Bilirubin Metobolisms

- Porphyrin → 4 pyrrol rings → linkage of 4 methyne
- Porphyrin form complex
  - iron → heme
  - cobalt → cobalamine
  - magnesium → cholorophyl
  - Soret band.
- Heme proteins = hemoglobin
  - myoglobin
  - cytochromes
  - catalase (H_2O_2 metabolism)
  - tryptophan pyrrolase

CATABOLIC product of Porphyrin

BILIRUBIN

Sources of Bilirubin

%85 → erythrocytes destroyed

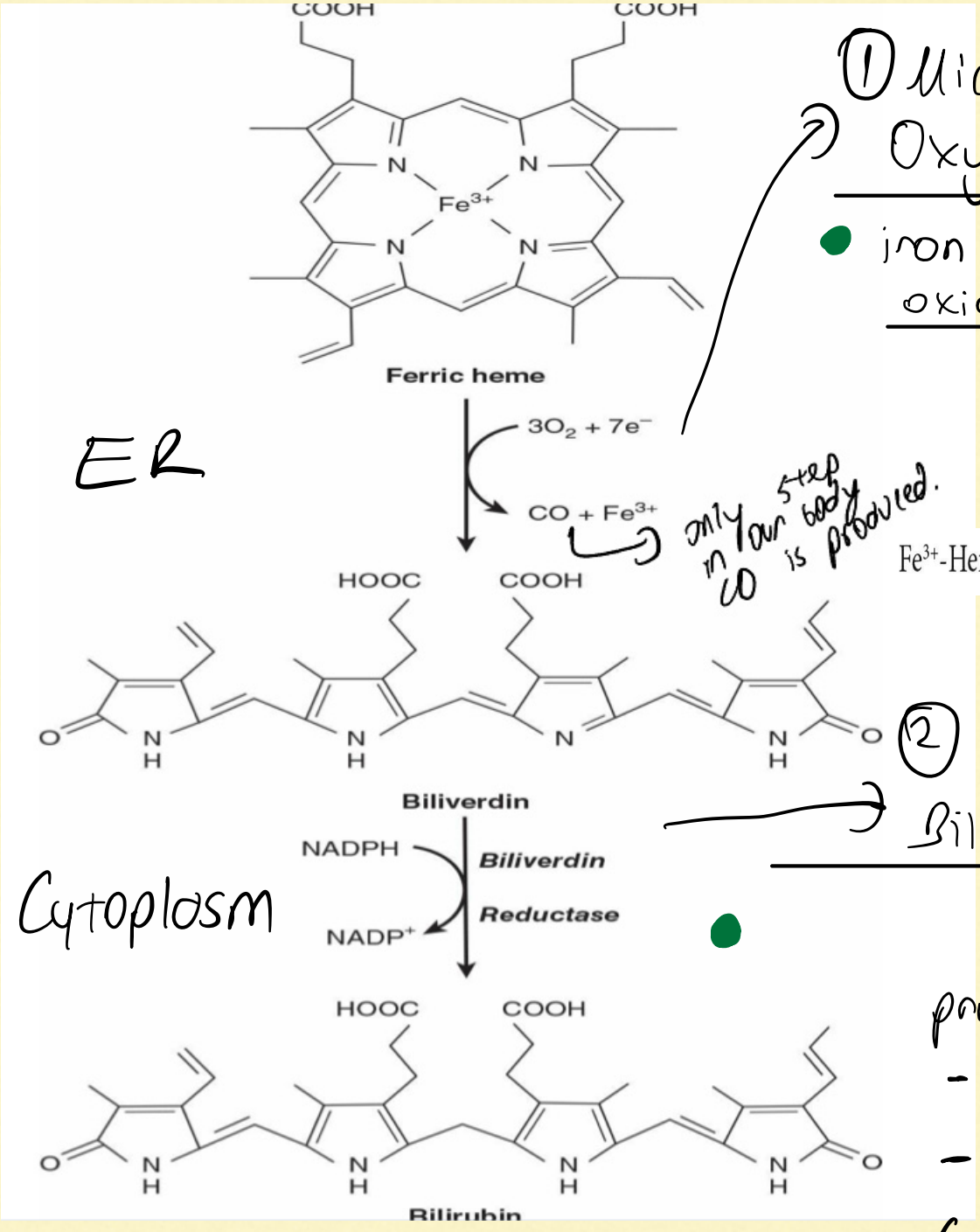
%15 → ineffective erythropoesis

degradation non-hem hem → myoglobin
catalase
peroxidase
cytochrom P5

Cytochrom p450

formation of Bilirubin

Reticuloendothelial system cells of liver
bone marrow
spleen.



ER

① Microsomal Heme Oxygenase

- iron of heme oxidized to → ferric form

Fe^{3+}-Heme + 3 O_2 + 7 e^- → biliverdin + CO + Fe^{3+}

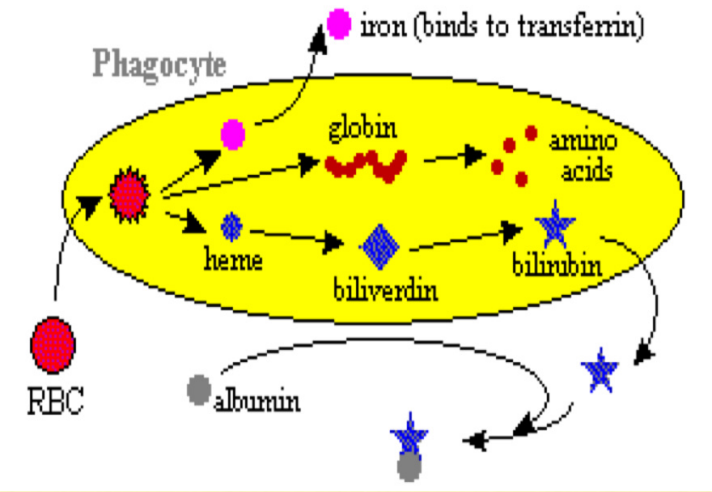
Cytoplasm

② Cytoplasmic Biliverdin Reductase

- provided by
  - NADPH
  - cytoplasmic enzyme (cytochrome p450 reductase)

What happens to products

1. Globin = find its way in aa pool
2. Iron = enter iron pool for reuse
3. CO = exhaled



BILIRUBIN FORMED → transfered → Why Where How

Transferred Why

Toxic characteristics

Transferred Where

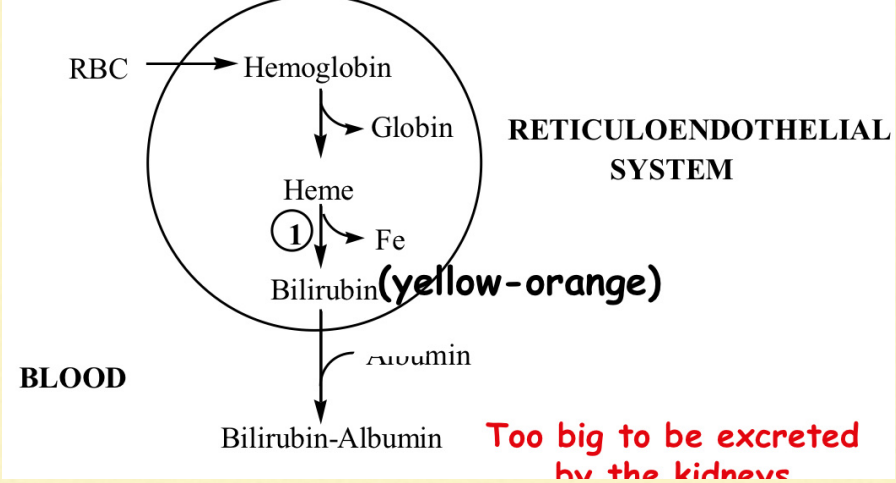
non polar molecule so

1. necessary enzymatic system increase polarity
2. anatomical structure to remove it bile canaliculus

in LIVER

Transferred How

Non-covalent binding to Albumin



Albumin → one high affinity
→ one low affinity sites

! a number of compounds such as drugs compete with bilirubin for high affinity binding site on albumin
↳ displace bilirubin from albumin → significant clinical effects

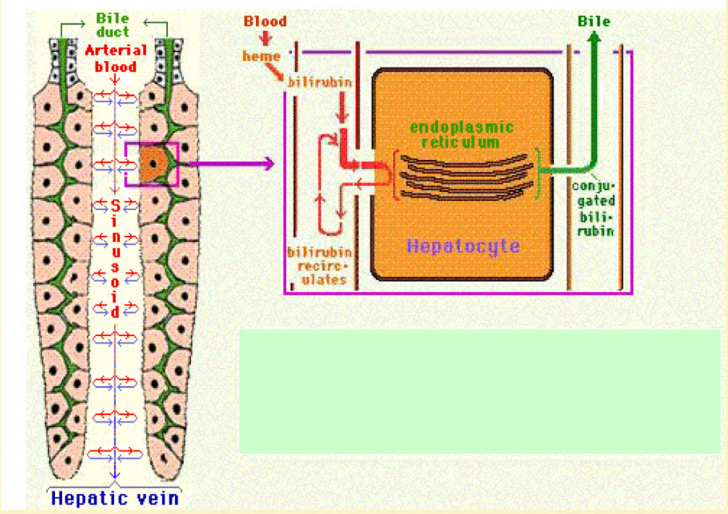
In the neonatal period if the the concentration of this bilirubin exeeds 20-25 mg/dL (which can be tightly bound by albumin) it becomes capable of penetrating the blood-brain barrier.
This can result in a hyperbilirubinemic toxic encephalopathy, or kernicterus, which can cause mental retardation.

LIVER takes up bilirubin.

II Entry = ① Bilirubin / detached from albumin / / taken up by sinusoidal surface of hepatocytes / by a carrier mediated saturable system /

! large capacity system = even in pathologic conditions not a rate limiting step

- organic anion binding protein used.

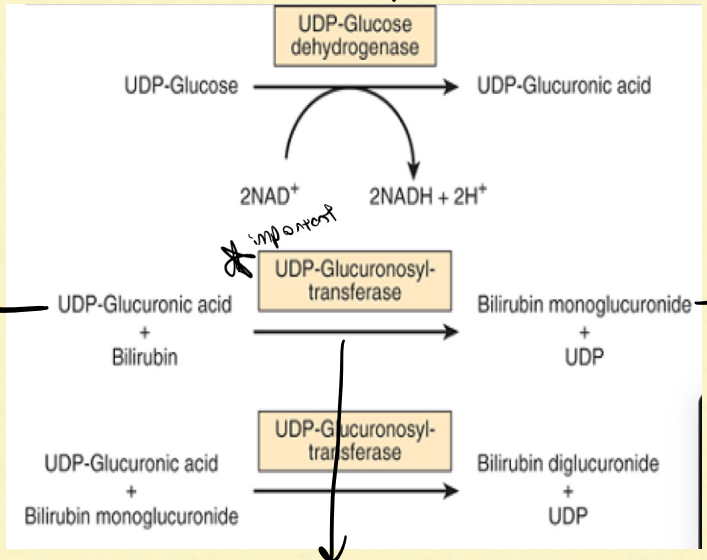


- net uptake of bilirubin dependent on removal of bilirubin via metabolic pathways

* in hepatocytes, cytosilic proteins keep them solubilized prior to conjugation.
→ Ligandin
→ Protein Y
also prevent efflux of bilirubin back to blood

2 Conjugation = bilirubin + glucuronic acid molecules

this is it ↖ ↳ polar form

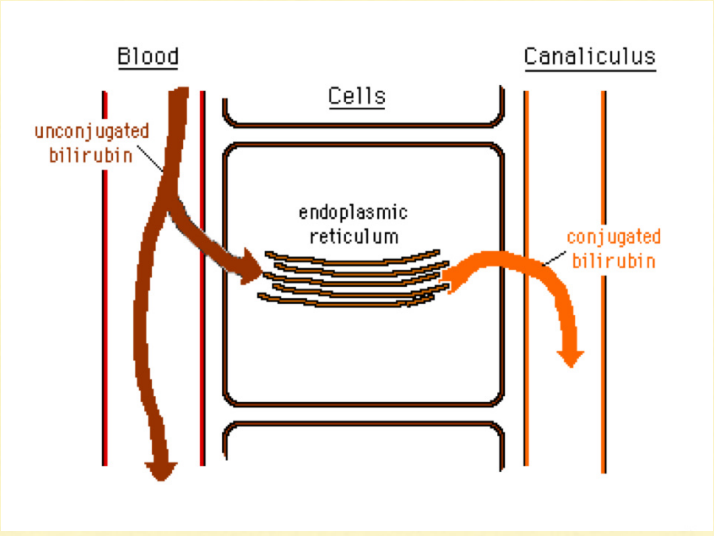


glucuronosyl donor ← UDP-Glucuronic acid + Bilirubin

Bilirubin monoglucuronide + UDP → (conjugated) bilirubin formed.

it means direct reacting

induced by drugs like phenobarbitol ← bilirubin UGT → located in ER



① %85 → glucuronidated
%10 → sulphated

② most of them diglucuronide

exit abnormally plasma in human plasma → monoglucuronides

3 Secreted into Bile

- active transport mechanism
- rate limiting

MRP2 → various tissue include brain → toxic effect of conjugated bilirubin

4 Conjugated Bilirubin is reduced urobilinogen by intestinal bacteria

Conjugated bilirubin —glucuronidases→ Unconjugated bilirubin —pigment reduced by fecal flora→ urobilinogen

in large intestine

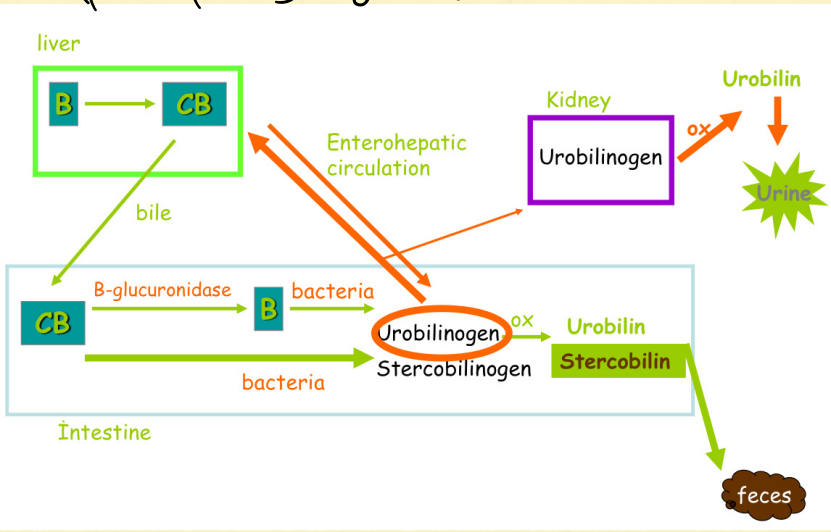
5 Fate of Urobilinogen

① small fraction of urobilinogen reabsorbed and reexcreted through liver to keep the cycle.

② small fraction be excreted in urine in the form of urobilin gives urine odour and colour.

↳ colourless urobilinogens —oxidized→ urobilins in fecal flora

* Darkening of feces on air due to this reaction



! Newborn → antibiotics destroy intestinal flora
decrease conversion of bilirubin to sterobin
Biliverdin ← Bilirubin
pale colored feces

Jaundice bilirubin diffuse into tissue

hyperbilirubinemia → increased production of bilirubin
→ failure of liver to conjugate or excrete bilirubin
→ obstruction of excretory ducts of liver

Delta bilirubin → conjugated bilirubin - Albumin complex
long lasting conjugated hyperbilirubi

- Why is it important do you think?
- it remains elevated during the recovery phase of obstructive jaundice after the remainder of the conjugated bilirubin has declined to normal levels

Unconjugated hyperbilirubinemias

① hemolytic anemia

liver large capacity handling bilirubin

↳ unconjugated hyperbili " slight in the event of extensive hemolysis

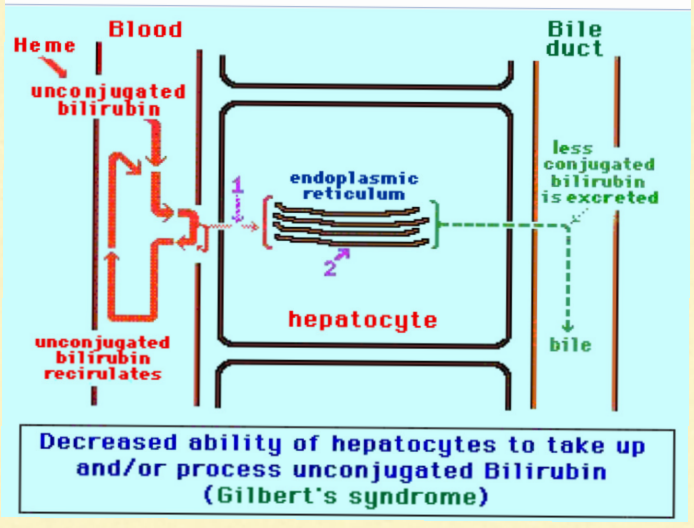
② Neonatal physiologic Jaundice

most common couse

Neonatal "Physiologic" Jaundice

- 1- accelerated hemolysis around the time of birth
- 2- immature hepatic system for the uptake (ligandin?),
- 3- conjugation,
  - A) reduced bilirubin-UGT activity
  - B) reduced synthesis of the substrate for that enzyme, UDP-glucuronic acid
- 4- decreased secretion of bilirubin.
- Since the bilirubin is unconjugated, it is capable of penetrating the blood-brain barrier when its concentration in plasma exceeds that which can be tightly bound by albumin (20-25 mg/dL) leading to hyperbilirubinemic toxic encephalopathy. 66

③ Gilbert Syndrome



④ Crigler Najjar syndrome

mutation gene coding bilirubin UGT

Type 1 = no activity

type 2 = some activity retained

⑤ Toxic hyperbilirubinemia

toxic, hepatic parenchymal cell damage

impairs conjugation

these are mediated by → phototherapy

exchange transfusion

phenobarbitol

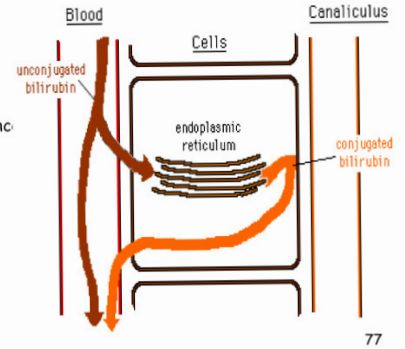
phototherapy → convert bilirubin to other derivatives excreted in bile

↳ bilirubin con. decreases

Conjugated hyperbilirubinemias

① Defective secretion of the bilirubin in to the bile

- Dubin-Johnson syndrome
  - MOABP mutation
  - MRP-2 (Multidrug resistanc associated protein)
- Rotor syndome
  - Rare
  - Genetic
  - harmless



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② Intrahepatic Cholestasis

↳ microobstruction of intrahepatic bile duct

- 60–70% bilirubin direct → cholestasis
- 30–40% Indirect bilirubin → decreased conjugation

① Extrahepatic obstruction

↳ blockage of hepatic or common bile ducts

— often gall stone or cancer of head of pancreas