Pharmaceutical Chemistry – II (Biochemistry)

faiq production

PORPHYRINS

_ Introduction:

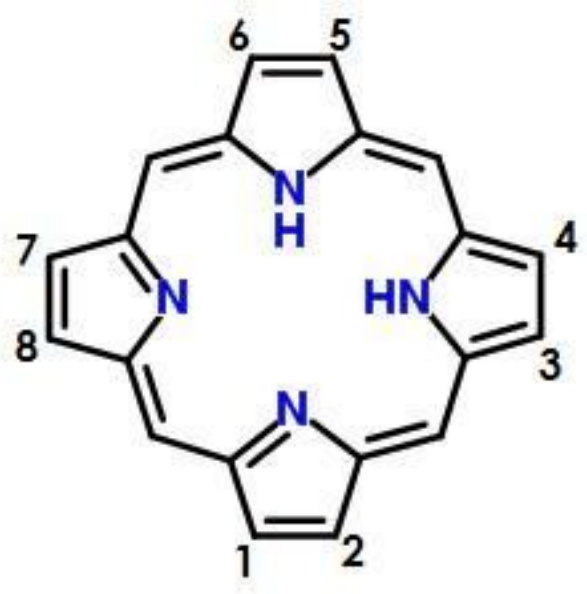
- Porphyrin is named from the ancient Greek word *porphura*, meaning purple.
- They're group of **heterocyclic** macrocycle organic compounds formed by fusion of four pyrrole rings joined at their alpha carbon atom via methine bridges (**=CH–**).
- The parent porphyrin is porphin, and substituted porphines are called porphyrins.
- They are aromatic and colored compounds.
- They have rigid, square-planer structure.
- They absorb the light intensity at or close to 410 nm.
- There are 26 electrons in conjugated system.

Chemistry:

- A porphyrin has four of its nitrogen atoms facing the centre, which can capture a metal ion to form a very suitable/stable organic metallic complex.
- When forming a complex, many metal ions accept six coordinating ligands to assume an octahedral configuration.
- They bind metals to form complexes. The metal ion usually has a charge of 2^+ or 3^+.
- For example: ○ Hemoglobin ○ Chlorophyll ○ Vitamins (B_{12})

Basic Structure:

Basic structure of porphyrins is as follows.



Classification:

Porphyrins are classified into six types.

I. Uroporphyrin – I
II. Uroporphyrin – III
III. Coproporphyrin – I
IV. Coproporphyrin – III V. Protoporphyrin – III
VI. Protoporphyrin – IX

Type	Uroporphyrin		Coproporphyrin		Protoporphyrin	
Position	**I**	**III**	**I**	**III**	**III**	**IX**
1	-A	-A	-M	-M	-M	-M
2	-P	-P	-P	-P	-V	-V
3	-A	-A	-M	-M	-M	-M
4	-P	-P	-P	-P	-V	-V
5	-A	-A	-M	-M	-M	-M
6	-P	-P	-P	-P	-P	-P
7	-A	-P	-M	-P	-M	-P
8	-P	-A	-P	-M	-P	-M

Where;

A = Carboxymethyl group ($-CH_2-COOH$)
P = Carboxyethyl group ($-CH_2-CH_2-COOH$)
M = Methyl group ($-CH_3$)
V = Vinyl Group ($-CH=CH_2$)

Explanation:

Porphyrins are extremely important group of organic compounds found in most living cells where they perform a wide variety of functions.

The special thing about porphyrins is that porphyrin molecule act as teeth and they grab and hold metal ions such as Mg, Zn, Fe, Ni and Ag etc.

Heme and Porphyrins:

When a porphyrin molecule holds a metal then it acquires different properties. Therefore, if a central metal is iron (Fe), the complex is called Ferro-protein or Heam, as the vital functioning of enabling of body cells to use oxygen.

In other cells, heme proteins are essential for respiration and perform many other functions especially in the liver, the transformation of many drugs and chemicals into biologically inactive substances.

Heme proteins containing iron which is present in hemoglobin which is a carrier of oxygen molecule in blood.

It supplies oxygen from higher concentration of O_2 to areas of low oxygen concentration. Heme plays an important role not only in blood, but it is also a component of enzyme called cytochrome P-450 (CYP), in organs such as liver.

Unlike hemoglobin to which a molecule of oxygen binds, it is highly single reactive molecule of oxygen that binds to iron that is located in centre of CYP.

When CYP ceases a potential target molecule, the enzyme oxidizes it by transferring its oxygen atom to it. The CYP enzyme come in many different types and their work places are diverse. One type plays a role in synthesis of important molecule like hormone while other type oxidizes foreign molecule to raise their water solubility and making excretion easier and this process is called as detoxification.

Chlorophyll and Porphyrins:

Plants also contain important component with porphyrin skeleton e.g. chlorophyll which is responsible of green pigment. It also contains Mg^{2+} as its central atom.

Vitamins and Porphyrins:

Vitamin B_{12} also contains porphyrin structure known as corrin. It is essential for production of nucleic acid while central metal atom is Zn.

Zinc Protoporphyrin (ZPP):

It is a compound found in RBCs where heme production is inhibited by Pb or by lack of iron. Instead of incorporating a ferrous ion to form heme, ProtoporphyrinIX, the immediate precursor of heme, incorporate Zn ion to form ZPP.

This reaction will insert ferrous ion into Protoporphyrin IX, catalyzed by enzyme ferrochelatase. Measure of ZPP in red cells has been used as screening test for Pb poisoning and for iron deficiency.

ZPP levels can be elevated and as a result the no. of conditions can occur such as:

- Anemia of chronic type
- Lead disease
- Iron deficiency
- Various types of cancer

Porphyrias:

- Porphyria is a group of diseases / disorders that can cause skin or nervous problems.
- It has two types.
    - **Cutaneous Porphyria**
        - Chronic disease caused by deficiency in uroporphyrinogen decarboxylase
        - Uroporphyrin accumulates in the urine
        - Most common Porphyria
        - Patients are photosensitive
        - **Acute Porphyria**
        - Characterized by acute attacks of gastrointestinal, neurologic/ psychiatric and cardiovascular symptoms.
- Cure of any kind of Porphyria is not available

Causes of Porphyria:

- Barbiturates
- Birth control pills
- Stress
- Sun exposure
- Hepatitis C
- Problems in production of heme

Treatment:

Treatment of Porphyria is not known but underlying conditions can be treated.

- Treatment of vomiting
- IV injections
- Low doses of anti-malarial drugs

Application of Porphyrins:

Applications of porphyrins are extended in various fields such as:

- Medicines
- Biomimetic catalysis
- Molecular electronics
- Supramolecular chemistry
- Organic geochemistry
- Toxicology

Applications of Porphyrins in Medicine or Pharmacy:

- Photodynamic therapy
- Near infrared (NIR) fluorescence
- MRI
- CT scan
- Photo acoustic imaging
- Porphyrin Hydrogels
- Anti-cancer treatment

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Pharmaceutical Chemistry – II (Biochemistry)

BIOSYNTHESIS AND METABOLISM OF HEME

Heme:

Heme or Heam is an iron-containing compound of the porphyrin class which forms the non-protein part of hemoglobin and some other biological molecules, such as myoglobin, cytochrome P-450.

When a porphyrin molecule holds a metal then it acquires different properties. Therefore, if a central metal is iron (Fe), the complex is called Ferro-protein or Heam, as the vital functioning of enabling of body cells to use oxygen.

Biosynthesis of Heme:

It is synthesized by almost all tissues of body e.g. in bone marrow and spleen. Heme biosynthesis is partly mitochondrial and partly cytoplasmic. Biosynthesis of heme is divided in seven steps.

Step 1:

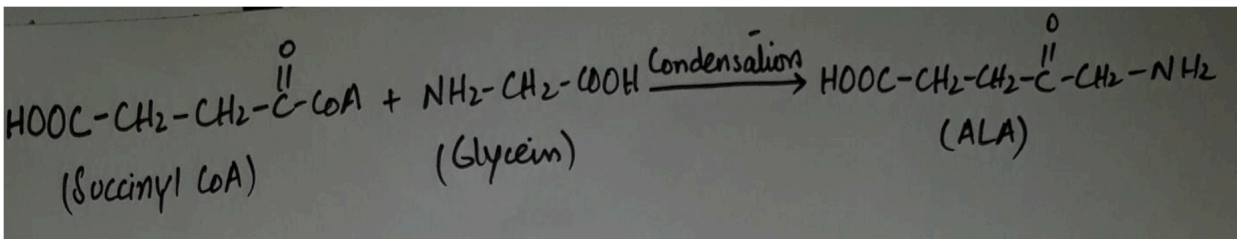
FORMATION OR SYNTHESIS OF ALA OR δ-AMINOLEVULINIC ACID

Site: Mitochondria

Enzyme: ALA synthase

Substrate: Succinyl CoA and Glycein (from Krebs cycle)

Product: ALA

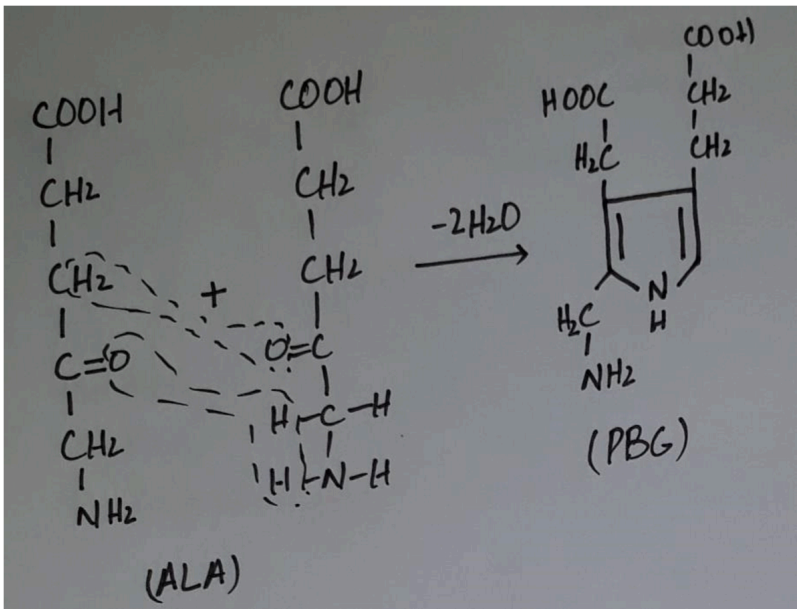


Step 2:

CONDENSATION OF TWO MOLECULES OF ALA

Site: Cytoplasm **Enzyme**: ALA dehydratase

Substrate: ALA **Product**: PBG (Porphobilinogen)



Step 3:

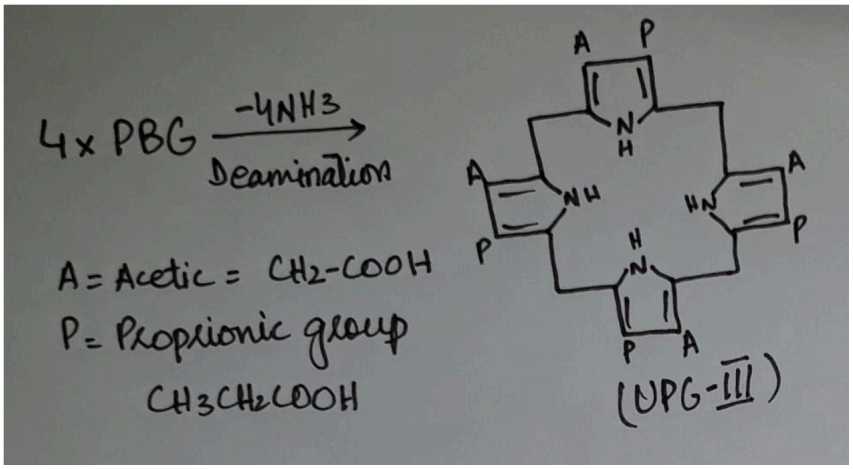
CONDENSATION OF FOUR MOLECULES OF PBG

Site: Cytoplasm **Substrate:** 4 molecules of PBG

Enzyme: PBG deaminase, Uroporphyrinogen-III co-synthase

Product: Uroporphyrinogen – III (UPG)

Intermediate: UPG-I (rapidly oxidized to Uroporphyrin-I and excreted in urine)

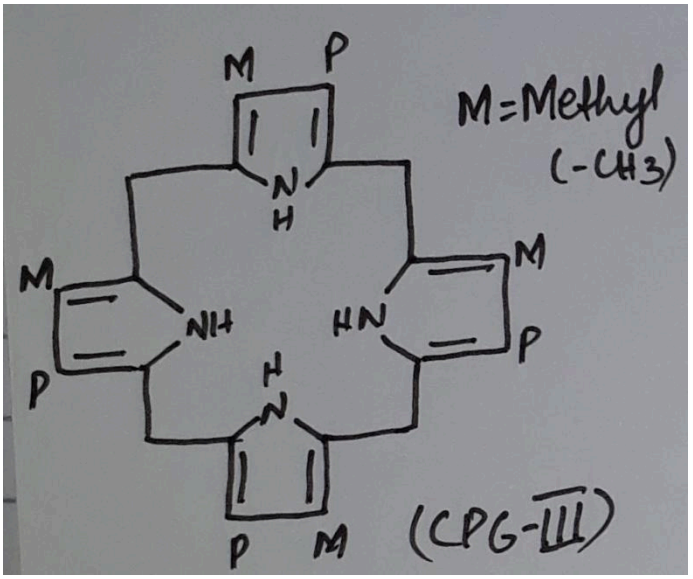


Step 4:

DECARBOXYLATION OF UPG-III

Site: Cytoplasm **Enzyme:** UPG decarboxylase

Substrate: UPG-III **Product:** Corprophyrinogen – III (CPG-III) **Intermediate:** CPG-I (rapidly metabolized and excreted in urine)



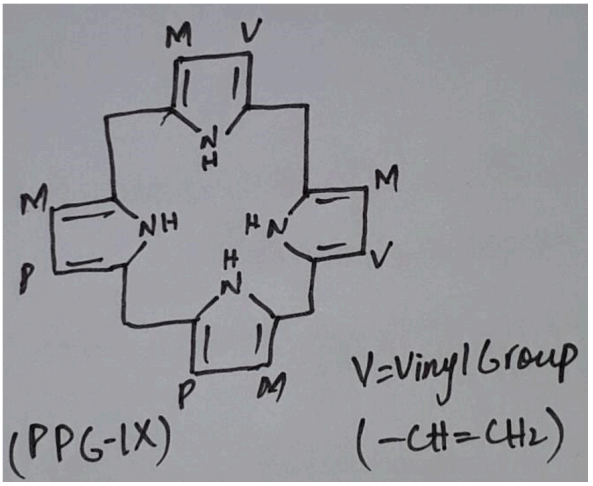
Step 5:

OXIDATION OF CPG-III

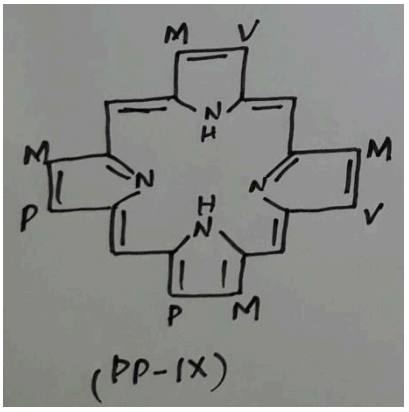
Site: Mitochondria **Enzyme:** CPG oxidase **Substrate:** CPG-III

Product: Protoporphyrinogen – IX (PPG-IX)

Mechanism: Two propionic acid side chains will be decarboxylated to vinyl group



Step 6:



OXIDATION OF PPG-IX

Site: Mitochondria

Enzyme: PPG oxidase

Substrate: PPG-IX

Product: Protoporphyrin – IX (PP-IX)

Mechanism: -CH_2 bridges are oxidized to methenyl bridges

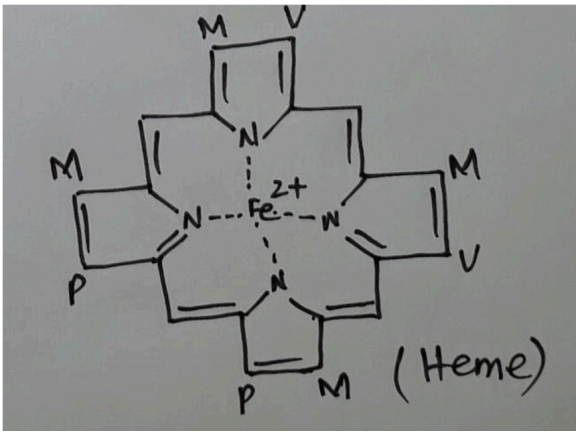
Step 7:

FORMATION OF HEME BY ATTACHMENT OF Fe^{2+} TO PP-IX

Site: Mitochondria **Enzyme:** Heme Synthase

Substrate: PP-IX **End Product:** Heme

$$Protoporphyrin - IX \xrightarrow{Fe^{2+}} Heme$$



Regulation of Heme Synthesis:

Heme synthesis is regulated precisely to meet the needs of heme containing proteins (globins).

Feedback Regulation by Heme:

Heme itself inhibits d-ALA synthase via repression (genetic) along with diminished transport of CPG-III from the cytosol to mitochondria and stimulates the synthesis of the protein part of hemoglobin / myoglobin (the globins).

Heme Metabolism:

Heme proteins are constantly synthesized and degraded. The major source of heme is hemoglobin found in RBCs. When the RBC ends its life after 120 days the hemoglobin molecule is degraded. The amino acid from the globin and iron are recycled while the porphyrin is degraded. Bilirubin is the end product of heme metabolism. Heme is degraded by reticulo-endothelial system (mononuclear phagocytic system)

Bilirubin:

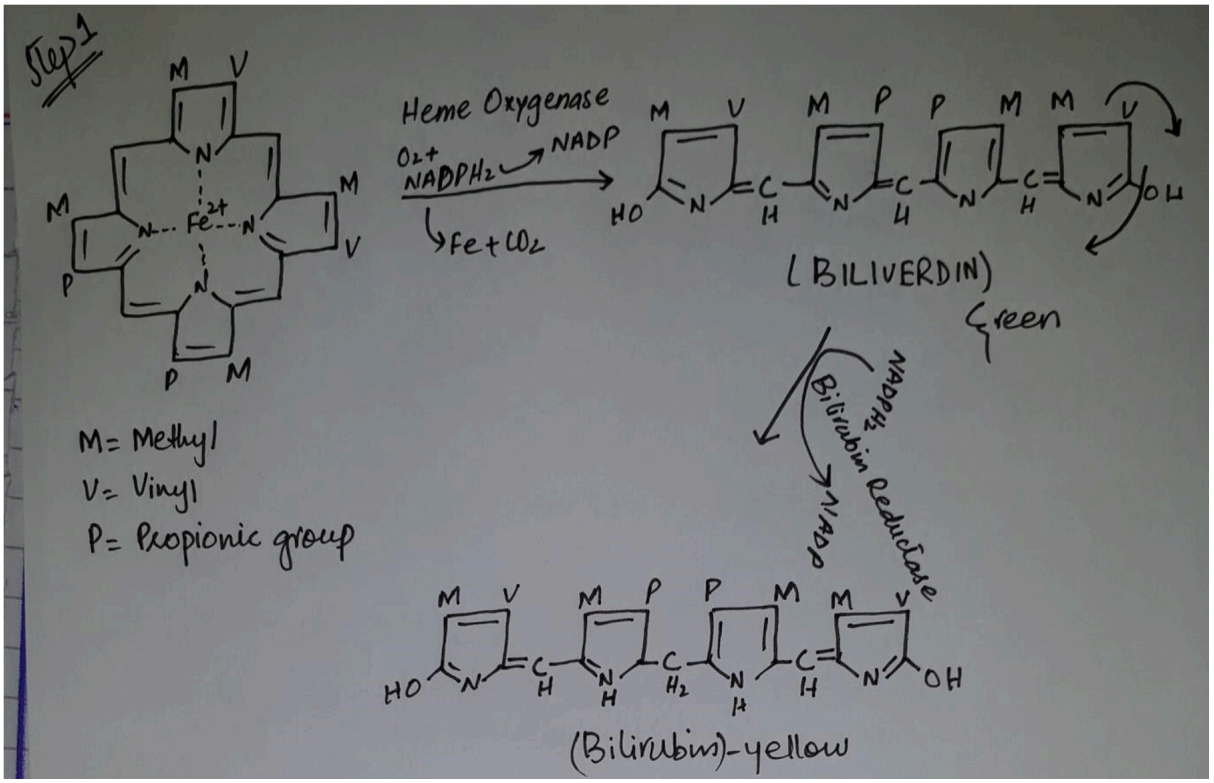
It is the yellow, water insoluble and highly toxic compound. It is transported bound to albumin in the plasma to the hepatocytes (liver). In the hepatocytes it is conjugated to the two molecules of glucuronic acid (hydrophilic).

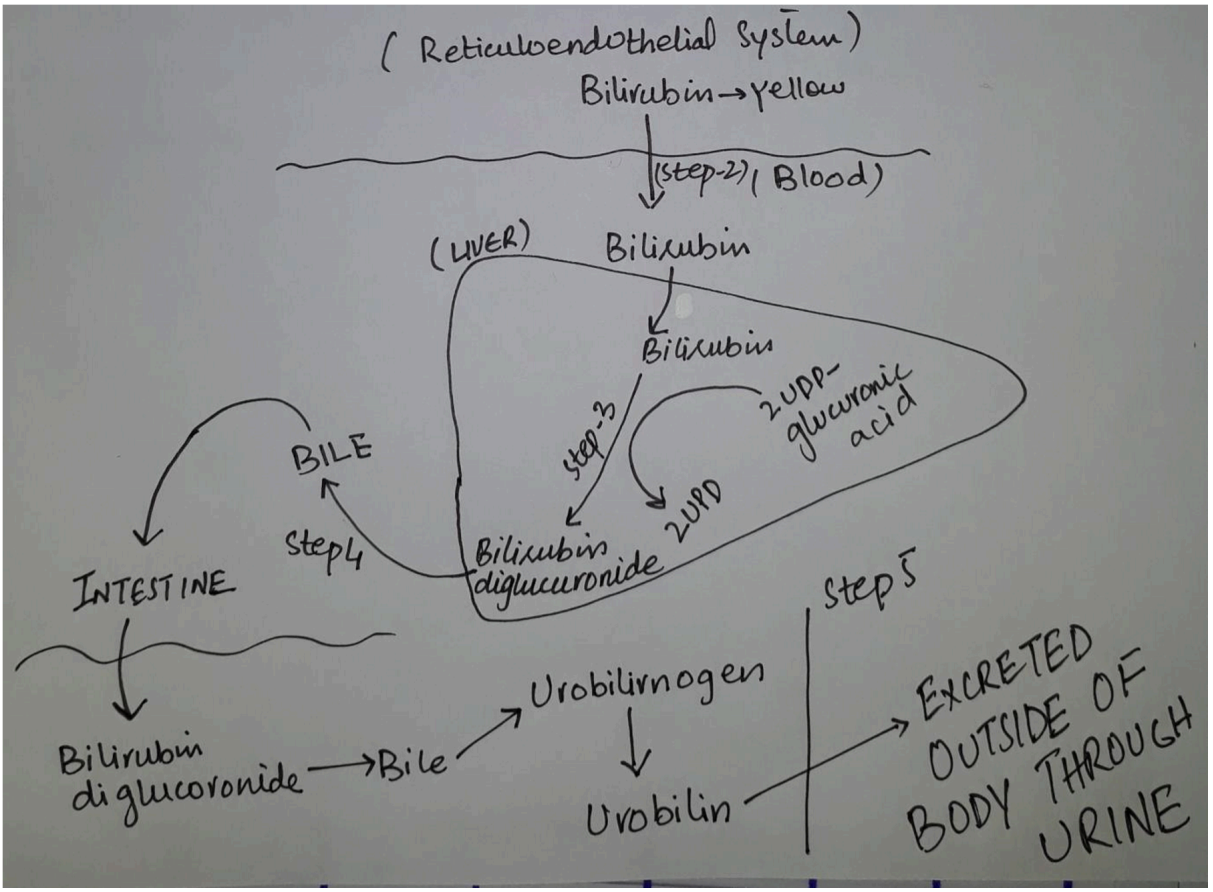
Steps of Heme Degradation:

Heme is degraded in five steps and is excreted through urine.

1. Formation of Bilirubin
2. Uptake of bilirubin by liver via blood
3. Formation of bilirubin diglucuronide
4. Secretion of bilirubin into bile

5. Formation of Urobilin in the intestine
6. Excretion through urine





Note:

- Bilirubin diglucuronide ○ Water soluble compound
  - ○ Reacts immediately with diazonium salts
- When bilirubin and bilirubin diglucuronide are mixed, it means liver is sick and it may be hepatitis.

Functions of Heme:

- Heme proteins containing iron which is present in hemoglobin which is a carrier of oxygen molecule in blood. It supplies oxygen from higher concentration of O_2 to areas of low oxygen concentration.
- Heme plays an important role not only in blood, but it is also a component of enzyme called cytochrome P-450 (CYP), in organs such as liver. Unlike hemoglobin to which a molecule of oxygen binds, it is highly single reactive molecule of oxygen that binds to iron that is located in centre of CYP.

Types of Heme:

Major forms or types of heme are:

- Heme A
- Heme C
- Heme I
- Heme B ○ Heme m ○ Heme D ○ Heme s

Diseases Related to Heme:

- Enlarged spleen
- Porphyria
- Urinary tract infection
- Thalassemia
- Hemolysis
- Anemia
- CO poisoning
- Biliary duct stone
- Jaundice

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