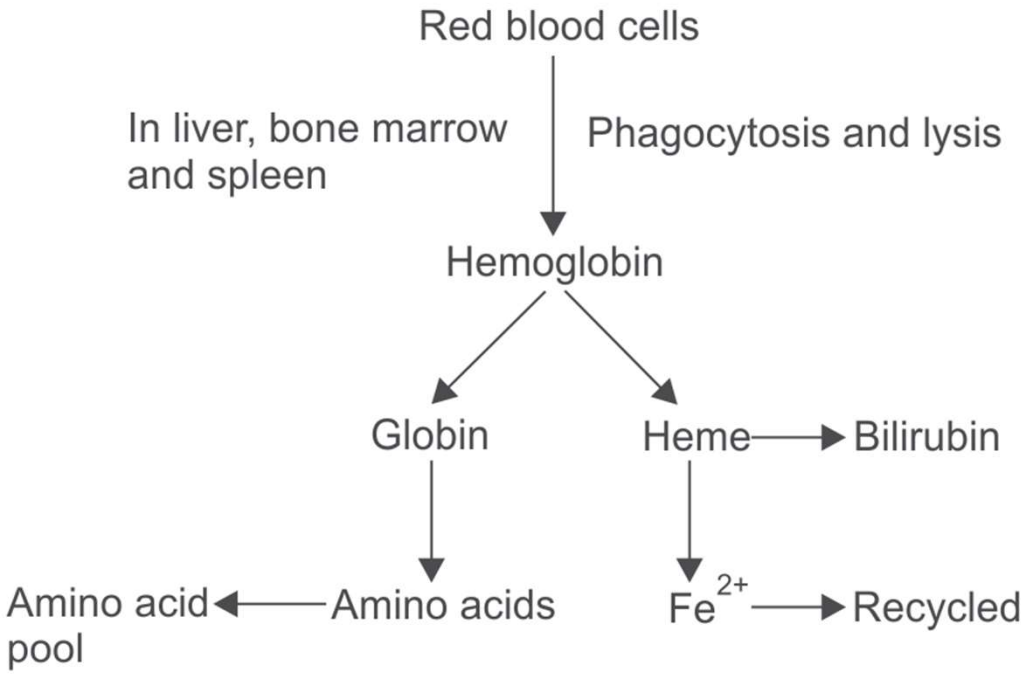
Hemoglobin Metabolism

bilirubin formed and excreted

Life span of mature red blood cells (RBCs) in bloodstream is around 60–120 days. In a 70 kg man, approximately 6 g/day of hemoglobin is liberated from breakdown of RBCs in the reticuloendothelial system. This hemoglobin is catabolized to form bilirubin. Bilirubin is further conjugated and excreted through bile.



Steps in Bilirubin Metabolism

i. Breakdown of heme into bilirubin in reticuloendothelial cells.

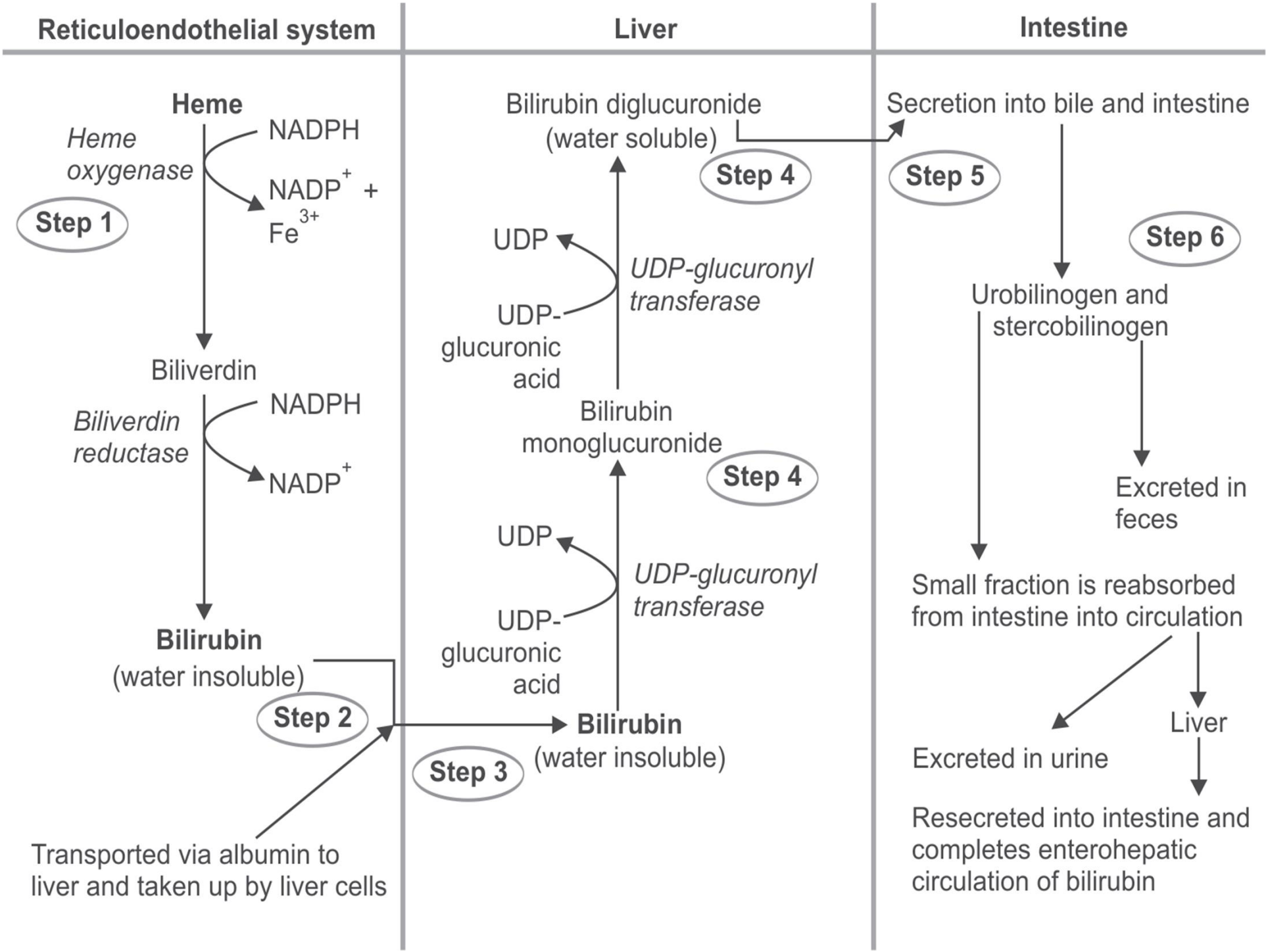
ii. Transport of bilirubin (unconjugated) bound to albumin to liver.

iii. Uptake of bilirubin into liver cells.

iv. Conjugation of bilirubin with glucuronide by uridine diphosphate (UDP)-glucuronyl transferase.

v. Secretion of bilirubin into bile → intestine.

vi. Conversion of bilirubin to urobilinogen followed by reabsorption and excretion


Reticuloendothelial system
Liver
Intestine
Heme
Heme oxygenase
NADPH
NADP+ + Fe3+
Step 1
Biliverdin
Biliverdin reductase
NADPH
NADP+
Bilirubin
(water insoluble)
Step 2
Transported via albumin to liver and taken up by liver cells
Step 3
Bilirubin
(water insoluble)
UDP-glucuronic acid
UDP
UDP-glucuronyl transferase
Bilirubin monoglucuronide
Step 4
UDP-glucuronic acid
UDP
UDP-glucuronyl transferase
Bilirubin diglucuronide
(water soluble)
Step 4
Secretion into bile and intestine
Step 5
Step 6
Urobilinogen and stercobilinogen
Excreted in feces
Small fraction is reabsorbed from intestine into circulation
Excreted in urine
Liver
Resecreted into intestine and completes enterohepatic circulation of bilirubin

Define jaundice. How can it be classified? Describe the biochemical investigations to differentiate different types of jaundice.

Definition: Jaundice is defined as yellowish discoloration of skin, nail beds and sclera. It is caused by deposition of bilirubin, secondary to increased bilirubin levels in the blood. When bilirubin concentration is more than 1 mg/dL, the condition is called hyperbilirubinemia. At a concentration of more than 2 mg/dL, bilirubin diffuses into tissues, which then becomes yellow, leading to jaundice or icterus.

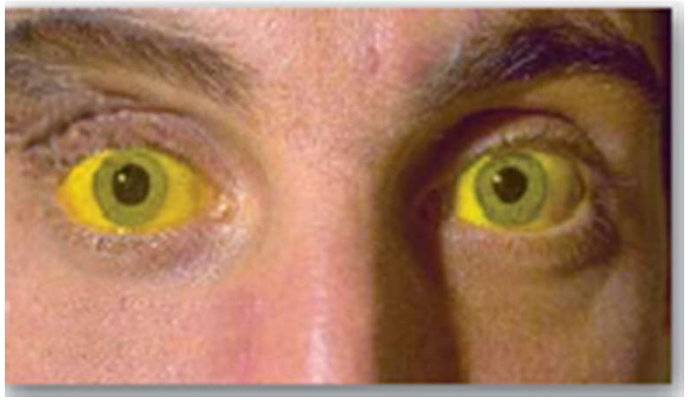
Classification

Jaundice is classified into three major types:

i. **Prehepatic (hemolytic):** Due to excessive hemolysis**,** bilirubin production exceeds the capacity of liver to conjugate it.

ii. **Hepatic:** Impaired uptake, conjugation or excretion of bilirubin.

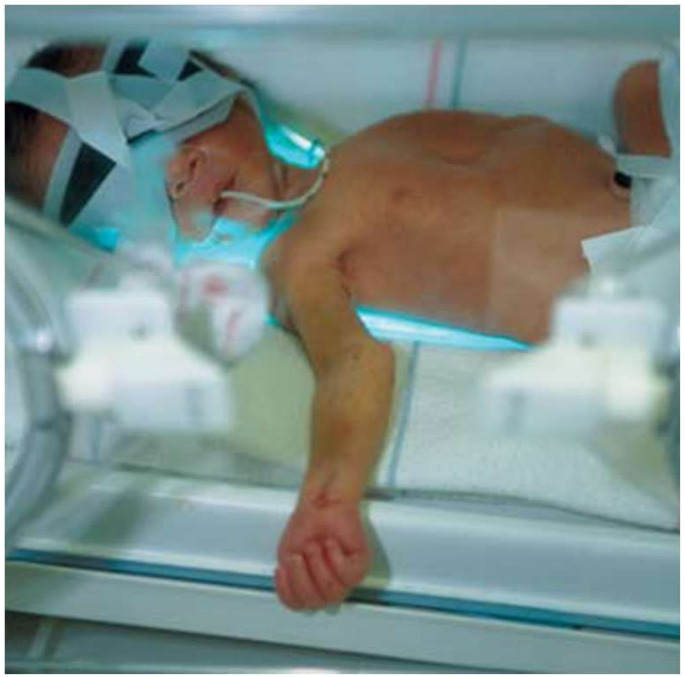
iii. **Posthepatic (obstructive):** Caused by an obstruction in the biliary tract

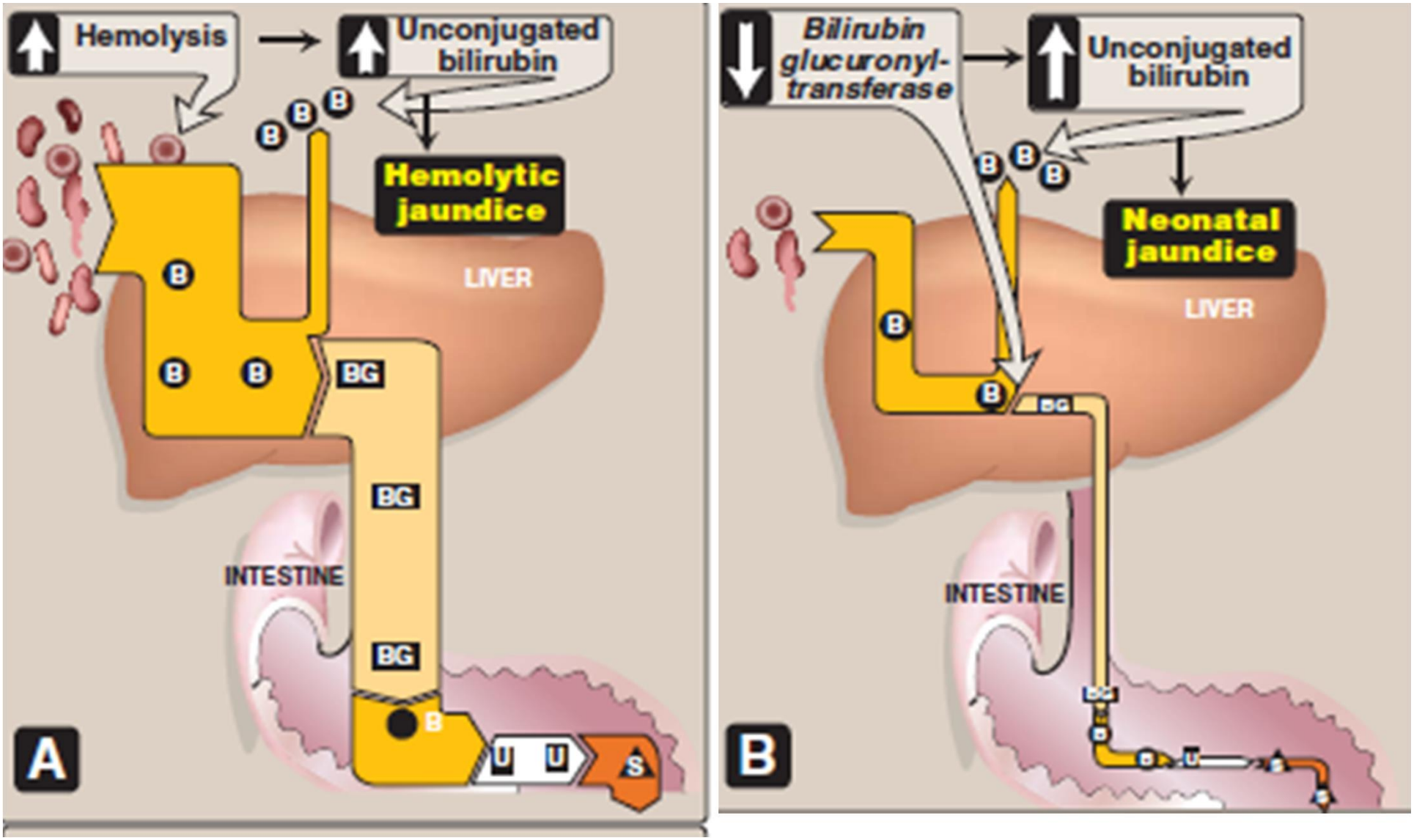


Jaundice in newborns

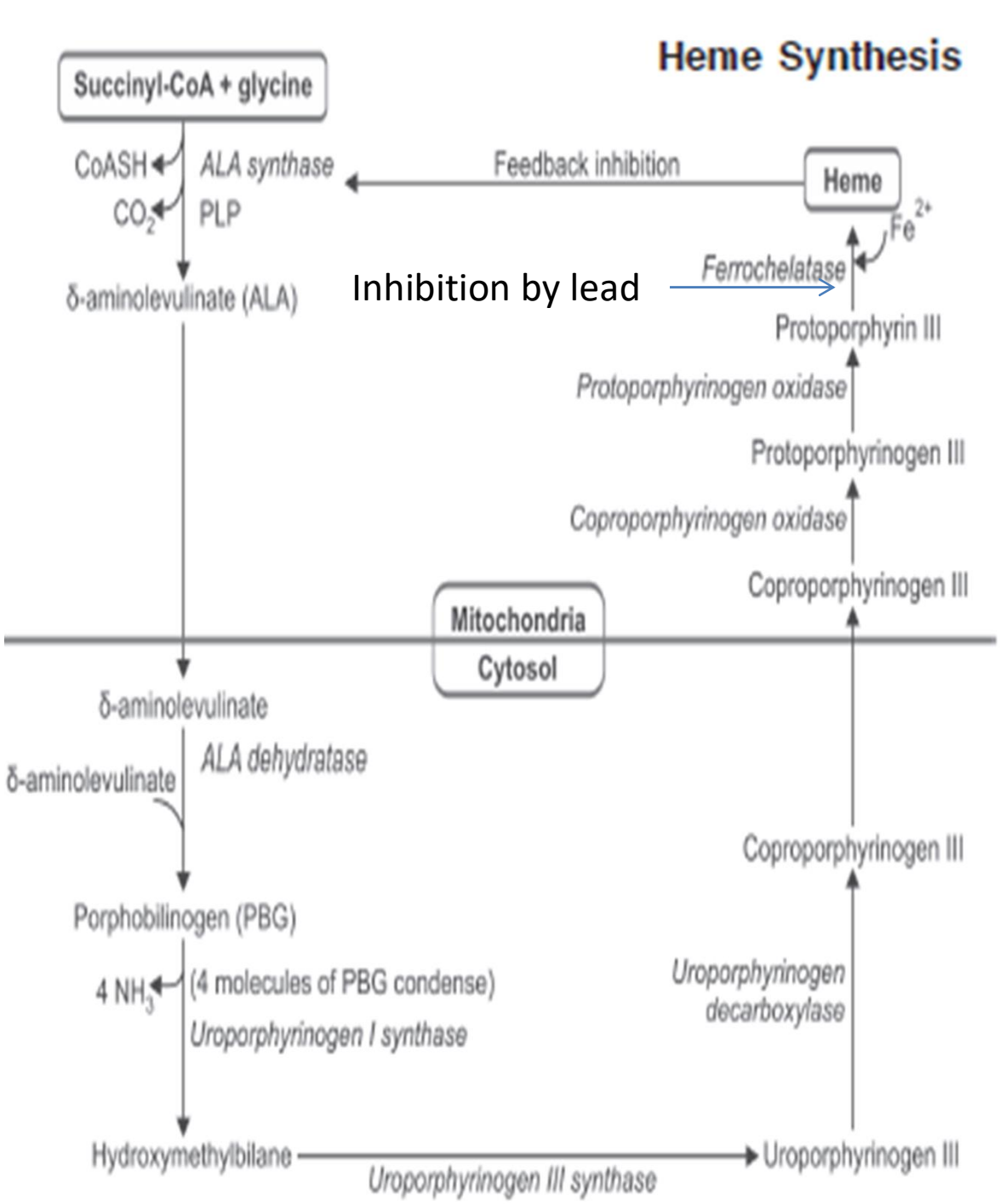
Newborn infants, particularly if premature, often accumulate bilirubin, because the activity of hepatic bilirubin glucuronyltransferase is low at birth—it reaches adult levels in about 4 weeks (Figures). Elevated bili rubin, in excess of the binding capacity of albumin, can diffuse into the basal ganglia and cause toxic encephalopathy (kernicterus). Thus, newborns with significantly elevated bilirubin levels are treated with blue fluorescent light (Figure), which converts bilirubin to more polar and, hence, water-soluble isomers. These photoisomers can be excreted into the bile without conjugation to glucuronic acid.

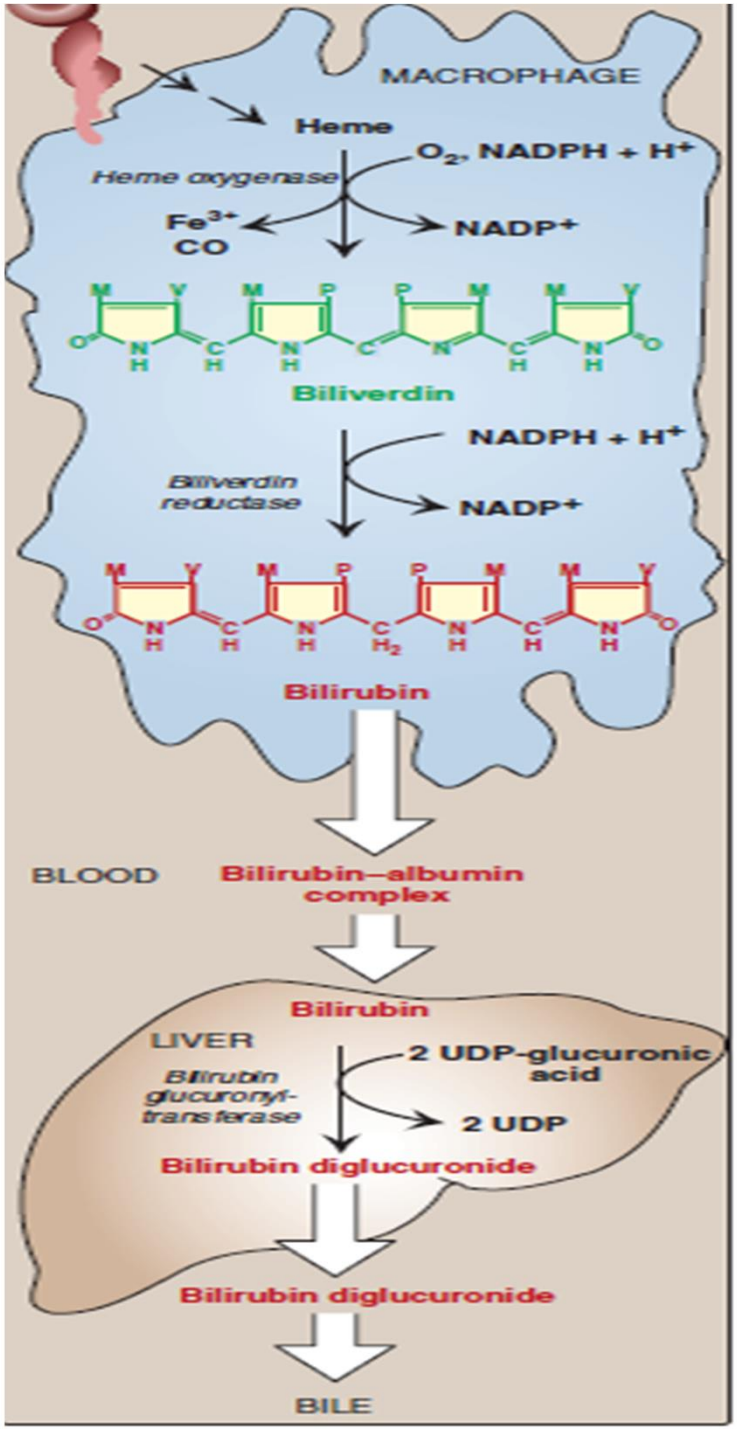
Phototherapy in neonatal jaundice





Alterations in the metabolism of heme.
A. Hemolytic jaundice. B. Neonatal jaundice.
BG = bilirubin glucuronide; B = bilirubin;
U = urobilinogen; S = stercobilin.


Heme Synthesis
Succinyl-CoA + glycine
CoASH
CO_2
ALA synthase
PLP
δ-aminolevulinate (ALA)
Feedback inhibition
Heme
Fe^{2+}
Ferrochelatase
Inhibition by lead
Protoporphyrin III
Protoporphyrinogen oxidase
Protoporphyrinogen III
Coproporphyrinogen oxidase
Coproporphyrinogen III
Mitochondria
Cytosol
δ-aminolevulinate
δ-aminolevulinate
ALA dehydratase
Porphobilinogen (PBG)
$4\ NH_3$
(4 molecules of PBG condense)
Uroporphyrinogen I synthase
Hydroxymethylbilane
Uroporphyrinogen III synthase
Uroporphyrinogen III
Uroporphyrinogen decarboxylase
Coproporphyrinogen III


MACROPHAGE
Heme
O_2, NADPH + H^+
Heme oxygenase
Fe^{3+}
CO
$NADP^+$
Biliverdin
NADPH + H^+
Biliverdin reductase
$NADP^+$
Bilirubin
BLOOD
Bilirubin–albumin complex
Bilirubin
LIVER
Bilirubin glucuronyl-transferase
2 UDP-glucuronic acid
2 UDP
Bilirubin diglucuronide
Bilirubin diglucuronide
BILE

Write short notes on neonatal jaundice.

Neonatal jaundice is seen in newborn infants, due to accelerated hemolysis and an immature hepatic system for bilirubin uptake, conjugation and secretion. It is commonly seen in premature infants and resolves within first 10 days of birth.

Causes

- Accelerated hemolysis
- Impaired glucuronyl transferase synthesis due to immaturity of liver
- Substrate UDP-glucuronic acid synthesis also may be inadequate.

Clinical Features

- Yellowish discoloration of skin and sclera due to elevated unconjugated bilirubin
- High levels (> 20 mg/dL) of unconjugated bilirubin are toxic to the newborn—due to its hydrophobicity, it can cross the blood-brain barrier and cause kernicterus, which causes mental retardation
- Mostly self-limiting; if serum bilirubin concentration exceeds 15 mg/dL for more than 15 days, it is usually pathological and needs to be further investigated.

Treatment

- If bilirubin levels are judged to be too high, then phototherapy is used to convert it to a water-soluble, non-toxic form (maleimide and geometric isomers) • Phenobarbital is useful in treatment—inducer of glucuronyl transferase
- If necessary, exchange blood transfusion—used to remove excess bilirubin.

Write briefly on thalassemia.

Definition: Thalassemia are a group of hereditary hemolytic diseases in which an imbalance occurs in the synthesis of globin chains. They are the most common single gene diseases in humans.

Classification

a. **α-thalassemia**—synthesis of α-chain of hemoglobin is decreased (Table 22.4).
b. **β-thalassemia**—synthesis of β-chain of hemoglobin is decreased (Table 22.5).