# Heme degradation

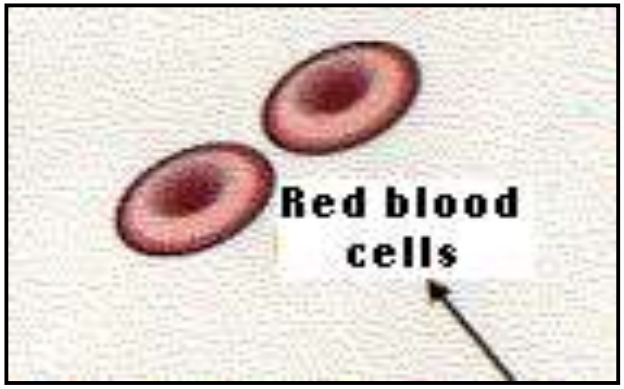
# Fate of RBCs

- Life span in blood stream is 90-120 days, RBCs are phagocytosed and/or lysed
- Normally, lysis occurs extravascularly in the ER of reticuloendothelial system (liver, spleen and bone marrow). subsequent to RBC phagocytosis.
- Lysis can also occur intravascularly (in blood stream).
- In the human body approx. 100 – 200 million RBCs are broken down every hour.
- $Fe^{2+}$ → transported with transferrin and used in the next heme biosynthesis.
- Not only Hb but other hemoproteins also contain heme groups which are degraded by the same pathway.

** Degradation of RBC and releasing all of it contents → Hemoglobin

- Globin is amino acids that will go to Amino acid pool in liver for reutilization.
(if it didn't go to liver, but passed to urinary tract and excreted by Kidney → **Aminoacidouria**, thus, it changes **urine PH**, leads to **precipitation of salts and crystals (such as Urate)** and **losing all amino acids** since they can pass glomerular filtration rate to be excreted in urine.

- $Fe^{2+}$ will go to iron pool, since it's difficult to be excreted and their existence in blood is toxic.




** First step of Heme degradation

**Phagocytosis & Lysis**

Hemoglobin

$Fe^{2+}$ | Globin | Heme

رح يتحول لـ

Iron pool | Amino acids | Bilirubin

عشان يصيرله

Amino acid pool | Excretion

NOT EXCRETED

# Handling of free (intravascular) hemoglobin

***Those 3 proteins scavenge iron***

- **Purposes:** 1- Scavenge iron 2- Prevent major iron losses
  3- Complex free heme (very toxic)

Hemoglobin still as it is. (no degredation)

1- **Haptoglobin:** hemoglobin-haptoglobin complex is readily metabolized in the liver and spleen forming an iron-globin complex and bilirubin.
**Prevents loss of iron in urine.** How? (this haptoglobin bind with haemoglobin to increase its molecular weight so it cant pass into the pores of glomural filtration in kidney. So if there is G6PD deficiency haptoglobin will be reduced)

2- **Hemopexin:** binds free heme. The heme-hemopexin complex is taken up by the liver (since it has high molecular weight so it can't pass through kidney) and the iron is stored bound to ferritin.

**if hemoglobin is degraded to Heme & Globin inside blood vessels.** **will bind with hemopexin since its toxic** **will be hydrolyzed in liver.**

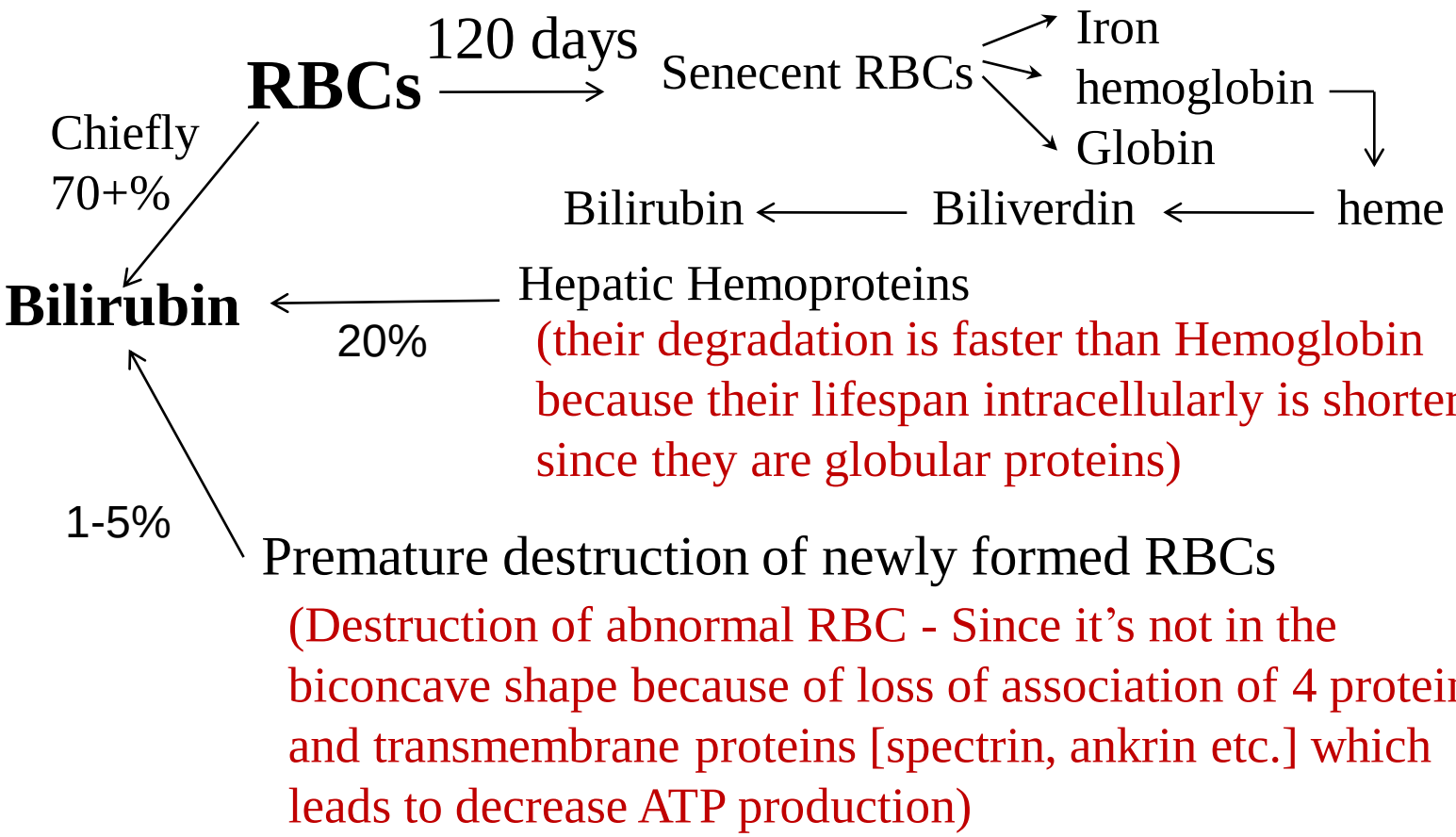
3- **Methemalbumin:** complex of oxidized heme (hemin) and albumin.
(if hemoglobin is degraded to heme & globin but heme is oxidized into hemin)

## Bilirubin metabolism

1) Bilirubin formation
2) Transport of bilirubin (unconjugated) in plasma
3) Hepatic bilirubin transport → A- Hepatic uptake, B- Conjugation, C- Biliary excretion
4) Enterohepatic circulation

# Bilirubin formation

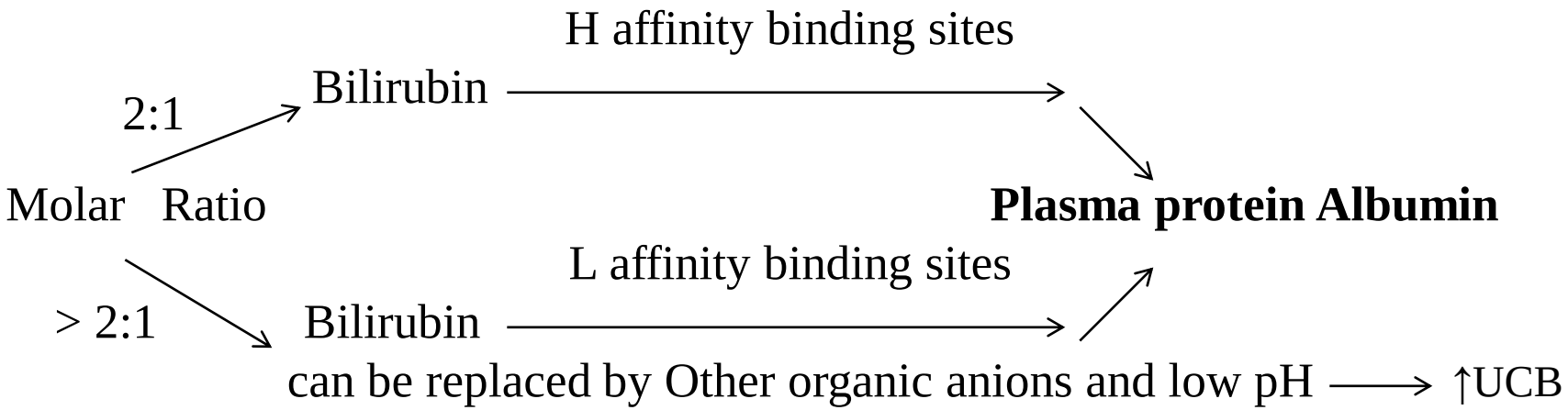
**Bilirubin is formed in 3 ways:**



# Transport of bilirubin in plasma

Unconjugated Bilirubin (UB) is hydrophobic

Albumin + UB ⟶ UB ~ Albumin Complex




** If it's 2:1 ratio between UB and Albumin, so albumin will carry all the UB within normal levels.

** if the ratio was >2:1, here albumin is not a specific carrier, thus, it has different competitors for binding of UB to Albumin such as Organic anions and Low pH and they will bind to Albumin instead, so rejecting some UB from binding sites of albumin.

- In uncontrolled diabetic patients who have yellow eye/skin discoloration → Ketone bodies is formed by Acetoacetic acid & Beta Hydroxybutyric acid and they are found in blood in ionized form, so H+ will be at higher level in circulation then pH will decrease and UB will be dissociated from binding sites on albumin and patient will show characteristic of Jaundice.

# Hepatic Bilirubin Transport

## 1. Hepatic uptake of bilirubin

UCB ~ Albumin complex separated

(be) taken up

Bilirubin ⟶ Plasma membrane of the liver

- Bilirubin uptake is reduced: in neonates, cirrhosis, some drugs effects

## 2.Conjugation of bilirubin

bound to Z protein (Ligandin)

UCB ⟶ carrier protein ⟶ ER

(Lipid soluble)
hydrophobic

Conjugation
(catalyzed by
UDPGT)

excreted ⟵ (Water soluble) CB ⟵ CBGA

## 3.Biliary excretion of bilirubin

Transfer across

CB ⟶ Bile canaliculus

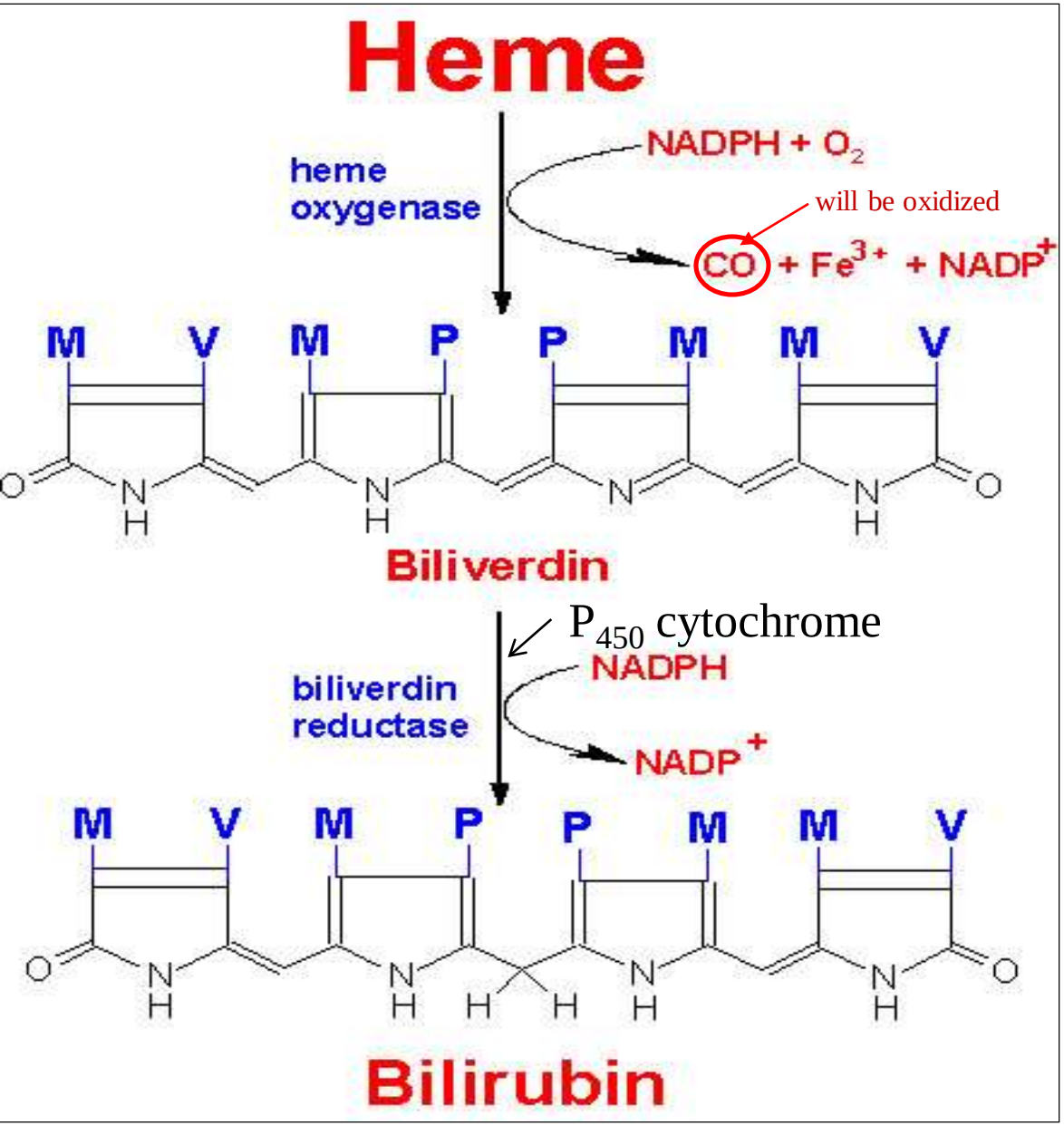
Microvillar membrane

**Physiologic Jaundice can happen when liver is not conjugating bilirubin (WHY?)**

Erythrocytes are not well developed, proteins in membrane are not well associated and liver is still immature and unable to uptake molecules and synthesize different type of proteins efficiently so conjugation reaction is not taken place efficiently in.

Maturation of membrane of erythrocytes and hemolysis decreases and maturation of liver to synthesize proteins, the patient symptoms will improve.

# Degradation of heme to bilirubin




-75% is derived from RBCs

- In normal adults this results in a daily load of 250-300 mg of bilirubin

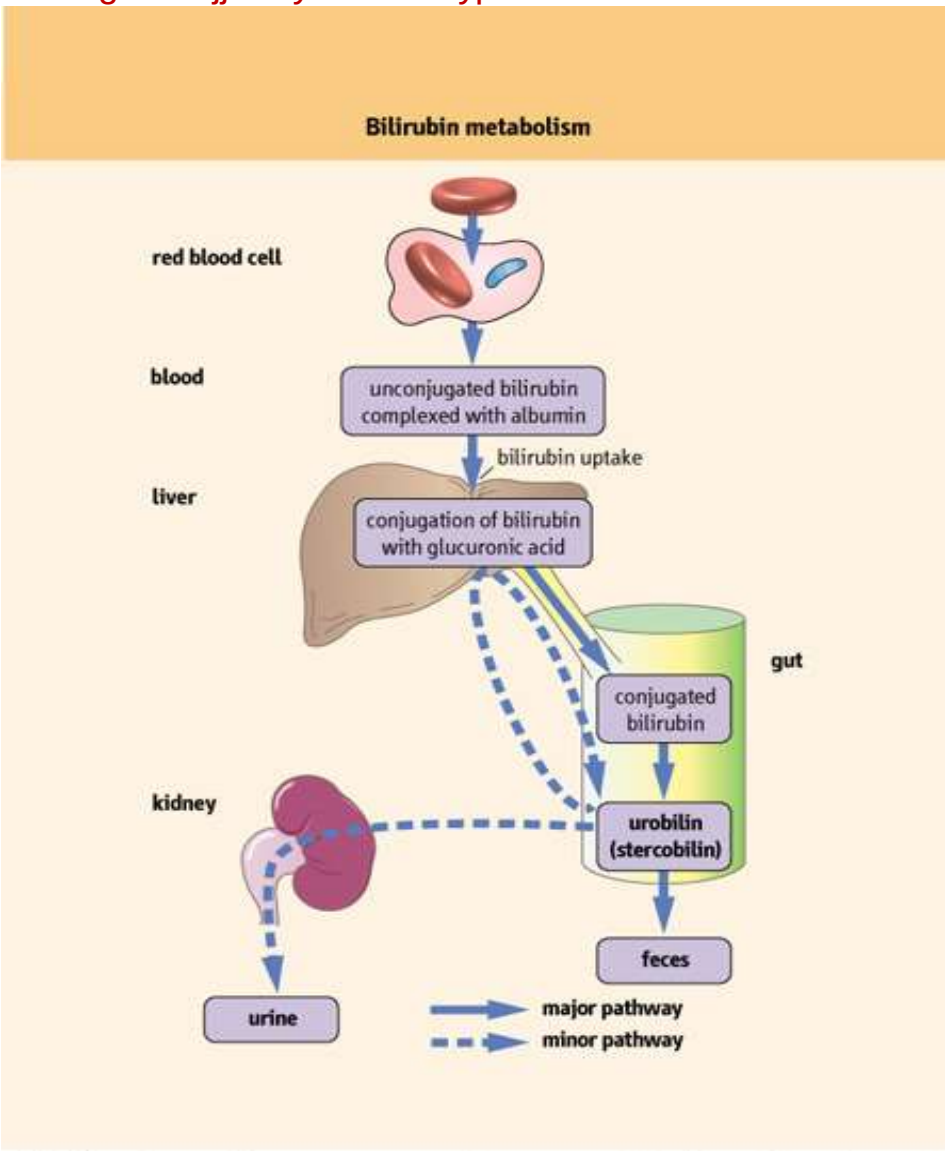
- Normal plasma concentrations are less then 1 mg/dL

- Hydrophobic – transported by albumin to the liver for further metabolism prior to its excretion

# Normal bilirubin metabolism

**Mutation of UDPGT leads to:**

- Gilbert syndrome
- Crigler-najjar syndrome type 1&2&3






- Uptake of bilirubin by the liver is mediated by a carrier protein (receptor)
- Uptake may be competitively inhibited by other organic anions
- On the smooth ER, bilirubin is conjugated with glucuronic acid, xylose, or ribose

- Glucuronic acid is the major conjugate – catalyzed by UDP glucuronyl transferase

-"Conjugated" bilirubin is water soluble and is secreted by the hepatocytes into the biliary canaliculi

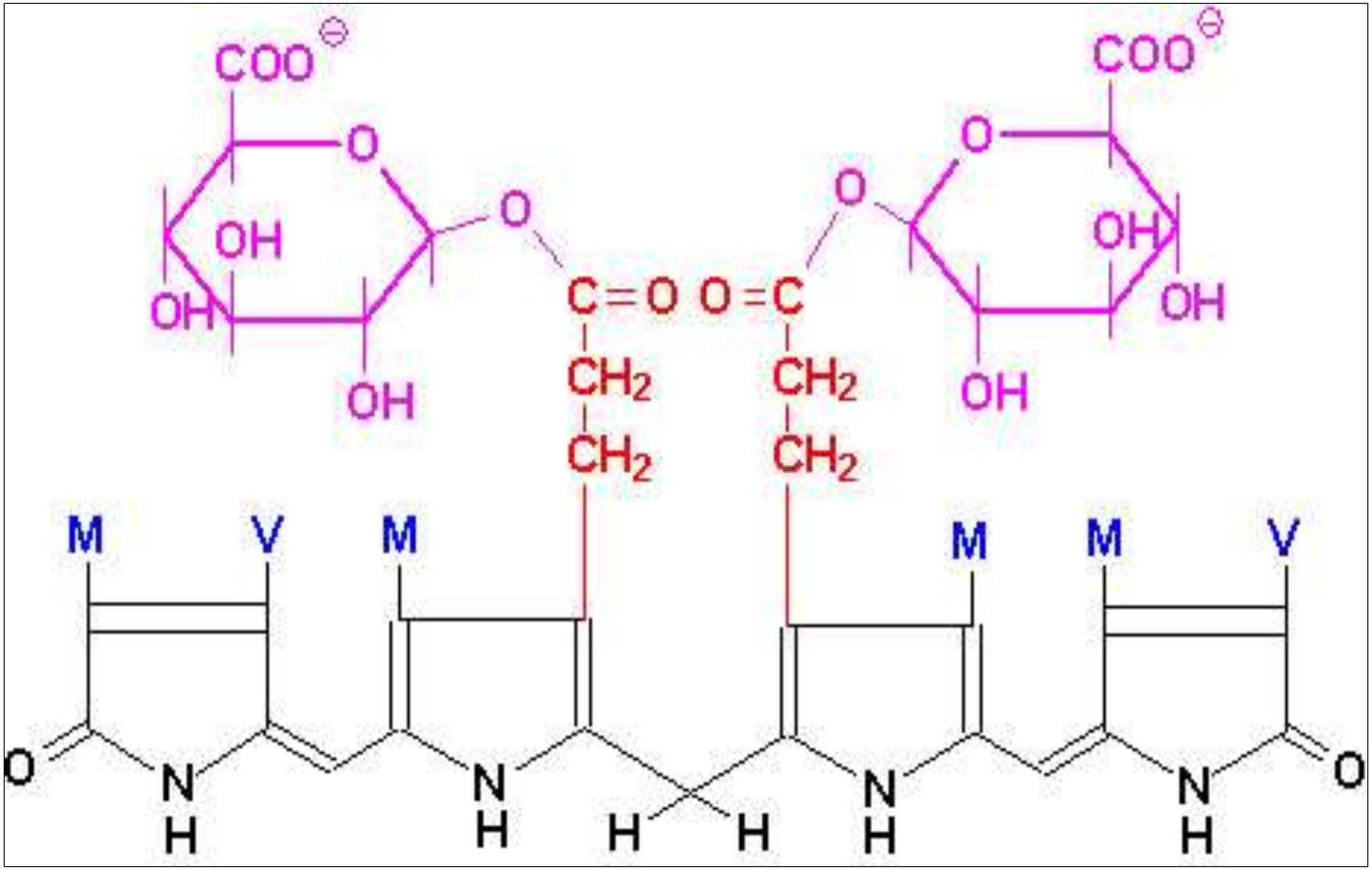
- Converted to stercobilinogen (urobilinogen) (colorless) by bacteria in the gut

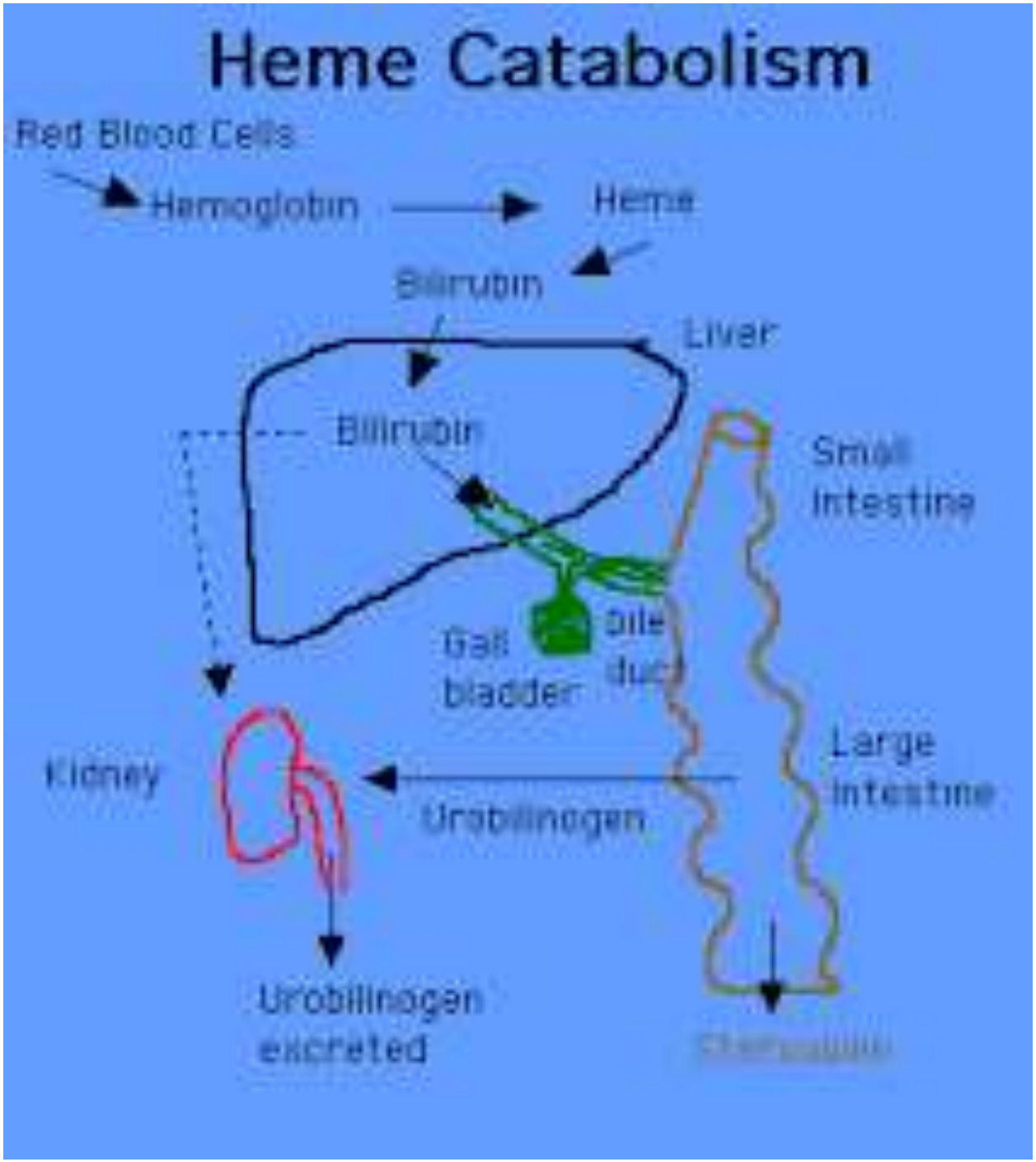
- Oxidized to stercobilin which is colored (brown) then excreted in feces

- Some stercobilin may be re-adsorbed through enterohepatic circulation by the gut and re-excreted by either the liver or kidney (yellow colored)

**bilirubin-diglucuronide = conjugated bilirubin**

is soluble in water → „**direct bilirubin**“




Heme Catabolism
Red Blood Cells
Hemoglobin
Heme
Bilirubin
Liver
Bilirubin
Small Intestine
Gall bladder
bile duct
Kidney
Large Intestine
Urobilinogen
Urobilinogen excreted

# Clinical correlations
# Determination of bilirubin (Bil) in serum

## Blood tests

- Bil reacts directly when reagents are added to the blood sample → conjugated bilirubin = **direct Bil** (up to 3.4 µmol/L)

- free Bil does not react to the reagents until alcohol (methanol) or caffeine is added to the solution. Therefore, the measurement of this type of bilirubin is indirect → unconjugated bilirubin = **indirect Bil** (up to 13.6 µmol/L)

-**Total bilirubin** measures both unconjugated and conjugated Bil (normal value up to 17 µmol/L).

| | **Results of Vanden Bergh** | **Type of Hyperbilirubinemia/Jaundice** |
|---|---|---|
| 1 | **Direct** Vanden Bergh's Reaction Positive | Conjugated Hyperbilirubinemia → **Obstructive Jaundice** |
| 2 | **Indirect** Vanden Bergh's Reaction Positive | Unconjugated Hyperbilirubinemia → **Hemolytic Jaundice** |
| 3 | Both **Direct** and **Indirect** Vanden Bergh's Reaction positive | Biphasic Hyperbilirubinemia means Both conjugated and Unconjugated Bilirubin increased → **Hepatic Jaundice**. |

# Bilirubin physiology

- Ligandins responsible for transport from plasma membrane to endoplasmic reticulum. They are necessary for intracellular transport of bilirubin, are also low at birth and reach adult levels by 3-5 days.

- Bilirubin conjugated in presence of UDPGT (uridine diphosphate glucuronyl transferase) to mono and diglucoronides, which are then excreted into bile canaliculi.

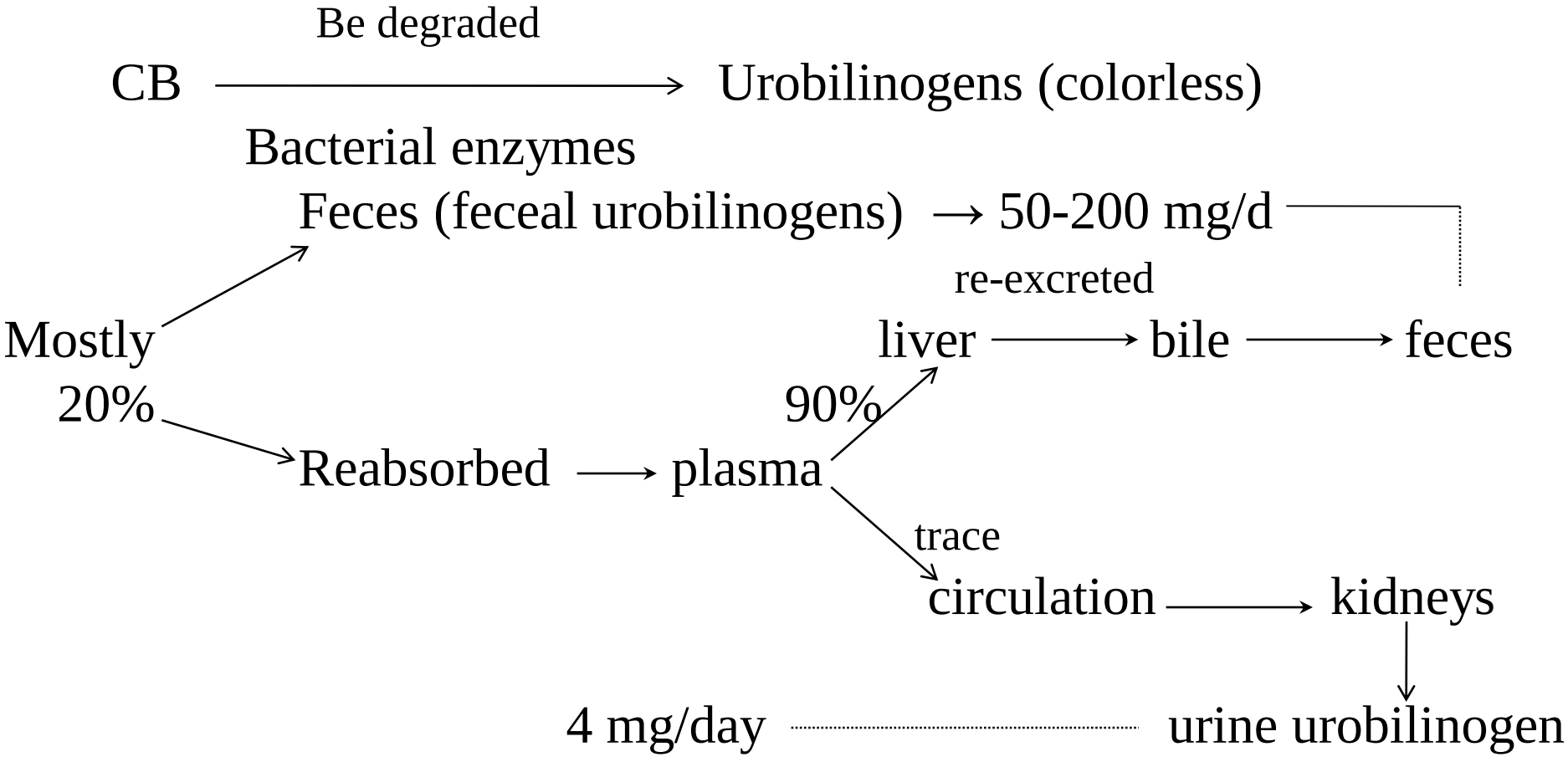
## Enterohepatic Circulation

- Conjugated bilirubin is unstable and easily hydrolyzed to unconjugated bilirubin.

-This process occurs nonenzymatically in the duodenum and jejunum and also occurs in the presence of **β glucuronidase**, an enteric mucosal enzyme, which is found in high concentration in newborn infants and in human milk.

In intestine, removal of 2 glucuronic acids of CB by **β glucuronidase**

# Entero - hepatic circulation




- The serum of normal adults contains ≤1 mg of bilirubin per 100 ml.
- In healthy adults → The direct fraction is usually <0.2 mg/100 ml
  The indirect fraction is usually <0.8 mg/100 ml