Metabolism

فريق طوفان الأقصى

Modified N: **19**

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Homocystinuria

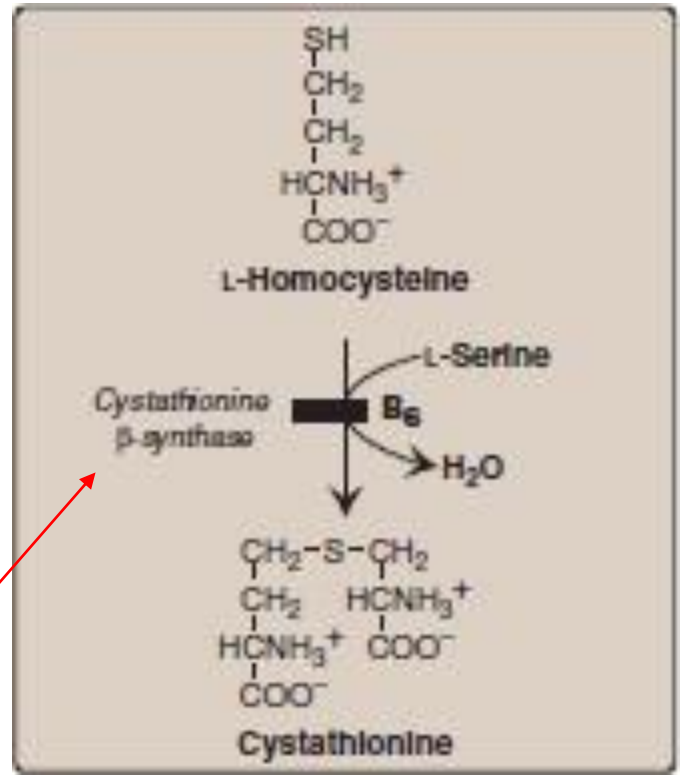
NOTE: affects the degradation of Met

Defects in the metabolism of homocysteine.

Mode of inheritance: AR

High plasma and urinary levels of homocysteine and Met and low levels of Cys.

The most common cause is a defect in cystathionine β-synthase that converts homocysteine to cystathionine



NOTE: If this enzyme is deficient due to a genetic mutation (autosomal recessive inheritance, we need both copies of the gene to inherit the disease) there will be accumulation of Homocysteine.

■ **The complement in this slide:**

Homocysteine, as you remember, is used to either

A- regenerate Methionine OR B- synthesize Cysteine through two steps

<u>Cysteine synthesis:</u>

Homocysteine first gets combined with Serine to form Cystathionine (by the enzyme: **Cystathionine β-synthase**).

In case of Homocysteine accumulation (genetic mutation), its level will increase in the plasma as well as in urine.

We give those patients Vitamin B6, B12 and folic acid supplements to increase the passage of homocysteine in the other pathway producing Methionine.

Maple syrup urine disease (MSUD)

Rare (1:185,000), autosomal recessive (AR) disorder, most cases are heterozygotes

Partial or complete deficiency in branched-chain α-keto acid dehydrogenase complex that decarboxylates Leu, Ile, and Val

Branched-chain amino acids are an important energy source in times of metabolic need

Accumulation in the blood causes a toxic effect that interferes with brain functions.

Signs and symptoms: feeding problems, vomiting, dehydration, severe metabolic acidosis, and a characteristic maple syrup odor to the urine.

If untreated, MSUD leads to mental retardation, physical disabilities, and even death.
Screening and diagnosis: prenatal diagnosis and neonatal screening are available.

Treatment: a synthetic formula that contains limited amounts of Leu, Ile, and Val to provide the branched-chain amino acids necessary for normal growth and development without producing toxic levels.

Early diagnosis and lifelong dietary treatment is essential for child normal development.

Telegraph.co.uk

Amino Acid Metabolism: Conversion of Amino Acids to Specialized Prod

D

NOTE:

We can use amino acids to make proteins
We can consume them by degradation
And we can also consume them by making other nitrogen containing compounds (eg: heme)

All images are taken from Lippincott's Biochemistry textbook except where noted

- **The complement in this slide:**

-Also autosomal recessive, rare

-It's named this way because in such case, the urine would smell like maple syrup

-Patients have a problem in branched AA metabolism (α-keto acid dehydrogenase, responsible for oxidative decarboxylation)

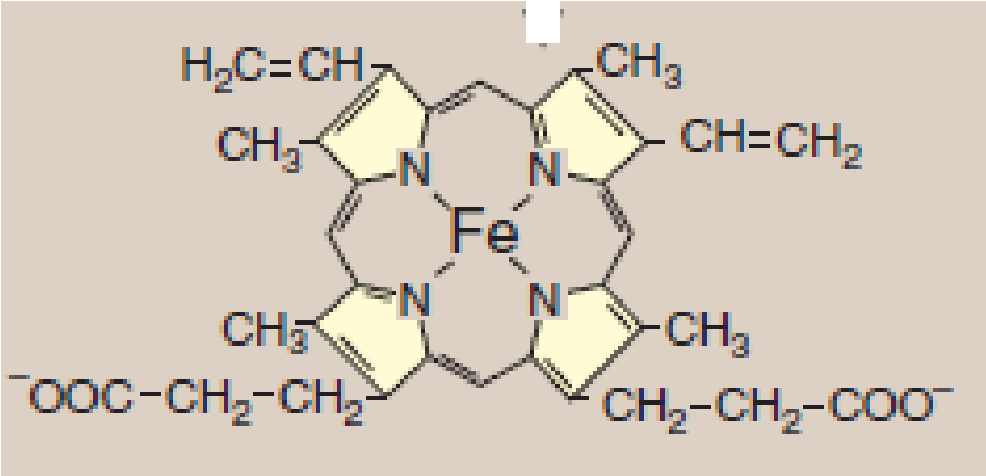
If this enzyme is deficient, then the degradation of these AA's will be compromised.

Their CNS will be affected because these AA's can be used to make neurotransmitters (both excitatory and inhibitory).

Another thing is that these branched AA's can be degraded in the peripheral tissues (like muscle), so they can provide some energy for these tissues under certain conditions, which will be reduced in the case of these patients.

PORPHYRIN

NOTE: a group of organic molecules that share a ring structure that is composed of 4 rings (tetrapyrrole rings).



Porphyrins are cyclic compounds that readily bind metal ions (Fe2+ or Fe3+)

The most prevalent metalloporphyrin in humans is heme

Heme is found in hemoglobin, myoglobin, the cytochromes, catalase, nitric oxide synthase, and peroxidase.

Hemeproteins are rapidly synthesized and degraded

6–7g of hemoglobin are synthesized each day to replace heme lost through the normal turnover of erythrocytes.

- **The complement in this slide:**

بتظهر الأعراض عن
طريق انه الطفل يرفض الرضاعة سواء طبيعية أو صناعية

Also vomiting and dehydration, but these could be due to many other reasons
In addition to acidosis and maple syrup odor of urine.
Traditionally, screening is done after birth or prenatal
These patients have to have dietary restrictions of branched chain AA's (remember that they're essential AA's and have to be obtained from diet), so it doesn’t exceed their needs or accumulate resulting in problems.

- **The complement in this slide:**

Each of these pyrrole rings is a 5 membered ring and has a Nitrogen that will be directed towards the center of the molecule and each of those rings has two side chains. These four rings are connected together. for Heme group we have Fe in the middle.

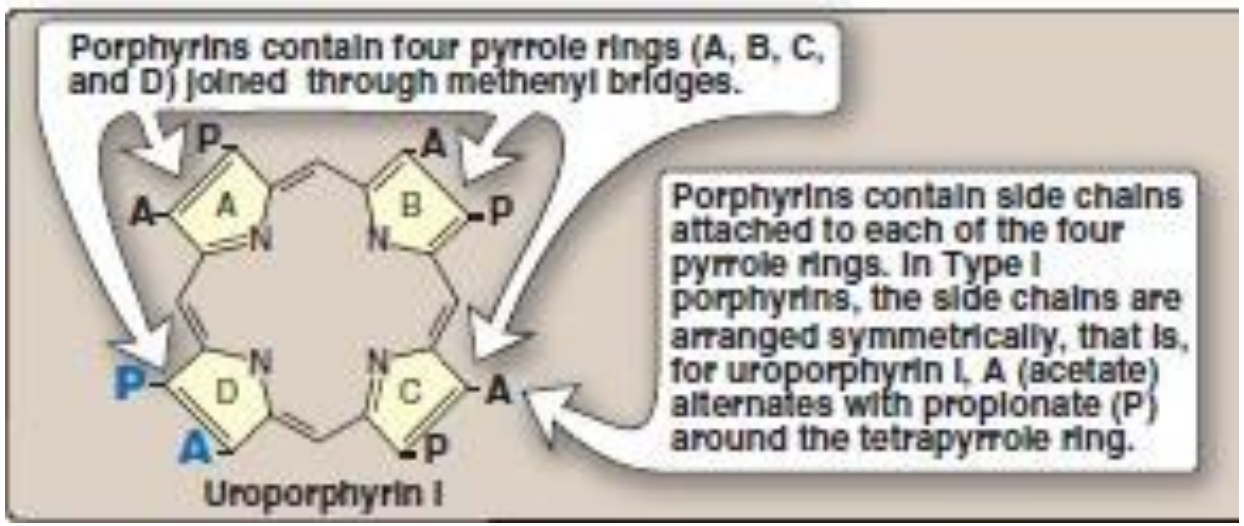
This Fe is bounded the four Nitrogens (four coordinates).

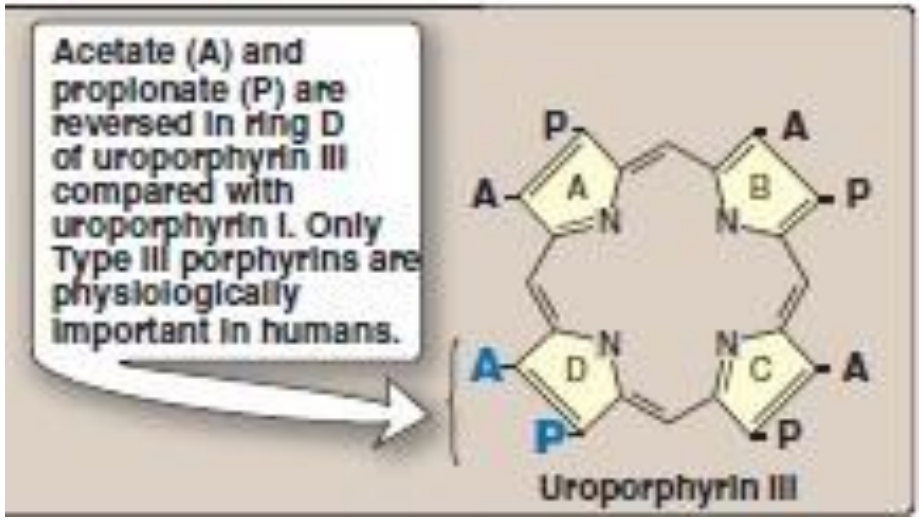
Also one bond with proximal Histidine, another one in case of binding to Oxygen.

Porphyrins are colored molecules, so the problems that are linked with porphyrin synthesis cause purple pigmentation of skin (porphyrias).

We need to synthesize Heme group for the regeneration of RBC's and all other Hemoproteins (Myoglobin, Cytochcrome P450, Catalase)

Structure of porphyrins

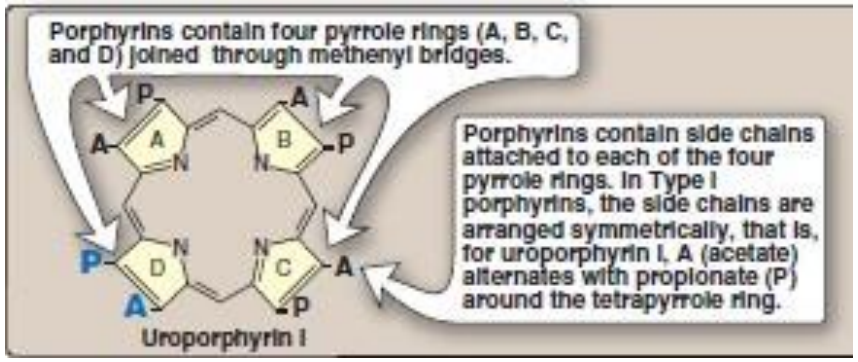


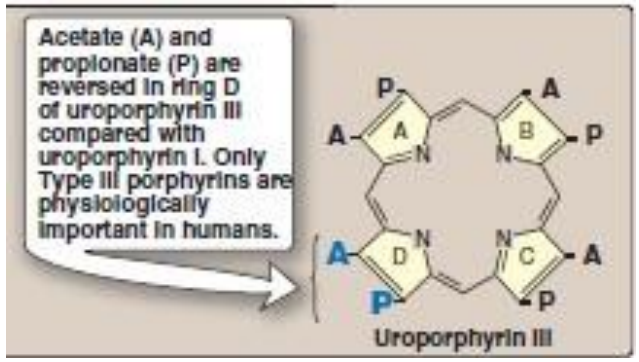


The medical significance of porphyrins is related to the following structural features of these molecules:

1. Nature of the side chains that are attached to each of the four pyrrole rings. Uroporphyrin contains acetate (–CH2–COO–) and propionate (–CH2–CH2–COO–) Coproporphyrin contains methyl (–CH3) and propionate groups Protoporphyrin IX (and heme) contains vinyl (–CH=CH2), methyl, and propionate groups.

Structure of porphyrins





The medical significance of porphyrins is related to the following structural features of these molecules:

2.Distribution of side chains around the tetrapyrrole nucleus. Four different ways (I to IV) Only Type III porphyrins (asymmetric substitution on ring D) are physiologically important in humans.

3.Porphyrinogens (porphyrin precursors) exist in a chemically reduced, colorless form, and serve as intermediates between porphobilinogen and the oxidized, colored protoporphyrins in heme biosynthesis.

- **The complement in this slide:**

What differs a porphyrin molecule from another?

For example, in the prev. slide we have "Uroporphyrin I". it has:

-Ring structure

-Pyrrole rings

-Nitrogens directed to the middle

-No Fe

-2 Side chains (4× acetate, 4× propionate)

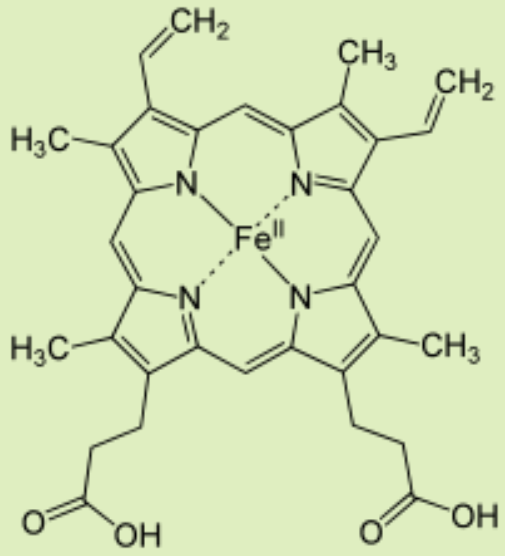
The nature of side chains can be different ⟶ indicating different types of porphyrins.

■ **The complement in this slide:**

Another factor that would affect the order of these side chains is as the following:
Notice the structure of another porphyrin, "Unoporphyrin III"
A: acetate, propionate / B: acetate, propionate / C: acetate, propionate /
BUT **D: propionate THEN acetate**
Order is changed ⟶ new molecule.

Compare that to Hemoglobin, what type of side chains does it contain?
Methyl, vinyl / methyl, vinyl / methyl, propionate / propionate, methyl
Here, we have 3 types of side chains;
2× propionate, 2× vinyl, 4× methyl
So they **don't always have to be just 2 types.**

In conclusion, porphyrins differ in the **nature** and **order** of side chains



Hemoglobin

# of hemeBiosynthesis

The major sites of heme biosynthesis are:

1. Liver (cytochrome P450), variable rate depending on demands for heme proteins

2. Erythrocyte-producing cells of the bone marrow (hemoglobin), more than 85% of all heme synthesis

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

The complement in this slide:

Another important information about porphyrins is that they are synthesized as precursors called "porphyrinogen" which is the generator of porphyrin. So, once they get modified to the porphyrins, they change in color, get oxidized, etc.

Where does Heme synthesis occur?

RBC's use the most Hemoglobin. Heme groups need to be synthesized because none of the components of RBC is going to be recycled as a molecule. EXCEPT for Fe.

The rest of the components will be digested to its monomers. Amino acids will be recycled, not the protein. Globin part, sugar.. All will be digested.

Back to the question, we need big amount of Hemoglobin. We are going to synthesize Heme group in the [1]hepatocytes of the liver, but these Heme groups are not going to be directed towards Hemoglobin protein. We can use them as Cytochrome P450 that is present in the liver and needs to renewed constantly. We can also use them for Catalase enzyme for Myoglobin but not for Hemoglobin. For Hemoglobin we need to make Heme groups in the [2]bone marrow where RBC's are going to be synthesized from stem cells.

- **The complement in this slide:**

The RBC itself doesn't have the machinery and organelles necessary for Heme group synthesis. That's why we need a regular cell. So when we trace its differentiation scheme, we find the presence of previous cells (before loss of nucleus and mitochondria). These cells are called Erythrocyte-producing cells (progenitor cells), and they produce Heme groups for Hemoglobin.

It has gotten better before, it will get better again. Just make sure you sustain your hope and motivation :))

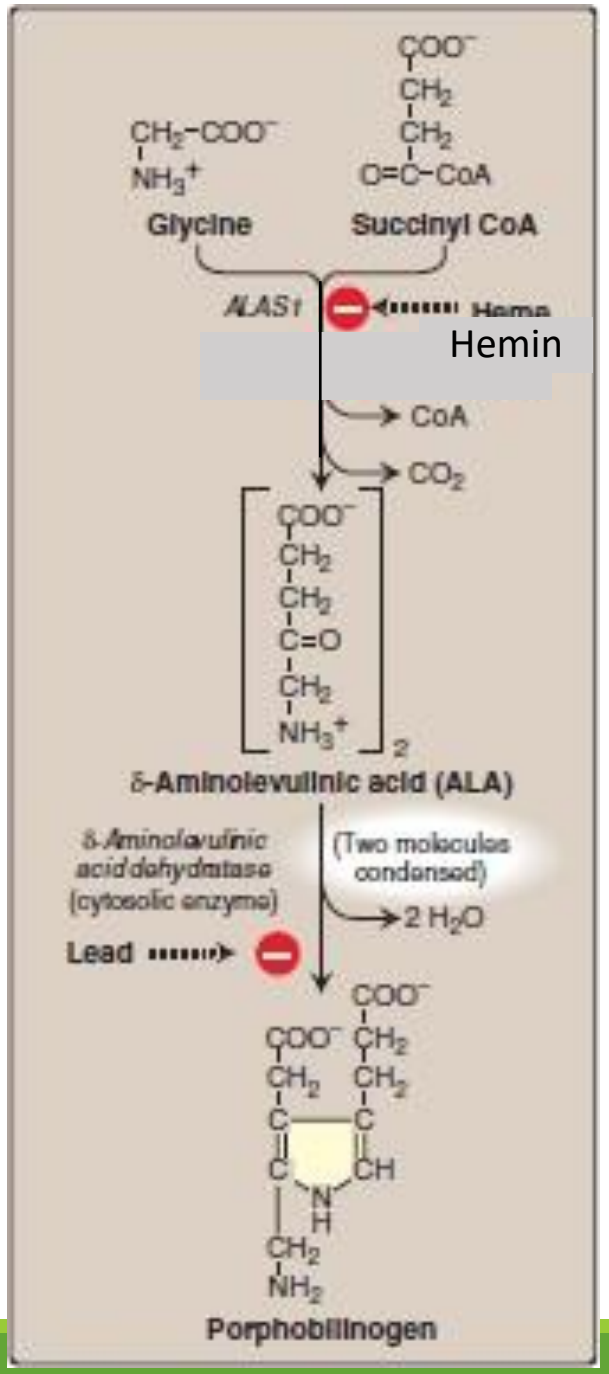
Biosynthesis of Heme

1. Formation of δ-aminolevulinic acid (ALA)

The rate-limiting step in porphyrin synthesis

2. Formation of porphobilinogen

ALA is elevated in the anemia seen in lead poisoning.



- **The complement in this slide:**

In some pathways, we use AA's as a precursor to produce Nitrogen-containing compounds. So in this pathway, the precursors are Glycine (AA) & Succinyl CoA (krebs cycle intermediate and a metabolite of amino acid).

As you noticed earlier, Hemoglobin's structure is very large... فعليًا فبدي اجمّع ذرات

The reactions or steps of Heme biosynthesis, some of them occur in the **mitochondria**, while others in the **cytosol**.

We start in the **mitochondria** ⟶ exit to **cytosol** ⟶ return back to **mitochondria**

The complement in this slide:

The first step of conjugating Succinyl CoA with Glycine (عملية تلزيق) occurs in the mitochondria. Catalyzed by **ALA Synthase,** releasing CoA, CO_2. Producing ALA that moves to the cytosol.

This is the slowest step of the pathway (**rate-limiting**), and it is regulated.

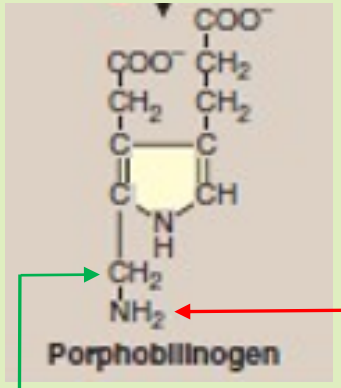
This rxn has to be repeated twice. We use another Glycine & another Succinyl CoA to make another ALA molecule. WHY?! To **condense** the two molecules of ALA (in the cytosol) into the **first pyrrole ring** (we put them next to each other and perform a condensation rxn). This ring structure, before modification, is called **porphobilinogen** (it's like an introduction to produce porphyrin).

Notice, to be able to combine these two aminolevulinic acids together, we have to **lose H_2O molecules.** Each of these ALA's has an amino group, one of these (N) will be incorporated into the structure of the pyrrole ring. The other N will be gotten rid of (we'll see how).

So far, we have a pyrrole ring (5-membered) with a Nitrogen, two side chains (acetate & propionate). But we're going to modify it in a bit.

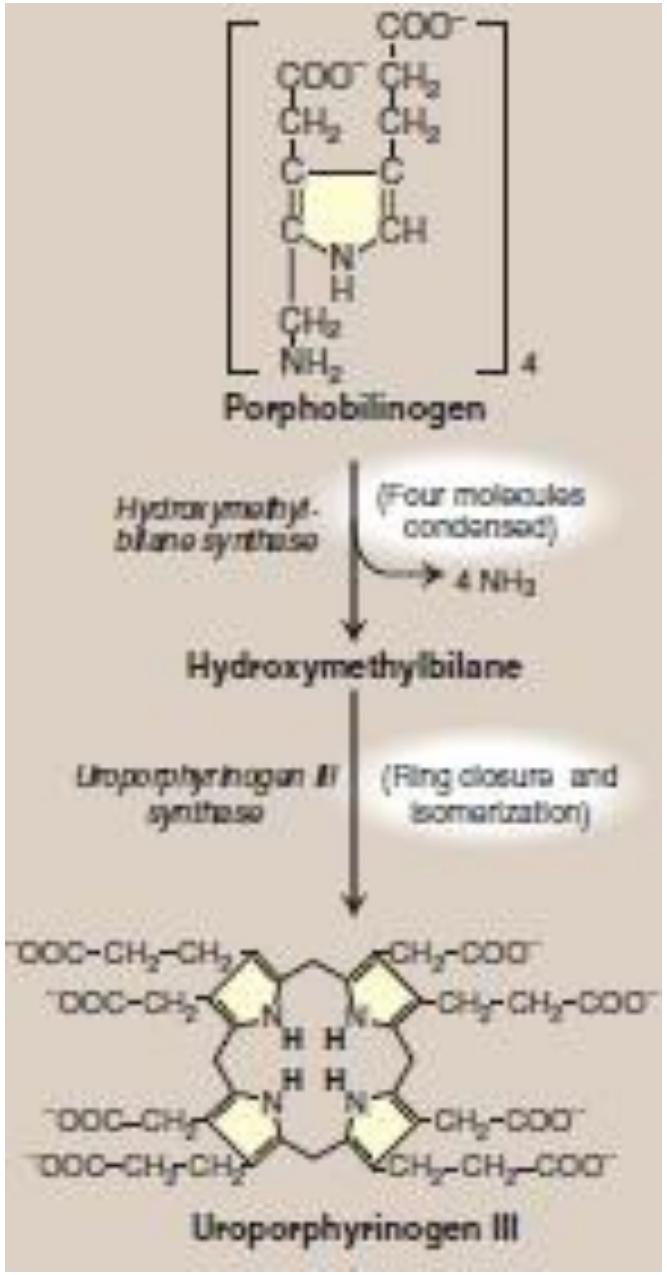
- **The complement in this slide:**

We need to repeat the previous steps multiple times to make 4 pyrrole rings (4 porphobilinogens). Which means that we're going to perform the 1st rxn **8 times**, and the 2nd one (condensation) **4 times**.



[read the following while checking on the pic on your left then the next slide]
We have our porphobilinogen, and 4 of them (produced by repetition of steps) will be condensed together to form porphyrin. BUT we have to remove **this** Nitrogen. So, we'll release it as 4× NH_3. Now, these 4 Porphobilinogens are condensed into **hydroxy-methylbilane**. Then we close the ring and form the first porphyrin structure (it's not really a porphyrin, that's why it's called **Uroporphyrinogen III**). Enzyme is called: **Uroporphyrinogen III synthase**. So far, we're still in the cytosol

الكربونة هاي بقدر استخدمها عشان اوصل بين ال pyrrole rings



Synthesis of heme

3. Formation of uroporphyrinogen:
The condensation of four porphobilinogens produces the linear tetrapyrrole, hydroxymethyl bilane

Hydroxymethyl bilane is isomerized and cyclized by uroporphyrinogen III synthase to produce the asymmetric uroporphyrinogen III.

These reactions occur in the cytosol.

- **The complement in this slide:**

If you look at the structure of Uroporphyrinogen III and compare it to Heme, what modifications do we need to make?

Ans:

1- on the side chains. In Uroporphyrinogen III we have acetate and propionate, we need to convert it to vinyl, methyl and propionate to reach Heme structure.

Propionate is already present, but we have 4 and we need only 2

2- we need to add Fe.

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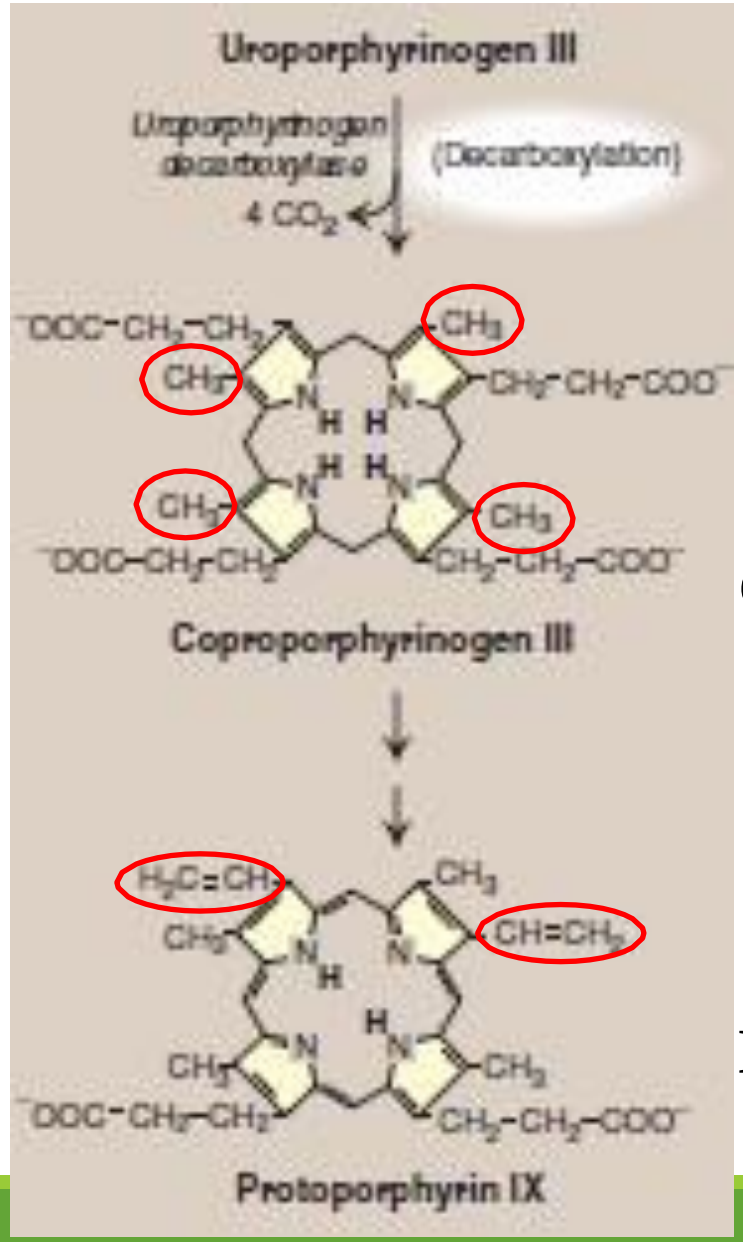
So, we have to get rid of the hydrogens then add Fe^{2+}



Synthesis of Heme*

Cytosol

The cyclic hydroxymethyl bilane is decarboxylated (of its acetate groups) generating coproporphyrinogen III

These reactions occur in the cytosol.

Mitochondria

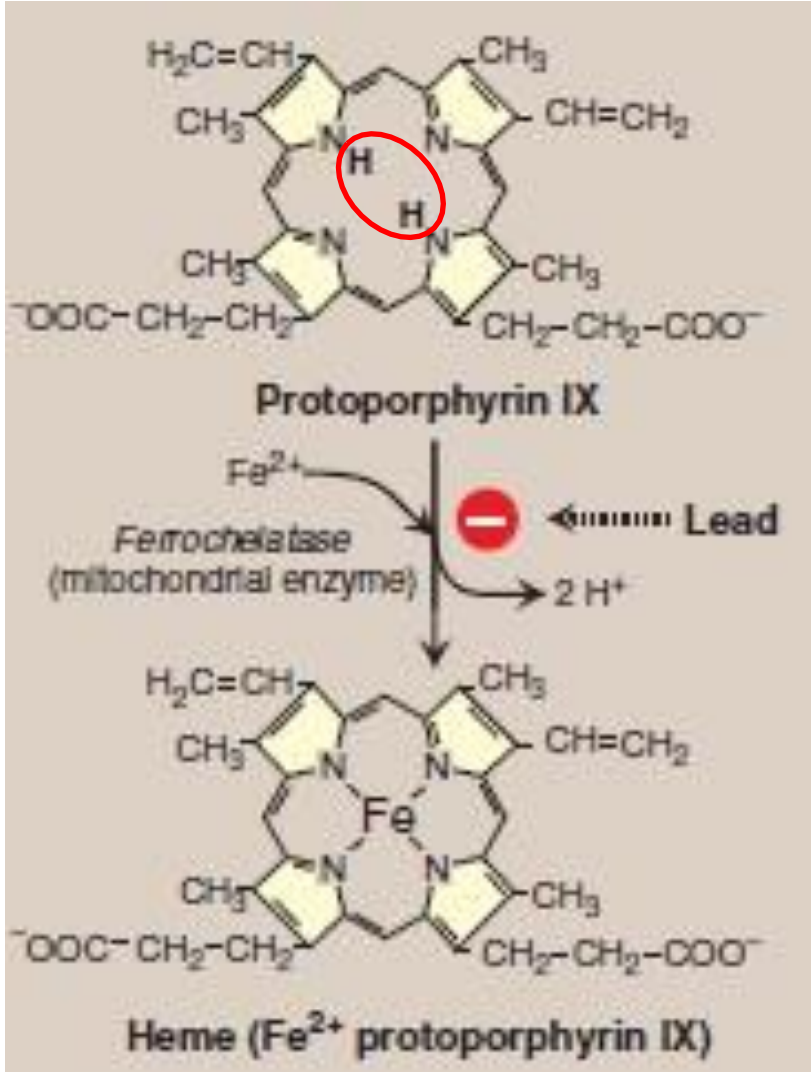
Coproporphyrinogen III enters the mitochondrion

Two propionate side chains are decarboxylated to vinyl groups generating protoporphyrin IX

- **The complement in this slide:**

In Uroporphyrinogen III, all the acetate is going to be **decarboxylated** to methyl groups. So now we have 4 Methyl groups. The resulting molecule is called **Coproporphyrinogen III.**
Enzyme: **Uroporphyrinogen III decarboxylase** (removed 4 CO_2).
Now, this **Coproporphyrinogen III** will move to the mitochondria to continue the rxns there till the end.
It will enter multiple steps, two of the propionates will be **decarboxylated** and **dehydrogenated** to create the vinyl groups.
Notice: multiple steps, and we removed 2 of the hydrogens from the center.
Now we have **Protoporphyrin IX** (first porphyrin. not gen, not a precursor)

Synthesis of Heme



4. Formation of heme:

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)

■ **The complement in this slide:**

What's left to do is the removal of the last 2 hydrogens, and addition of Fe^{2+}.

Enzyme: Ferrochelatase (mitochondrial enzyme)

Producing: Fe^{2+} Protoporphyrin IX or Heme ✓ 🎉

ليش شلناهم بالتقسيط؟ علشان ما يفضى المكان ويرتبط اشي ثاني غير **الحديد**

We do that in the same step.

Now Heme is ready to be added to the globin part making Hemoglobin or added to Myoglobin.

- **The complement in this slide**: Regulation of heme synthesis occurs on the rate limiting steps:

  1. ALA synthase is inhibited by high concentration of Hemin; it is heme group bound with Fe^{+3}(ferric),the oxidized form of heme.

  2. we have other effectors are not found normally in this pathway, like Lead → lead poisoning, which causes anemia and ALA accumulation. Lead inhibits ALA dehydratase & ferrochelatase.

Heme Degradation

RBCs are degraded by the reticuloendothelial system (liver and spleen)

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

1. **Formation of bilirubin:**

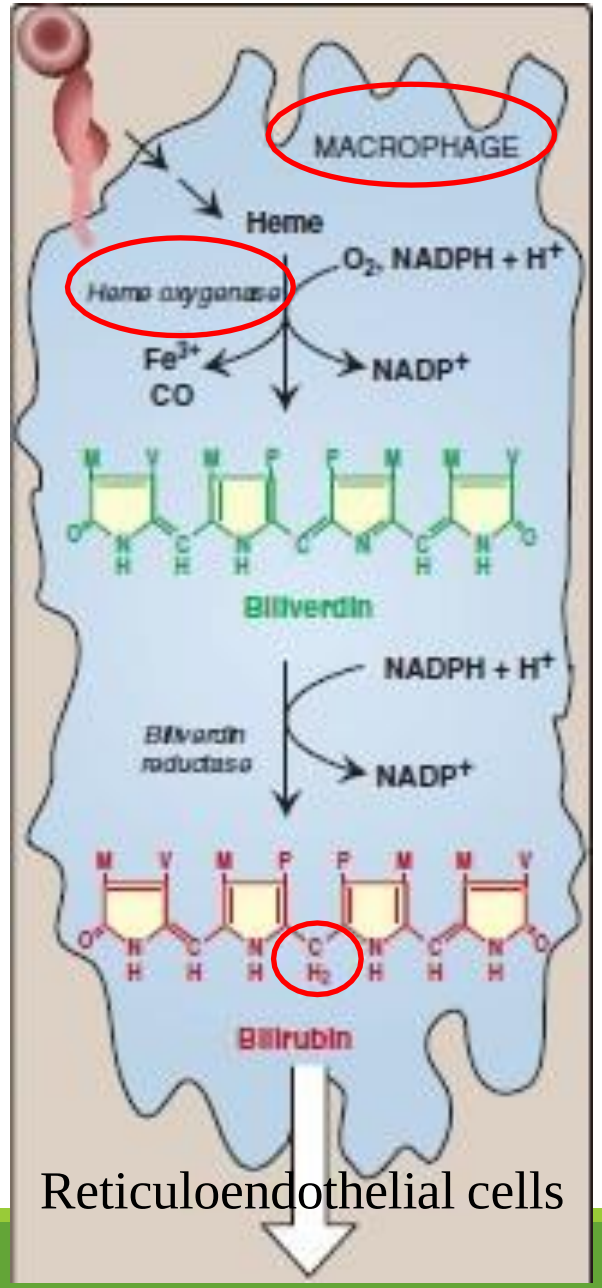
A. Biliverdin formation by the addition of an OH to the methenyl bridge between two pyrrole rings, and then a second oxidation by the same enzyme system to cleave the porphyrin ring.

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

B. Biliverdin reduction to bilirubin (redorange)

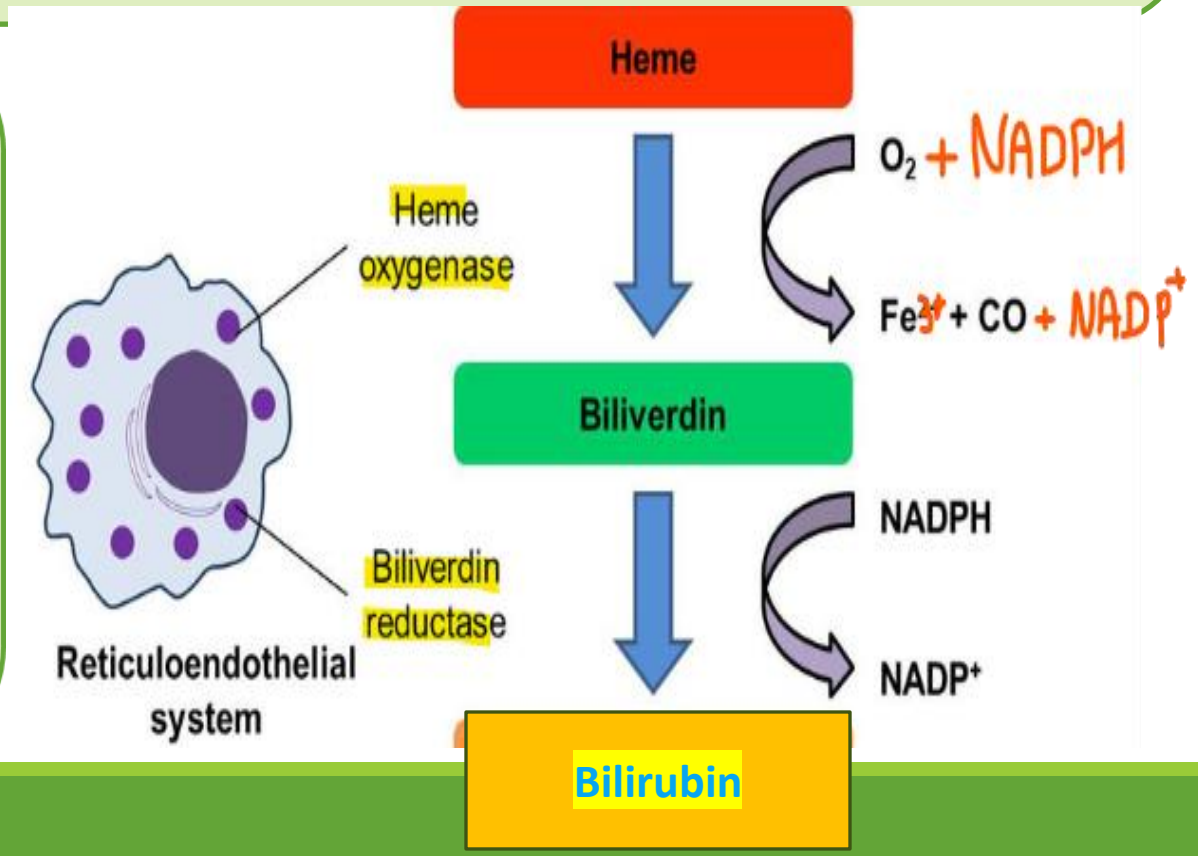
Bilirubin and its derivatives are called bile pigments.

Bilirubin functions as an antioxidant (oxidized to biliverdin)



- **The complement in this slide:** When RBCs need to be regenerated after 120 days, hemoglobin enter degradation pathway, in which heme group are degraded and Fe is recycled.
- Heme groups are degraded in macrophages of reticuloendothelial system, if the hemeproteins want to be degraded in any tissue, the macrophages of that tissue will deal with them.
- But the hemoglobin in RBCs are degraded by macrophages of the spleen (major site)
- RBCs will be completely degraded , the protein part will be simplified into amino acids and so on, but the atom that will be recycled is the iron (Fe).

1. The first step in the degradation of heme is catalyzed by microsomal heme oxygenase in macrophages, some changes will occur:
   1) release of Fe^{+3}
   2) opening the ring structure
   3) O2 and NADPH are used
2. Biliverdin, a green pigment, is reduced, forming the red-orange bilirubin By Biliverdin reductase



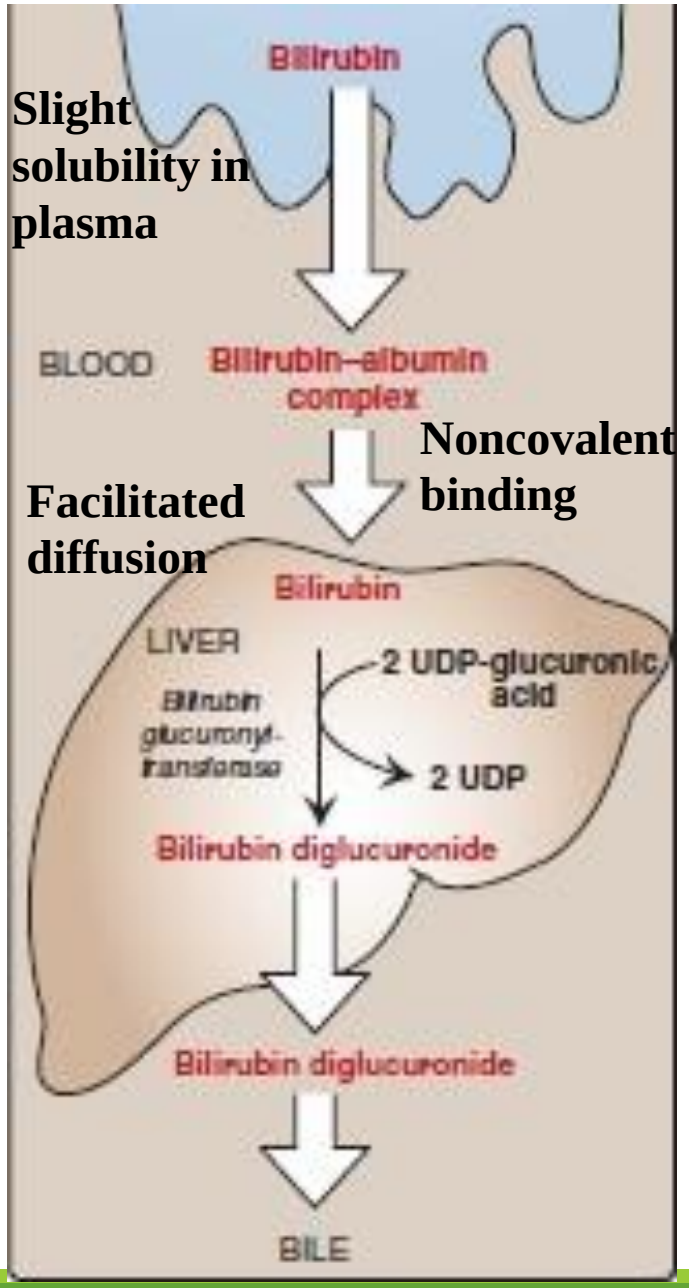
Heme Degradation

2. Uptake of bilirubin by the liver:

In hepatocytes, bilirubin binds to intracellular proteins, such as, ligandin.

3. Formation of bilirubin diglucuronide: two molecules of glucuronic acid are added to increase solubility (conjugation) by bilirubin glucuronyl-transferase.

Deficiency of this enzyme results in Crigler-Najjar I and II (more severe) and Gilbert syndrome (common).



2. Uptake of bilirubin by the liver:

- Bilirubin is red-orange in color and mostly hydrophobic molecule, so, bilirubin is insoluble in plasma, we can't excrete on that form. Therefore, it is transported through blood to the hepatocytes (liver) by binding noncovalently to albumin, Bilirubin dissociates from the carrier albumin molecule, enters a hepatocyte via facilitated diffusion.

3. Formation of bilirubin diglucuronide:

- bilirubin solubility is increased by the addition of two molecules of glucuronic acid in a process called conjugation. UDP is used to transfer glucuronic acid (big structure) forming bilirubin diglucuronide (or conjugated bilirubin).

- Conjugated bilirubin --> soluble
- UnConjugated bilirubin --> insoluble

Heme Degradation

4. Secretion of bilirubin into bile:

Conjugated bilirubin is **actively transported** into the bile canaliculi and then into the bile.

The rate-limiting step (energy-requiring step). The active transport is the rate limiting step.

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

Unconjugated bilirubin is normally not secreted.

Heme Degradation

5. Formation of urobilins in the intestine:

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

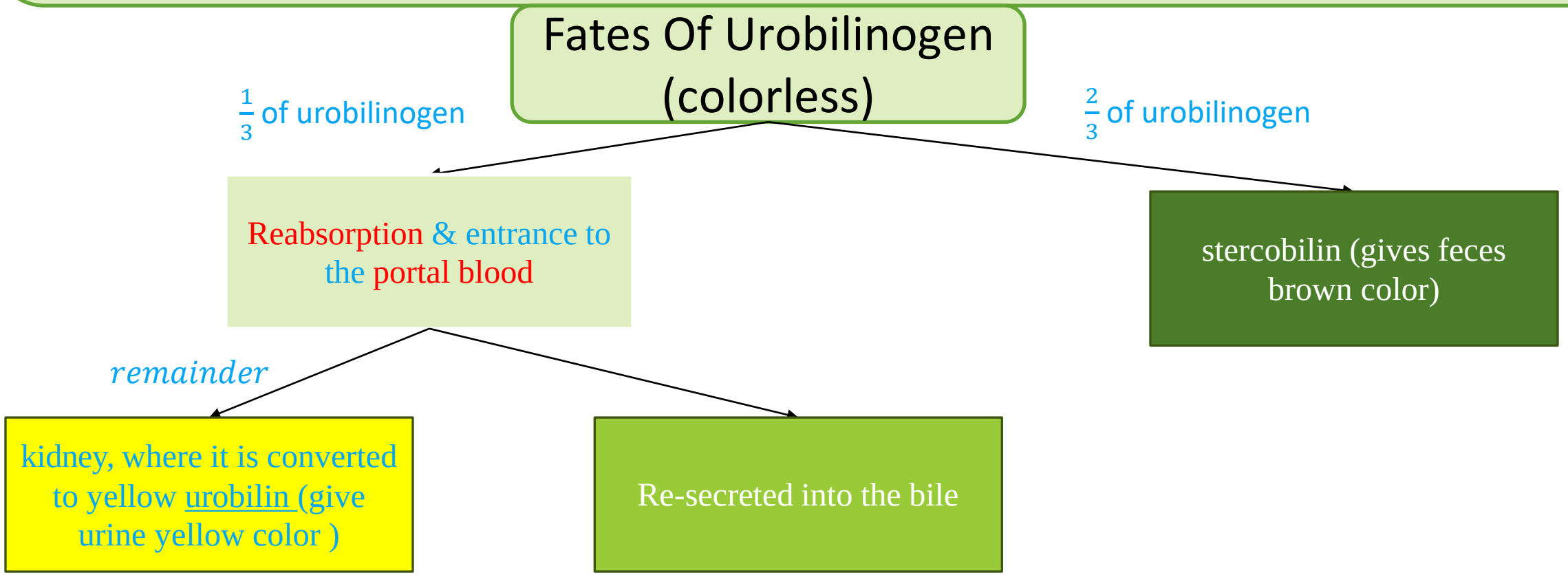
Urobilinogen fates:

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

2. Reabsorption from the gut and entrance to the portal blood.

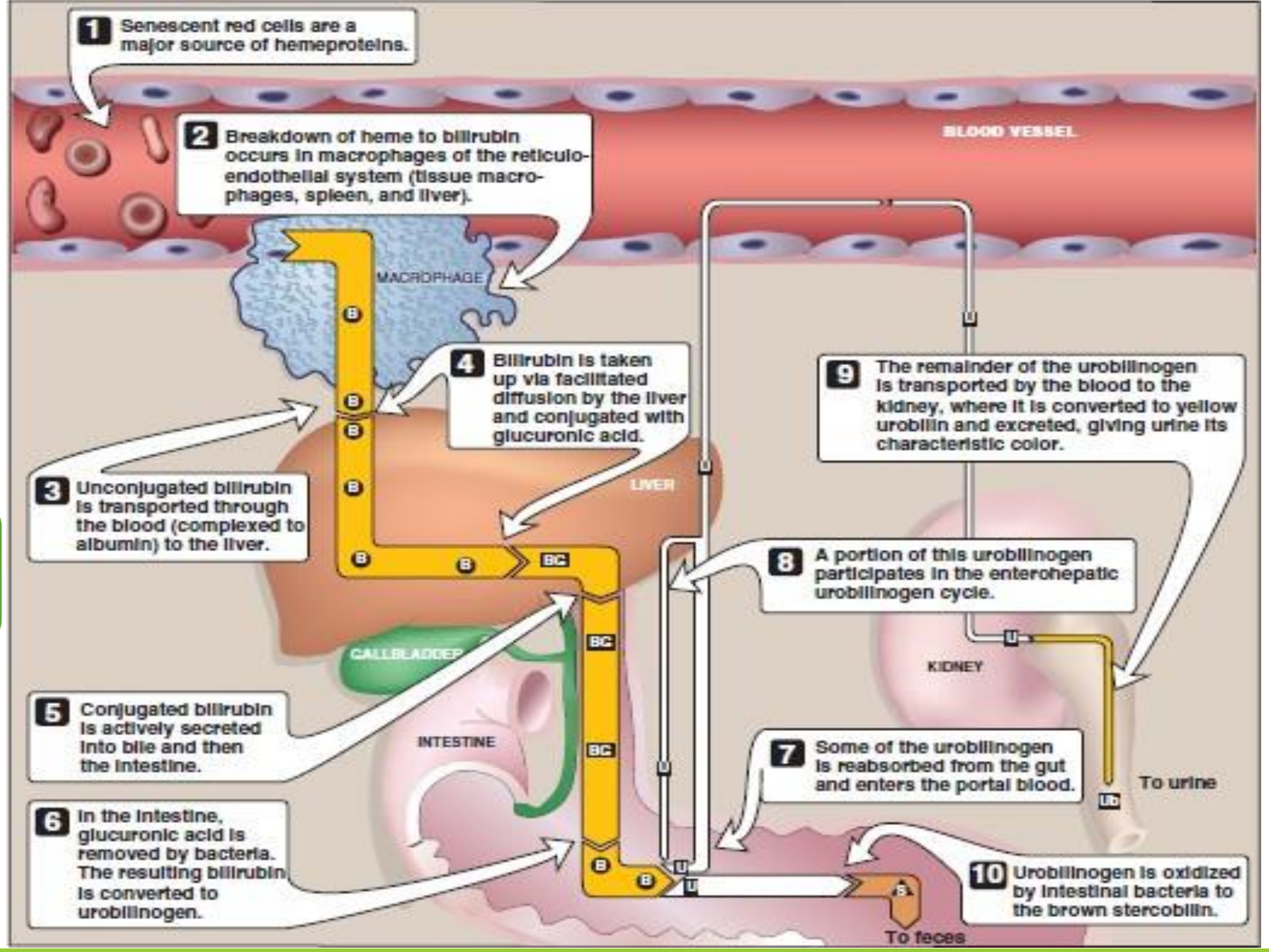
a. Some urobilinogen participates in the enterohepatic urobilinogen cycle where it is taken up by the liver, and then resecreted into the bile.
b. The remainder is transported by the blood to the kidney, where it is converted to yellow urobilin and excreted, giving urine its characteristic color.

- **The complement in this slide:** after the bilirubin is actively transported into the gallbladder, it gives its yellow color. Once it is secreted with bile + salts in small intestine, they work as emulsifier for the lipids. (as we took in LIPIDS)
- Then bilirubin diglucuronide (conjugated bilirubin) is reduced by bacteria (normal flora in gut) → urobilinogen (generator of urobilin)



Catabolism of heme

- **NOTE:** **Summary of Heme Degradation.**
- **Helpful for revision** ☝



B = bilirubin; BC = bilirubin diglucuronide; U = urobilinogen; Ub = urobilin; S = stercobilin.

اللهم انصر أهل غزة وثبت أقدامهم اللهم احرس أهل غزة بعينك التي لا تناماللهُم كُن لأهل غزة عونًا ونصيرًااللهم إنا لا نملك لفلسطين إلا الدعاء فيارب لا ترد لنا دعاء ولا تخيب لنا رجاء وأنت أرحم الراحمين