DOCTOR 2020 | JU

METABOLISM

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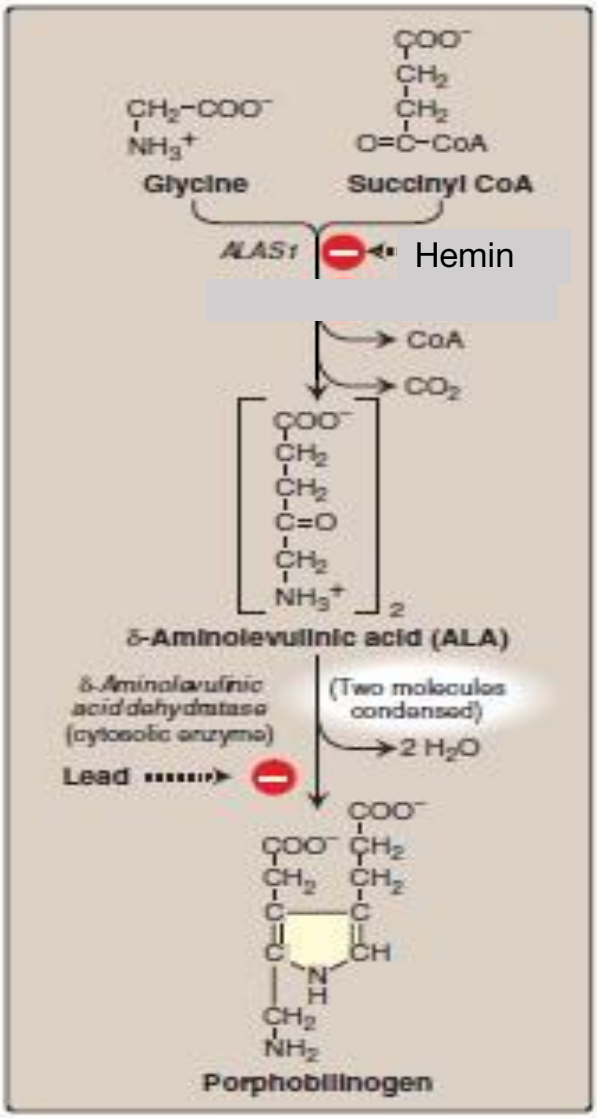
Biosynthesis of Heme



A very large structure that belongs to porphyrin, Derived from amino acids such as:

Glycine and succinyl CoA

Succinyl CoA is not an amino acid instead it is a metabolite of many amino acids, that is a final product of their metabolism.

We need to join atoms of heme from Different sources, one source is glycine and succinyl CoA, which combine together in mitochondria by *δ-aminolevulinic acid synthase (ALAS1)* (In liver) which release CoA and CO2 and combines other atoms in a molecule called δ-aminolevulinic acid (ALA), The rate-limiting step in porphyrin synthesis

***Note: Hemin (Heme with ferric(Fe^{+3})) is a negative regulator of ALAS1**

When heme present in high concentration, Fe^{+2} gets oxidised to Fe^{+3}.

this reaction is repeated twice to obtain 2 ALA molecules

Cytosolic reactions

these 2 molecules align next to each other and interact in a Dehydration reaction, releasing 2 H2O molecules, by enzyme *δ-aminolevulinic acid dehydratase*

Now, we have a ring structure (the first pyrrole ring structure was formed which is a 5-membered ring with nitrogen just like in heme group, two side chains upward acetate and propionate, one side chain downward methylamine).

***The ring structure is called Porphobilinogen (-gen means precursor)**

***Note: lead is external regulator for this step.**

***The major sites of heme biosynthesis are*:**

1. **Liver (cytochrome P450), variable rate depending on demands for heme proteins. >> *ALAS1***
2. **Erythrocyte-producing cells of the bone marrow (hemoglobin), more than 85% of all heme synthesis. >>*ALAS2***

The initial and last steps in porphyrins formation occur in mitochondria The intermediate steps occur in the cytosol

Mature RBCs lack mitochondria and are unable to synthesize heme

*** ALA is elevated in the anemia seen in lead poisoning.**

Now, in next reaction we will repeat the two steps how many times? 4 times

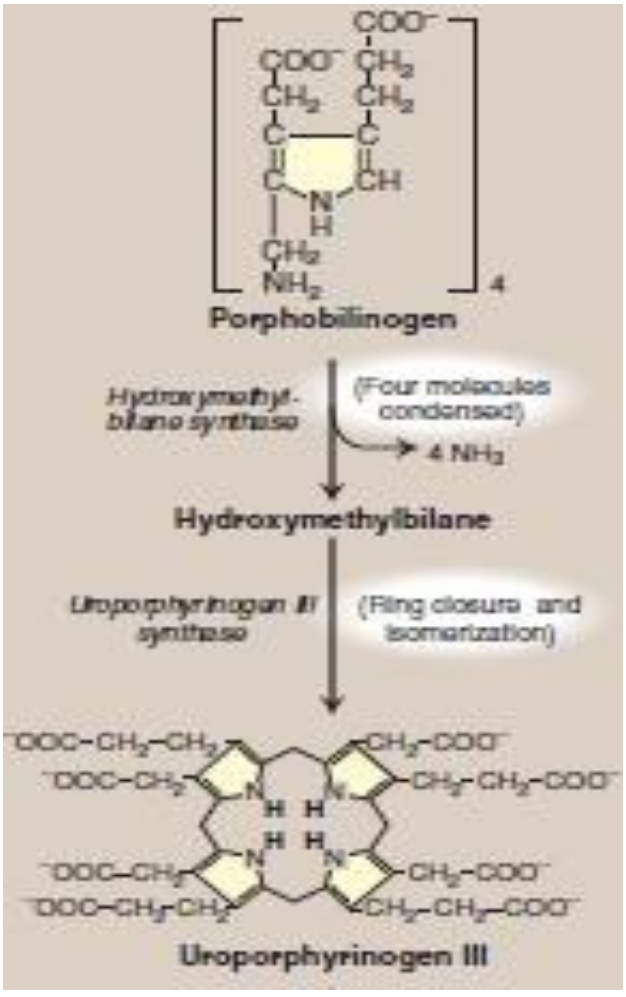
How many ALA molecules we need? 8

(i.e the first step is repeated 8 times (8 ALAs) and second one 4 times so I have 4 Porphobilinogen molecules)

Now, we will condense these 4 molecules together so they can form the large porphyrin ring structure, this happen in multiple steps first remove nitrogen from downward side chain by *hydroxymethyl bilane synthase* forming the linear tetrapyrrole, hydroxymethylbilane

***notice that the terminal CH2 molecule will connect two pyrrole rings together.**

hydroxymethylbilane is isomerized and cyclized (ring closure) by *uroporphyrinogen III synthase* to produce the asymmetric uroporphyrinogen III.



We still in precursor stage #3

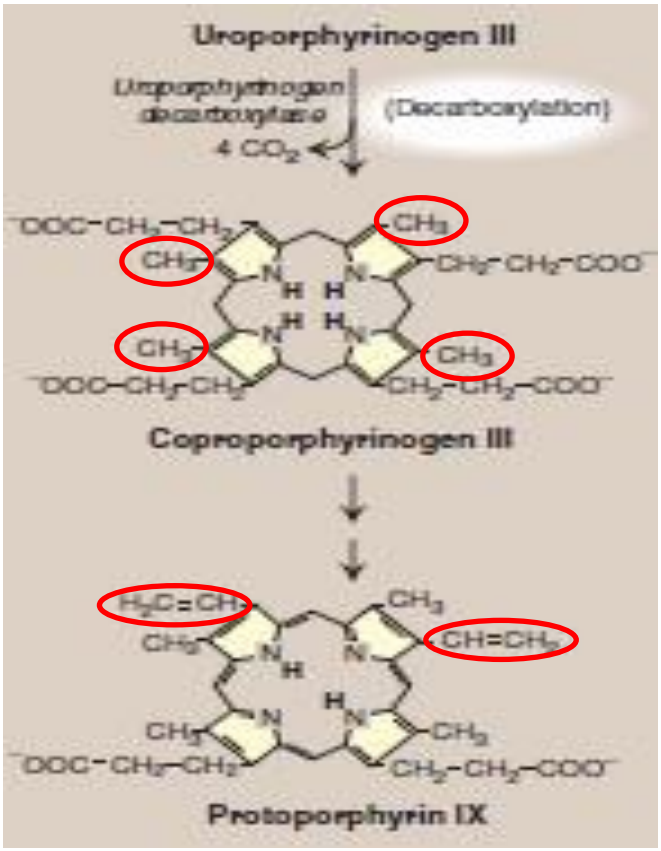
Side chains need modifications plus there is no Fe^{+2}(rather we have four H atoms centrally)

Side chains present in heme group are methyl, vinyl and propionate

But here we still have acetate and propionate so we need to generate methyl and vinyl.

Uroporphyrinogen III (cyclic hydroxymethylbilane) is decarboxylated of its acetate groups and they become methyl groups generating coproporphyrinogen III by

Uroporphyrinogen decarboxylase



Mitochondrial reactions

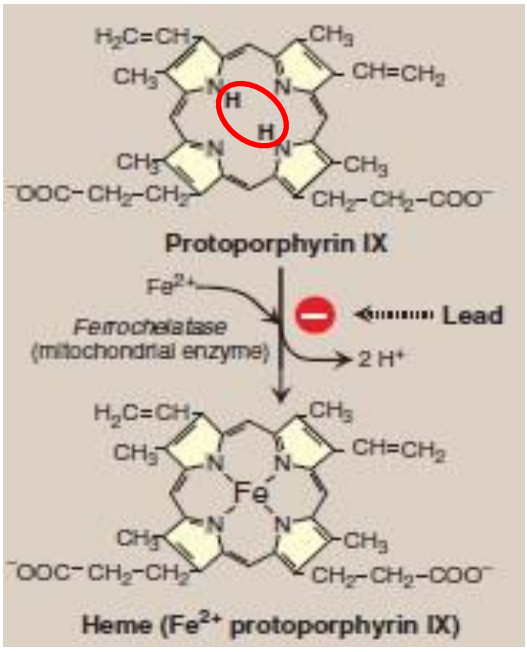
Coproporphyrinogen III enters the mitochondrion

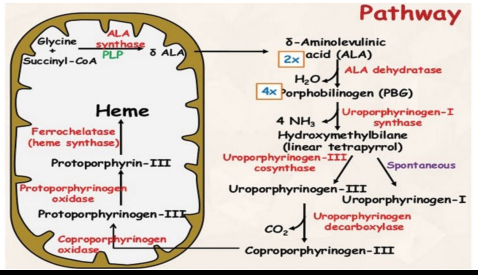
Two propionate side chains are decarboxylated to vinyl groups generating protoporphyrin IX also two hydrogens were lost.

Protoporphyrinogen IX is oxidized to protoporphyrin IX.

The introduction of iron (as Fe2+) into protoporphyrin IX occurs spontaneously

The rate of Fe addition is enhanced by *ferrochelatase* (an enzyme that is inhibited by lead)





*this helpful pic to understand synthesis of heme and not included in doctor slides.

Heme Degradation

The primary heme degradation pathway is through RBCs degradation, whenever they become senescent(120 days), they going to be targeted for degradation

~85% of degraded heme comes from senescent RBCs
~15% of degraded heme comes from immature RBCs turnover and cytochromes of nonerythroid tissues.

RBCs are degraded by the reticuloendothelial system (macrophages distributed in several organs throughout the body (liver and spleen..etc))

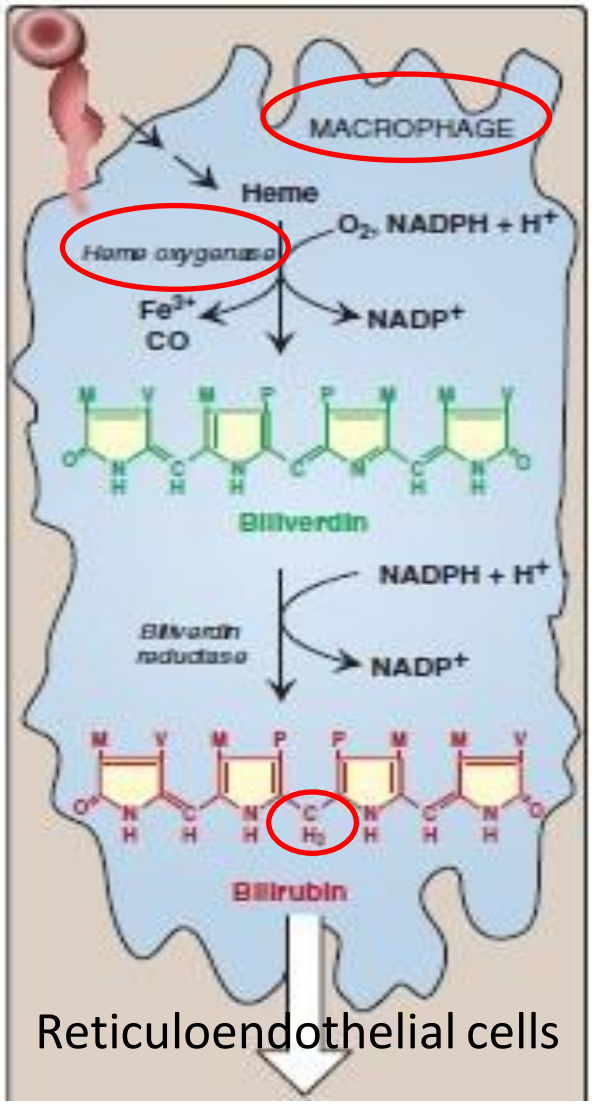
1. Formation of bilirubin:

A. **Biliverdin (green) formation by the addition of an OH to the methenyl bridge between two pyrrole rings by the enzyme *heme oxygenase* (needs O_2 and NADPH), and then a second oxidation by the same enzyme system to cleave the porphyrin ring.**

Products: the green pigment biliverdin, ferric iron (Fe3+) and CO

Biliverdin reduction to bilirubin (redorange), Bilirubin and its derivatives are called bile pigments.

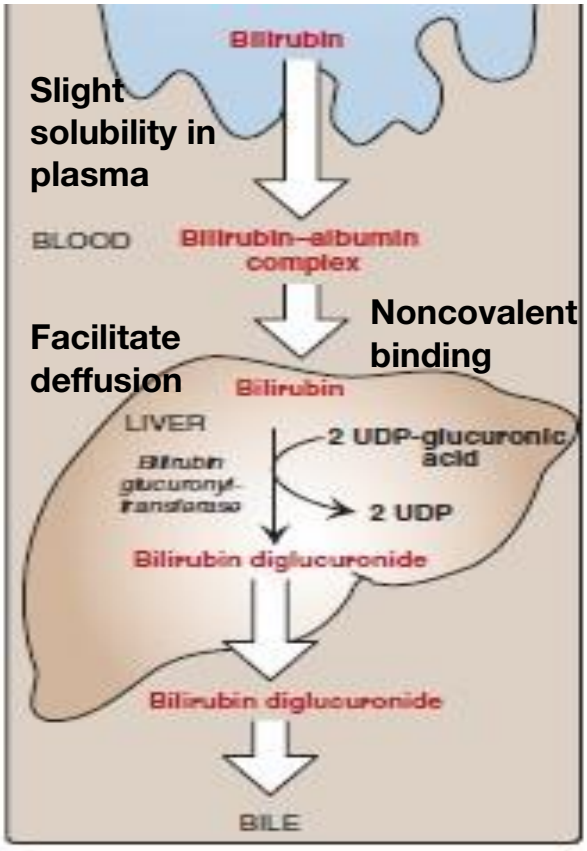
B. **Bilirubin is generally hydrophopic and functions as an antioxidant (oxidized to biliverdin)**



2. Uptake of bilirubin by the liver:

In hepatocytes, bilirubin binds to intracellular proteins, such as, ligandin. for easier metabolism and excretion of this molecule we convert it to be more soluble, this happens outside macrophage (in hepatocyte) by a carrier especially albumin (non covalently) then bilirubin is taken by hepatocytes by facilitated diffusion.

3. Formation of bilirubin diglucuronide:



two highly polar molecules (glucuronic acids) carried by nucleotide UDP will be added to bilirubin forming bilirubin diglucuronide (conjugated bilirubin) by enzyme

Bilirubin glucuronyl transferase

***Deficiency of this enzyme results in Crigler-Najjar I and II (more severe) and Gilbert syndrome (relatively common mild syndrome, patients of which suffer from fasting difficulty).**

4. Secretion of bilirubin into bile:

Now, it becomes soluble so can move easily Conjugated bilirubin is actively transported (ATP Needed) into the bile canaliculi (biliary system) and Gallbladder then into the bile cuz it is part of biliary secretion.

The rate-limiting step of this pathway (energy-requiring step).

***Note: bile color comes from bilirubin.**

***Dubin-Johnson syndrome results from a deficiency in the transport protein of conjugated bilirubin.**

Unconjugated bilirubin is normally not secreted.

Now bilirubin is part of gallbladder secretions and goes into small intestine

5. Formation of urobilins in the intestine:

Bilirubin diglucuronide is hydrolyzed and reduced by bacteria in the gut (normal flora) to yield urobilinogen (colorless).

Urobilinogen fates:

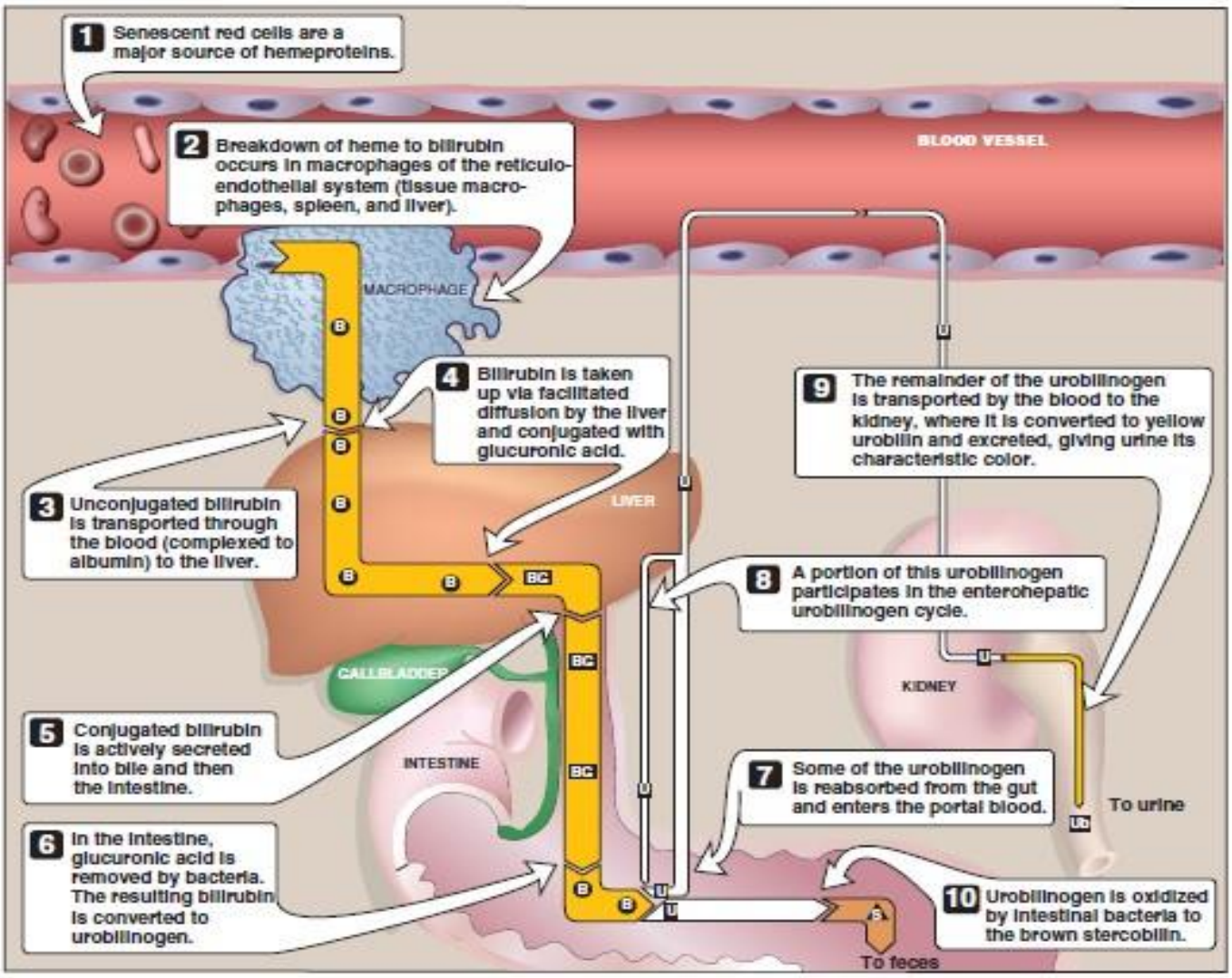
1. **Oxidation by intestinal bacteria to stercobilin (gives feces the characteristic brown color). (large portion)**

2. **Reabsorption from the gut and entrance to the portal blood then to liver. (small portion)**

    a. **Some urobilinogen participates in the enterohepatic urobilinogen cycle where it is taken up by the liver, and then resecreted into the bile.**

    b. **The remainder is transported by the blood to the kidney, where it is converted to yellow urobilin and excreted, giving urine its characteristic color.**

Catabolism of heme



Now it is your roll to link what you have learnt with this pretty pic, Enjoy!

***Hint: arrow's color represents color of transported molecule**

BC=conjugated bilirubin

Jaundice

اليرقان **Jaundice (or icterus) is the yellow color of skin, nail beds, and sclera due to bilirubin deposition secondary to hyperbilirubinemia**

***Jaundice is a symptom not a disease**

Jaundice has different types due to causes that result in this symptom:

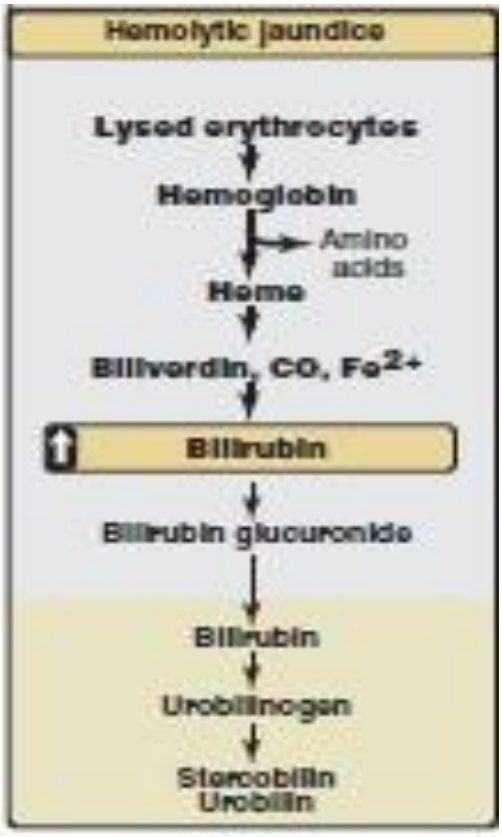
1. Hemolytic jaundice:

More hemolysis→more unconjugated bilirubin in the liver→hemolytic jaundice

Bilirubin conjugation and execretion capacity of the liver is >3,000 mg/day

If there is more bilirubin, this will result in accumulation of unconjugated ones.

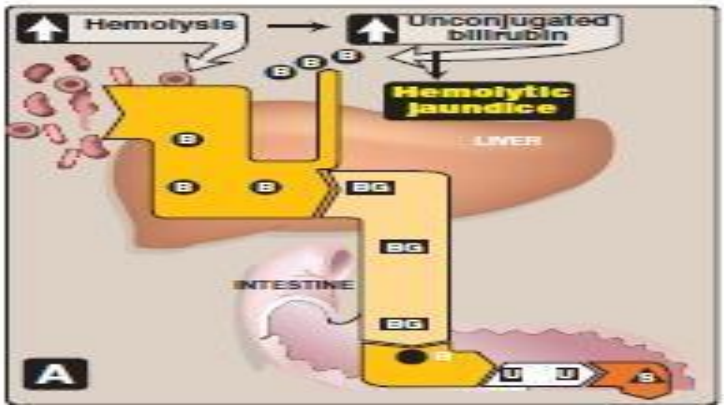
300 mg/day of bilirubin produced



Diseases that are related to this type of jaundice:

Sickle cell anemia→more hemolysis process beyond the capacity of the liver

pyruvate kinase or glucose-6-phosphate dehydrogenase deficiency



BG = bilirubin glucuronide; B = bilirubin; U = urobilinogen; S = stercobilin.

2. Hepatocellular jaundice

due to damage to liver cells

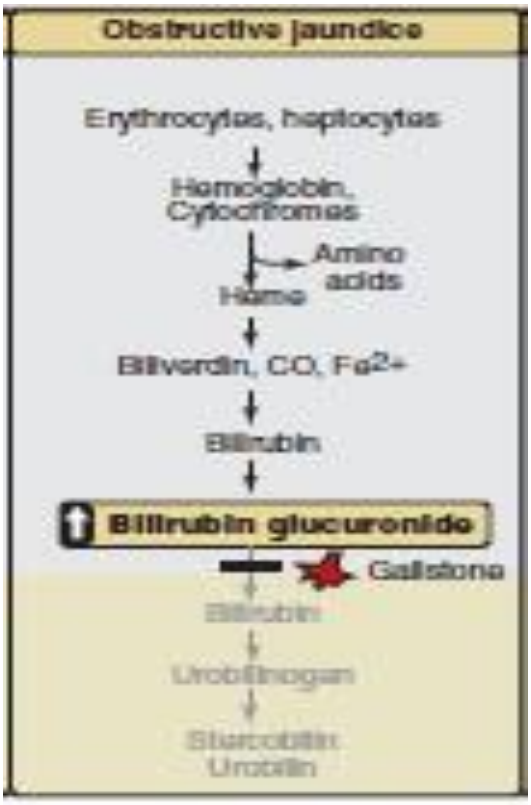
more destruction of the liver→

More unconjugated bilirubin levels in the blood

Urobilinogen is increased in the urine (the enterohepatic circulation is reduced) resulting in dark urine.

Stools may have a pale, clay color.

3. Obstructive jaundice: Obstruction of the bile duct



(extrahepatic cholestasis) due to a tumor or bile stones, preventing bilirubin passage into the intestine.

No overproduction of bilirubin or decreased conjugation

Signs and symptoms: GI pain and nausea, pale clay color stool, and urine that darkens upon standing.

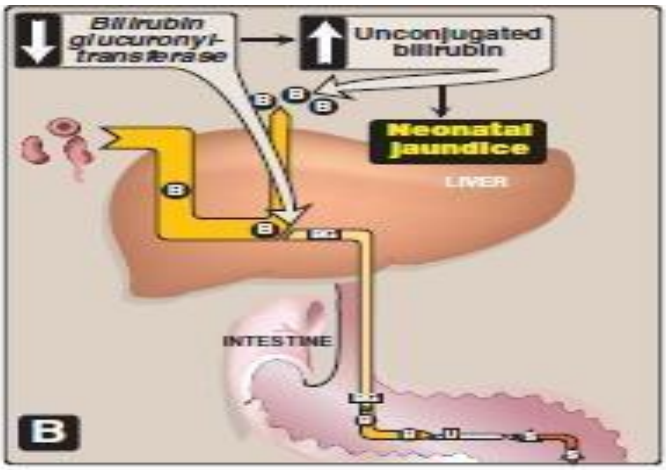
Hyperbilirubinemia, bilirubin execretion in the urine, no urinary urobiloinogen.

Prolonged obstruction of the bile duct can damage the liver and increase unconjugated bilirubin

***Note: conjugated and unconjugated bilirubin can cause jaundice.**

Jaundice in newborns especially in preterm newborns

Newborn infants, particularly if premature, often accumulate bilirubin, because the activity of *hepatic bilirubin glucuronyltransferase* is low at birth



BG = bilirubin glucuronide; B = bilirubin; U = urobilinogen; S = stercobilin.

Enzyme adult levels are reached in ~4 weeks (so it is just a time issue)

It depends on degree or level of bilirubin,

High bilirubin above the binding capacity of albumin, can diffuse into the basal ganglia and cause toxic encephalopathy (kernicterus) in CNS

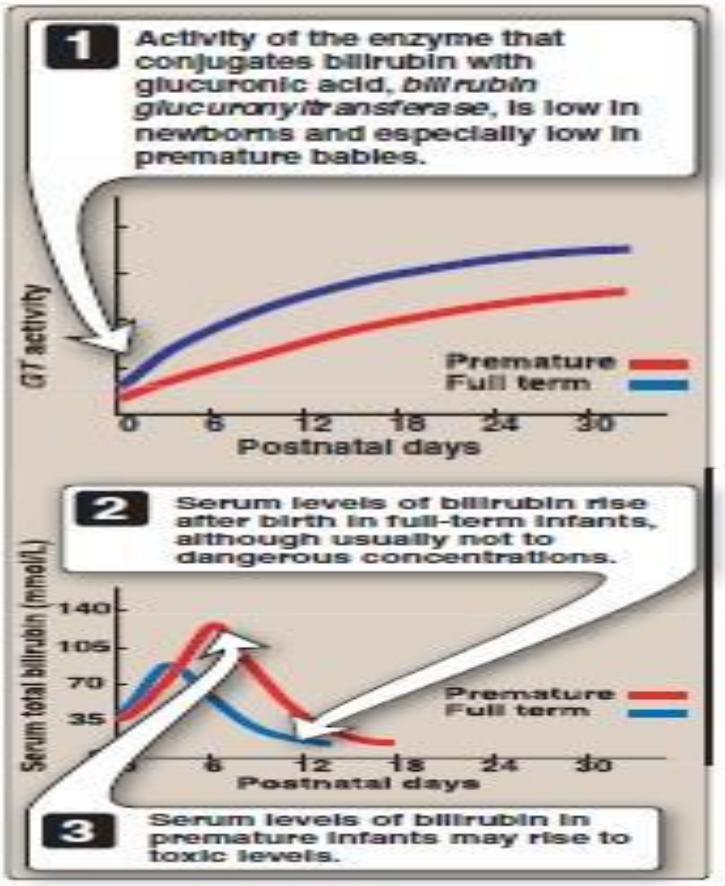
So, our concern about newborns is not to pass their BBB by bilirubin.

صلِّ على النبي

In incubator, blue fluorescent light is used that converts unconjugated bilirubin to more polar water-soluble isomers.

(notice that their eyes are covered)

The resulting photoisomers can be excreted into the bile without conjugation to glucuronic acid.



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