Physiology of *Gastrointestinal System* (L8)

Bilirubin Metabolism

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LEARNING OBJECTIVES

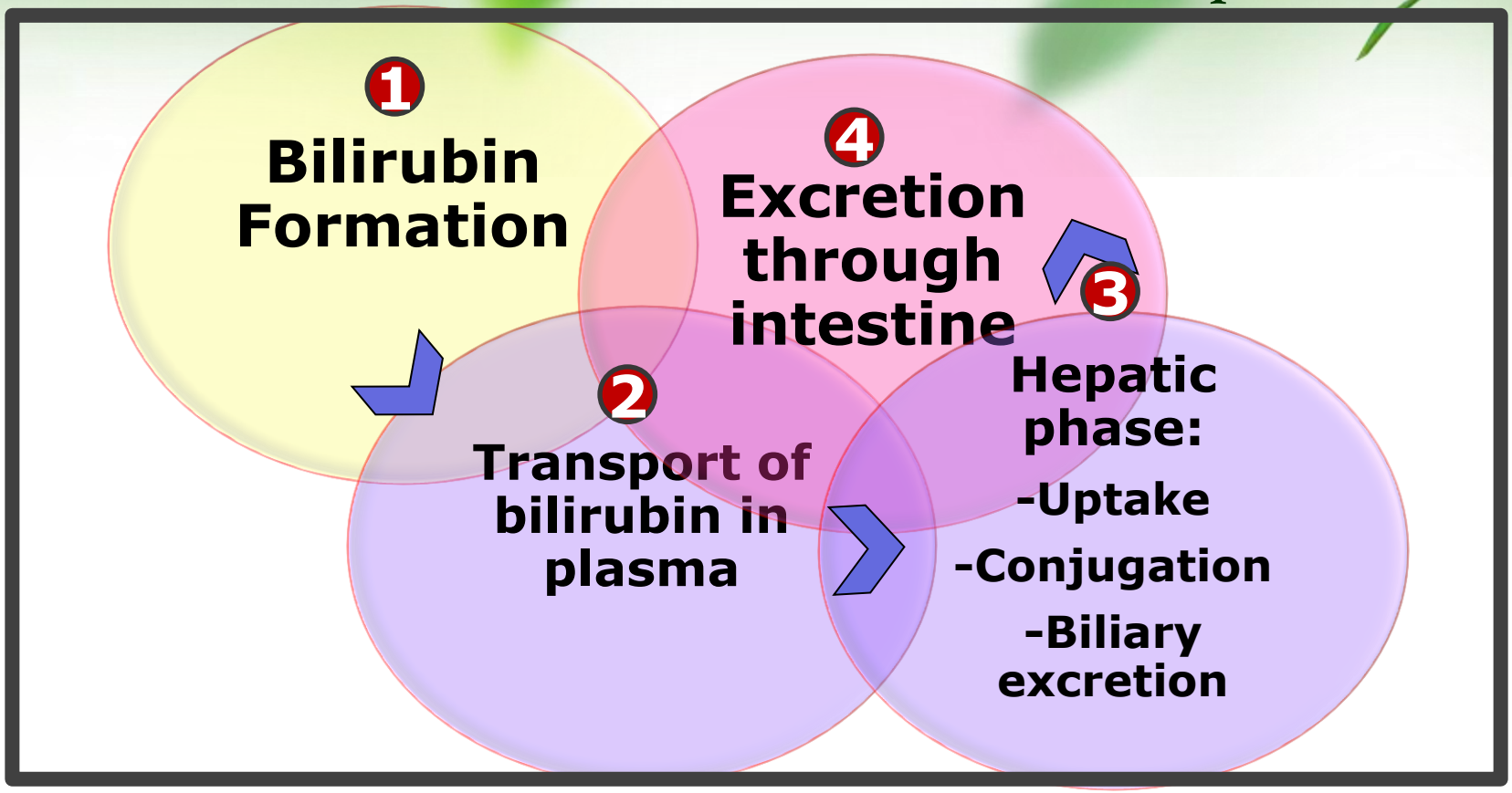
- *Definition of Bilirubin*
- *Bilirubin Metabolism: formation, Transport in Plasma, Hepatic Transport, Excretion Through Intestine*
- *Other Substances Conjugated By Glucuronyl Transferase.*
- *Differentiation Between Conjugated & Unconjugated Bilirubin*
- *Causes and Pathogenesis of Jaundice*

Definition of Bilirubin

- It is the greenish yellow pigment excreted in bile, urine & feces.
- It is water insoluble breakdown product of 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, peroxidase, myoglobin)
- Bilirubin 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

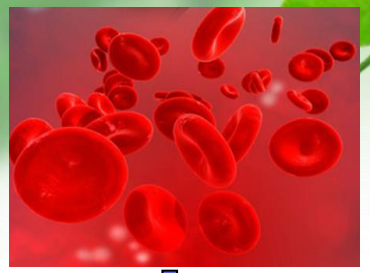
Bilirubin metabolism involves four discernible steps:

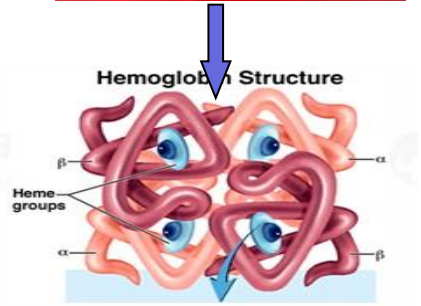


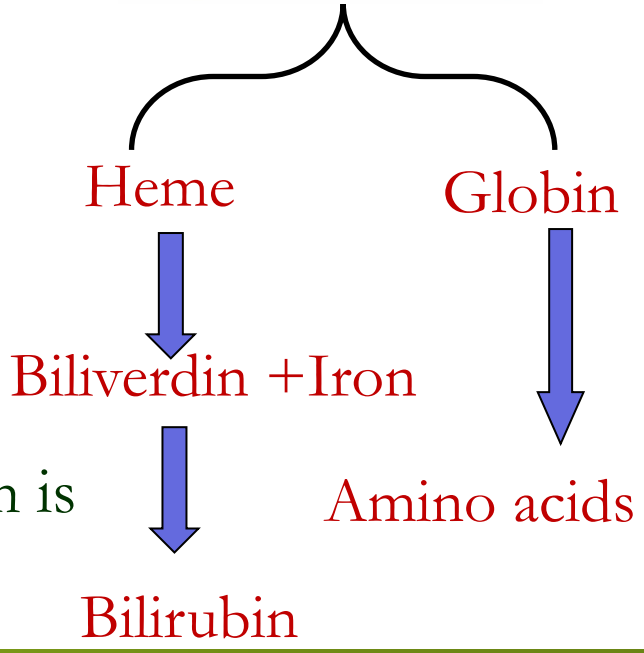
- The four steps are finely balanced. Therefore:
  - Reduction at any step may cause hyperbilirubinemia.
  - Enhancement of the throughput requires induction of multiple gens, coordinated by nuclear receptors.

Bilirubin Formation

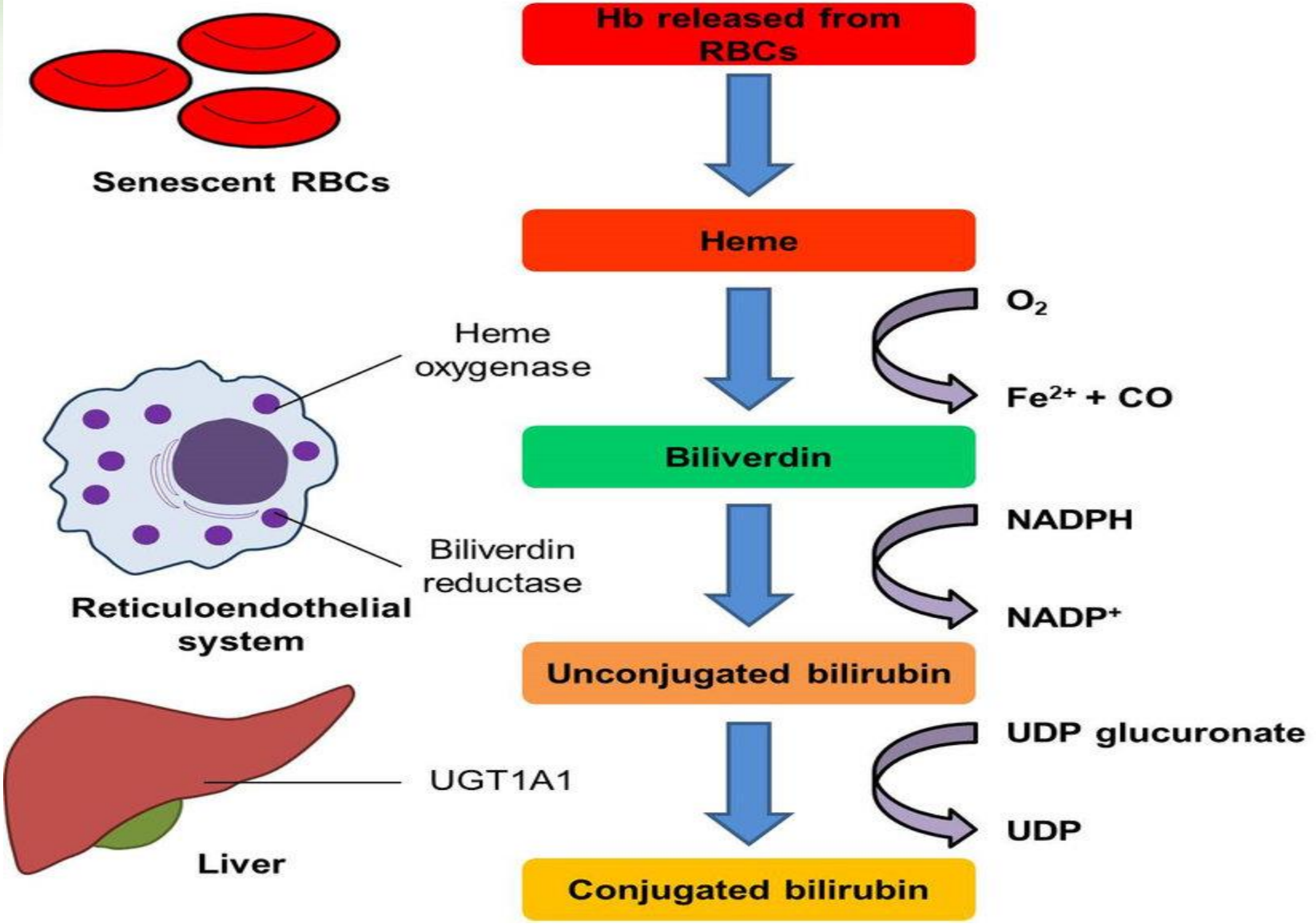
- Life span of RBCs is 60-120 days.
- Senescent RBCs are phagocytosed intravascularly or extravascularly in the reticulo-endothelial system.
- The hemoglobin is first split into globin & heme.
- The AA formed from breakdown of globin are stored in the body.
- The heme ring is opened to give:
  - **Free iron:** Transported in the blood by transferrin and stored in the body as a reservoir for erythropoiesis.
  - **Bile pigments (biliverdin):** Reduced by biliverdin reductase to free bilirubin which is gradually released into the plasma.



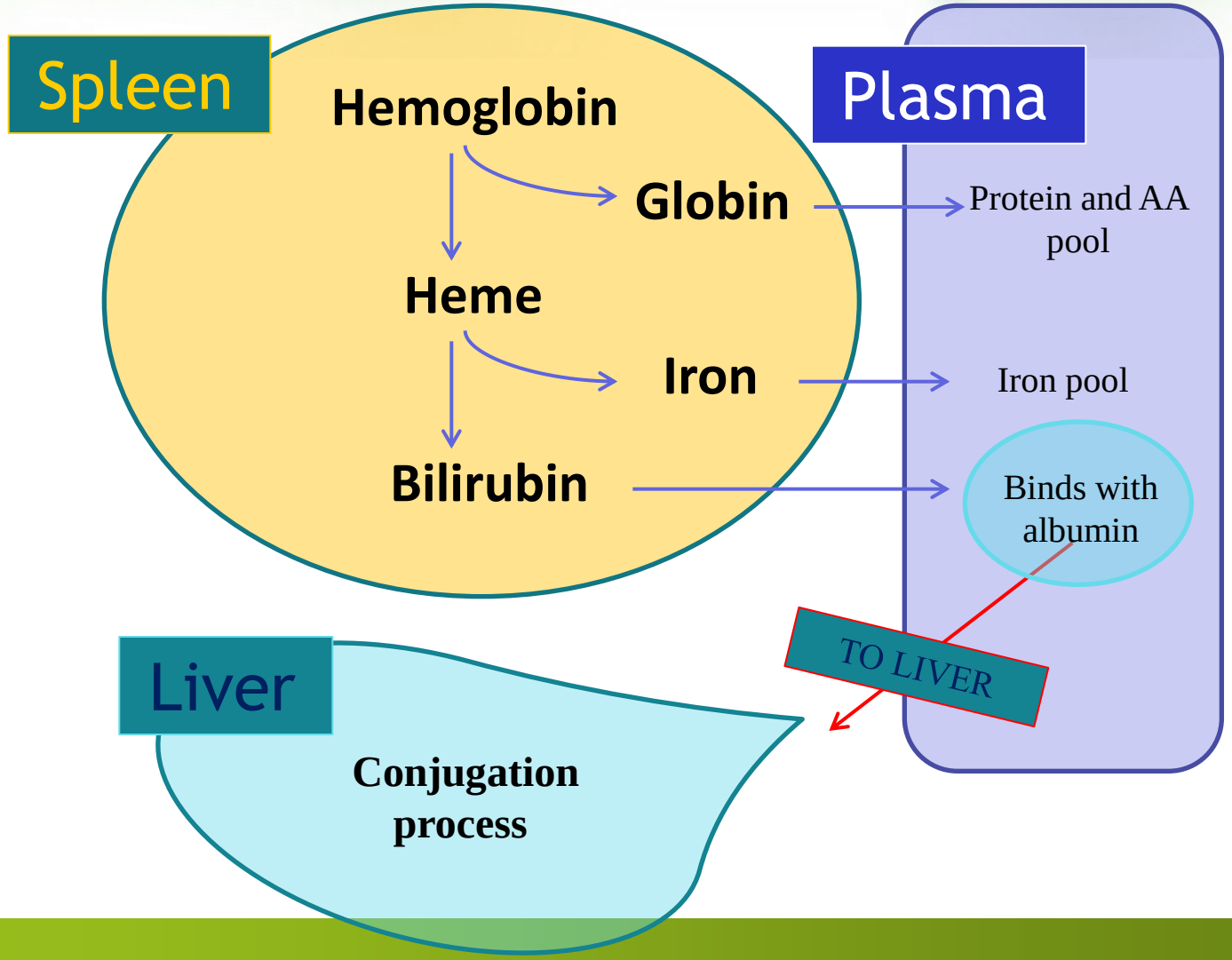




Bilirubin Formation

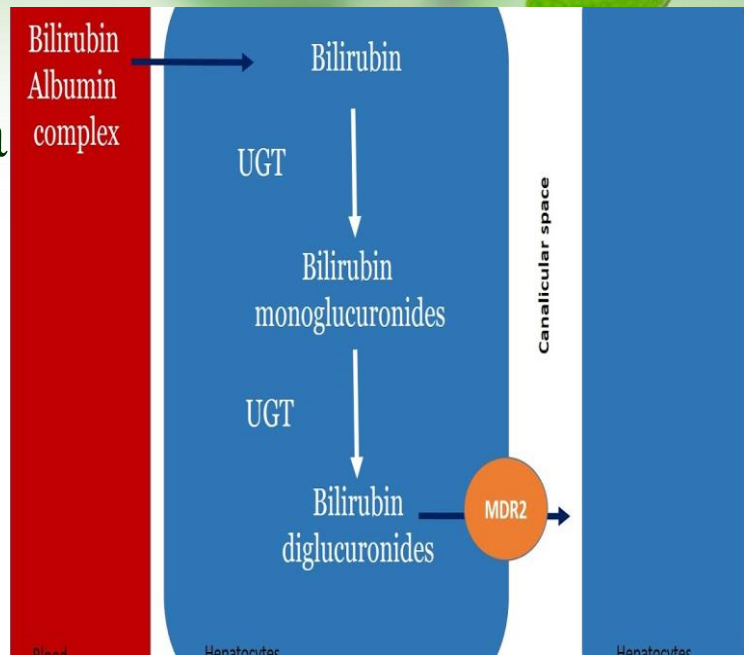


Hemoglobin Degrading and Bilirubin Formation



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, indirect bilirubin (hemobilirubin)

Transport of Bilirubin in Plasma (Cont.)

Significance: of bilirubin binding to albumin:

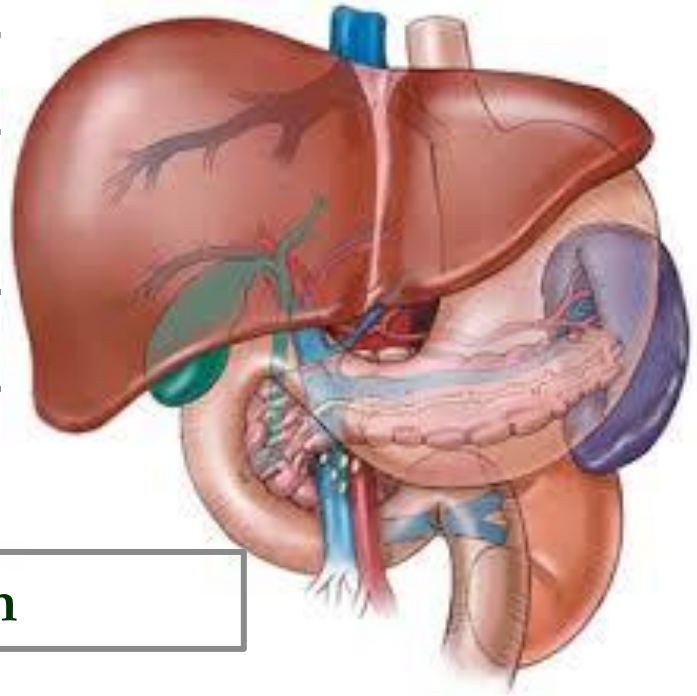
- Increase the solubility of whole molecule.
- Prevent unconjugated bilirubin freely come into other tissue, cause damage.

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 Bilirubin Uptake**
- **B- Bilirubin Conjugation**
- **C- Bilirubin Biliary Excretion**



A- Hepatic Uptake

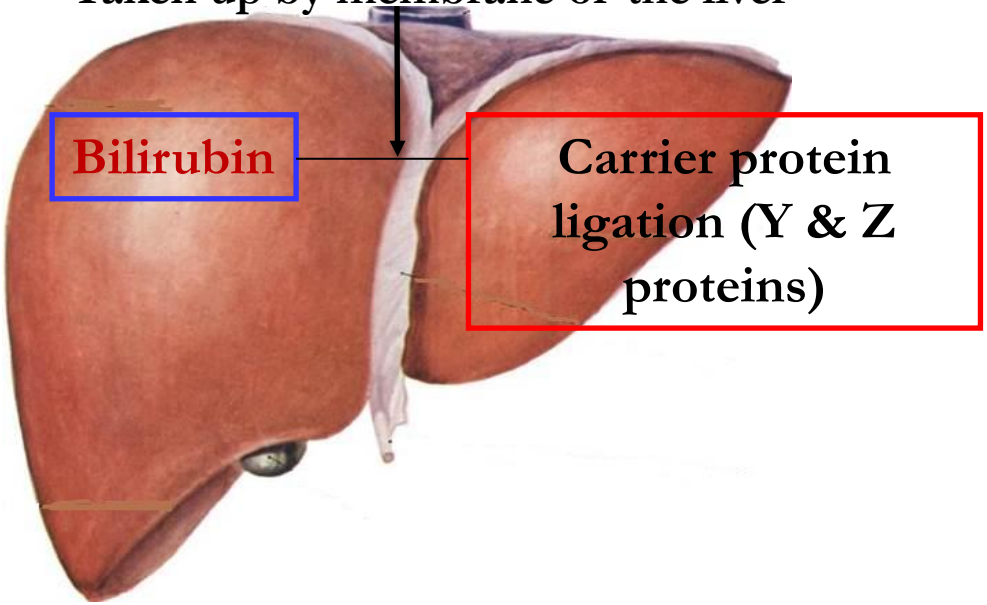
Bilirubin ~ Albumin Complex

Albumin

Bilirubin

(lipid soluble)

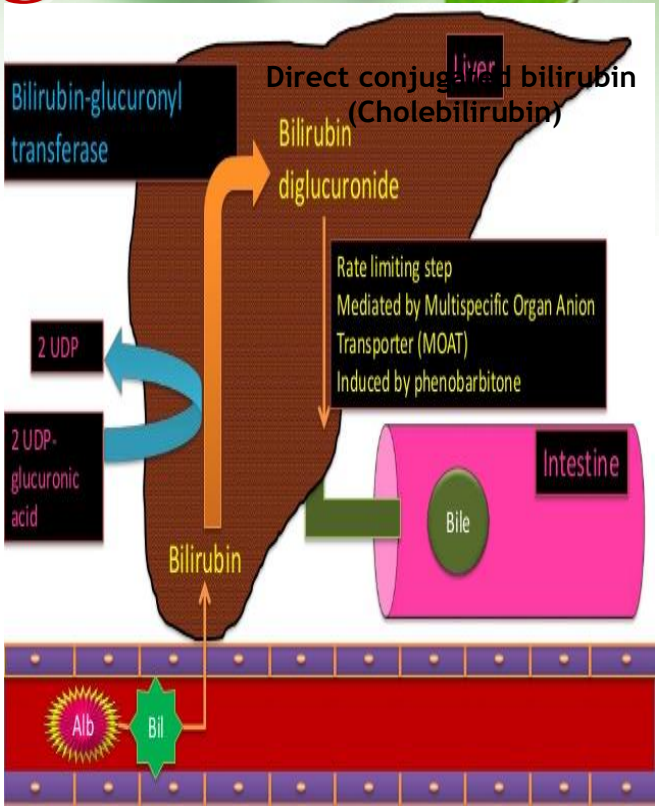
Taken up by membrane of the liver



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

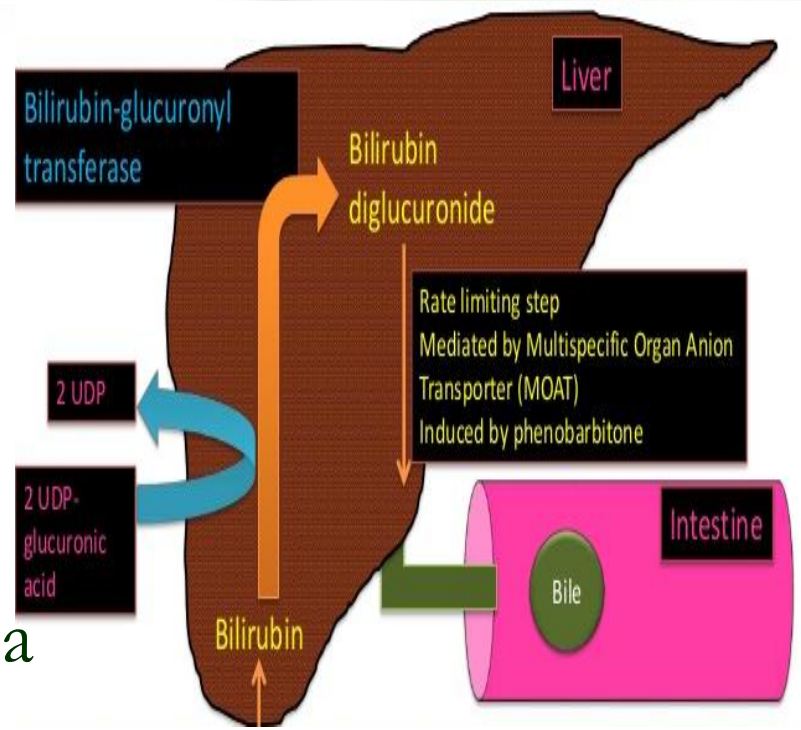
- In the smooth ER of hepatocytes, about 80% of bilirubin conjugates with uridine diphospho-glucuronic acid (UDPGA).



- Each bilirubin molecule reacts with 2 UDPGA molecules catalyzed by the enzyme glucuronyl transferase to form bilirubin diglucuronide (cholebilirubin, direct, conjugated bilirubin)
- Cholebilirubin is more water soluble than free bilirubin.
- Inherited glucuronyl transferase deficiency causes jaundice.
- 20% conjugate with sulphate or other substances.

C- Bilirubin Secretion in Bile

- Cholebilirubin is actively secreted into the bile canaliculi through an active carrier-mediated process giving bile its color.
- This energy-dependent, rate – limiting step is susceptible to impairment in liver disease.
- In normal adults this results in a daily load of 250-300 mg of bilirubin.
- Uncojugated bilirubin is normally not excreted.

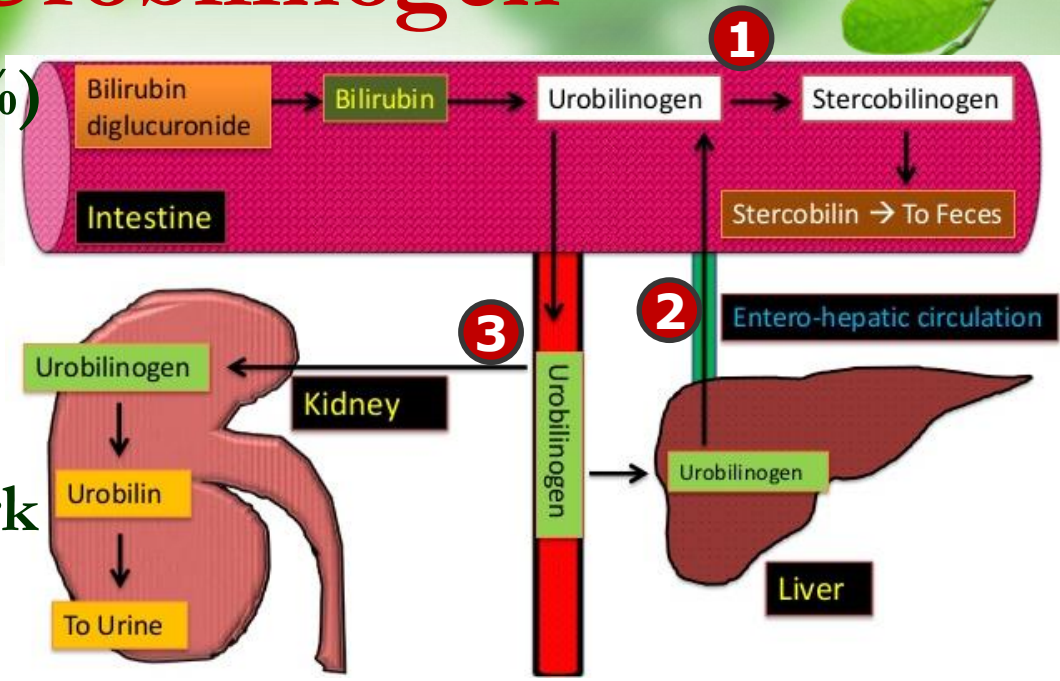


Fate of conjugated bilirubin

- 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 in the small intestine and absorbed 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%) is converted into stercobilinogen in the intestine , 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.

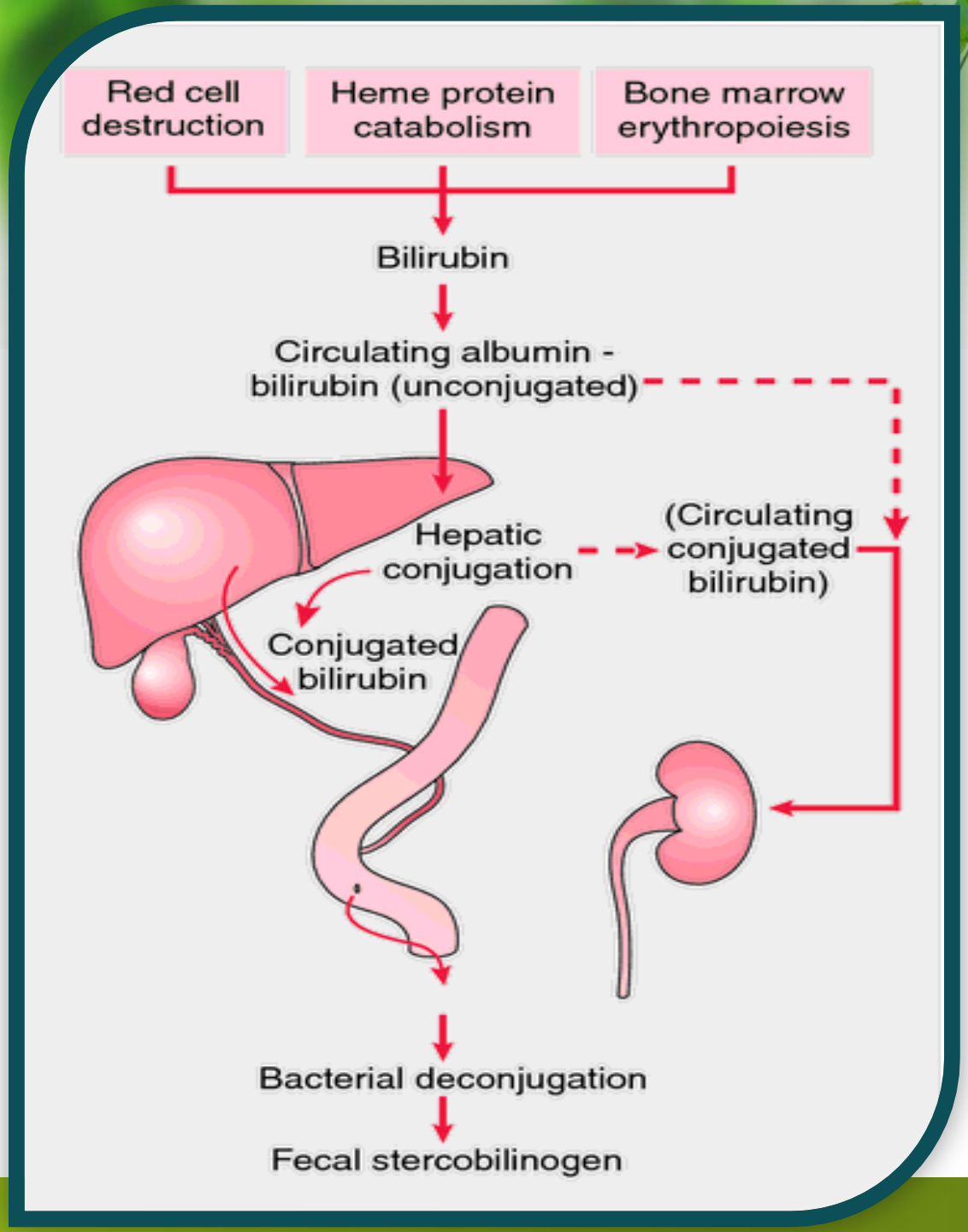
Other Substances Conjugated By Glucuronyl Transferase

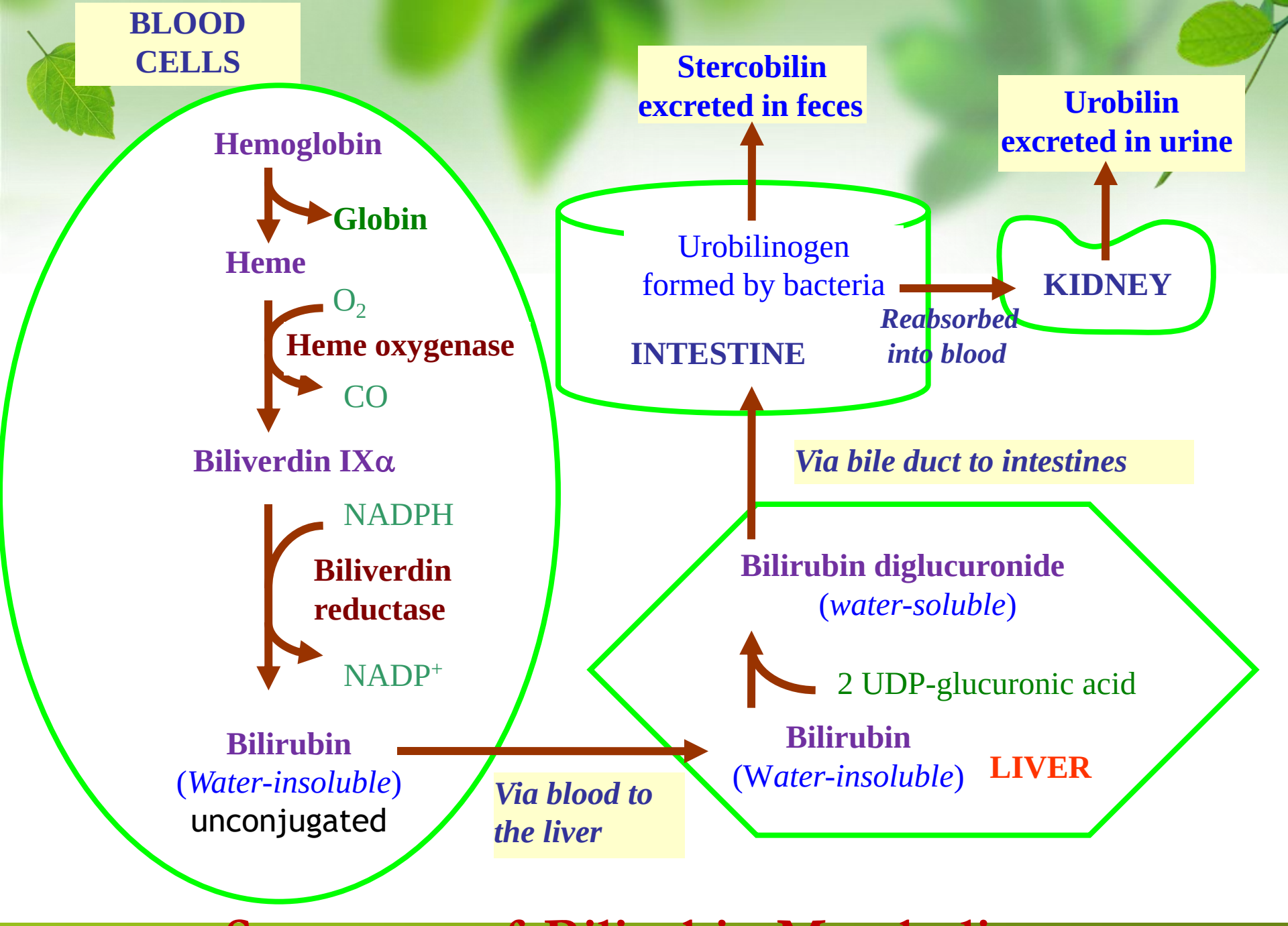
- The glucuronyl transferase system in the smooth endoplasmic reticulum catalyzes the formation of the glucuronides of a variety of substances in addition to bilirubin.
- The list includes steroids & various drugs.
- These compounds can compete with bilirubin for the enzyme system when they are present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

Substances that increase hepatic glucuronyl transferase activity

- Several substances as barbiturates, antihistamines and anticonvulsants 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 2 UDP-glucuronyl transferase.

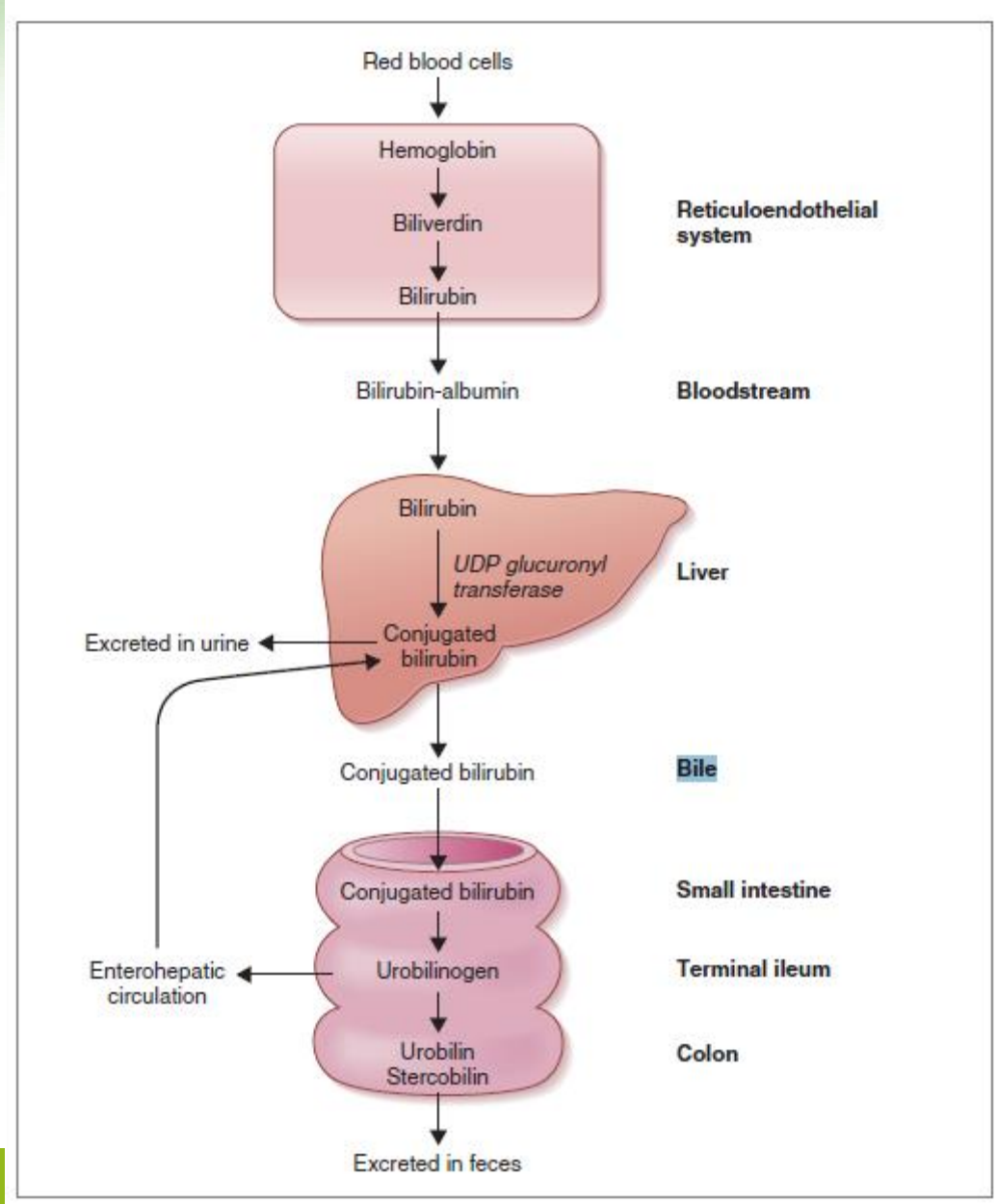
Normal Bilirubin Metabolism





Summary of Bilirubin Metabolism

Summary of Bilirubin Metabolism



Types of Bilirubin in the 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.

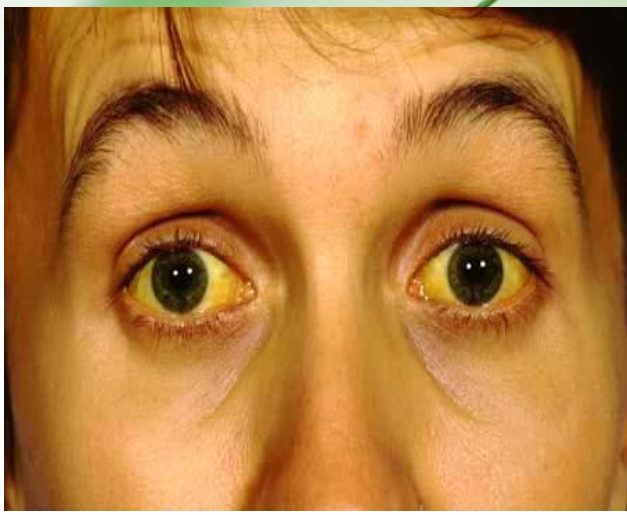
Major Differences Between Unconjugated And Conjugated Bilirubin

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
Renal excretion	Absent	Present
Affinity to brain tissue	Present (kernicterus), toxic	Absent, less toxic

Other Substances Excreted in The Bile

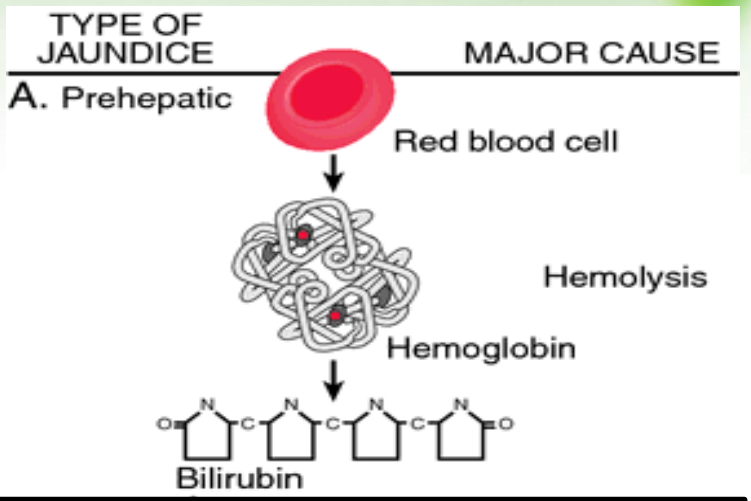
- Cholesterol & alkaline phosphatase are excreted in the bile.
  - In patients with jaundice due to intra or extra hepatic obstruction of the bile duct, the blood levels of these 2 substances usually rise.
  - A much smaller rise is generally seen when the jaundice is due to non obstructive hepatocellular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

Hyperbilirubinemia (Jaundice, Icterus)

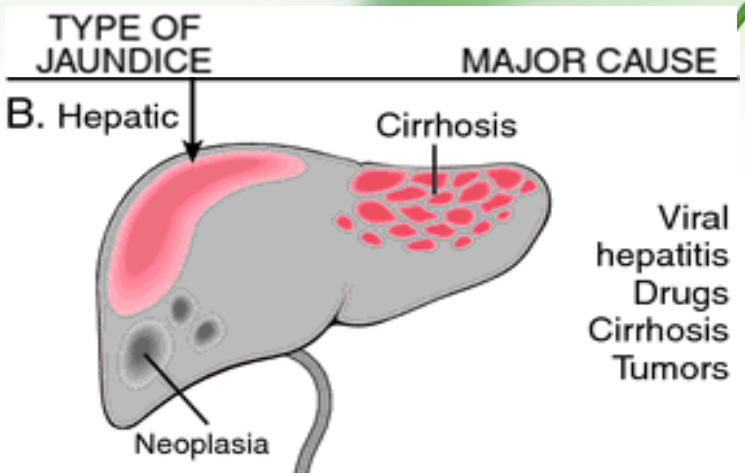


- It is the yellow coloration of the skin, sclera, mucous membranes and deep tissues
- The usual cause is large quantities of bilirubin in the ECF, either free or conjugated bilirubin.
- The normal plasma concentration of total bilirubin is 0.3-1.2 mg/dl of blood
- The skin usually begins to appear jaundiced when the concentration of total bilirubin in the plasma is > than 2 -2.5 mg/dl.
- Bilirubin level from 1 to 2 mg/dl is called subclinical (occult jaundice).

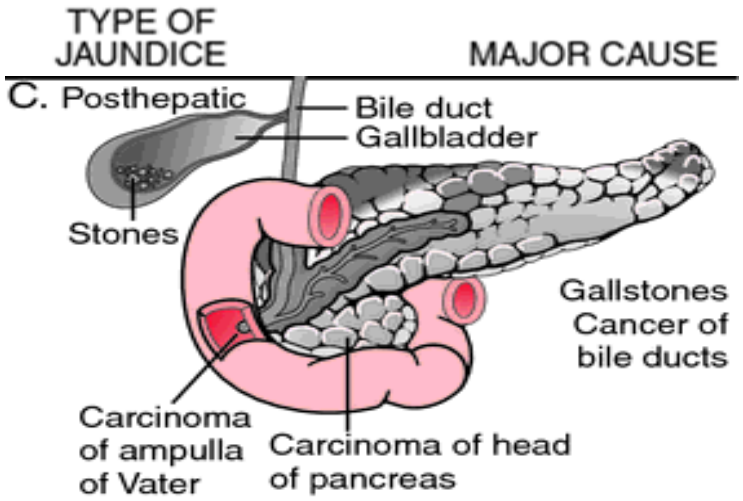
Classification of Jaundice



Prehepatic (hemolytic) jaundice



Hepatic (hepatocellular) jaundice



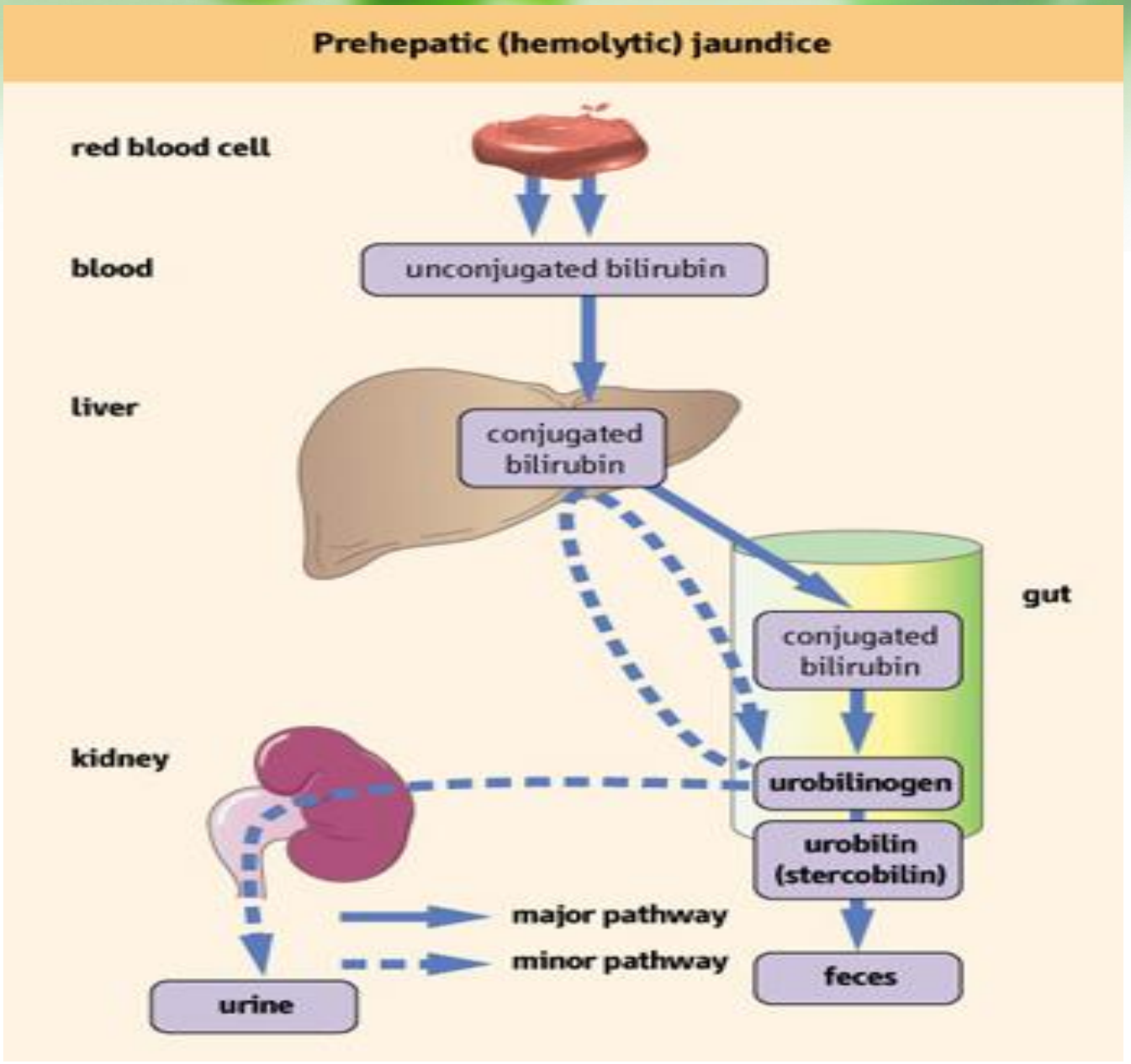
Poshepatic (obstructive) jaundice

Prehepatic (Hemolytic) Jaundice

- **In hemolytic jaundice, the excretory function of the liver is not impaired.**
- **It results from excess production of bilirubin (beyond the livers ability to conjugate it) following hemolysis.**
- **Excess RBC lysis is commonly the result of:**
  - Autoimmune disease
  - Hemolytic disease of the newborn
  - Rh- or ABO- incompatibility
  - Structurally abnormal RBCs (Sickle cell disease)
  - Breakdown of extravasated blood.

Prehepatic (Hemolytic) Jaundice…Cont.

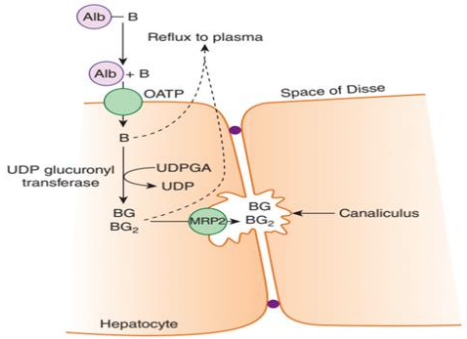
- Therefore the plasma concentrations of free bilirubin (hemobilirubin) rises to levels much above normal but it is not filtered through the kidney.
- The urine is free from bilirubin (acholuric jaundice).
- The stools appear darker than the normal color due to excessive stercobilin formation.


Prehepatic (hemolytic) jaundice
red blood cell
blood
unconjugated bilirubin
liver
conjugated bilirubin
gut
conjugated bilirubin
kidney
urobilinogen
urobilin (stercobilin)
major pathway
minor pathway
feces
urine

Hepatic (Hepatocellular) Jaundice

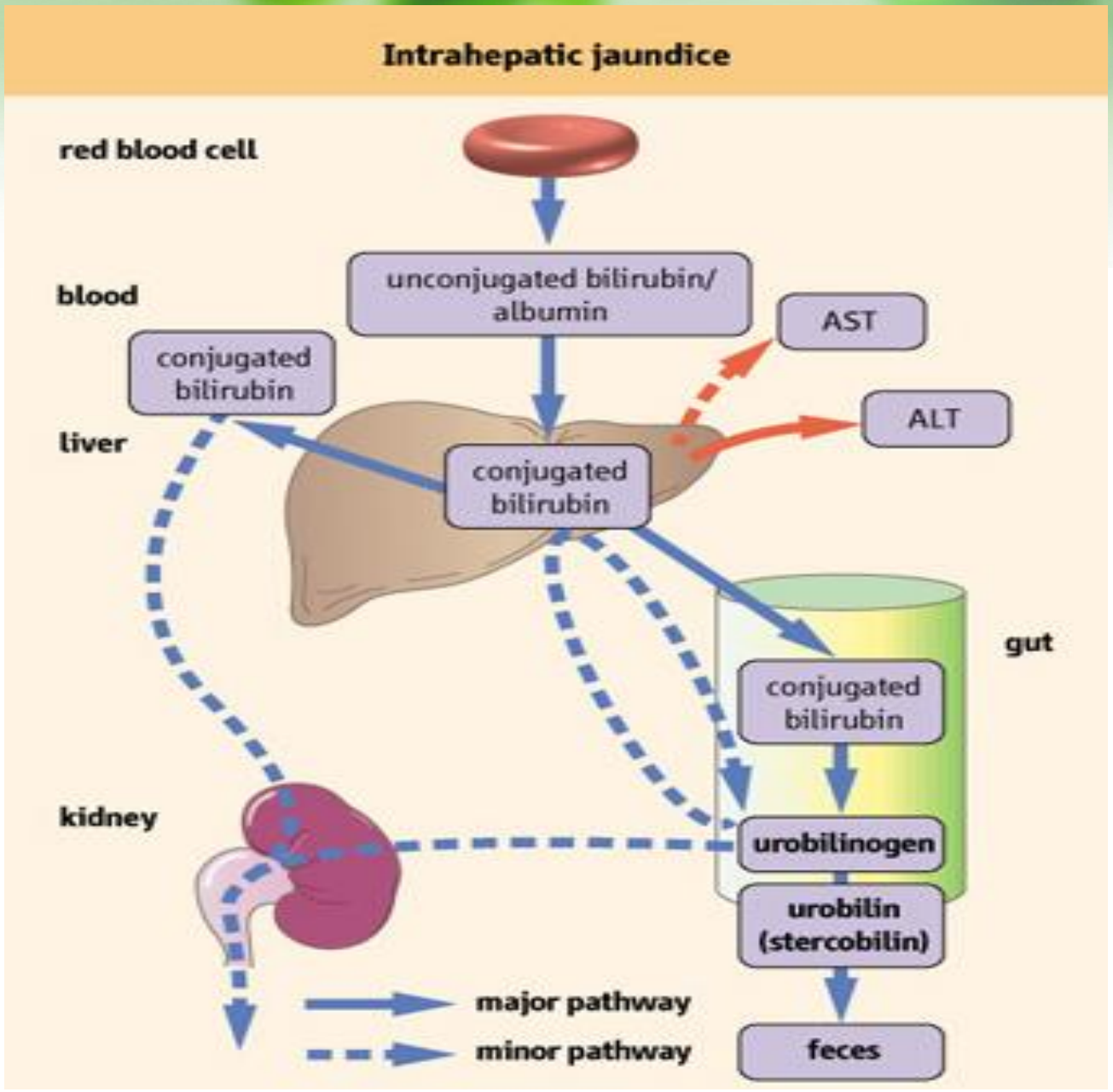
Causes:

- Damage of liver cells e.g., viral hepatitis, autoimmune hepatitis, drugs, chemical, alcohol, or toxins.
- Impaired uptake of bilirubin into hepatic cells.
- Disturbed intracellular protein binding or conjugation.
- Genetic errors in bilirubin metabolism.
- Disturbed active secretion of bilirubin into bile canliculi.
- Genetic errors in specific proteins.
- Gilbert syndrome: 7% of population, autosomal dominant, decreased activity of hepatic uridine diphosphate glucuronyl transferase (UDPGA) activity.
- Crigler-Najjar syndrome: Inherited disorder of bilirubin conjugation due to absence of UDPGTferase in liver



Hepatic Jaundice…Cont.

- The diseased liver cells are unable to take all the unconjugated hemobilirubin, ⇧ its blood concentration.
- Also, there is intrahepatic biliary duct obstruction that leads to regurgitation of conjugated bilirubin to blood.
- ⇧ blood concentration of both conjugated & unconjugated bilirubin.
- Stools appear pale grayish in color due to ⇩ stercobilin.
- Urine appears dark brown due to filtration of excess conjugated bilirubin through the kidney.
- Hyperbilirubinemia is usually accompanied by other abnormalities in biochemical markers of liver function {Alanine amine transferase (ALT, SGPT) & Aspartate amine transferase (AST, SGOT}.


Intrahepatic jaundice
red blood cell
blood
unconjugated bilirubin/ albumin
AST
conjugated bilirubin
ALT
liver
conjugated bilirubin
gut
conjugated bilirubin
kidney
urobilinogen
urobilin (stercobilin)
major pathway
minor pathway
feces

Posthepatic (Obstructive) Jaundice

Caused by an obstruction of the biliary tree:

1- Intrahepatic bile duct obstruction e.g

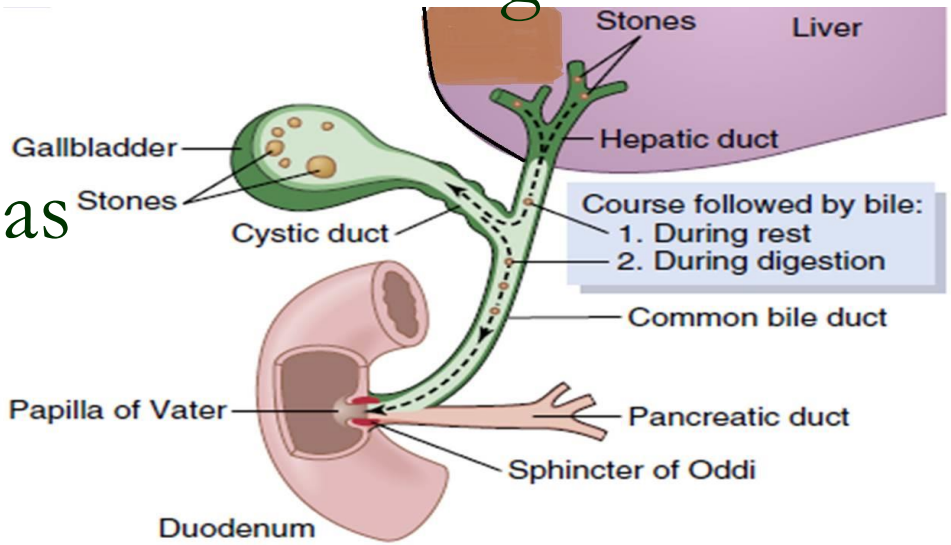
* Drugs
* Primary biliary cirrhosis
* Cholangitis.

2- Extrahepatic bile duct obstruction e.g

*Gall stones.

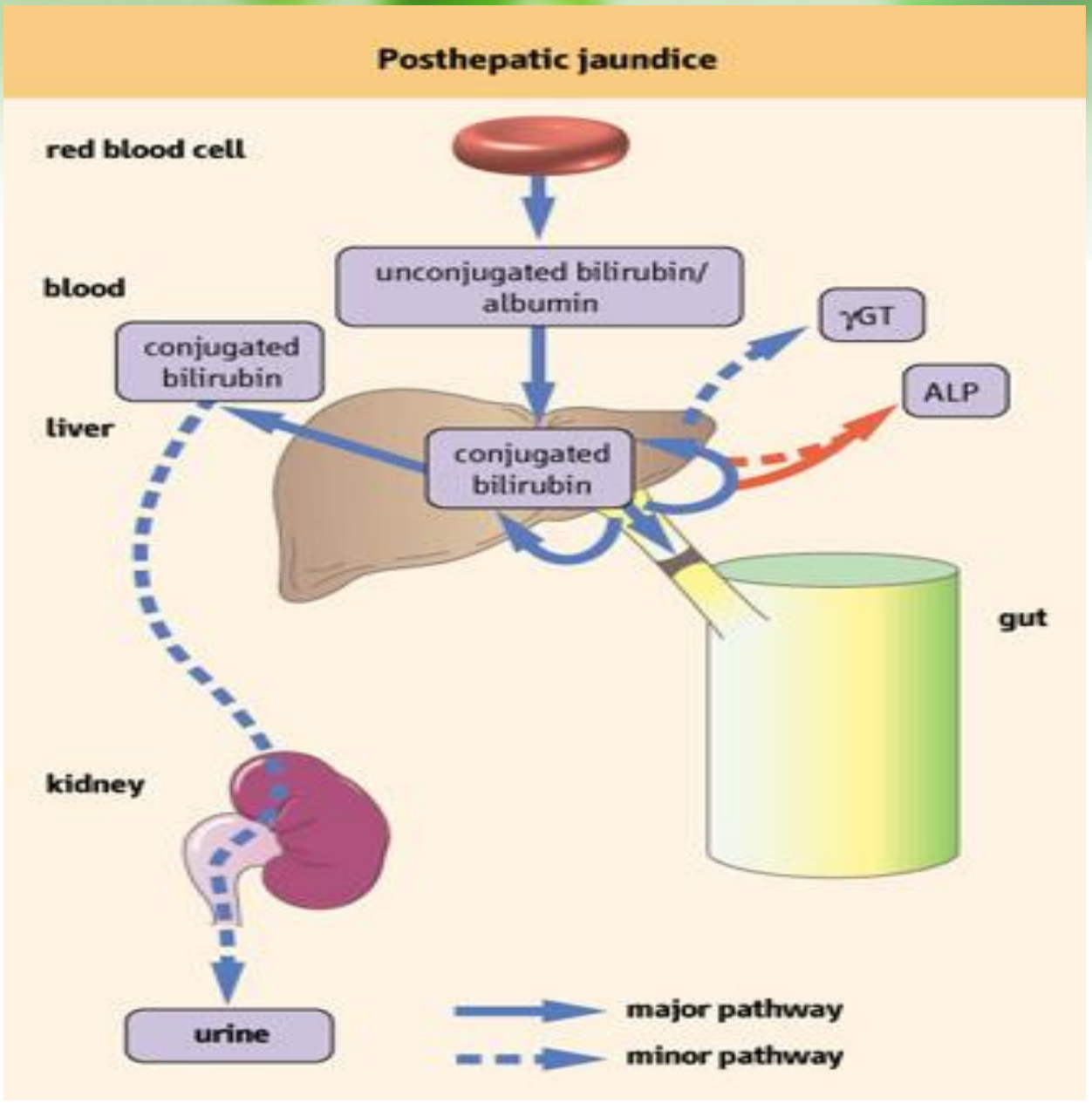
*Cancer head of pancreas

*Cholangiocarcinoma.



Posthepatic Jaundice…Cont.

- The rate of bilirubin formation is normal.
- Bilirubin enters the liver cells and become conjugated in the usual way.
- The conjugated bilirubin formed simply cannot pass into small intestine and it returns back into blood.
- In this type of jaundice, conjugated bilirubin is filtered through the kidney and appears in urine giving it dark brown color.
- Urine is free from urobilinogen.
- Stools are clay color due to absence of stercobilin.


Posthepatic jaundice
red blood cell
blood
unconjugated bilirubin/ albumin
γGT
conjugated bilirubin
ALP
liver
conjugated bilirubin
gut
kidney
urine
major pathway
minor pathway

	Prehepatic (Hemolytic)	Hepatic (Hepatocellular)	Posthepatic (Obstructive)
Unconjugated	↑	↑	Normal
Conjugated	Normal	↑	↑
Bilirubin	Indirect	Both	Direct
AST & ALT	Normal	↑	Normal
ALP & (y glutamyl transpeptidase)	Normal	Normal	↑
Urine bilirubin (Urine color)	Absent	Present (dark brown)	Present (dark brown)
Urine urobilinogen	Present	Present	Absent
Stercobilin (Stool color)	↑ Darker	↓ Pale grayish	Absent (Clay Color)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