

# Billirubin Metabolism

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# Pendahuluan

- Jaundice (jaune = means yellow color in french) Bilirubin is yellow in color
- Jaundice, or icterus, is a yellowish discoloration of tissue resulting from the deposition of bilirubin.
- The degree of serum bilirubin elevation can be estimated by physical examination
- Slight increases in serum bilirubin level are best detected by examining the sclerae ( $51 \mu\text{mol/L}$  ( $3 \text{ mg/dL}$ ), which have a particular affinity for bilirubin due to their high elastin content.
- A second site to examine jaundice is underneath the tongue.



# Jaundice



Elevation of bilirubin  
in the plasma



Overproduction of  
Billirubin,  
Hemolytic anemias



Excretion failure  
of Billirubin,  
Hepatitis,  
Pancreas cancer

## The Concept of Jaundice

# Human & Animal **Hemoprotein** (protein containing heme)

<b>Protein</b>	<b>Function</b>
Hemoglobin	Transport oxygen in blood
Myoglobin	Storage oxygen in muscle
Cytochrome C	Involvement in electron transport chain
Cytochrome p450	Hydroxylation of xenobiotics
Catalase	Degradation of hydrogen peroxide
Tryptophan pyrolase	Oxidation of tryptophan

# Catabolism of Heme Produces Bilirubin

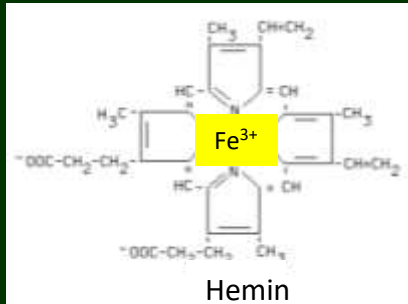
- In the human adult  $1 - 2 \times 10^8$  erythrocytes are destroyed per hour:
  - In one day, a 70 kg human turn over  $\pm 6$  gr of hemoglobin
  - When hemoglobin is destroyed, globin is degraded to its constituent aminoacids and iron for reuse
  - Free iron porphyrin also degrade, mainly in reticuloendothelial cells of the liver, spleen, and bone marrow
- The catabolism of heme is carried out in the microsomal fraction of cells by a complex enzyme system called **heme oxygenase**

# Heme

# Heme

# Catabolism to form Bilirubin

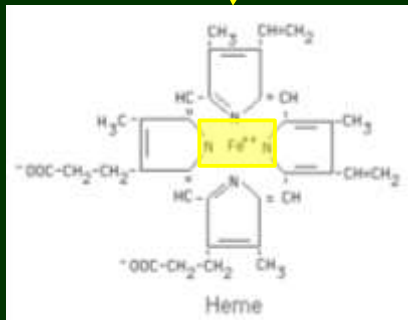
Microsomal heme oxygenase system



Hemin

NADPH

NADP

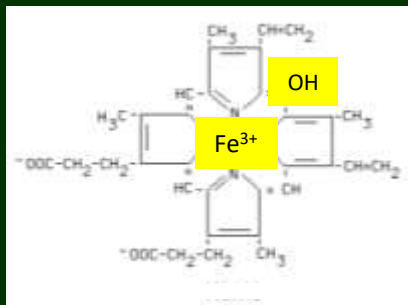


Heme

NADPH

NADP

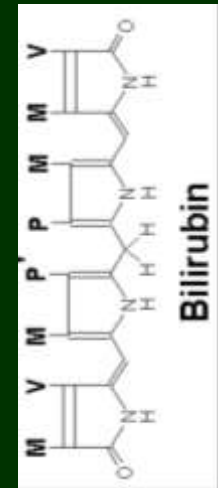
$O_2$



Biliverdin

$Fe^{3+}$  (reutilized) CO exhaled

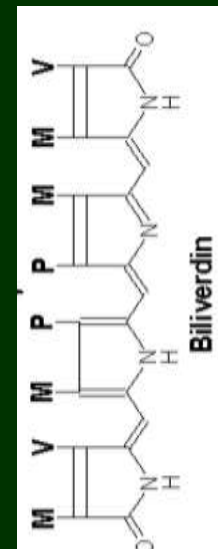
$O_2$



Bilirubin

NADP

NADPH



Biliverdin

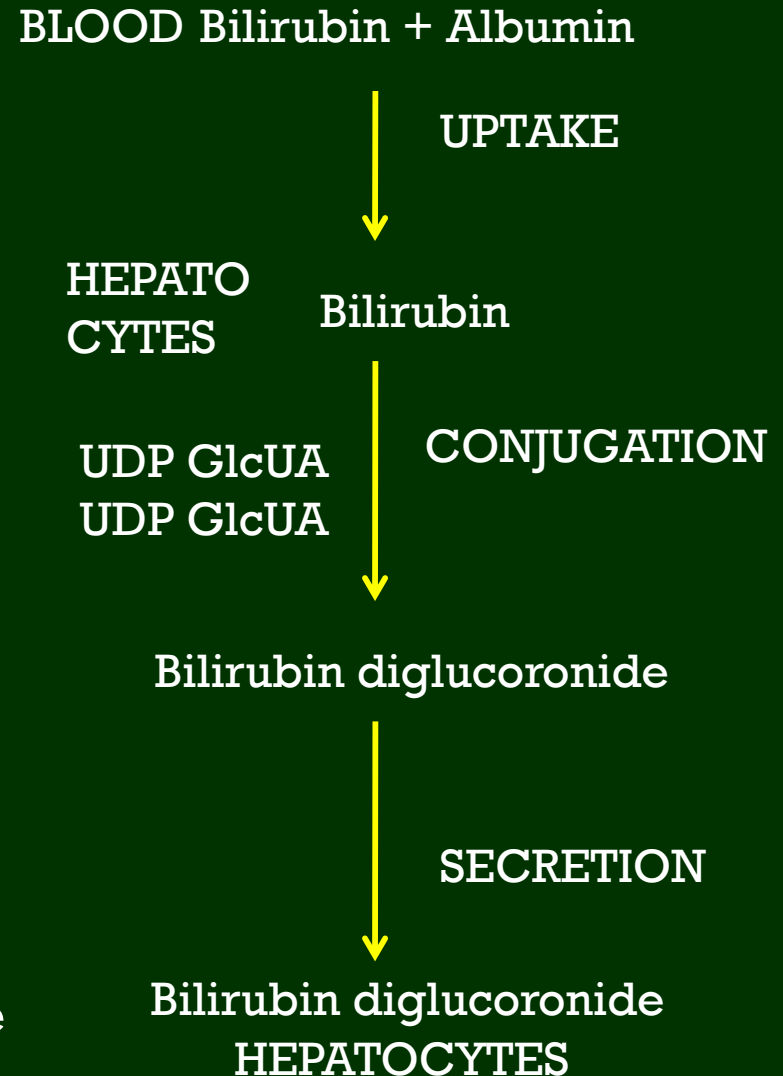
Its estimated that each 1 gr of hemoglobin yield 35 mg of bilirubin

The daily bilirubin formation in human adult is  $\pm 250 - 350$  mg, deriving from Hb, ineffective erythropoiesis, and cytochrome P450

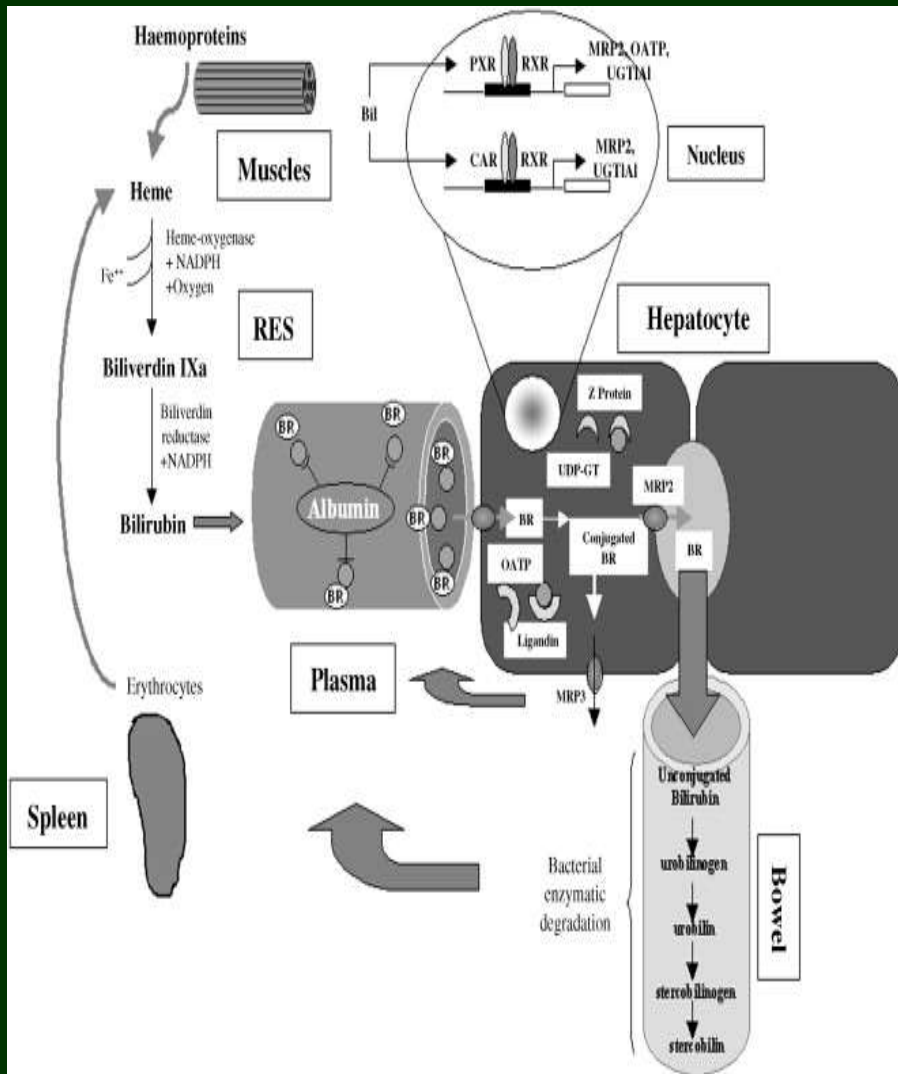
Bilirubin formed in peripheral tissues is transported to the liver by plasma albumin and further metabolized by liver

The Bilirubin metabolism process can be divided into three step:

1. uptake bilirubin by parenchymal liver cells
2. Conjugation of bil with glucoronate in the endoplasmic reticulum
3. Secretion of conjugated bil into the bile



# Bilirubin Uptaken by Liver

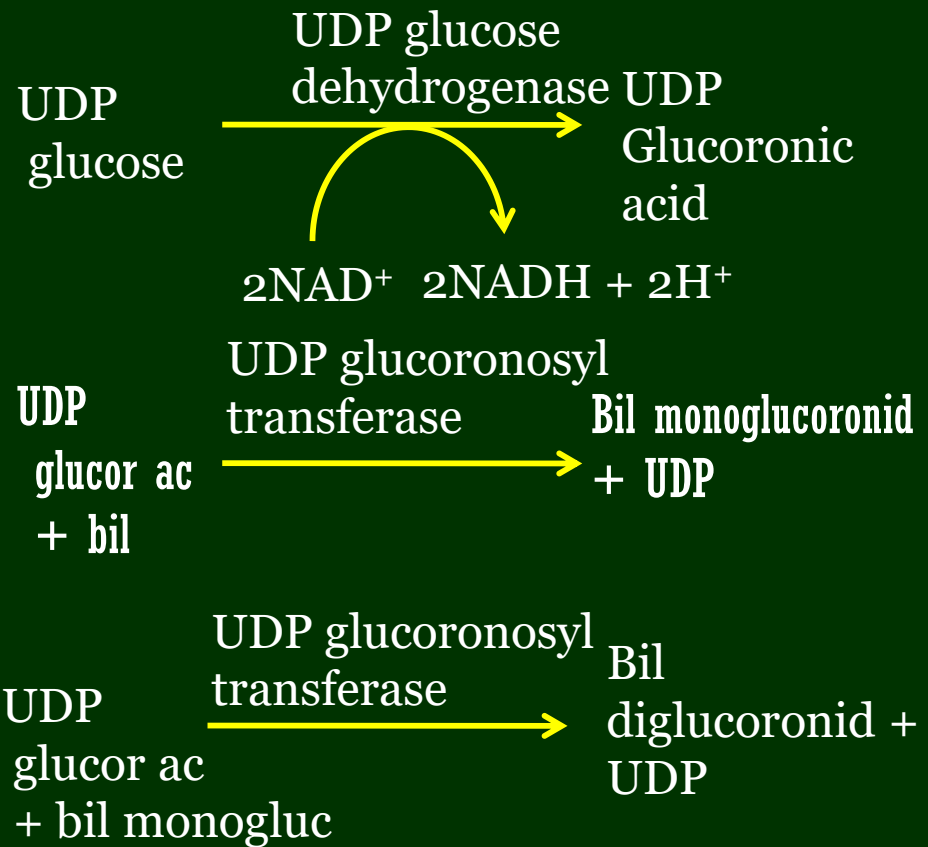


- One high affinity side One low affinity side
- 25 mg tightly bound/100ml Plasma; more loosely bound
- Antibiotics and other drugs can compete with bilirubin for the high-affinity binding side of albumin
- Bilirubin removed from albumin mediated by facilitated transport system
- Once bilirubin enter hypatocytes , it can bind cytosolic protein (ligandin; glutathion transferase family)
  - Prevent efflux of bilirubin back into the blood stream



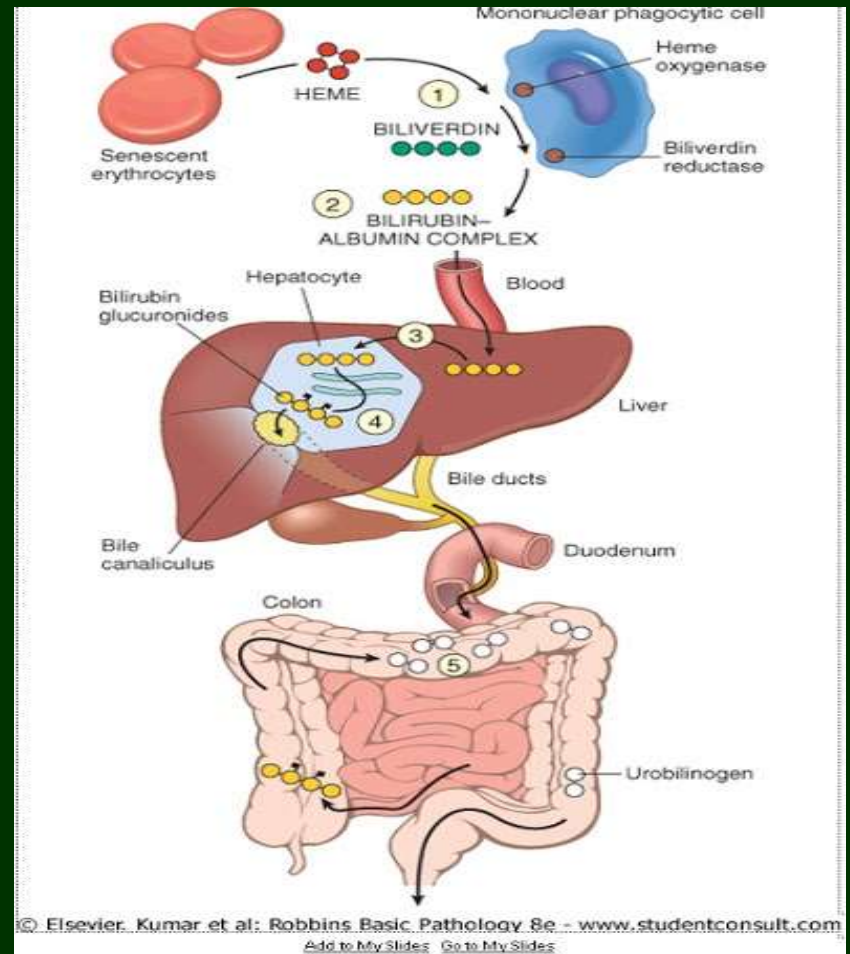
# Bilirubin conjugation

- Hepatocytes convert bilirubin to polar form
  - Readily excreted in the bile by adding glucuronic acid (conjugation) → bilirubin monoglucuronide → bilirubin diglucuronide (mostly excreted in bile)
- Enzyme that needed at the reaction is glucoronyl transferase (located in ER)

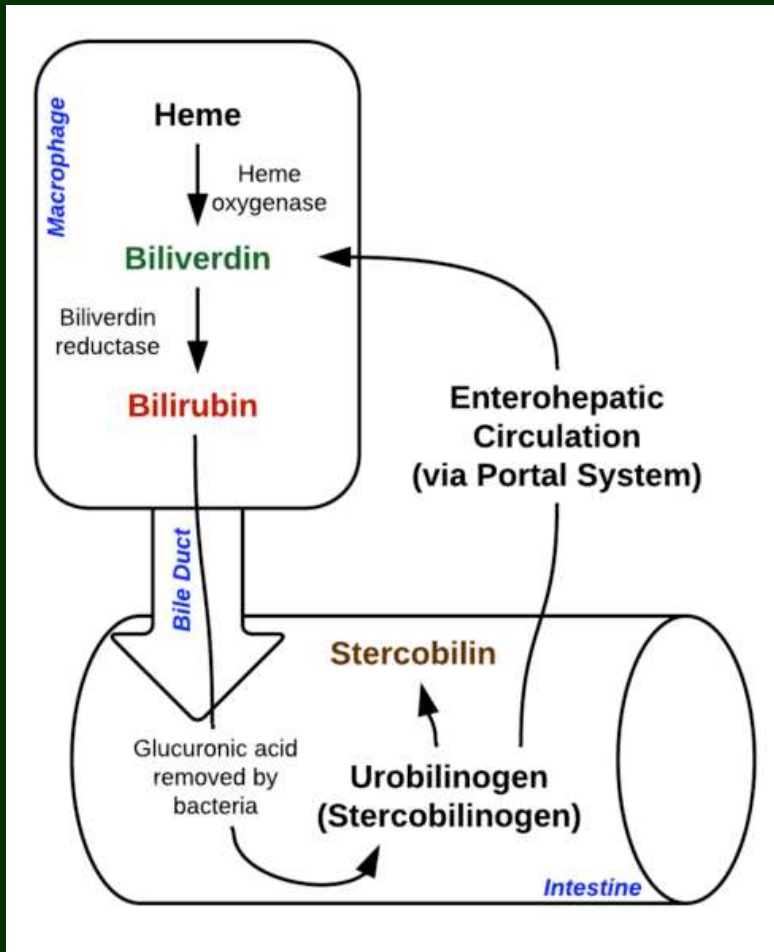


# Bilirubin is Secreted into Bile

- By active transport (rate limiting)
  - MRP-2 (multidrug-resistance like protein-2) = MOAT (multispecific organ anion transporter) located in membrane of bile canalicular – a member ATP binding cassette family transporter



# Conjugated Bilirubin is reduced by Bacteria in Intestinal



- Glucoronide are removed by Beta glucuronidase (bacterial enzyme) → urobilinogen (colourless)
- Urobilinogen is partly reabsorbed and reexcreted through the liver (enterohepatic urobilinogen cycle)
- Normally urobilinogen are oxidized to urobilin (colored) and excreted in faeces
  - Darkening of faeces upon standing in air is due to the oxidation of residual urobilinogens to urobilins

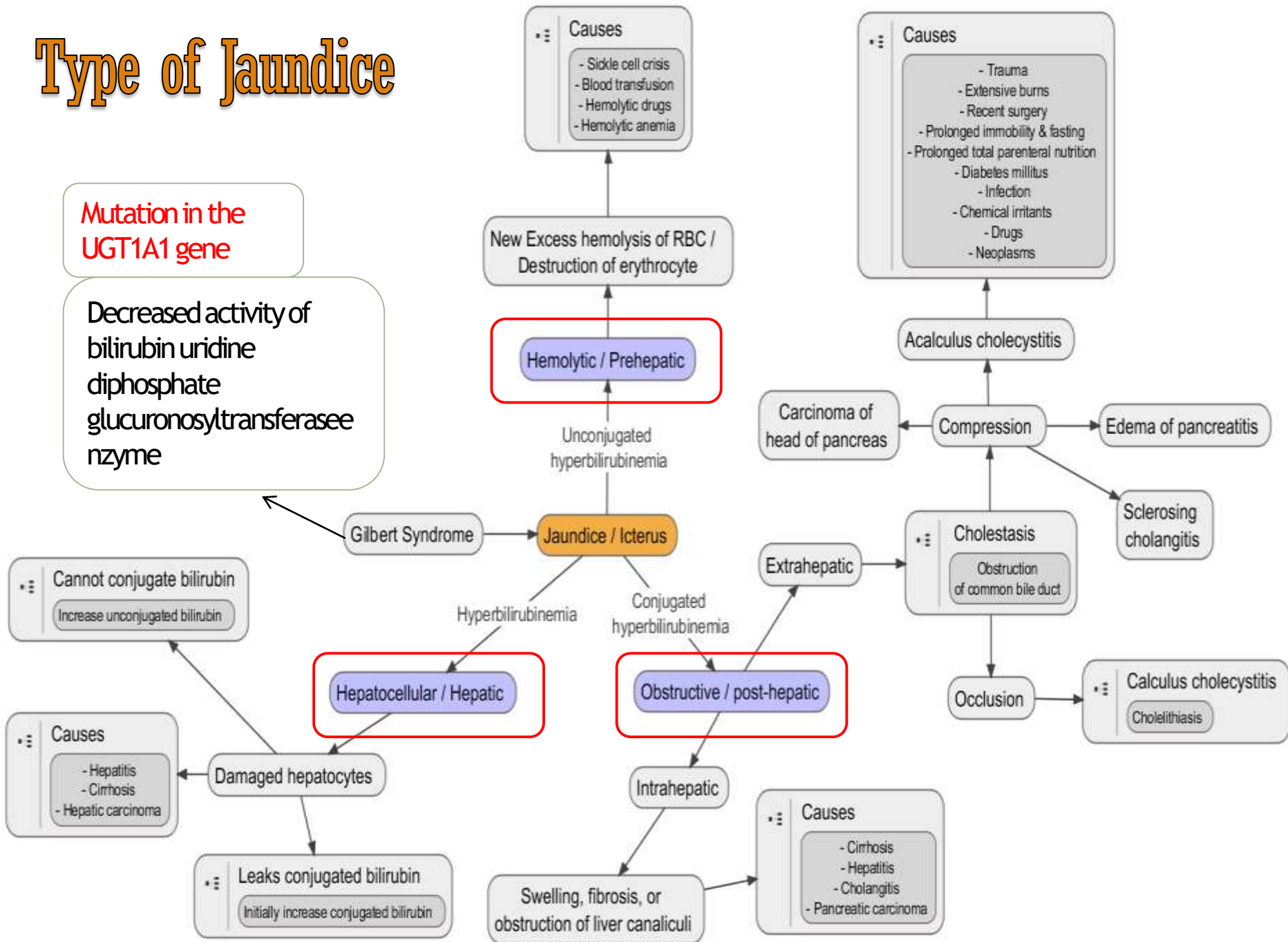
# Jaundice

- When bilirubin in blood more than 1 mg/dl (17.1  $\mu\text{mol/L}$ )  $\rightarrow$  hyperbilirubinemia
  - When concentration of bilirubin exceeds 2 – 2.5 mg/dl, can diffuse into the tissues, which then become yellow (jaundice)
- There are two types of hyperbilirubinemia
  - **Retention hyperbilirubinemia**
    - Unconjugated (hydrophobicity) – can cross blood brain barrier  $\rightarrow$  encephalopathy
    - Acholuric jaundice only occur in this type of hyperbilirubinemia
  - **Regurgitation hyperbilirubinemia**
    - Conjugated bilirubin (water solubility), can appear in urine
    - Choluric jaundice (bile pigment in urine) only occur in this type of hyperbilirubinemia

# Type of Jaundice

Mutation in the UGT1A1 gene

Decreased activity of bilirubin uridine diphosphate glucuronosyltransferase enzyme

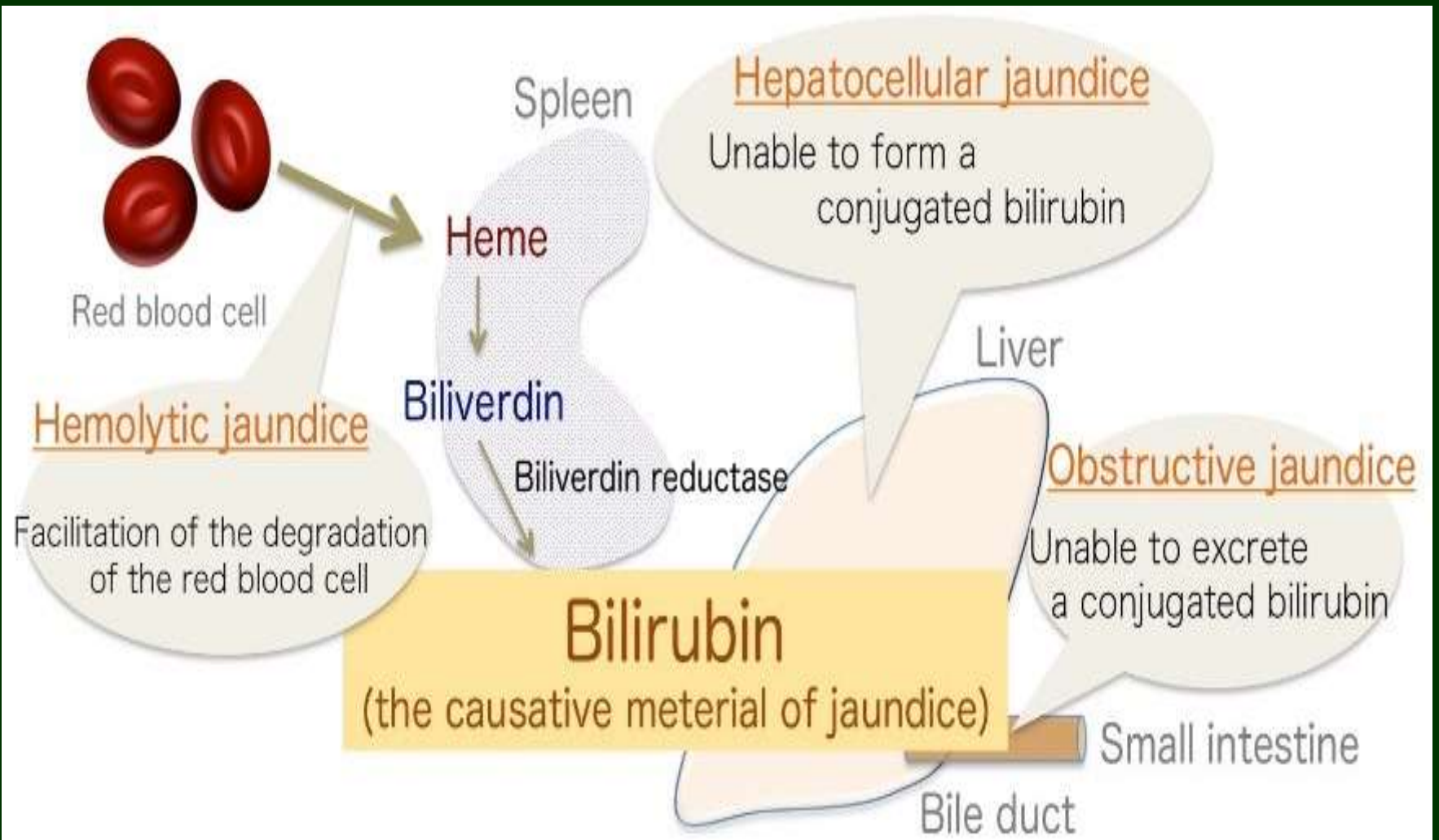


# Type of Jaundice

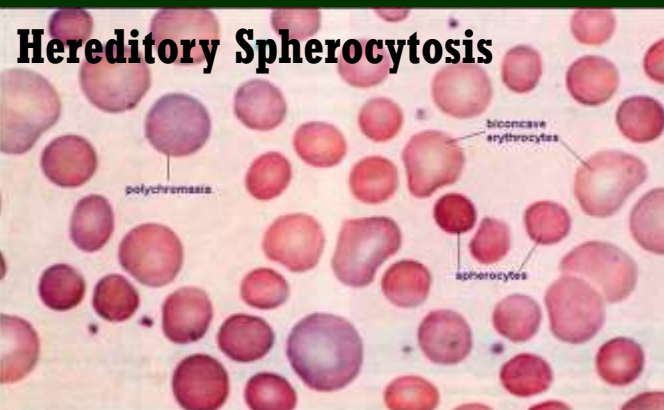
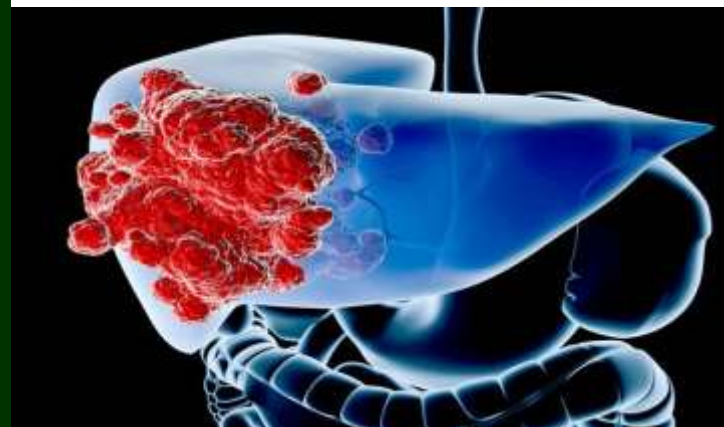
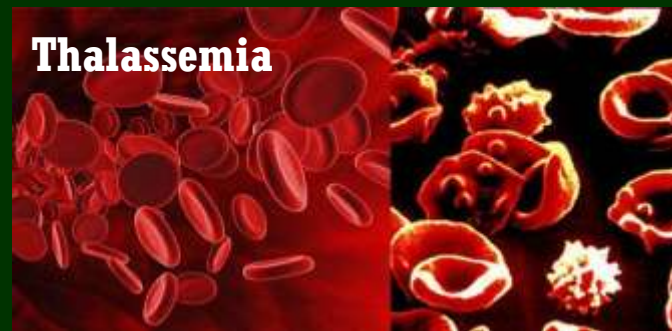
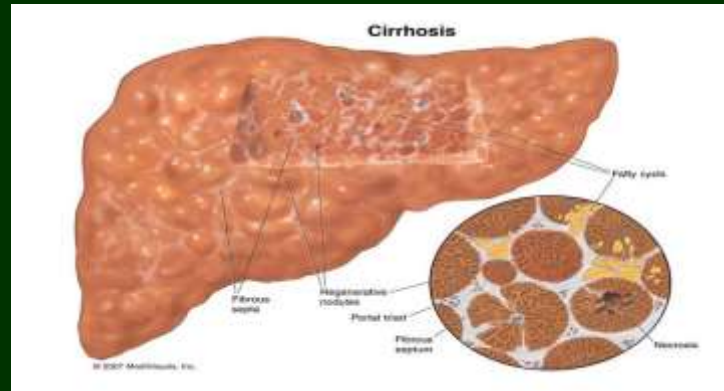
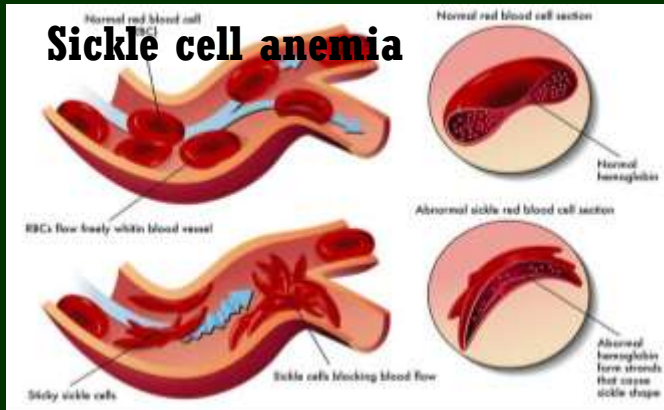
<b>Category</b>	<b>Definition</b>
<b>Pre-hepatic/hemolytic</b>	The pathology is occurring prior to the liver due to either: A. Intrinsic defects in RB cells B. Extrinsic causes external to RB cells
<b>Hepatic/hepatocellular</b>	The pathology is located within the liver caused due to disease of parenchymal cells of liver.
<b>Post-hepatic/cholestatic</b>	The pathology is located after the conjugation of bilirubin in the liver caused due to obstruction of biliary passage



# Cause of Jaundice



# Causes of Jaundice (Prehepatic)





# Diagnostic test

Function test	↕ Pre-hepatic jaundice ↕	Hepatic jaundice	↕ Post-hepatic jaundice ↕
Total bilirubin	Normal / increased	Increased	
Conjugated bilirubin	Normal	Increased	
Unconjugated bilirubin	Normal / increased	Increased	Normal
Urobilinogen	Normal / increased	Decreased	Decreased / negative
Urine color	Normal <sup>[21]</sup>	Dark (urobilinogen + conjugated bilirubin)	Dark (conjugated bilirubin)
Stool color	Normal	slightly pale	Pale
Alkaline phosphatase levels	Normal	Increased	
Alanine transferase and aspartate transferase levels		Increased	
Conjugated bilirubin in urine	Not present	Present	
Large spleen	Present	Present	Absent

**Sekian Dulu**