krebs-Henseleit urea cycle
- Ornithine is the first member of the reaction it is also called as ornithine cycle.
- Urea is synthesized in liver & transported to kidney for excretion in urine.



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Disorder of Urea Cycle :-

Urea formation is adversely affected in various inherited disorder. The disorder result due to deficiency of enzyme required in urea cycle.

- Following metabolic defects associated with these enzyme.

① Hyper Ammonemia Type-I :-

This disorder occur due to deficiency of Carbamoyl phosphate Synthetase I which leads to mental retardation.

② Hyper Ammonemia Type-II :-

Deficiency of the enzyme ornithine transcarbamoylase causes accumulation of Carbamoyl phosphate and diverts to pyrimidine formation. It leads to excretion of oroticacid and uracial in the urine.

③ Citrullinemia :-

In this deficiency of the enzyme arginosuccinate Synthetase causes accumulation of citrulline in the blood and its excreation in urine.

④ Argininosuccinic Aciduria :-

In this Condition argininosuccinate enzyme remains absent which causes accumulation of argininosuccinate in the blood and its excretion in urine.

⑤ Hyperarginemia :-

Low arginase activity causes accummulation of arginine and its excreation in urine.

⑥ N-Acetyl Glutamate Synthetase Deficiency.

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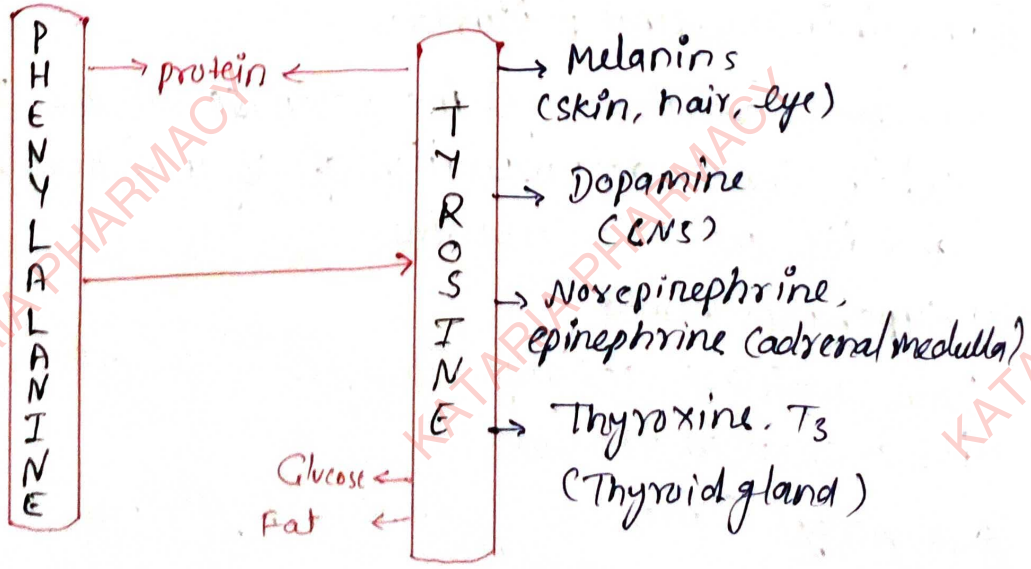
✱ Catabolism of phenylalanine and tyrosine :-

- phenylalanine and tyrosine are aromatic amino acid with structural similarities.
- phenylalanine belongs to essential and tyrosine to non-essential catagory of amino acid.
- phenylalanine metabolism takes place by tyrosine.
- Tyrosine is incorporated into proteins and participates in the synthesis of many significant biological compounds like · epinephrine, nore-epinephrine, dopamine (catecholamine) melanin (pigment) and thyroid hormones.
- on degradation phenylalanine and tyrosine become metabolites acting as precursors for glucose and fat synthesis.
- Thus, both these amino acids functions as glucogenic and ketogenic amino acids.
- phenylalanine and tyrosine metabolism ↴



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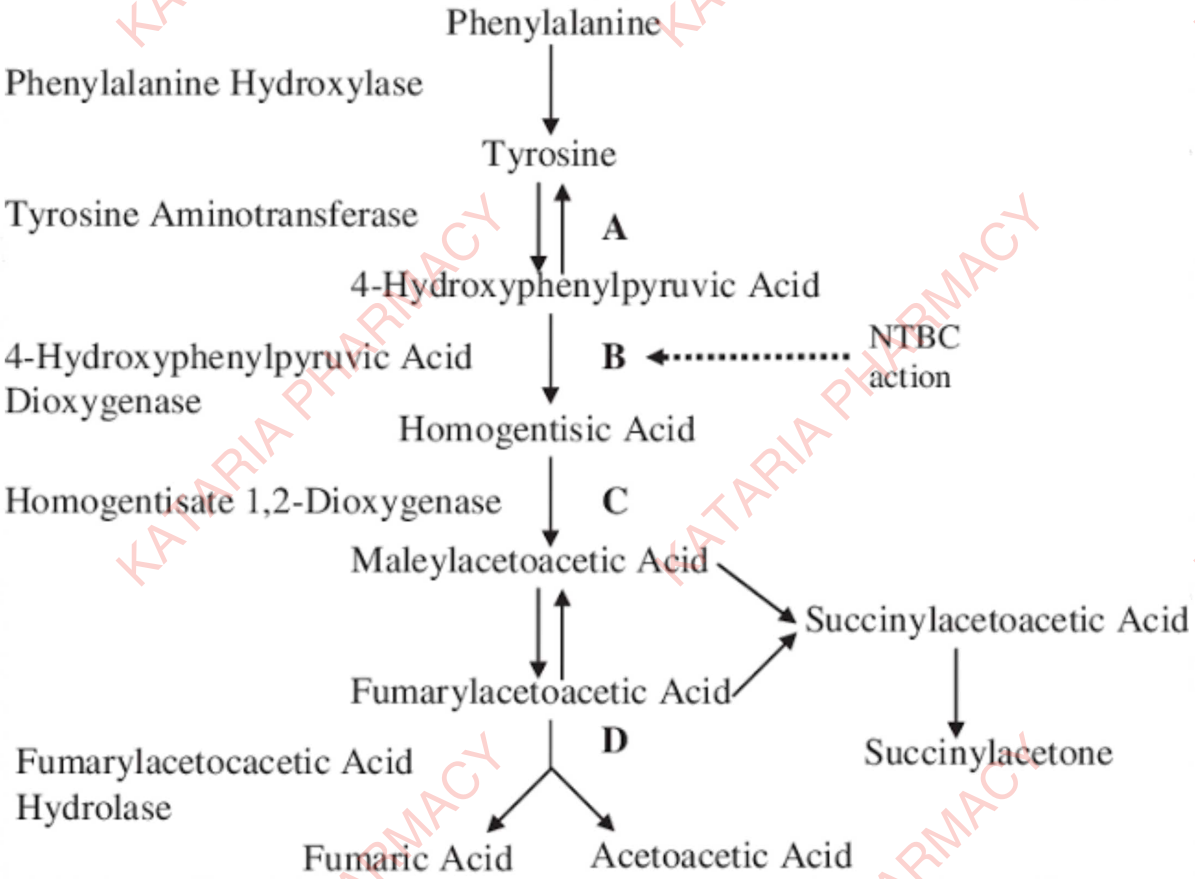
pathway :-



Metabolic disorder :-

- phenylalanine and tyrosine both are metabolised in the cytosol

① phenyketonuria :-

- phenylketonuria is a congential or inborn error of phenylalanine metabolism, related with the inability to convert phenylalanine to tyrosine.
- The pku is a genetic disorder and is inherted in an autosomal recessive manner.
- The rate of incidence of pku is about 1 in 20,000 new-borns.
- In pku, phenylanine is accumulated in tissue and blood.

② Albinism :-

Albinism is a group of conditions, in which error occurs in tyrosine metabolism and thus defective melanine synthesis occurs.

Such individual have little or NO Colour (pigment) in the skin, hair and eys.

③ Alkeptonuria :- (Black urine disease)

Alkeptonuria is a rare genetic disorder involving Less production of enzyme Homo-Gentisic-Dioxygenase (HGD)

- This enzyme is utilised in the degradation of a toxic substance called homogentisic acid.
- Lack of HGD causes accumulation of homogentisic acid in the body.

④ Tyrosinemia :-

Tyrosinemia is a hereditary metabolic disorder which involves body's inability to effectively breakdown amino acid tyrosine.

- This inability to breakdown the amino acid tyrosine is resulted due to the deficency of the Fumaryl Acetoacetate hydrolase (FAH) enzyme, essential for tyrosine metabolism.
- If not treated, tyrosine and its by-product accumulate in the tissue and organs.
- This Condition May leads to Severe Medical Condition with liver, kidney and CNS (mental retardation)

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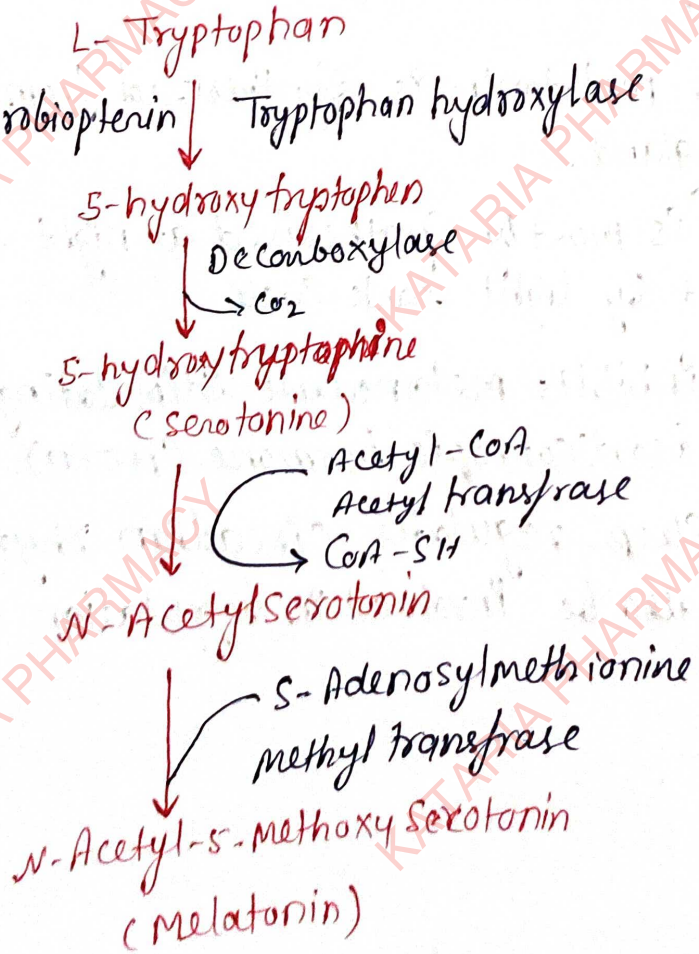
✱ Synthesis and Significance of biological Substance :-

1. 5-HT
2. Melatonin
3. dopamine
4. nonadrenaline
5. adrenaline

① 5-HT (Hydroxy Tryptophan) :-

Tryptophan is metabolised through Serotonin pathway to yield 5-hydroxy Tryptophan.

#pathway :-



Significance of 5-HT :-

- Clinically, Serotonin is responsible for Mood fluctuations, depression and carcinoid tumours.
- In the brain it acts as transmitter in Serotonergic neurons. Serotonine is involved its various behavioural patterns in humans like.
  1. Sleep
  2. perception of pain
  3. Social behaviour
  4. Schizophrenia
  5. Mental depression.

(2) Melatonin :-

The hormone melatonin is synthesized from Serotonin by the pineal gland.

- Melotonin is mostly synthesised at night and its synthesis is regulated by light dark cycle.
- Melatonine inhibits melanocyte Stimulating Hormone (MSH) and Adrenocorticotropic hormone (ACTH).
- It induce sleep, regulates circadian rhythm of body and may also be involved in regulation of reproductive function.

pathway — ✓ Next

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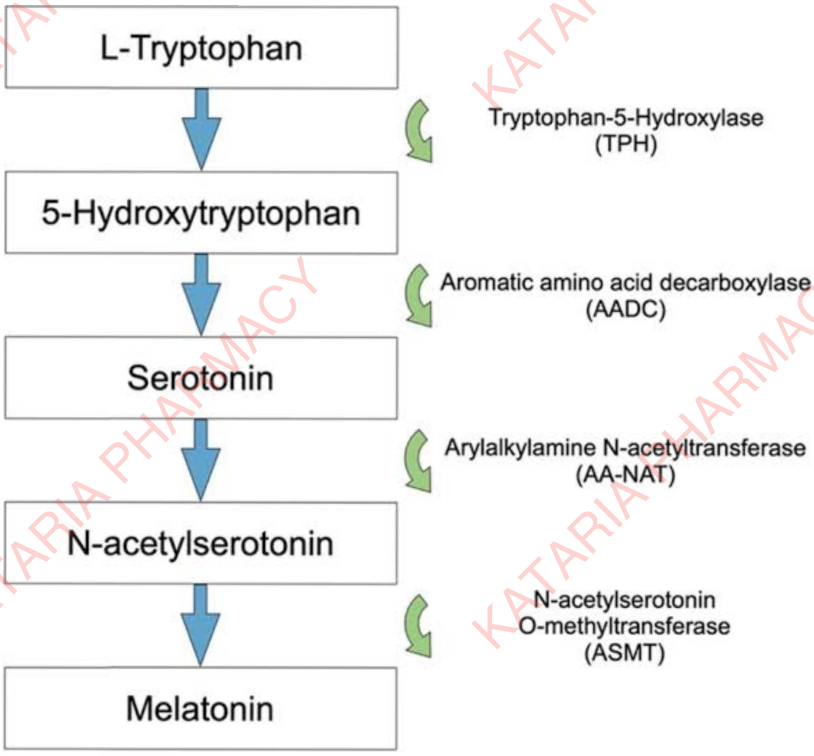
pathway :-



Significance of Melatonin :-

- Involved in circadian rhythums or diurnal variation of the body.
- It plays a significant role in sleep and wake process.
- It inhibit the production of MSH and ACTH hormones.
- Melatonin also performs a neurotransmitter function.

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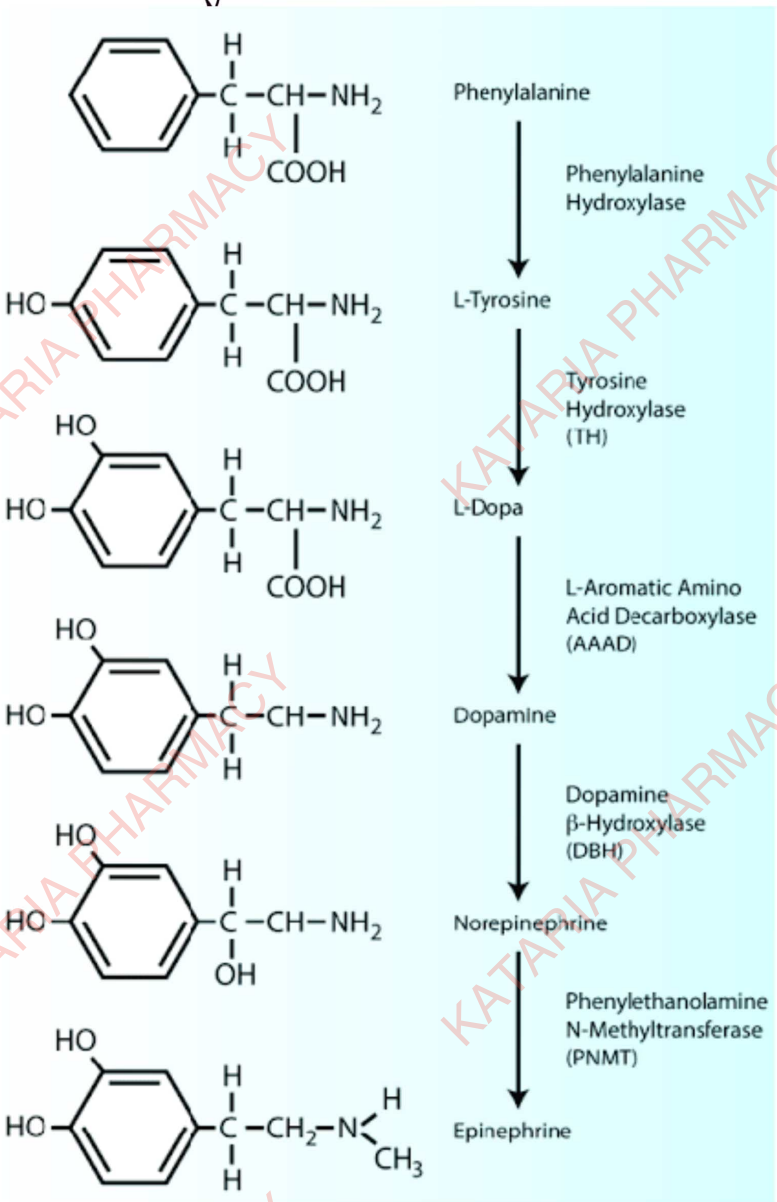
(3) Catecholamine (Dopamine, Norepinephrine & Epinephrine) :-

- The Compounds with dihydroxylated phenyl ring are referred as Catechol and the amine derivatives of Catechol are named as Catecholamines.
- Various Catecholamines, namely dopamine, norepinephrine and epinephrine (adrenaline) are Synthesised from amino acid Tyrosine.
- Tyrosine Converts into Catecholamines in adrenal medulla and central nervous System.

pathway :-



Significance of Catecholamine :-

- Norepinephrine and epinephrine control metabolism of carbohydrates and lipid.
- Degradation of triglycerol and glycogen is stimulated by these hormones.
- They are also responsible for increase in the blood pressure.
- Dopamine and norepinephrine function as neurotransmitter for brain and autonomous nervous system

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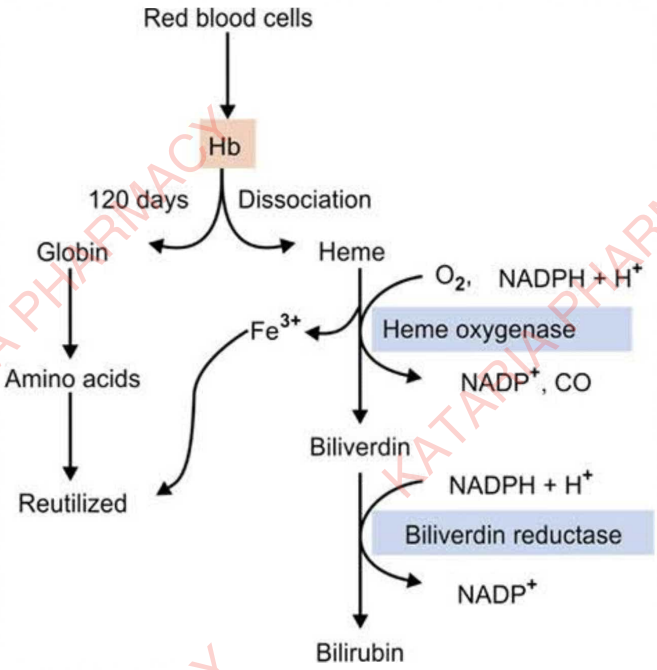
★ Catabolism of heme :-

Heme is present as prosthetic group in various proteins (such as haemoglobin, myloglobin, cytochrome, and cytochrome P450) and enzymes (such as Catalase Certain peroxidase and Tryptophan pyrrolase).

- Heme is synthesised in almost all the cells but largely in the bone marrow and liver cells because here heme requirement is high as it incorporated haemoglobin and Cytochromes.
- Heme biosynthesis has three stages

1. Biosynthesis of δ-Aminolevulinate (ALA) from the precursor Glycine Succinyl-CoA.
2. Formation of porphobilinogen (PBG) from two molecules of δ-aminolevulinate.
3. Conversion of the porphobilinogen to the Cyclic tetrapyrrol porphyrin ring and heme.

Pathway -



(71)

- Heme is Catabolised in the microsomal fractions of Cells in the presence of Complex enzyme system called heme oxygenase, by the NADPH and O_2.
- A green pigment, biliverdin is formed with the release of ferric ion and Carbon Monoxide (CO). Biliverdin is them reduced to give bilirubin (reddish orange Colour) Bile pigment Comprise of bilirubin and its derivatives.

✱ Hyperbilirubinaemia :-

The normal Concentration of serum bilirubin is :

1) Total bilirubin = 0.1 to 1.0 mg/dL
2) Conjugated (direct) bilirubin = 0.1 to 0.4 Mg/dL
3) Unconjugated (indirect) bilirubin = 0.2 to 0.7 mg/dL

- The Serum bilirubin Concentration rises due to any disease or Condition that obstructs the bilirubin Synthesis
- If bilirubin Concentration in blood is increased to 1 mg/dL, the Condition is known as hyperbilirubinaemia
- Hyperbilirubinaemia may result due to

1. Increased bilirubin production
2. Decreased hepatic uptake
3. Decreased hepatic Conjugation
4. Decreased excretion of bilirubin into bile.

* Jaundice :-

Jaundice refers to yellow Colouration of the skin, the mucosa and the Sclera (white of the eye), resulting from accumulation of bilirubin in the skin and mucous membranes.

Types :-

① Pre-Hepatic Jaundice :-

This type of jaundice is due to a defect in the functioning of liver to adequately remove the increase levels of bilirubin from the blood (due to haemolysis of red blood cells).

② Hepatic Jaundice :-

This type of jaundice is due to a defect in the functining of liver to properly metabolise and excrete bilirubin (due to a defect in capturing, conjugating and excreting bilirubin by liver.

③ post-Hepatic jaundice :-

This type of jaundice is due to an obstruction in the flow of bile (due to the obstruction of extra hepatobiliary system.

Symptoms :-

- weakness
- Diarrhoea
- Anaemia
- weight loss
- Itching of skin
- Fatigue
- yellowing of skin, eye, nails.