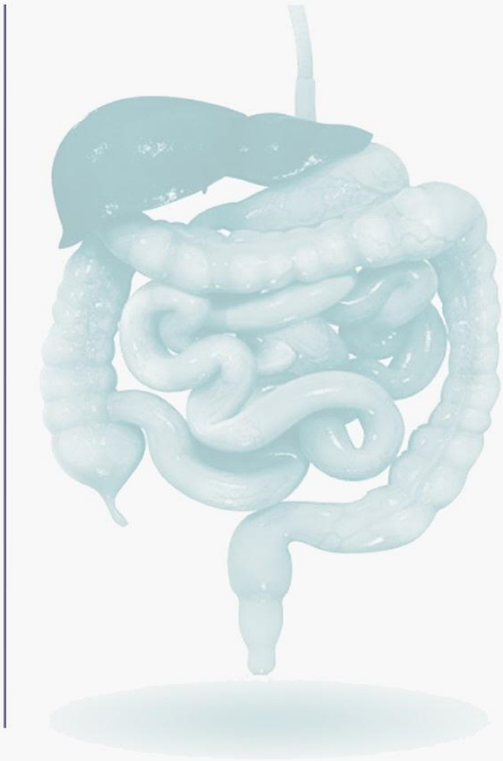
#7 Bilirubin metabolism



objectives :

- **Definition of bilirubin**
- **The normal plasma concentration of total 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 Jaundice**
- **Classification of jaundice (Prehepatic / Hepatic / poat-hepatic).**

Doctors' notes

Extra

Important

Revised by
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Resources: 435 Boys' & Girls' slides | Guyton and Hall 12th & 13th edition

Editing file

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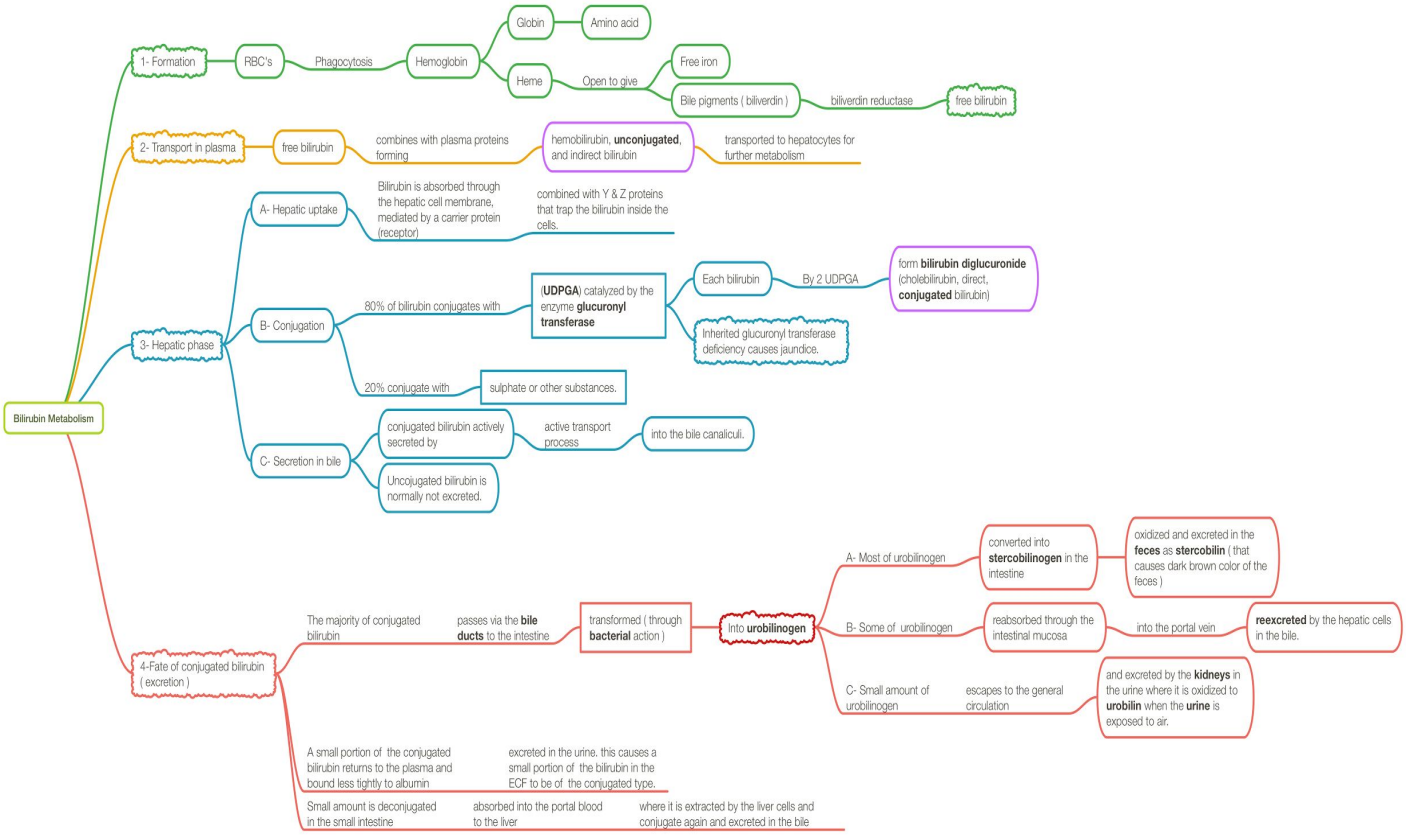
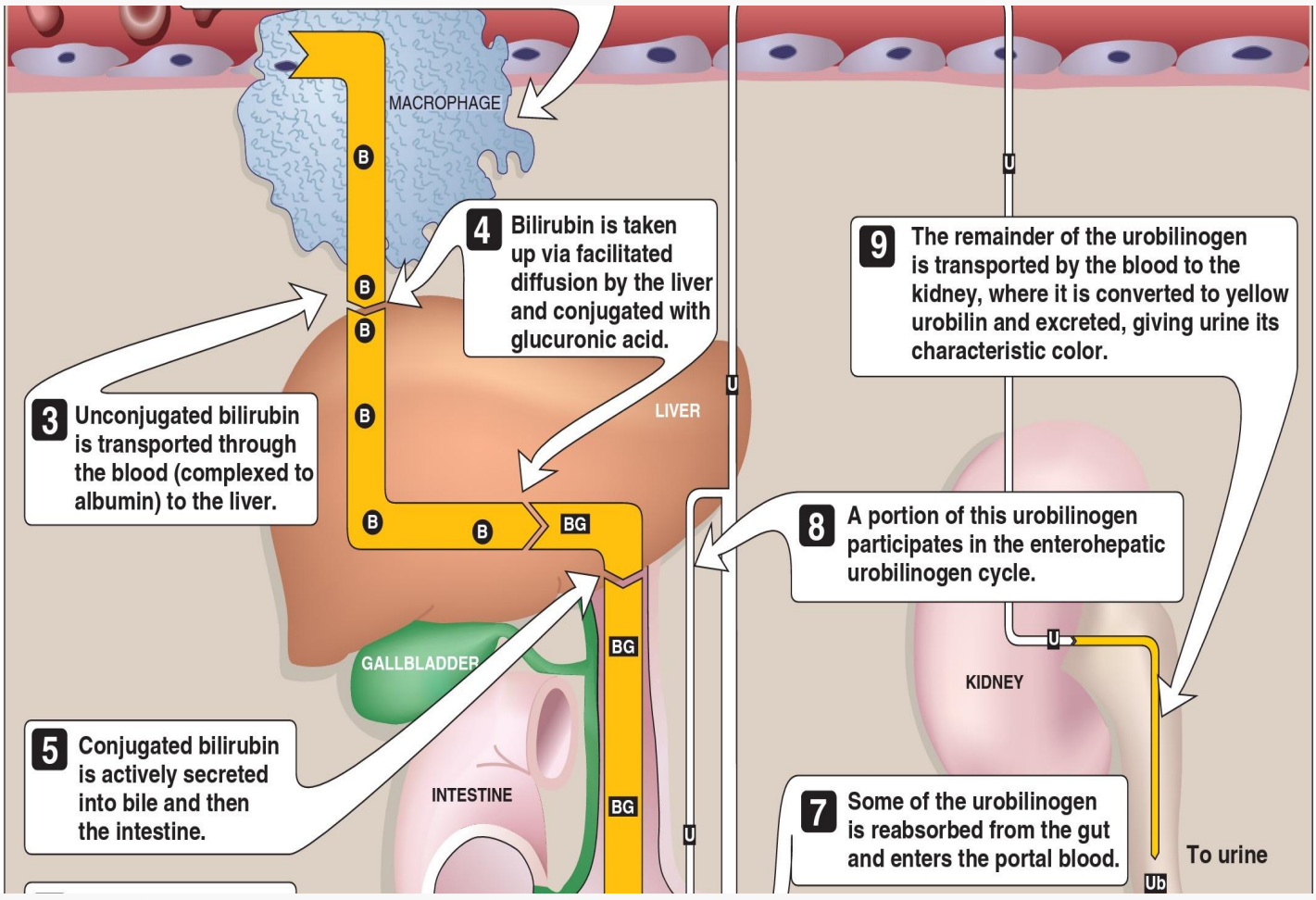
Overview- mind map





Porphyrin Metabolism (Boys' slides) :

- Porphyrins are cyclic compounds that readily bind metal ions usually Fe^{2+} or Fe^{+3} which can carry O_2.
- Porphyrins are heterocyclic macrocycles composed of four modified pyrrole (a colorless, toxic, liquid, five-membered ring compound, C4 H5 N) subunits interconnected at their α carbon atoms via methine bridges (=CH-).
- The most prevalent porphyrin in the human is heme, which consists of one ferrous (Fe^{2+}) iron ion coordinated in the center of tetrapyrrole ring of protoporphyrin IX.
- Structure of Hemoglobin showing the polypeptides backbone that are composed of four subunits: 2 α and 2 β subunits. Every subunit is consisted of one ferrous (Fe^{2+}) iron ion coordinated in the center porphyrin compound.

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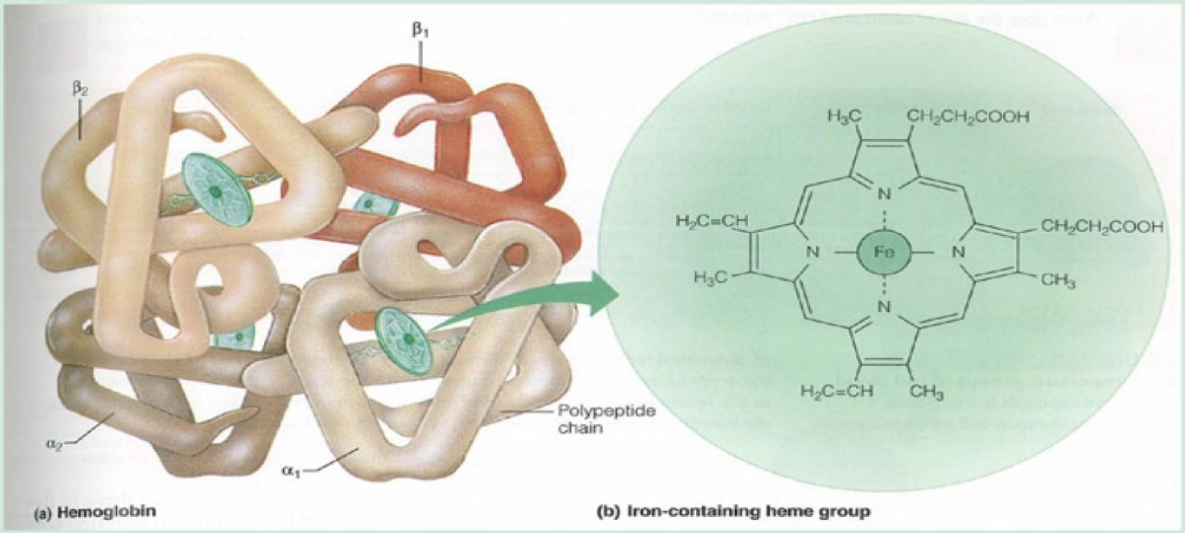


MARIEB 18.4 Structure of hemoglobin. (a) The intact hemoglobin molecule is composed of the protein globin bound to the iron-containing heme pigments. Each globin molecule has four polypeptide chains: two alpha (α) chains and two beta (β) chains. Each chain is complexed with a heme group shown as a green beaded structure. (b) Structure of a single heme group **[ie a porphyrin with a central iron]**

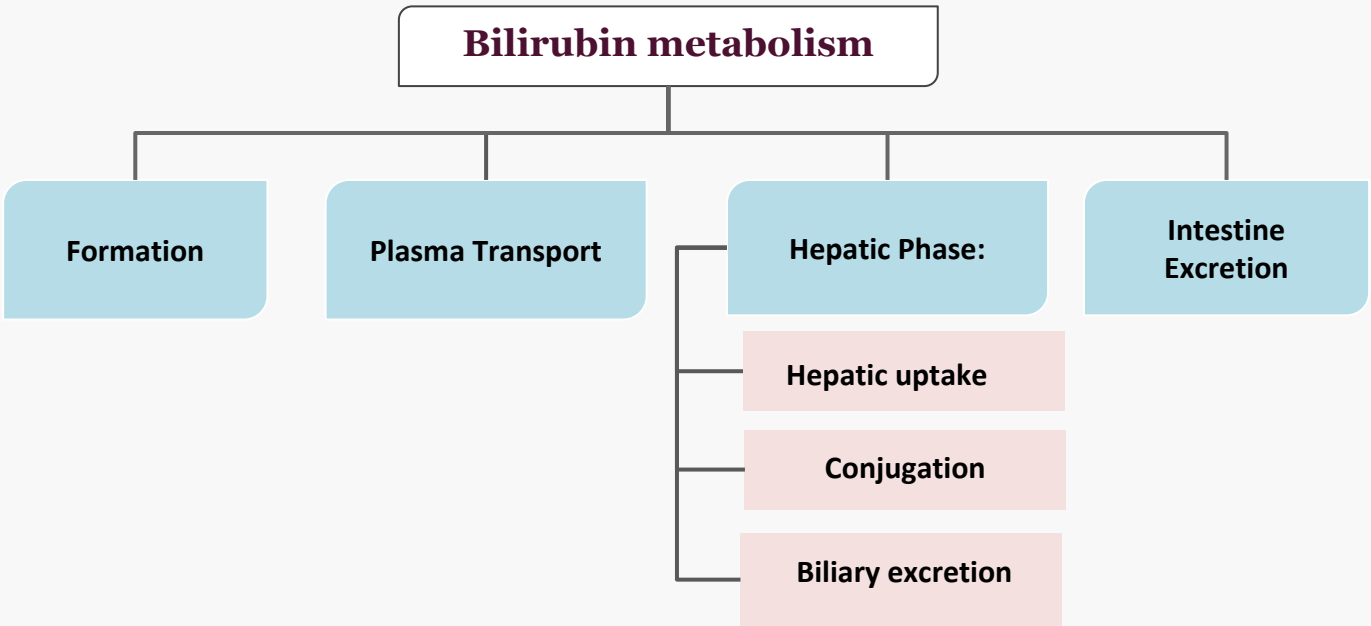
The most prevalent porphyrin in the human is heme

Definition of bilirubin :

- **Bilirubin** is the end product of heme degradation derived from breakdown senescent (aging) erythrocytes by mononuclear phagocytes system specially in the spleen, liver and bone marrow. (It is the **water insoluble** breakdown product of normal heme catabolism).
- Bilirubin is the greenish yellow pigment excreted in **bile**, **urine** and **feces**.
- The major pigment present in bile is the orange compound bilirubin.
- 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.
- It is highly soluble in all cell membranes (hydrophobic) and is also very **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. It's one of the Liver function tests

Bilirubin metabolism :

❖ Bilirubin metabolism involves four discernible steps:



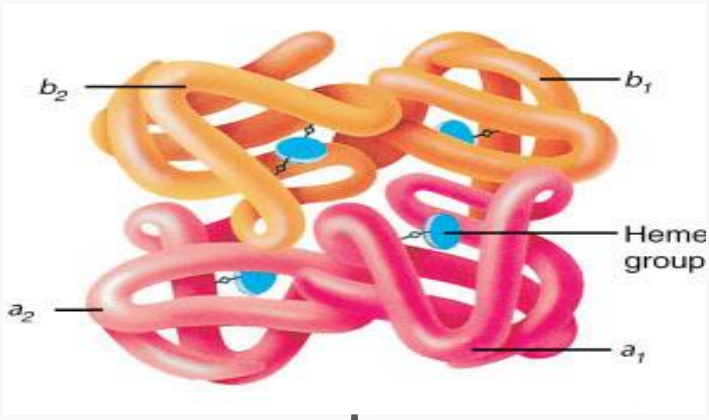
❖ The four steps are finely balanced, therefore:

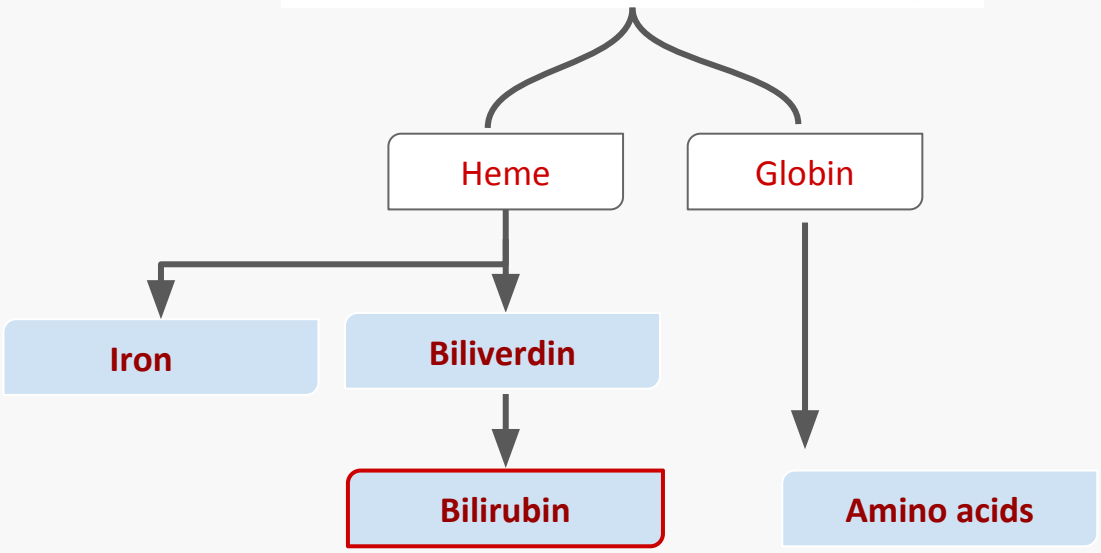
- Reduction at any step may cause **hyperbilirubinemia.**
- Enhancement of the throughput requires induction of multiple genes, probably coordinated by nuclear receptors.

1) Bilirubin formation :

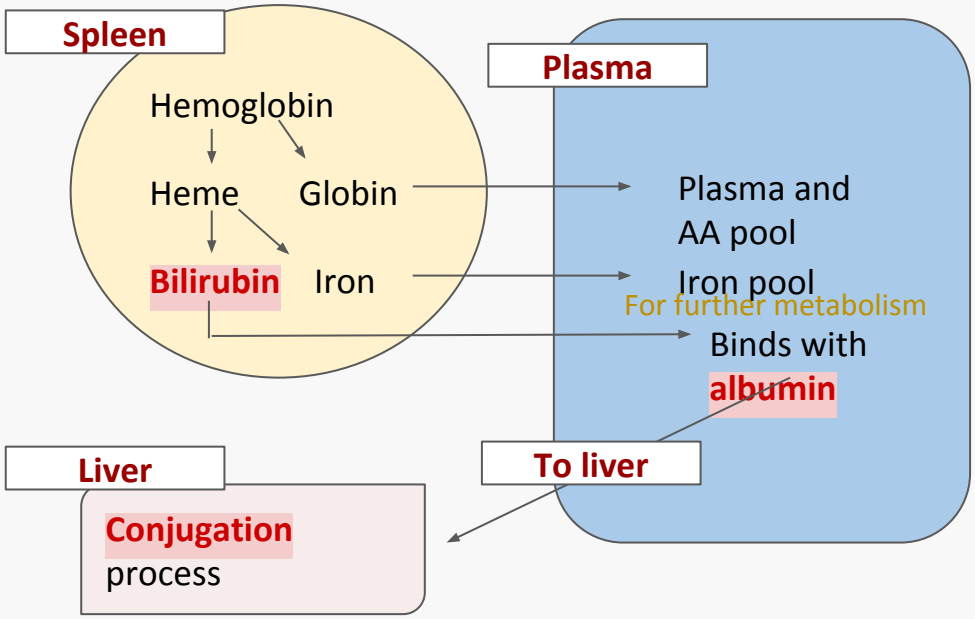
- Life span of RBCs is **60-120** days.
- Senescent "old" RBCs are phagocytosed **intravascularly** or **extravascularly** in the reticulo-endothelial system. "Mainly extravascularly"
- The hemoglobin is first split into globin & heme.
- The Amino acids formed from breakdown of globin are **stored in 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)	"it's the first bile pigment formed" Reduced by biliverdin reductase to free bilirubin which is gradually released into the plasma.





❖ Hemoglobin degrading and bilirubin formation :



2) Transport of bilirubin in plasma :

- Bilirubin is formed in spleen .
- 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.**

هنا لازم نعرف إن البيلروبين لما يوصل للبلازما يكون هيدروفوبيك (كاره للماء) بعدين يرتبط بمركب يخفف كرهه للماء إلى حدٍ ما (ألبيومن) فلما يرتبطون مع بعض مانقدر نقول إن المركب الناتج صار هيدوفيليك (محب للماء) لكن نقدر نقول إنه صار أقل كرهاً للماء وأكثر تقبلاً له

Albumin + Free Bilirubin ⇌ **Bilirubin ~ Albumin Complex**

↓

Unconjugated bilirubin
(hemobilirubin)

❖ Significance of bilirubin binding to albumin:

1. Increase the solubility of whole molecule. "قلنا " إلى حدٍ ما"
2. **Prevent** unconjugated bilirubin freely come into other tissue, cause damage.
   - ➔ 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.**"it's common in babies because of their incomplete formation of blood brain barrier"

3) Hepatic phase :

Hepatic phase

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

"Any problem in these steps can lead to high bilirubin"

Hepatic uptake

Bilirubin -Albumin complex dissociate in plasma of liver into hemebilirubin & free albumin .

Dissociation of hemebilirubin Inside hepatocytes into free bilirubin and free protein .

The Free Bilirubin is absorbed through the hepatic cell membrane, mediated by a carrier protein (receptor)

* bilirubin enters a hepatocyte via facilitated diffusion, and binds to intracellular proteins, particularly the protein ligandin.

combined with Y & Z proteins that trap the bilirubin inside the cells. Any genetic defect in carriers will lead to failure of hepatic uptake of bilirubin.

Conjugation

In hepatocytes :

*about **80%** of bilirubin conjugates with uridine diphospho- glucuronic acid (UDPGA) catalyzed by the **enzyme glucuronyl transferase** in the smooth ER.

"To make it water soluble and facilitate its excretion"

*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.

"hemobilirubin"

20% conjugate with sulphate or other substances.

Inherited glucuronyl transferase deficiency causes jaundice.

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.

- It is Very important to understand this concept:
- ★ unconjugated is a lipid soluble but when it combines with plasma protein it increases its water solubility but it still lipid soluble.
- ★ conjugated is a water soluble

Very helpful

Fate of conjugated bilirubin

1-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.	**2-**Small amount is deconjugated in the small intestine and absorbed into the portal blood to the liver	**3-**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

3a- 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."Patients with obstruction of bile duct won't have stercobilin in their stool making it pale & grayish in color"	**3b-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).	**3c-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.Only urobilin and conjugated bilirubin can be found in urine. NOT the unconjugated form.

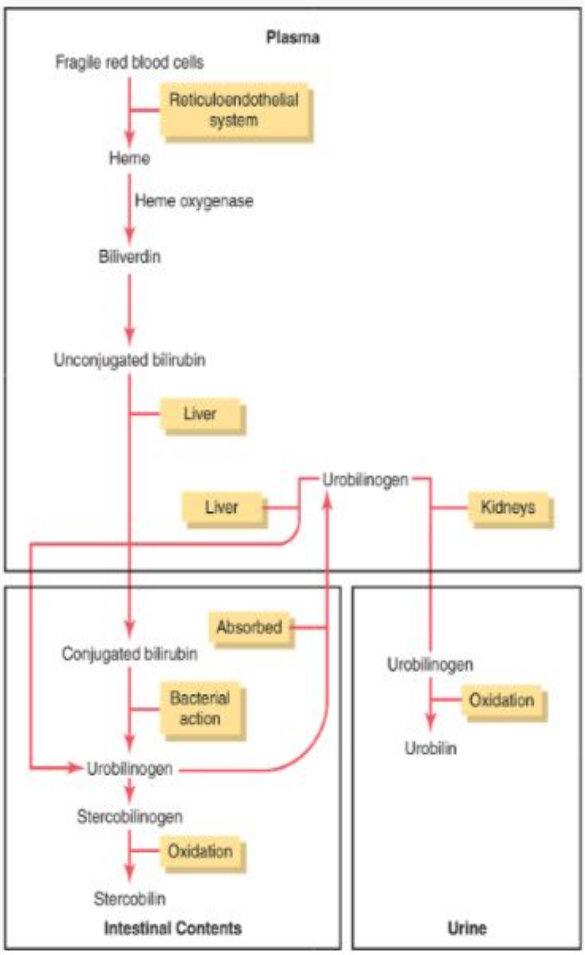
- **Guyton corner :**

Briefly, when the red blood cells have lived out their life span (on average, 120 days) and have become too fragile to exist in the circulatory system, their cell membranes rupture, and the released hemoglobin is phagocytized by tissue macrophages (also called the *reticuloendothelial system*) throughout the body. The hemoglobin is first split into *globin* and *heme*, and the heme ring is opened to give (1) free iron, which is transported in the blood by transferrin, and (2) a straight chain of four pyrrole nuclei, which is the substrate from which **bilirubin** will eventually be formed. The first substance formed is *biliverdin*, but this is rapidly reduced to *free* ***bilirubin***, also called *unconjugated* ***bilirubin***, which is gradually released from the macrophages into the plasma. This form of **bilirubin** immediately combines strongly with plasma albumin and is transported in this combination throughout the blood and interstitial fluids.

Within hours, the unconjugated **bilirubin** is absorbed through the hepatic cell membrane. In passing to the inside of the liver cells, it is released from the plasma albumin and soon thereafter conjugated about 80 percent with glucuronic acid to form ***bilirubin****glucuronide*, about 10 percent with sulfate to form ***bilirubin*** *sulfate*, and about 10 percent with a multitude of other substances. In these forms, the **bilirubin** is excreted from the hepatocytes by an active transport process into the bile canaliculi and then into the intestines.

Formation and Fate of Urobilinogen.

Once in the intestine, about half of the "conjugated" **bilirubin** is converted by bacterial action into the substance *urobilinogen*, which is highly soluble. Some of the urobilinogen is reabsorbed through the intestinal mucosa back into the blood. Most of this is re-excreted by the liver back into the gut, but about 5 percent is excreted by the kidneys into the urine. After exposure to air in the urine, the urobilinogen becomes oxidized to *urobilin*; alternatively, in the feces, it becomes altered and oxidized to form *stercobilin*.



Summary of bilirubin metabolism :

1) Senescent **red** cells are major source of hemeproteins

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

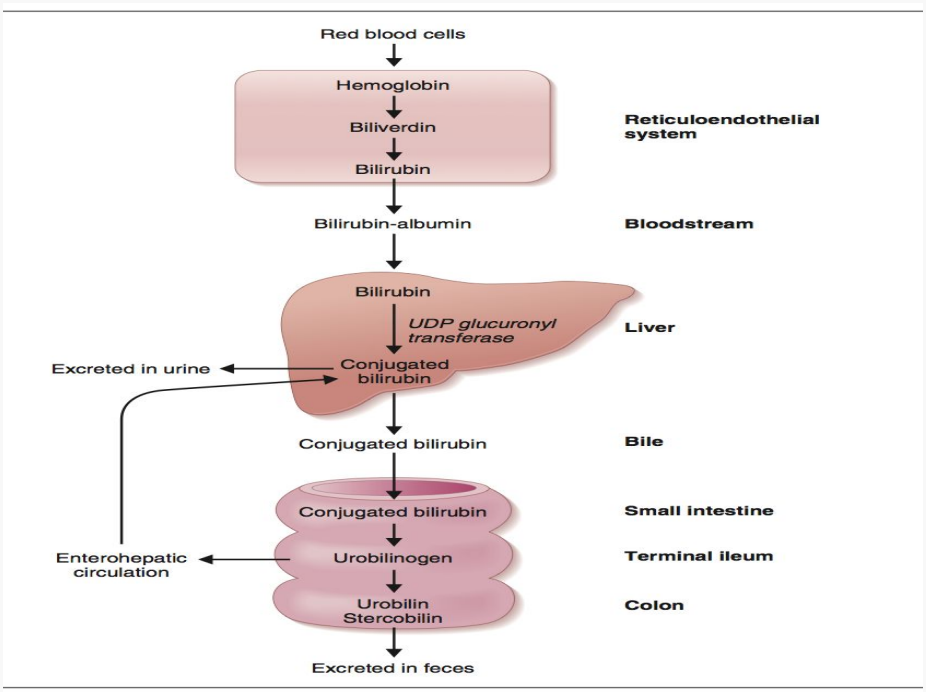
3) **Unconjugated** bilirubin is transported through blood (complex to albumin) to **liver**.

4) Bilirubin is taken into liver and conjugate with **glucuronic acid.**

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

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

7) Urobilinogen is oxidized by intestinal bacteria to the brown **stercobilin**.



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. Therefore, Bilirubin won't be conjugated and excreted in bile leading to excess bilirubin in blood and aggravating clinical condition of jaundice
- 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).**

Types of bilirubin in serum :

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). السبب خلف تسميتهم direct & indirect هو حسب تفاعلهم مع الكاشف إذا كان بشكل مباشر مثل conjugated أو غير مباشر مثل unconjugated
Total bilirubin	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 importance.We can specify the type jaundice if its pre-hepatic, hepatic, or post-hepatic

Normal Range of bilirubin		
Normal	**Occult** pre-clinical jaundice (not seen clinically)	**Jaundice**
<1 mg/dl 1～16 **mol/l** (0.1 ～1**mg/dl**) ➔ 4/5 are unconjugated bilirubin, others are conjugated bilirubin. "We'll find mainly hemobilirubin in serum"	**1-2 mg/dl**	**>2 mg/ dl**
	Hyperbilirubinemia	

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.

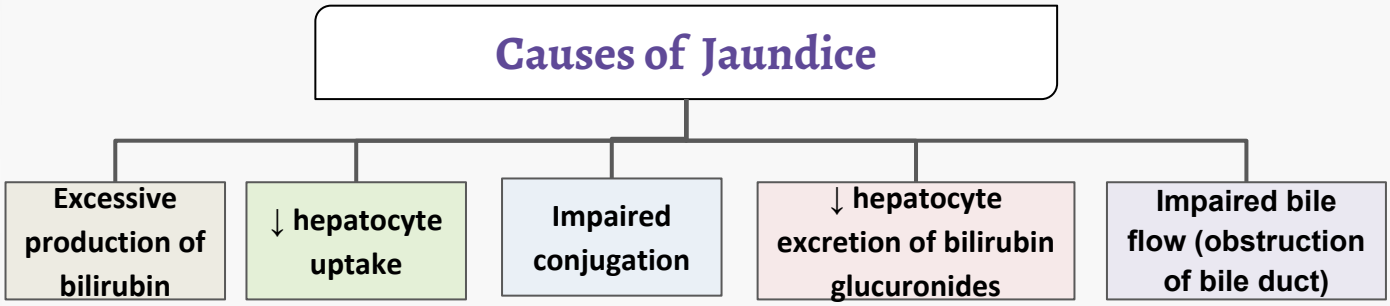
- **Adrenocortical**, other **steroid hormones & a number of drugs** are excreted in the bile and subsequently reabsorbed **(enterohepatic circulation).** Impairment of this metabolic function can increase estrogen in men causing gynecomastia

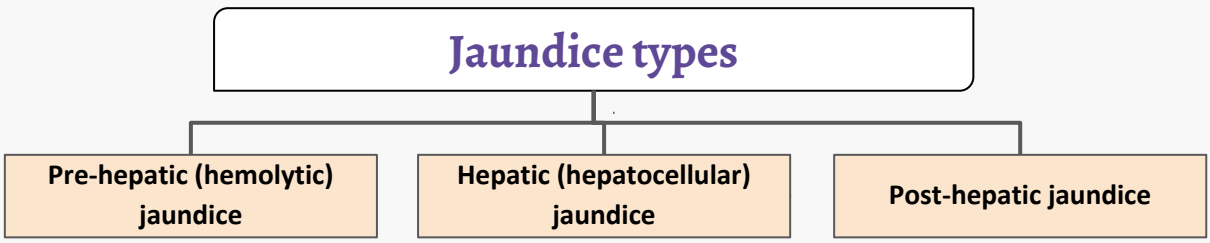
Major differences between unconjugated and conjugated bilirubin : (very important)

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 (Water soluble)
Affinity to lipids	Present	Absent
Binding	Bind to albumin	Bind to glucuronic acid
Reaction to reagents	Indirect (Total minus direct)	Direct
Renal excretion	Absent (Not filtered through renal glomeruli, is not excreted in urine)	Present (Filtered through renal glomeruli and excreted in urine)
Affinity to brain tissue	Present (kernicterus), toxic	Absent , less toxic
Toxicity	Toxic	Non-toxic

Jaundice : (Boys' slides)

- 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.
- However, in certain abnormal conditions this can rise up to **40 mg/dl** of blood. **But the skin usually begins to appear jaundiced when the concentration of total bilirubin in the plasma is greater than 2 - 2.5 mg/dl of blood.** مثل ماقلنا بالجدول السابق
- Bilirubin level from **0.5 to 2 mg/dl** is called **subclinical jaundice.**





1) Pre-hepatic (hemolytic) jaundice

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

- Therefore, the plasma concentrations of free bilirubin rises to levels much above normal but it is **NOT** filtered through the kidney, because they are **unconjugated bilirubin.**
- **The urine is free from bilirubin.**
- The stools appear **darker** than the normal color due to **excessive stercobilin formation.**

2) Hepatic (hepatocellular) jaundice

- **Hyper-bilirubinemia** (increased levels of bilirubin in the blood) may be due to:
  - Impaired uptake of bilirubin into hepatic cells.
  - Disturbed intra cellular protein binding or conjugation.
  - Disturbed active secretion of bilirubin into bile canaliculi.
- The main causes of Hepatic jaundice are:
  - Damage of liver cells: e.g., viral hepatitis, drugs, chemical, alcohol, or toxins.
  - Genetic errors in bilirubin metabolism.
  - Genetic errors in specific proteins.
  - Autoimmune hepatitis.

- The diseased liver cells are unable to take all the unconjugated bilirubin formed, increasing its concentration in the blood.
- Also, there is intrahepatic biliary duct obstruction that leads to regurgitation of conjugated bilirubin to blood (swelling of cells and edema due to inflammation cause mechanical obstruction of intrahepatic biliary tree).
- BOTH types of bilirubin (conjugated & unconjugated) are present in blood in high concentration.

clinical Features

- Stools appear **pale grayish** in color due to deficiency of stercobilin.
- Urine appears **dark brown** due to filtration of excess conjugated bilirubin through the kidney (probably by rupture of the congested bile canaliculi and direct emptying of the bile into the lymph leaving the liver).
- In this case, hyper-bilirubinemia is usually accompanied by other abnormalities in biochemical markers of liver function such as: Alanine amine transferase (ALT), Aspartate amine transferase (AST), alkaline phosphatase (ALP) and Gamma-glutamyltransferase (GGT).
- By looking at the ratio between these different liver enzymes, we can distinguish the causes of jaundice whether it is from biliary (cholestatic) or liver (hepatic). The main diagnostic tip is in the biliary obstruction: the ALT goes up and down (pulsatile increase) and the bilirubin concentration in the blood is high. But in hepatic jaundice, ALT shows persistent increase for along period of time (months).

3) Post-hepatic jaundice

Caused by an obstruction of the biliary tree :

Intra-hepatic bile duct obstruction	Extrahepatic bile duct obstruction
- Drugs - Primary biliary cirrhosis - Cholangitis.	- Gallstones. - Cancer at the head of pancreas. - Cholangiocarcinoma.

- The rate of bilirubin formation is normal. bilirubin enters the liver cells and become conjugated in the usual way.
- The conjugated bilirubin formed simply can not 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 (mud) color due to **absence of stercobilin.**

Liver Secretion of Cholesterol and Gallstone Formation :

- Under **abnormal conditions**, the cholesterol may precipitate in the gallbladder, resulting in the formation of *cholesterol gallstones*. The amount of cholesterol in the bile is determined partly by the quantity of fat that the person eats, because liver cells synthesize cholesterol as one of the products of fat metabolism in the body. For this reason, people on a high-fat diet over a period of years are prone to the development of gallstones.

- Inflammation of the gallbladder epithelium, often resulting from low-grade chronic infection, may also change the absorptive characteristics of the gallbladder mucosa, sometimes allowing excessive absorption of water and bile salts but leaving behind the cholesterol in the bladder, and then progressing to large gallstones.

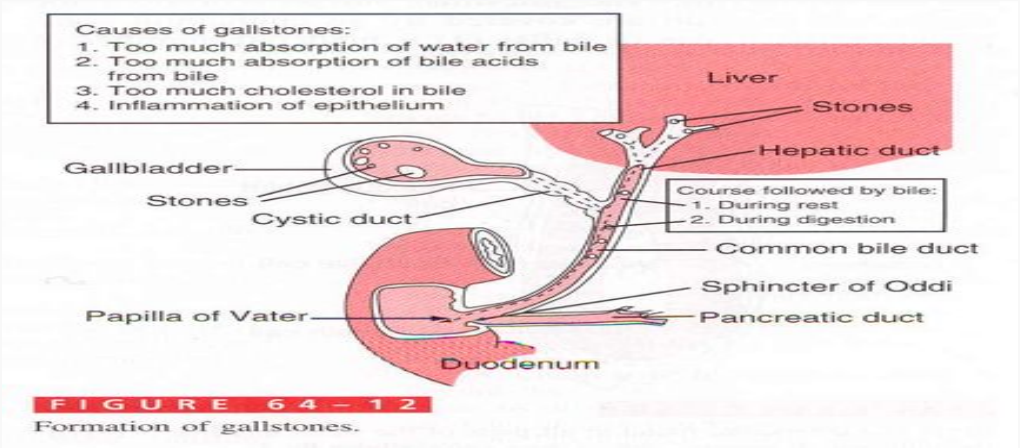


FIGURE 64–12
Formation of gallstones.

SUMMARY (IMPORTANT/ READ IT)

❖ Bilirubin Is the Major Component of Bile Pigments, (Steps of Excretion):

1. **Hemoglobin is first dissociated into heme and globin.**
2. **In the presence of NADPH and O_2, the Heme oxygenase enzyme hydroxylates Heme, with a concomitant oxidation of ferrus Fe^{2+} iron to ferric Fe^{+3} , and converts it into Biliverdin.**
3. **Biliverdin is then reduced or converted into bilirubin by biliverdin reductase enzyme. Bilirubin is transported in blood bound to albumin forming a water soluble compound called hemobilirubin (unconjugated bilirubin, free bilirubin) which is rapidly transported to hepatocytes for further metabolism (even when bound to albumin, it's called free bilirubin).**
4. **The liver removes bilirubin from the circulation rapidly, mediated by a carrier protein (receptor), and conjugates it with glucuronic acid. This reaction is catalyzed by the enzyme glucuronyl transferase in the smooth endoplasmic reticulum to have conjugated bilirubin, which is more water soluble than bilirubin.**
5. **The bilirubin-glucuronide (conjugated bilirubin) is secreted into the bile canaliculi through an active carrier-mediated process. (Note: the unconjugated bilirubin is normally not secreted.)**
6. **In the small intestine, bilirubin glucuronide is poorly absorbed. In the gut, however, bacteria deconjugate it back to bilirubin, and convert it to the highly soluble colorless compound called Urobilinogen.**
7. **Only 20% of Urobilinogen can be absorbed by the small intestine (this represents the enterohepatic circulation of bile pigments). 70% of the Urobilinogen can be oxidized in the large intestine to Stercobilin (by bacteria).**

➔ **Urobilinogen is excreted in either urine (where it is converted to yellow urobilin in the kidney) or fesses (after it is converted to Stercobilin which is responsible for the brown color of fesses).**

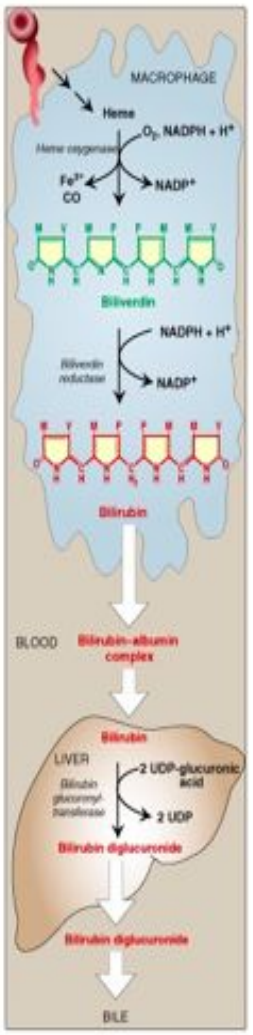


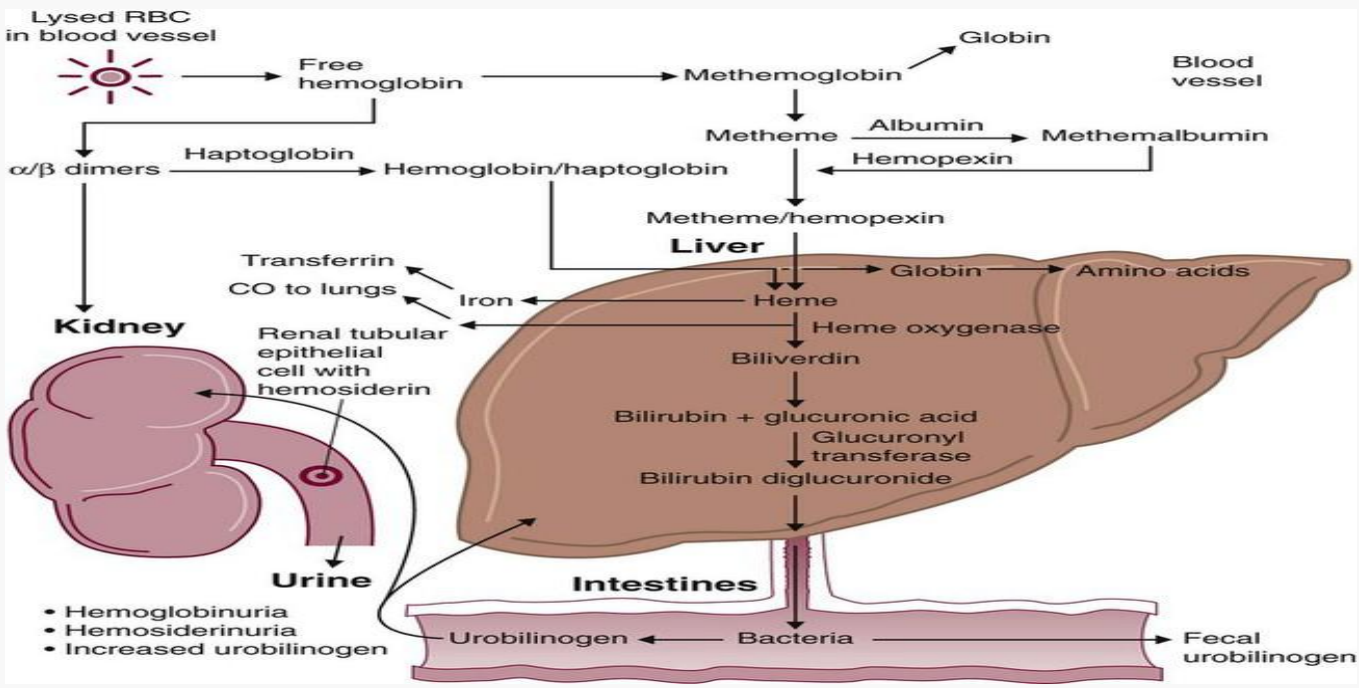
Figure 21.8
Formation of bilirubin from heme

❖ Fate of the bilirubin-glucuronide (conjugated bilirubin) after they leave the hepatocytes (liver):

- **A small portion of the conjugated bilirubin returns to the plasma either directly into the liver sinusoids or indirectly by absorption into the blood from the bile ducts or lymphatics. This represents 10% only).**
- **This causes a small portion of the bilirubin in the extracellular fluid always to be of the conjugated type rather than of the free type. These conjugated bilirubin that escaped into the blood, they bind less tightly to albumin & are excreted readily in the urine.**
- **Small amount of bilirubin glucuronide (20%) is de-conjugated (and converted to Urobilinogen) and absorbed by the small intestine into the portal blood to the liver where it is extracted by the liver cells and is conjugated again and excreted in the bile (enterohepatic circulation of bile pigments).**

SUMMARY

Bilirubin formation	RBCs lysis in spleen or blood strem >hemoglobin> bile pigment (biliverdin)--(by biliverdin reductase) >free bilirubin (hydrophopic)
Transport of Bilirubin in Plasma	Bilirubin in spleen> go to bood strem > combines with(mainly albumin and globulin)> hemobilirubin, unconjugated bilirubin (hydrophilic)
Hepatic phase	**Hepatic uptake:** Bilirubin absorbed through the hepatiocytes membrane and traped inside the cell by Y & Z proteins **Conjugation :** Bilirubin + 2 uridine diphospho-glucuronic acid– (by glucuronyl transferase) > bilirubin diglucuronide (cholebilirubin, direct, conjugated bilirubin) (highly hydrophilic) **Bilirubin Secretion in Bile :** Cholebilirubin secreted by the liver cells by an active transport process into the bile canaliculi Unconjugated bilirubin normally not excreted in bile
Fate of conjugated bilirubin	majority of conjugated bilirubin transformed through bacterial action into > urobilinogen > stercobilin > feces . Small amount deconjugated back by circulation > enterohepatic circulation small amountof conjugated bilirubin returns to the plasma and bound less tightly to albumin > excreted in the urine



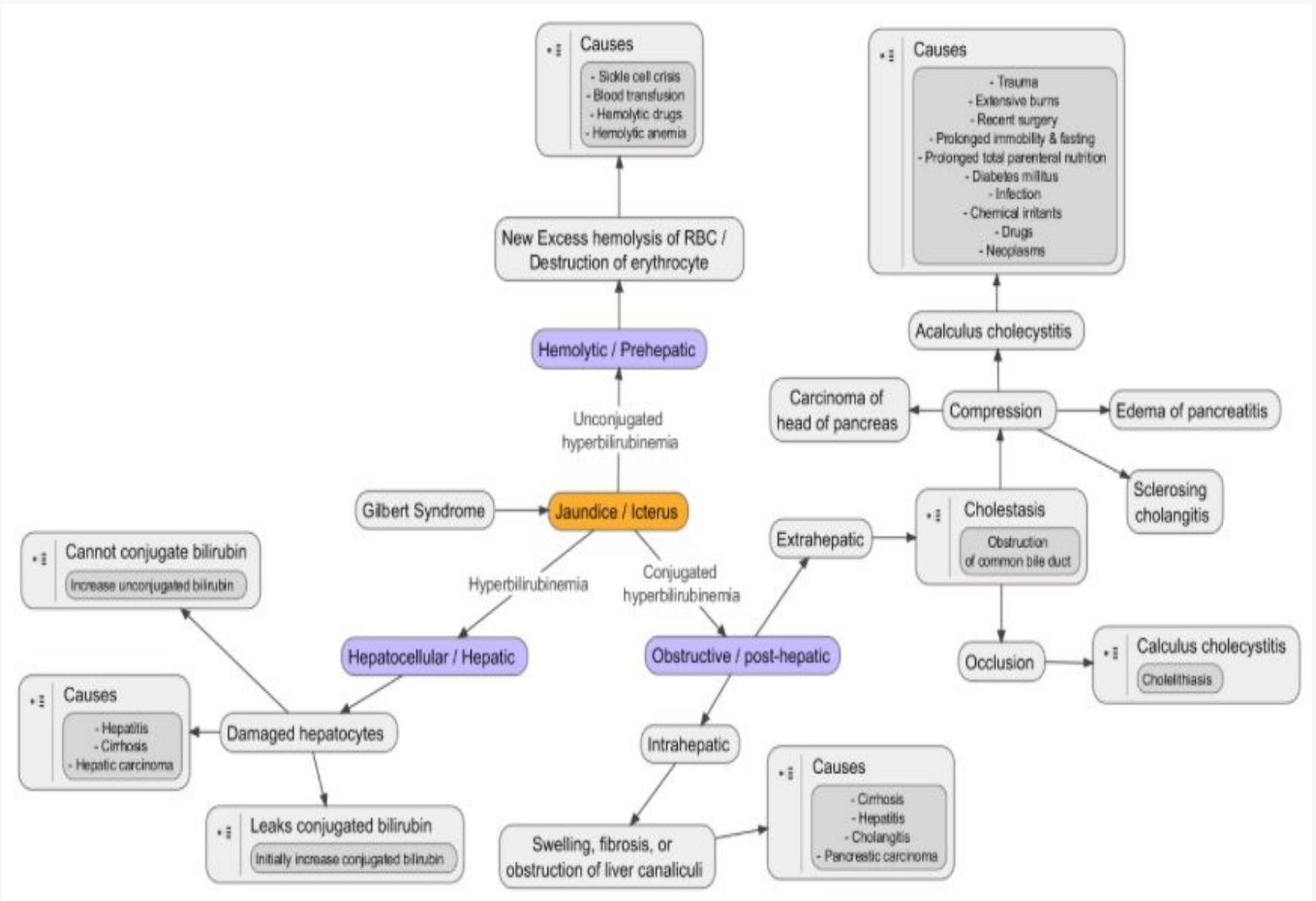
SUMMARY (GUYTON)

Jaundice—Excess Bilirubin in the Extracellular Fluid

Jaundice refers to a yellowish tint to the body tissues, including a yellowness of the skin and deep tissues. The usual cause of **jaundice** is large quantities of bilirubin in the extracellular fluids, either unconjugated or conjugated bilirubin. The normal plasma concentration of bilirubin, which is almost entirely the unconjugated form, averages 0.5 mg/dl of plasma. In certain abnormal conditions, this can rise to as high as 40 mg/dl, and much of it can become the conjugated type. The skin usually begins to appear **jaundice**d when the concentration rises to about three times normal—that is, above 1.5 mg/dl.
The common causes of **jaundice** are (1) increased destruction of red blood cells, with rapid release of bilirubin into the blood, and (2) obstruction of the bile ducts or damage to the liver cells so that even the usual amounts of bilirubin cannot be excreted into the gastrointestinal tract. These two types of **jaundice** are called, respectively, *hemolytic* ***jaundice*** and *obstructive* ***jaundice***. They differ from each other in the following ways.

Hemolytic Jaundice Is Caused by Hemolysis of Red Blood Cells.
In hemolytic **jaundice**, the excretory function of the liver is not impaired, but red blood cells are hemolyzed so rapidly that the hepatic cells simply cannot excrete the bilirubin as quickly as it is formed. Therefore, the plasma concentration of free bilirubin rises to above-normal levels. Likewise, the rate of formation of *urobilinogen* in the intestine is greatly increased, and much of this is absorbed into the blood and later excreted in the urine.

Obstructive Jaundice Is Caused by Obstruction of Bile Ducts or Liver Disease.
In obstructive **jaundice**, caused either by obstruction of the bile ducts (which most often occurs when a gallstone or cancer blocks the common bile duct) or by damage to the hepatic cells (which occurs in *hepatitis*), the rate of bilirubin formation is normal, but the bilirubin formed cannot pass from the blood into the intestines. The unconjugated bilirubin still enters the liver cells and becomes conjugated in the usual way. This conjugated bilirubin is then returned to the blood, probably by rupture of the congested bile canaliculi and direct emptying of the bile into the lymph leaving the liver. Thus, *most of the bilirubin in the plasma becomes the conjugated type* rather than the unconjugated type.



MCQs

1:Bilirubin is absorbed through the hepatic cell membrane by:

A. secondary cotransport with amino acid.
B. Carrier protein combined with albumin
C. Carrier protein combined with Y & Z proteins
D. none of them

2:The intestinal mucosa is relatively impermeable to.....bilirubin but permeable to .....bilirubin:

A. unconjugated –conjugated
B. conjugated –unconjugated

3:Urobilinogen is converted to ……., which is excreted in the feces:

A. Stercobilinogen
B. Urobilin
C. A&B

4 :The direct bilirubin (conjugated) is converted to _____ by bacteria in the intestine:

A. Biliverdin
B. Urobilin
C. Urobilinogen
D. Cholebilirubin

5: what would be the result from reduction of one step of Bilirubin metabolism:

A. Hyperbilirubinemia
B. Hypobilirubinemia
C. Anemia
D. Increase bilirubin solubility

6:The effect of steroid:

A. Compete with bilirubin on conjugation
B. proliferation of the smooth endoplasmic reticulum in the hepatic cells
C. increase in hepatic glucuronyl transferase activity
D. none of them

7: enzyme responsible to change biliverdin into free bilirubin:

A. Bilirubin anhydrease
B. biliverdin reductase
C. heme oxygenase
D. Biliverdin activator

8: Which of the following can be found in urine:

A. Unconjugated bilirubin
B. urobilin
C. Conjugated bilirubin
D. B&C

9: combining of bilirubin to albumin result in:

A. Conjugated bilirubin
B. Unconjugated bilirubin
C. Cholebilirubin
D. Direct bilirubin

10: most of conjugated bilirubin will convert into:

A. Deconjugated
B. Urobilin
C. Strecobilin
D. Excreted in urine

11: most abundant form of bilirubin in blood is:

A. Conjugated
B. Unconjugated

answer key: 1:C , 2:B , 3:A , 4:C , 5:A , 6:A , 7:B , 8:D , 9:B , 10:C , 11:B.

خولة العمَّاري
نجود الحيدري
نورة الطويل
لولوة الصغير
لجين السواط
رزان السبتي
ربى السليمي
ديما الفارس
خولة العريني
ملاك الشريف
منيرة الحسيني
مروج الحربي
أفنان المالكي
دلال الحزيمي
رناد القحطاني
سارة الخليفة
فرح مندوزا
مي العقيل
نورة الخراز
سارة الخليفة
نورة الخيال
رغد النفيسة
منيرة السلولي
نوف العبدالكريم
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