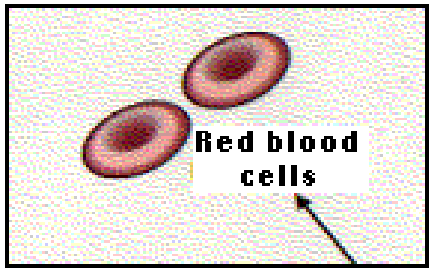
Heme degradation

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.



Phagocytosis & Lysis

Hemoglobin

Fe^{2+} Globin Heme

Iron pool Amino acids Bilirubin

Amino acid pool Excretion

Handling of free (intravascular) hemoglobin

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

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.

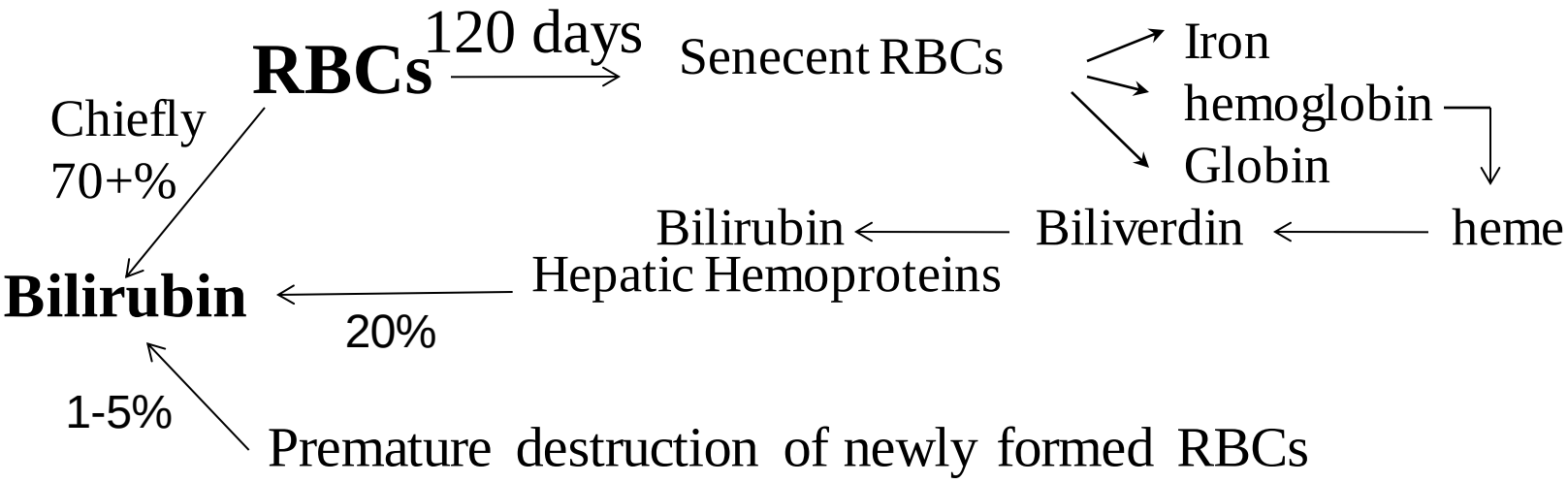
2- Hemopexin: binds free heme. The heme-hemopexin complex is taken up by the liver and the iron is stored bound to ferritin.

3- Methemalbumin: complex of oxidized heme and albumin.

Bilirubin metabolism

- Bilirubin formation
- Transport of bilirubin in plasma
- Hepatic bilirubin transport
  A- Hepatic uptake B- Conjugation C- Biliary excretion
- Enterohepatic circulation

Bilirubin formation



Transport of bilirubin in plasma

Albumin + UB ⟶ UB ~ Albumin Complex

H affinity binding sites

Bilirubin ⟶

2:1

Molar Ratio

Plasma protein Albumin

L affinity binding sites

> 2:1 Bilirubin ⟶

can be replaced by Other organic anions and low pH ⟶ ↑UCB

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

UCB ⟶ carrier protein ⟶ ER

(Lipid soluble)

Conjugation (catalyzed by UDPGT)

(Water soluble) CB ⟵ CBGA

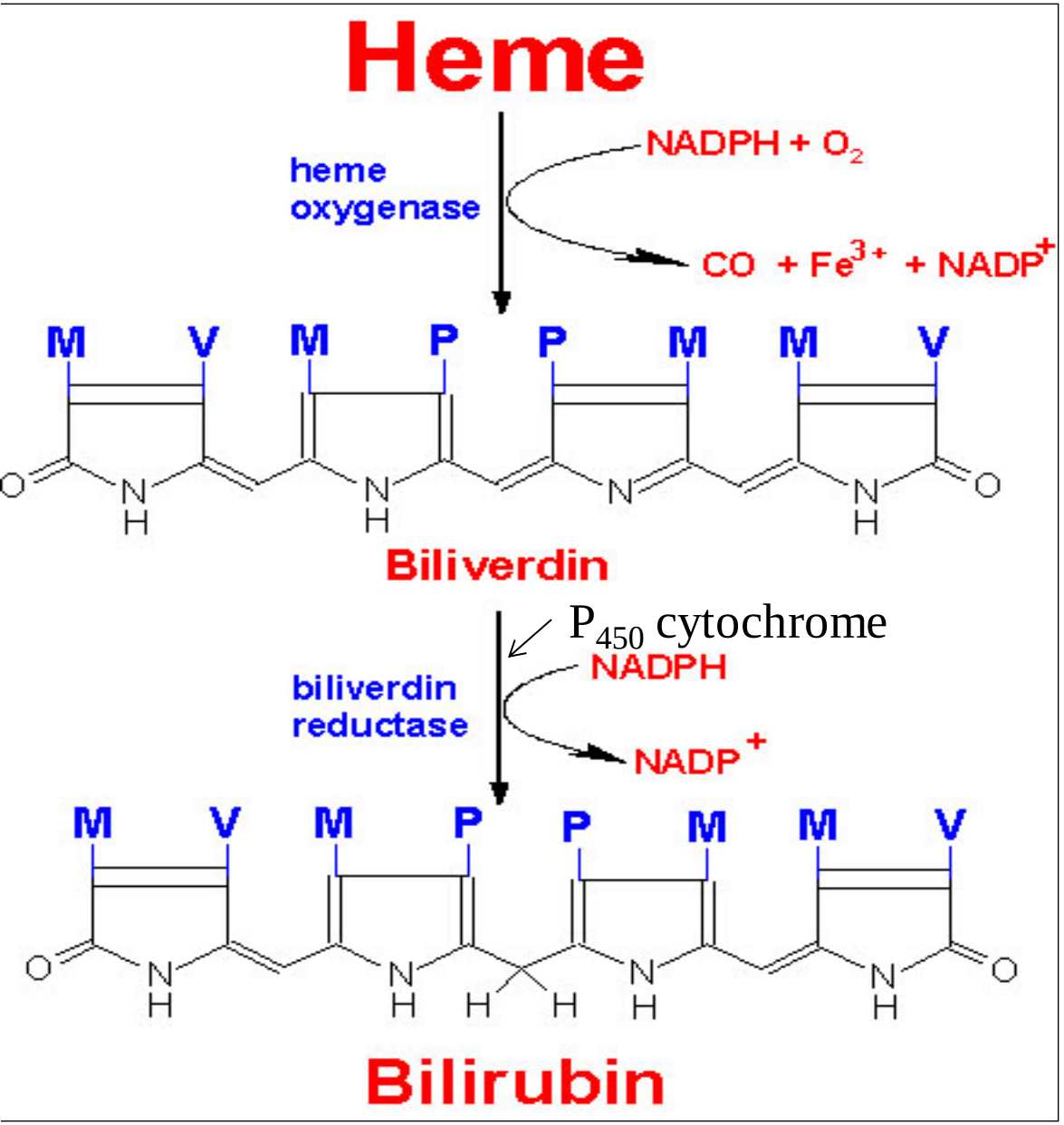
3. Biliary excretion of bilirubin

Transfer across

CB ⟶ Bile canaliculus

Microvillar membrane

Degradation of heme to bilirubin



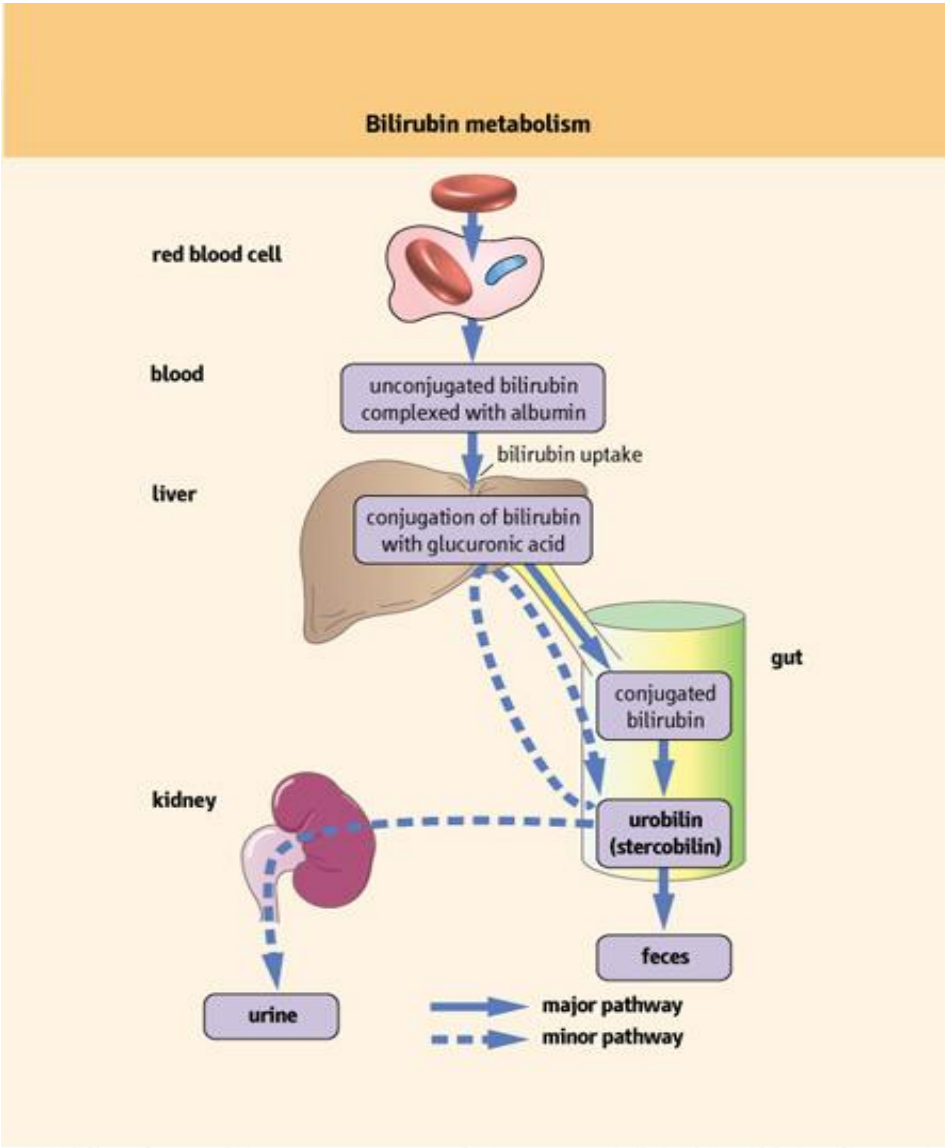
-75% is derived from RBCs

- 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



- 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

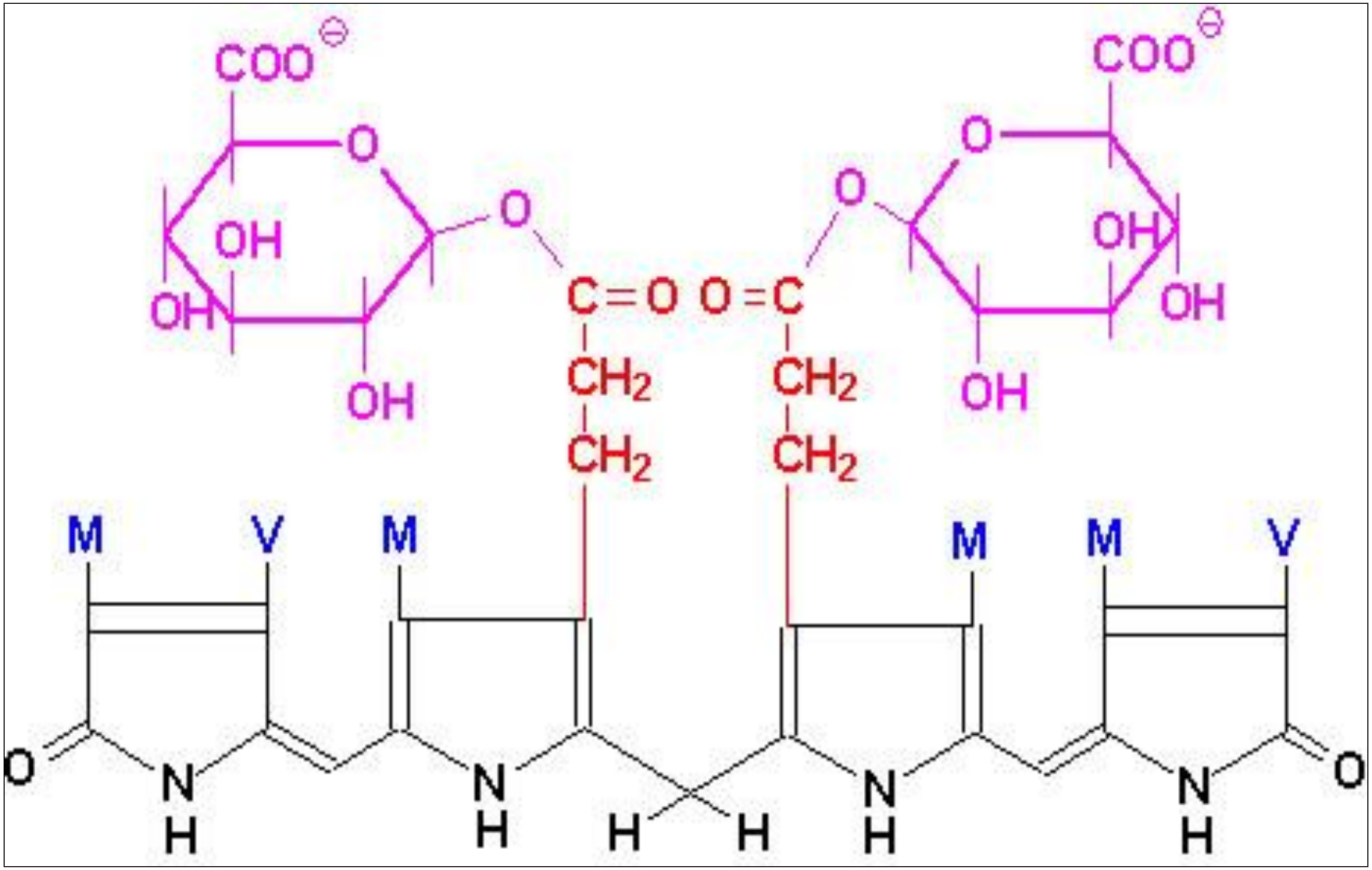
- Oxidized to stercobilin which is colored

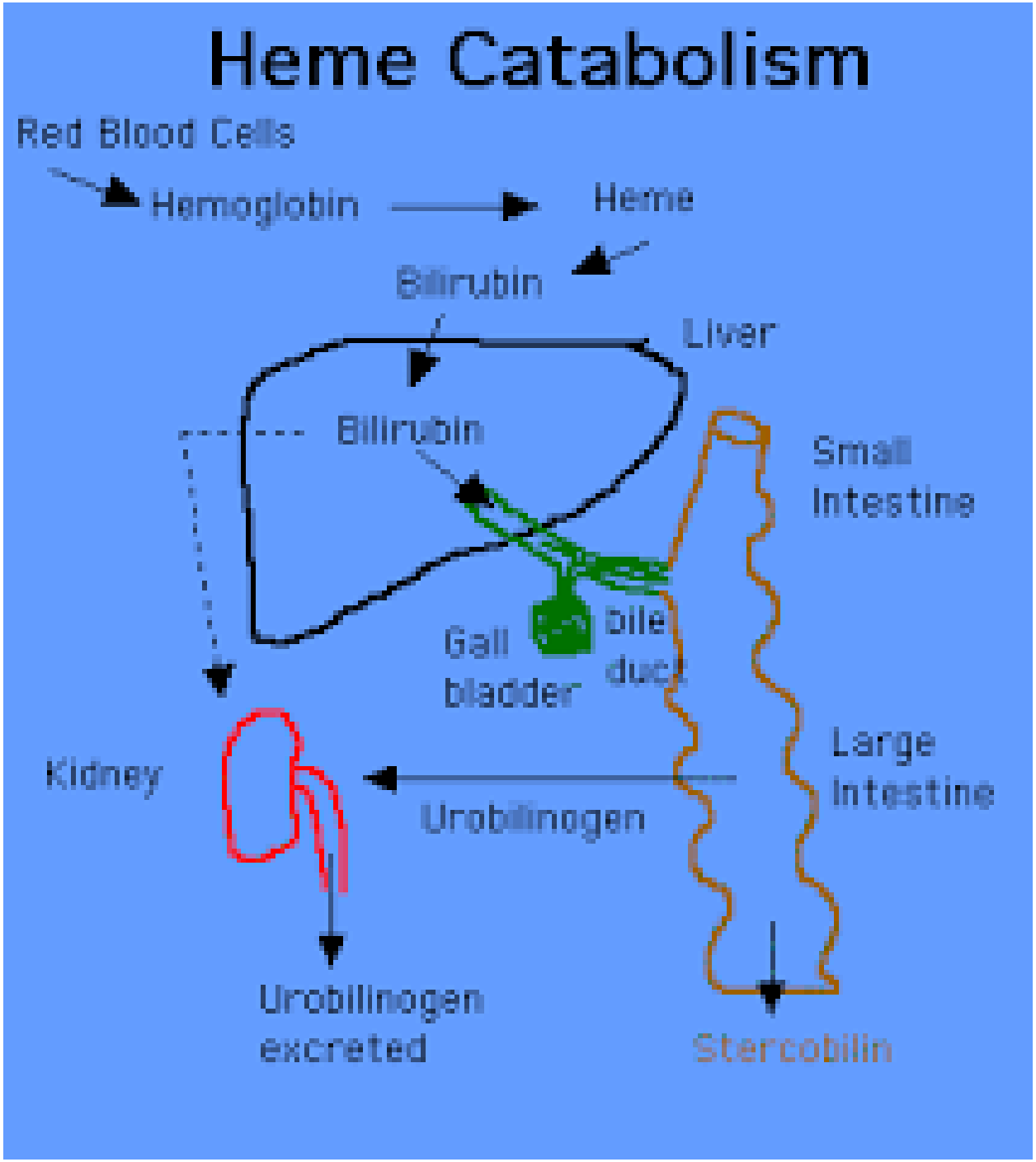
- Excreted in feces

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

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
Stercobilin

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.

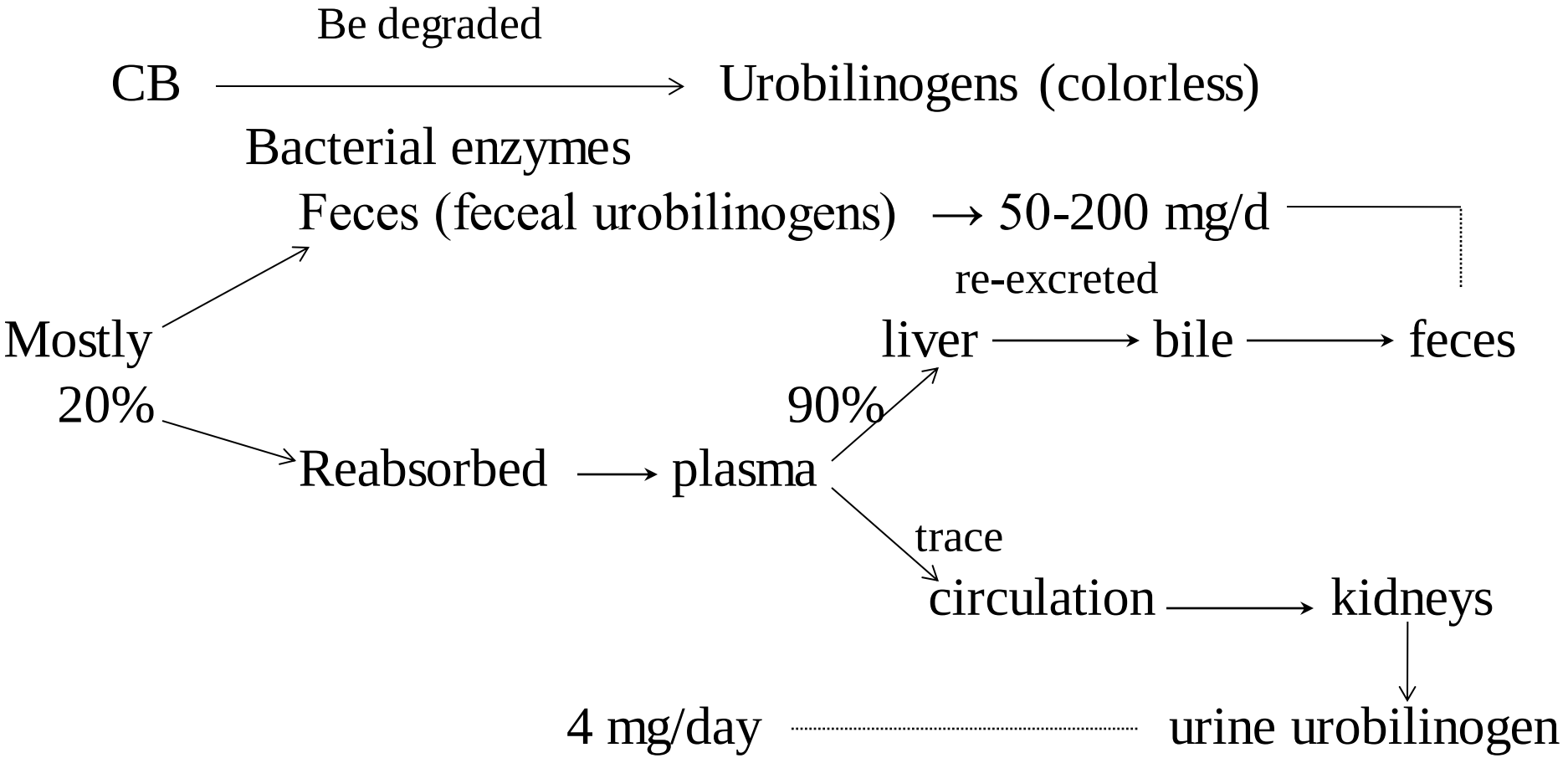
- Bilirubin conjugated in presence of UDPGT (uridine diphosphate glucuronyl transferase) to mono and diglucoronides, which are then excreted into bile canaliculi.

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.

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