GASTROINTESTINAL PHYSIOLOGY

(LECTURE 7)
BILIRUBIN METABOLISM

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LEARNING OBJECTIVES

- Definition of bilirubin
- Bilirubin metabolism
  - Bilirubin formation
  - Transport of bilirubin in plasma
  - Hepatic bilirubin transport
  - Excretion through intestine
- Other substances conjugated by glucuronyl transferase.
- Differentiation between conjugated & unconjugated bilirubin
- Other substances excreted in the bile

Definition of bilirubin

- Bilirubin is the greenish yellow pigment excreted in bile, urine and feces.
- It is the water insoluble breakdown product of normal heme catabolism
- Heme is found in hemoglobin, a principal component of RBCs [Heme: iron + organic compound "porphyrin"].
- Heme source in body:
  - 80% from hemoglobin
  - 20% other hemo-protein: cytochrome, catalase, peroxidas, myoglobin)
- It is toxic, therefore, its excretion in the bile is one of the very important functions of the liver.
- Serum bilirubin level is an important clinical marker of hepatobiliary excretory function.

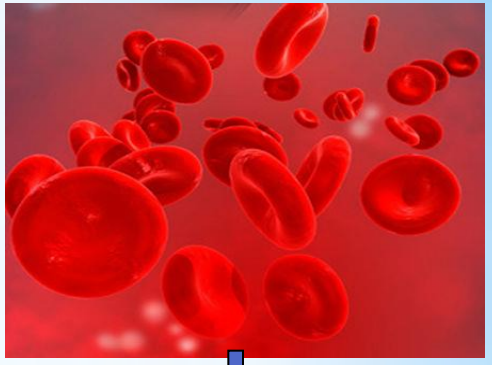
Bilirubin Metabolism

- Bilirubin metabolism involves four discernible steps:

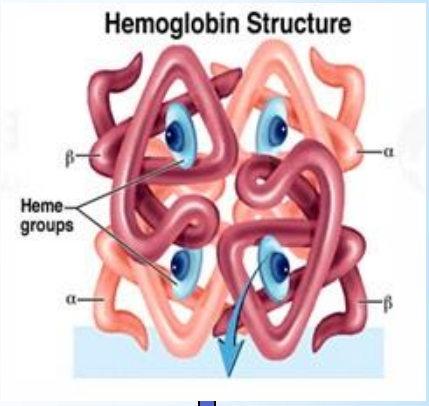
Formation	Plasma Transport	Hepatic Phase	Intestine Excretion
		▪ Hepatic uptake ▪ Conjugation ▪ Biliary excretion	

- The four steps are finely balanced. Therefore:
  - Reduction at any step may cause hyperbilirubinemia.
  - Enhancement of the throughput requires induction of multiple genes, probably coordinated by nuclear receptors.

BILIRUBIN FORMATION



- Life span of RBCs in blood stream is 60-120 days.
- Senescent RBCs are phagocytosed extravascularly in the reticulo-endothelial system.
- RBCs lysis can also occur intravascularly in blood stream.
- The hemoglobin is first split into globin & heme.
- The AA formed from breakdown of globin are stored in the body.



Iron+Bile pigments ← Heme

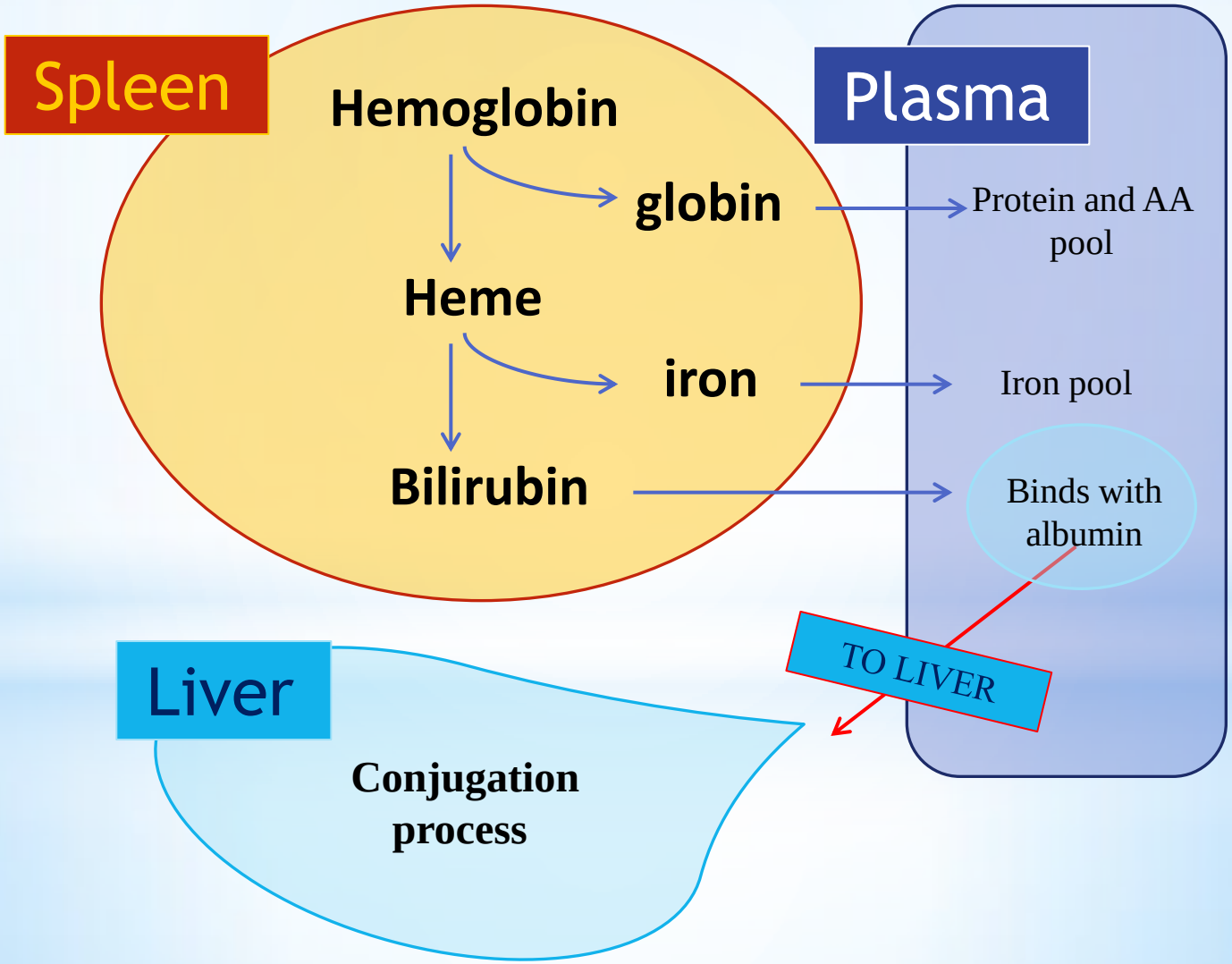
Amino acids ← Globin

BILIRUBIN FORMATION (CONT.)

The heme ring is opened to give:

- **Free iron:** Transported in the blood by transferrin and stored in the body as a reservoir for erythropoiesis.
- **Bile pigments:** The 1st pigment is biliverdin but it is rapidly reduced by biliverdin reductase to free bilirubin which is gradually released into the plasma.

Hemoglobin degrading and bilirubin formation



Transport of Bilirubin in Plasma

- The free bilirubin is hydrophobic, immediately combines with plasma proteins (mainly albumin and globulin) forming a water soluble compound (**hemobilirubin,** unconjugated, indirect bilirubin) which is rapidly transported to hepatocytes for further metabolism. Even when bound to albumin it's called free bilirubin.

Albumin + Free Bilirubn ⟷ **Bilirubin ~ Albumin Complex**

Unconjugated bilirubin

Transport of Bilirubin in Plasma (Cont.)

Significance: of bilirubin binding to albumin:

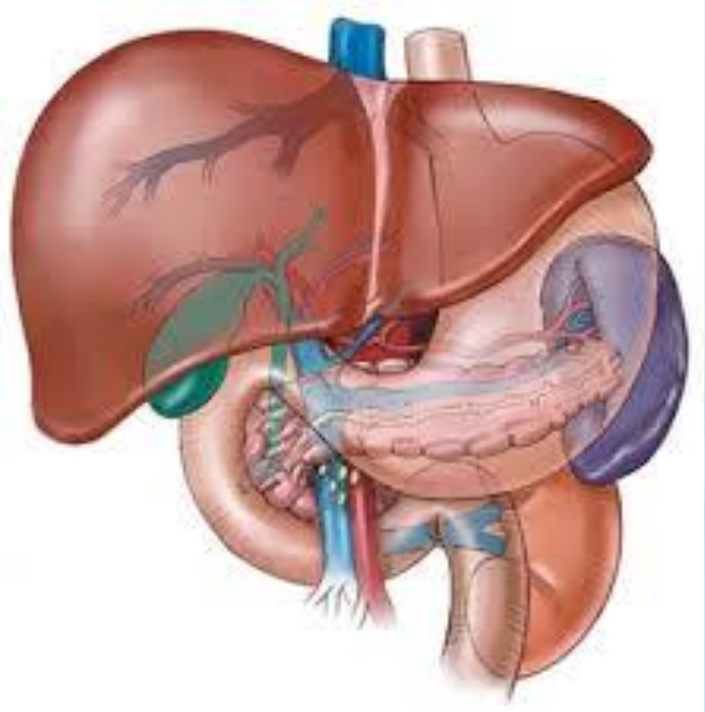
- Increase the solubility of whole molecule.
- Prevent unconjugated bilirubin freely come into other tissue, cause damage.

N.B: Certain drugs as sulfonamides and salicylates compete with bilirubin for albumin binding and displace bilirubin to enter into the brain in neonates and increase the risk of kernicterus (a type of brain damage that can result from high levels of bilirubin in a baby's blood). It can cause cerebral palsy and hearing loss.

Hepatic phase

On coming in contact with the hepatocyte surface, unconjugated bilirubin is preferentially metabolized which involved 3 steps:

- A- Hepatic uptake
- B- Conjuation
- C- Secretion in bile



A- Hepatic uptake

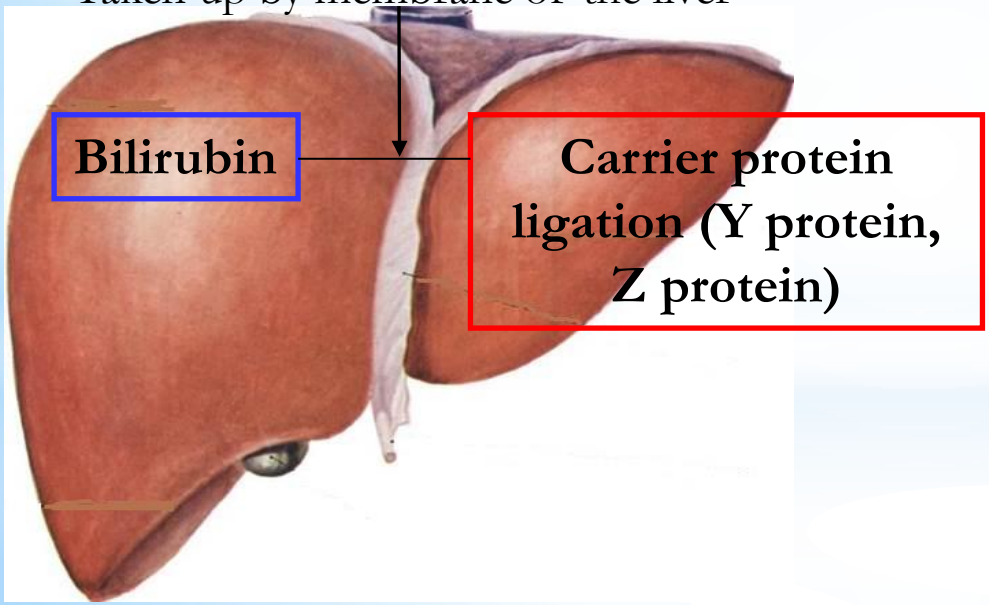
Bilirubin ~ Albumin Complex

Albumin

Bilirubin

(lipid soluble)

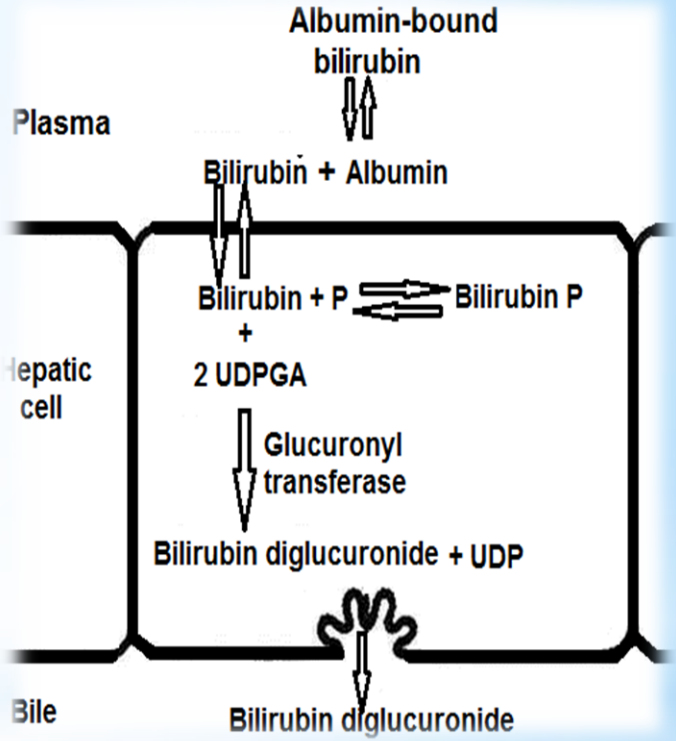
Taken up by membrane of the liver



Bilirubin is absorbed through the hepatic cell membrane, mediated by a carrier protein (receptor) & combined with Y & Z proteins that trap the bilirubin inside the cells.

B- Bilirubin Conjugation

- In the liver cells hemobilirubin dissociates into protein and free bilirubin.
- About 80% of bilirubin conjugates with uridine diphospho-glucuronic acid (UDPGA) catalyzed by the enzyme glucuronyl transferase in the smooth ER.
- Each bilirubin molecule reacts with 2 UDPGA molecules to form bilirubin diglucuronide (cholebilirubin, direct, conjugated bilirubin) which is more water soluble than the free bilirubin.
- Inherited glucuronyl transferase deficiency causes jaundice.
- 20% conjugate with sulphate or other substances.



B- Bilirubin Secretion in Bile

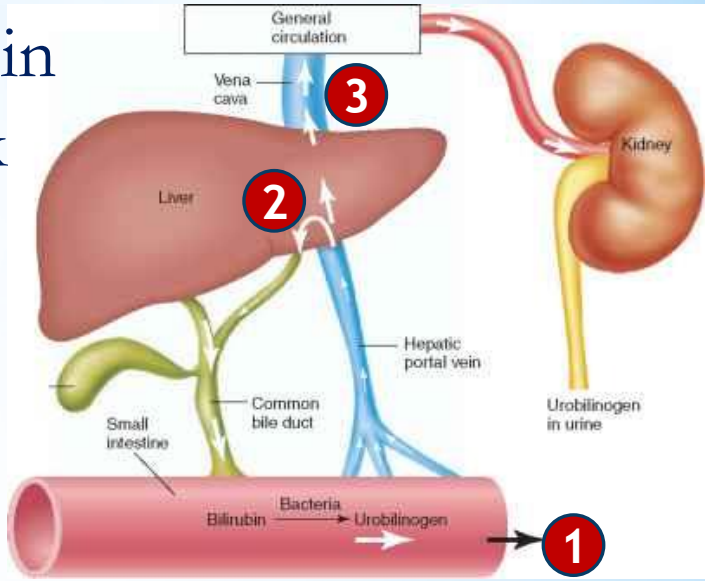
- Cholebilirubin (conjugated bilirubin) is actively secreted by the liver cells by an active transport process into the bile canaliculi.
- This energy-dependent, rate –limiting step is susceptible to impairment in liver disease.
- Uncojugated bilirubin is normally not excreted.
- The color of bile is due to bilirubin.
- In normal adults this results in a daily load of 250-300 mg of bilirubin.

C- Fate of conjugated bilirubin

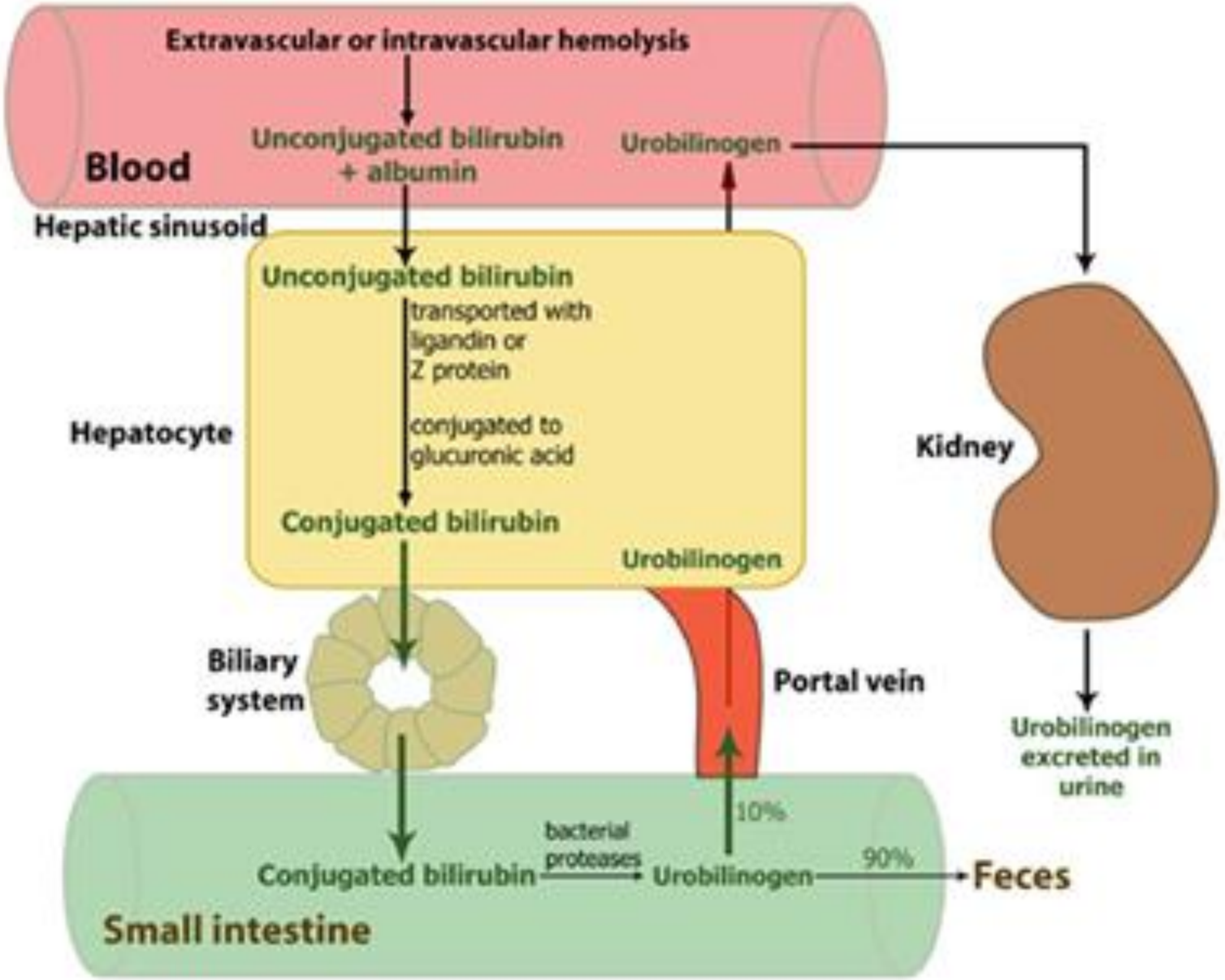
- A small portion of the conjugated bilirubin returns to the plasma and bound less tightly to albumin & is excreted in the urine. this causes a small portion of the bilirubin in the ECF to be of the conjugated type.
- Small amount is deconjugated and absorbed by the small intestine into the portal blood to the liver where it is extracted by the liver cells and conjugate again and excreted in the bile (enterohepatic circulation of bile pigments).
- The majority of conjugated bilirubin passes via the bile ducts to the intestine where it is transformed through bacterial action into urobilinogen which is highly soluble.

Fate of Urobilinogen

- Most of urobilinogen (70%) in the intestine is converted into stercobilinogen, oxidized and excreted in the feces as stercobilin that causes dark brown color of the feces.



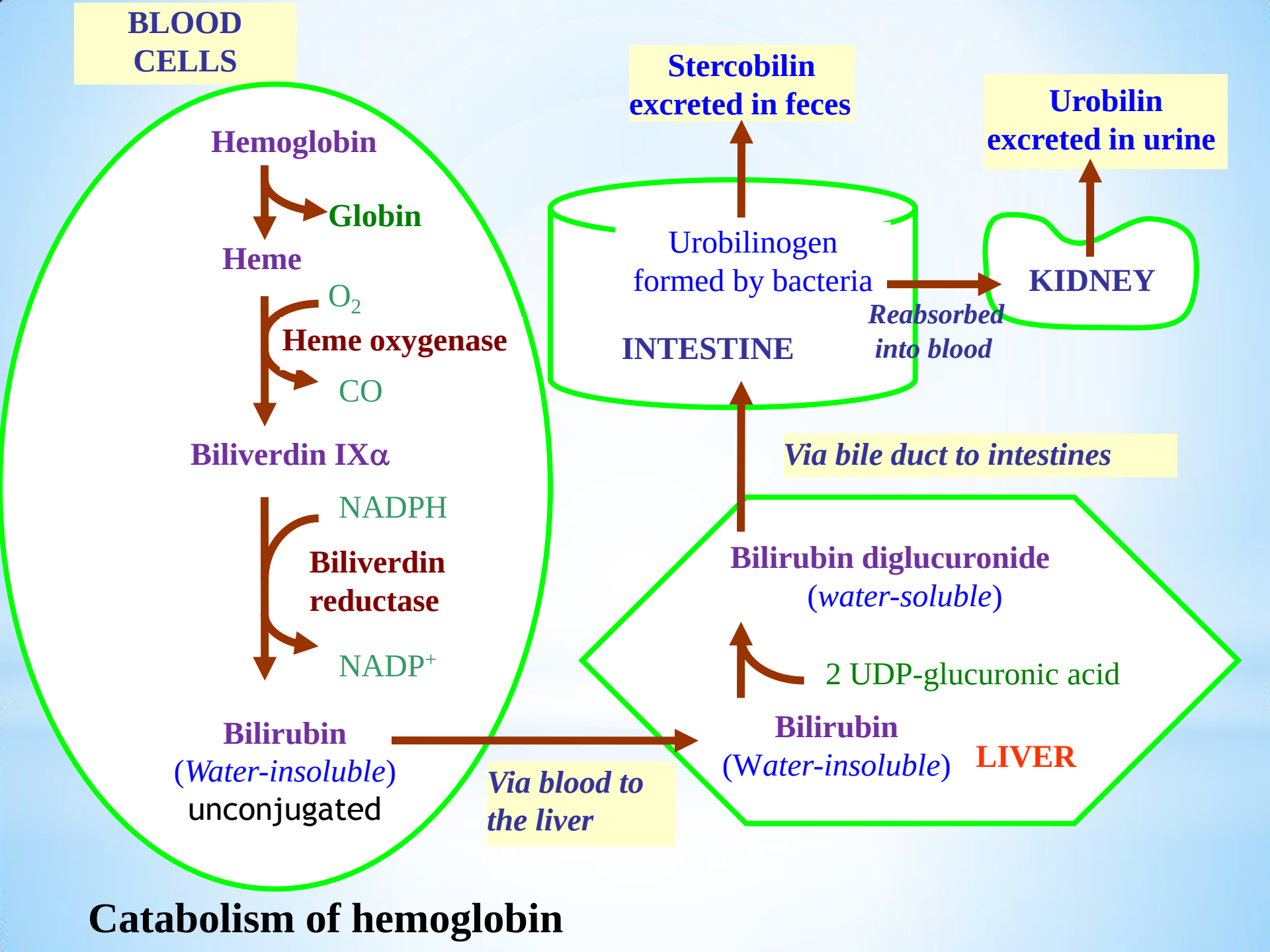
- Some of urobilinogen (20 %) is reabsorbed through the intestinal mucosa into the portal vein and reexcreted by the hepatic cells in the bile (enterohepatic circulation).
- Small amount of urobilinogen escapes to the general circulation and excreted by the kidneys in the urine where it is oxidized to urobilin when the urine is exposed to air.


Extravascular or intravascular hemolysis
Blood
Unconjugated bilirubin
+ albumin
Urobilinogen
Hepatic sinusoid
Unconjugated bilirubin
transported with
ligandin or
Z protein
Hepatocyte
conjugated to
glucuronic acid
Conjugated bilirubin
Urobilinogen
Kidney
Biliary
system
Portal vein
Urobilinogen
excreted in
urine
10%
bacterial
proteases
Conjugated bilirubin
Urobilinogen
90%
Feces
Small intestine

Other Substances Conjugated By Glucuronyl Transferase

- The glucuronyl transferase system in the smooth endoplasmic reticulum catalyzes the formation of the glucuronides of a variety of substances in addition to bilirubin.
- The list includes steroids & various drugs.
- These other compounds can compete with bilirubin for the enzyme system when they are present in appreciable amounts.

- In addition several barbiturates, antihistamines, anticonvulsants and other compounds can cause marked proliferation of the smooth endoplasmic reticulum in the hepatic cells, with a concurrent increase in hepatic glucuronyl transferase activity.
- Phenobarbital has been used successfully for the treatment of a congenital disease in which there is a relative deficiency of glucuronyl transferase (type 2 UDP-glucuronyl transferase deficiency).



Catabolism of hemoglobin

Summary of bilirubin metabolism

Senescent red cells are major source of hemeproteins

↓

Breakdown of heme to bilirubin occur in macrophage of reticuloendithelial system (tissue macrophages, spleen and liver).

↓

Unconjugated bilirubin is transported through blood (complex to albumin) to liver.

↓

Bilirubin is taken into liver and conjugate with glucuronic acid.

↓

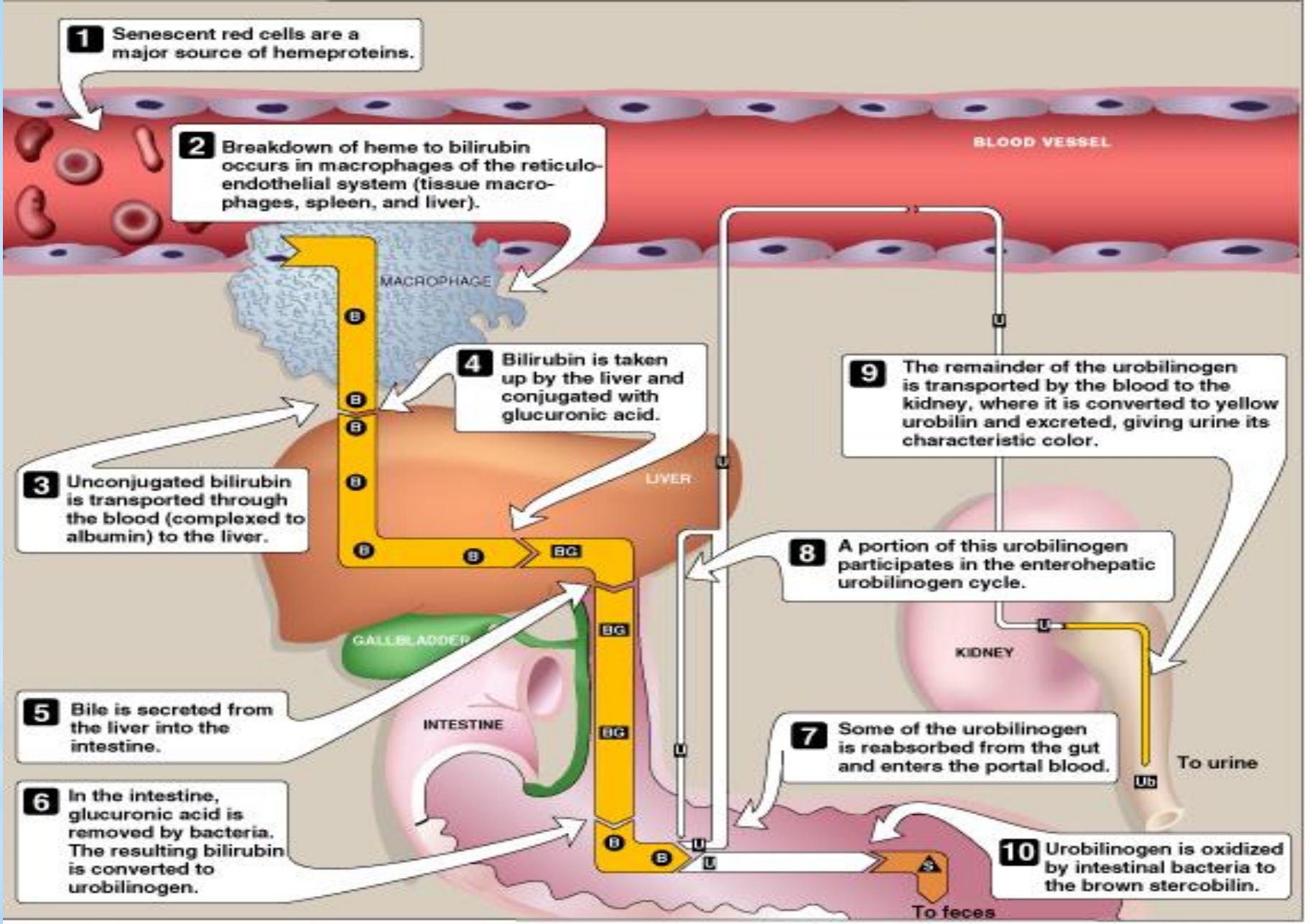
Bile is secreted into intestine where glucuronic acid is removed and the resulting bilirubin is converted to urobilinogen.

↓

A portion of urobilinogen is reabsorbed into blood, where it is converted to the yellow urobilin and excreted by kidneys.

↓

Urobilinogen is oxidized by intestinal bacteria to the brown stercobilin.



Catabolism of heme B = bilirubin; BG = bilirubin diglucuronide; U = urobilinogen; Ub = urobilin; A = stercobilin.

Types of bilirubin in serum

- ✓ Direct bilirubin: is conjugated (water soluble) bilirubin, it reacts rapidly with reagent (direct reacting).
- ✓ Indirect bilirubin: is unconjugated (water insoluble) bilirubin because it is less soluble, it reacts more slowly with reagent (reaction carried out in methanol).

  - in this case both conjugated and unconjugated bilirubin are measured given **total bilirubin**. Unconjugated will calculated by subtracting direct from total and so called indirect.

- ✓ Total bilirubin = D+ ID

Knowing the level of each type of bilirubin has diagnostic important.

Normal Range of bilirubin

1～16μmol/l (0.1 ～1mg/dl)

4/5 are unconjugated bilirubin, others are conjugated bilirubin.

<1mg/dl	**Normal**	
1-2mg/dl	**Occult**	Hyperbilirubinemia
>2mg/ dl	**Jaundice**	

Major differences between unconjugated and conjugated bilirubin

Feature	Unconjugated bilirubin (Hemobilirubin)	Conjugated bilirubin (Cholebilirubin)
Normal serum level	The chief form of bilirubin in the blood	Present in low conc. in the blood
Water solubility	Absent	Present
Affinity to lipids	Present	Absent
Binding	Bind to albumin	Bind to glucuronic acid
Reaction to reagents	Indirect (Total minus direct)	Direct
Reanal excretion	Absent	Present
Affinity to brain tissue	Present (kernicterus), toxic	Absent, less toxic

OTHER SUBSTANCES EXCRETED IN THE BILE

- Cholesterol & alkaline phosphatase are excreted in the bile.
  - In patients with jaundice due to intra or extra hepatic obstruction of the bile duct, the blood levels of these 2 substances usually rise.
  - A much smaller rise is generally seen when the jaundice is due to non obstructive hepatocellular disease.
- Adrenocortical, other steroid hormones & a number of drugs are excreted in the bile and subsequently reabsorbed (enterohepatic circulation)


Thank You