CATABOLISM OF HEME

Heme - degraded into bilirubin **by reticulo-endothelial cells** (in Microsomal fraction & in cytoplasm sequentially).

Bilirubin- principal bile pigment - is excreted via liver into intestine

Steps

Destruction of RBC to release Heme → **Reticuloendothelial system**

Degradation of heme into biliverdin → Lysosome

Reduction of biliverdin into bilirubin → Microsomal system

Transportation of bilirubin in blood → Cytoplasm

Hepatic uptake of bilirubin

Conjugation of bilirubin in liver

Deconjugation of bilirubin in intestine

Excretion

1. Destruction of RBC:

In **intravascular hemolysis** RBCs lyse in the circulation releasing hemoglobin into the plasma. Causes include mechanical trauma, complement fixation, and other toxic damage to the RBC. The fragmented RBCs are called schistocytes.

RBC's are phagocytized by macrophages in the spleen, bone marrow and Reticulo endothelial cell of liver.

In **extravascular hemolysis**

When old red blood cell (after 120 days) are destroyed, the globin portion is split off, the heme portion is converted to biliverdin and after that it is converted to bilirubin.

2.Degradation of Heme into Biliverdin by Heme oxygenase

In microsomal fraction of macrophage
Requires- 4—5 mols $NADPH_2$ and 3mols O_2

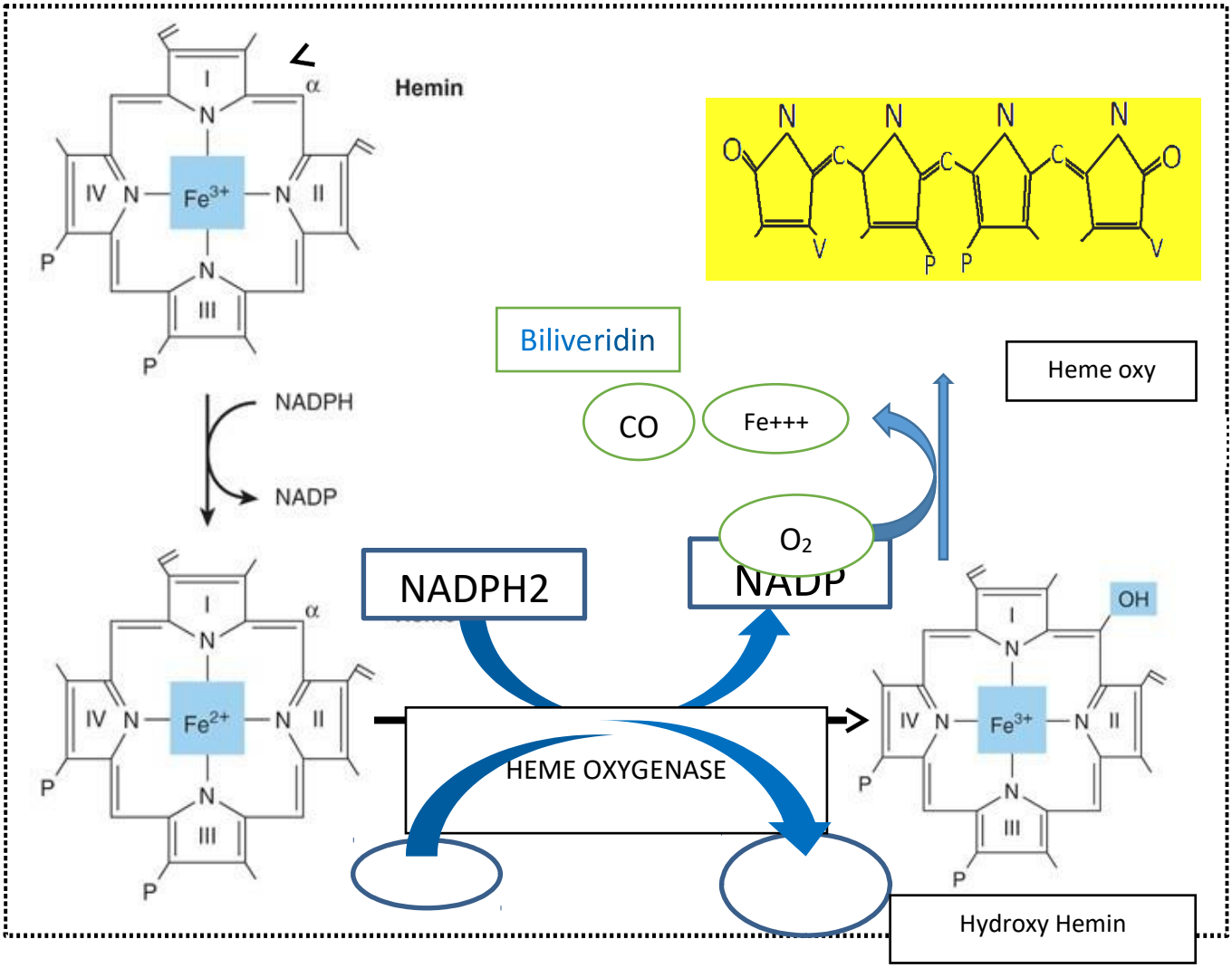
HEME CATABOLISM: STEPS
• Process
a. Hydroxylation of α-Methenyl bridge [----CH===] between I&II rings.

b. Concomitantly, oxidation of Fe^{++} to Fe^{+++}.

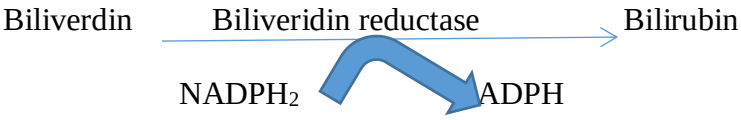
c. Oxidation of 'C' of Methenyl bridge into CO→→ bridge breaks.

d. Release of CO & ferric iron□ latter joins iron pool.

• In this way, closed tetrapyrrole ring of Heme is opened into open tetrapyrrole structure— Biliverdin



3.Reduction of biliverdin into bilirubin (In cytoplasm)



Methyne bridge in the structure is getting changed to methylene bridged

4.Transport of bilirubin

α-Bilirubin is transported by albumin. About 100 ml plasma (3.5-5.5gm/dl alb) can bind 25mg of bilirubin. It binds bilirubin tightly but non-covalently.

4. Uptake of Bilirubin-albumin complex by liver

Bilirubin is taken up at the sinusoidal surface of hepatocytes by a carrier mediated process and albumin is released back to plasma.
Inside hepatocyte cytoplasm, bilirubin binds with Ligandin-Y & Z (belong to Glutathione-S-Transferase family) that keep it solubilized and prevent efflux of it. Bilirubin enters endoplasmic reticulum

5. Conjugation of Bilirubin in liver

This process is carried out by- Uridine Di-Phosphate Glucuronosyl Transferase
This enzyme is found in endoplasmic reticulum of hepatocytes.

This enzyme transfers Glucuronosyl group of UDP- Glucuronic acid to COOH group of Propionic acid of bilirubin; process is called conjugation of Bilirubin.

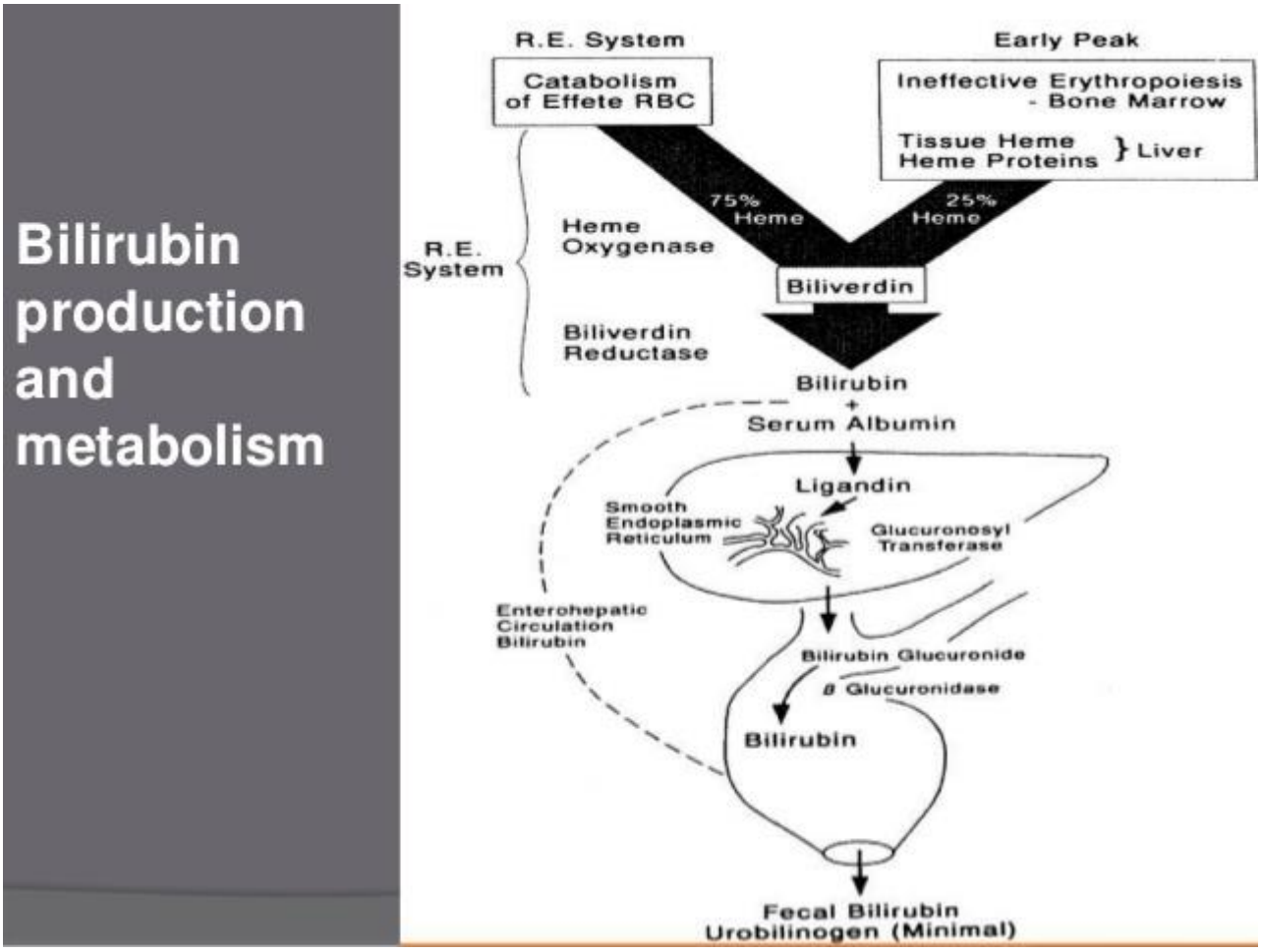
Bilirubin is converted initially into mono conjugated bilirubin [Bilirubin Monoglucuronide] and finally into Di-conjugated bilirubin [Bilirubin Diglucuronide] and render them water soluble

6. Secretion of Conjugated bilirubin in bile canaculi

After the formation of conjugated bilirubin is entered into the bile canaliculus as part of bile and thus delivered to the small intestine. Bacteria in the intestinal lumen metabolize bilirubin to a series of other compounds which are ultimately eliminated either in feces or, after reabsortion, in urine.

8.Deconjugation of bilirubin into intestine

There, colonic bacteria (beta glucuronidase) deconjugate the bilirubin diglucuronide to bilirubin and glucuronic acid and metabolize the bilirubin into colorless urobilinogen, which can be oxidized to form urobilin and stercobilin. Urobilin is excreted by the kidneys to give urine its yellow color and stercobilin is excreted in the faeces giving stool its characteristic brown color.



HYPERBILIRUBINEMIA

Conjugated (Direct): Bilirubin is converted from unconjugated to conjugated bilirubin in the liver. This happens when sugar attaches to the unconjugated bilirubin. The unconjugated bilirubin turns into bile and enters the small intestines. It is eventually eliminated through a person's stool.

Hyperbilirubinemia is a condition in which there is too much bilirubin in the blood. When red blood cells break down, a substance called bilirubin is formed. Babies are not easily able to get rid of the bilirubin and it can build up in the blood and other tissues and fluids of the baby's body.

The predominant causes of conjugated hyperbilirubinemia are intrahepatic cholestasis(Cholestasis is defined as a decrease in bile flow due to impaired secretion by hepatocytes or to obstruction of bile flow through intra-or extrahepatic bile ducts) and extrahepatic obstruction of the biliary tract, with the latter preventing bilirubin from moving into the intestines. Viruses, alcohol, and autoimmune disorders are the most common causes of hepatitis

JAUNDICE

Jaundice - clinical sign characterized by yellow discoloration of sclera, skin & mucosa due to deposition of bilirubin in state of hyperbilirubinemia.

TYPES OF JAUNDICE

Neonatal jaundice

Jaundice is common in newborn babies. It occurs as a result of the liver being underdeveloped and not fully functional. In most cases, neonatal jaundice is nothing to worry about. It requires no treatment and usually disappears after a week. Jaundice in adults and older children Jaundice that occurs in adults and older children is usually a sign of an underlying health problem. There are three types of jaundice.

Hepatocellular jaundice

Hepatocellular jaundice is the most common type of jaundice. It occurs when bilirubin is unable to leave the liver cells and cannot be removed from the body by the kidneys.

Hepatocellular jaundice is usually caused by liver failure, liver disease (cirrhosis), hepatitis (inflammation of the liver) or by taking certain types of medication.

Haemolytic jaundice

Haemolytic jaundice is when too much bilirubin is produced as a result of a large number of red blood cells being broken down. This can be due to a number of conditions, such as anaemia or a problem with the metabolism (the way that the body produces and uses energy).

Obstructive jaundice

Obstructive jaundice occurs when there is an obstruction (blockage) in the bile duct, which prevents bilirubin from leaving the liver. This type of jaundice is usually caused by a gallstone, a tumour or a cyst in the bile duct or pancreas

Bilirubin levels in adults

Bilirubin type	Bilirubin level
Total bilirubin	0.0–1.4 mg/dL or 1.7–20.5 mcmol/L
Direct bilirubin	0.0–0.3 mg/dL or 1.7–5.1 mcmol/L
Indirect bilirubin	0.2–1.2 mg/dL or 3.4–20.5 mcmol/L