CATABOLISM OF HEME
The end products of heme catabolism are bile pigments (bilirubin & biliverdin).

Catabolism takes place in macrophages of reticuloendothelial system of spleen and liver.

6g of Hb is broken down per day, from which 250mg of bilirubin is formed.
Figure 21.8
Formation of bilirubin from heme.

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Figure 2. Catabolism of hemoglobin

- **BLOOD CELLS**
  - Hemoglobin
    - Globin
    - Heme
    - Oxygenase
    - CO
    - Biliverdin IXα
    - NADPH
    - Biliverdin reductase
    - NADP+
    - Bilirubin (water-insoluble)

- **LIVER**
  - Bilirubin diglucuronide (water-soluble)
  - 2 UDP-glucuronic acid

- **INTESTINE**
  - Bilirubin (water-insoluble)
  - Stercobilin excreted in feces
  - Urobilinogen formed by bacteria
  - Urobilin excreted in urine

- **KIDNEY**
  - Urobilinogen formed by bacteria
  - Urobilin excreted in urine
1. Senescent red cells are a major source of heme proteins.

2. Breakdown of heme to bilirubin occurs in macrophages of the reticuloendothelial system (tissue macrophages, spleen, and liver).

3. Unconjugated bilirubin is transported through the blood (complexed to albumin) to the liver.

4. Bilirubin is taken up by the liver and conjugated with glucuronic acid.

5. Bile is secreted from the liver into the intestine.

6. In the intestine, glucuronic acid is removed by bacteria. The resulting bilirubin is converted to urobilinogen.

7. Some of the urobilinogen is reabsorbed from the gut and enters the portal blood.

8. A portion of this urobilinogen participates in the enterohepatic urobilinogen cycle.

9. The remainder of the urobilinogen is transported by the blood to the kidney, where it is converted to urobilin and excreted, giving urine its characteristic color.

10. Urobilinogen is oxidized by intestinal bacteria to form the brown stercobilin.
HYPERBILIRUBINEMIAS
Jaundice (icterus)

hyperbilirubinemia
- causes yellow color of skin, nail beds and sclerae

- not a disease, but symptom of underlying disorders
Hemolysis

Production of bilirubin

Jaundice

Excretion of bilirubin

Liver damage

Bile duct obstruction
Types of Jaundice

**hemolytic jaundice**
- liver can handle 3000 mg bilirubin/day - normal is 300
- massive hemolysis causes more than can be processed
  - can’t be conjugated
  - increased bilirubin excreted into bile, urobilinogen is increased in blood, urine
  - unconjugated bilirubin in blood increases = jaundice

**obstructive jaundice**
- obstruction of the bile duct
  - tumor or bile stones
  - gastrointestinal pain - nausea
  - pale, clay-colored stools
  - can lead to liver damage and increased conjugated bilirubin
Types of Jaundice

Hepatocellular Jaundice
- liver damage (cirrhosis or hepatitis) cause increased bilirubin levels in blood due to decreased conjugation
- conjugated bilirubin not efficiently exported to bile so diffuses into blood
- increased urobilinogen in enterohepatic circulation
  - so urine is darker and stool is pale, clay-colored
- AST and ALT levels are elevated
- nausea and anorexia
Jaundice in Newborns

Premature babies often accumulate bilirubin due to late onset of expression of bilirubin glucuronyltransferase.
- Maximum expression (adult level) at ~ 4 weeks
- Excess bilirubin can cause toxic encephalopathy (kernicterus)
- Treated with blue fluorescent light
  - Converts bilirubin to more polar compound
  - Can be excreted in bile without conjugation
Figure 21.13
Phototherapy in neonatal jaundice.

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Figure 21.11
Alterations in the metabolism of heme. A. Hemolytic jaundice. B. Neonatal jaundice. [Note: The enterohepatic circulation of urobilinogen is omitted for simplicity.] BG = bilirubin glucuronide; B = bilirubin; U = urobilinogen; S = stercobilin.

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Determination of bilirubin concentration

van den Bergh reaction (aqueous)
- conjugated bilirubin reacts readily - direct reaction
- unconjugated, hydrophobic, reacts slowly
- both conjugated and unconjugated react same in methanol - gives total bilirubin value
- subtraction of direct from total gives indirect

in normal serum - only 4% is conjugated -

SGOT, SGPT levels elevated in hepatic jaundice.
ALP levels elevated in obstructive jaundice
γ-GT levels elevated in chronic alcoholics
CONGENITAL HYPERBILIRUBINEMIAS

1. CRIGLER-NAJJAR SYNDROME TYPE-I
   - DEFECT IN CONJUGATION
   - ENZYME DEFECT:-
     UDP-glucuronyltransferase
   - Jaundice appears within 24hr. Of life
   - Unconjugated bilirubin increases to more than 20mg/dl.
   - Children die first two years of life.
2. **CRIGLER-NAJJAR SYNDROME TYPE-II**
   - Less severe than type-I
   - Defect in bilirubin conjugation
   - Bilirubin levels will be below 20mg/dl

3. **GILBERT’S DISEASE**
   - It is inherited as an autosomal dominant trait.
   - Defect is in the uptake of bilirubin, impairment in conjugation, decreased hepatic clearance of bilirubin
   - Bilirubin level around 3mg/dl
   - It is asymptomatic condition.
4. DUBIN JOHNSON’S SYNDROME

- It is an autosomal recessive trait
- Defect in excretion of conjugated bilirubin & increased conjugated bilirubin in blood.
- Bilirubin deposited in liver & appears black (black liver jaundice)

5. Rotor syndrome

- Bilirubin excretion is defective, but no deposition in liver.
ACQUIRED HYPERBILIRUBINEMIAS

- NEONATAL-PHYSIOLOGICAL JAUNDICE:
  - It is caused by increased hemolysis.
  - UDP-glucuronyl transferase activity is low.
  - Bilirubin level less than 5mg/dl.
  - It disappears by 2\textsuperscript{nd} week of life.
Table 2- Genetic Disorders of Bilirubin Metabolism

<table>
<thead>
<tr>
<th>Condition</th>
<th>Defect</th>
<th>Bilirubin</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crigler-Najjar syndrome</td>
<td>severely defective UDP-glucuronyltransferase</td>
<td>Unconjugated bilirubin ↑↑↑</td>
<td>Profound jaundice</td>
</tr>
<tr>
<td>Gilberts syndrome</td>
<td>reduced activity of UDP-glucuronyltransferase</td>
<td>Unconjugated bilirubin ↑</td>
<td>Very mild jaundice during illnesses</td>
</tr>
<tr>
<td>Dubin-Johnson syndrome</td>
<td>abnormal transport of conjugated bilirubin into the biliary system</td>
<td>Conjugated bilirubin ↑↑</td>
<td>Moderate jaundice</td>
</tr>
</tbody>
</table>
Porphyria

Tammy Evans

The Woman Who has the "Vampire Disease"
A True Story