Bilirubin Metabolism

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Objectives:

1. To outline the basic metabolic pathway of bilirubin breakdown and conjugation

2. To state the basic metabolic pathways of urobilinogens formation and excretion

3. To state the basic metabolic pathway for Elimination of Bilirubin

4. To define inherited hyperbilirubinemia
An understanding of the mechanisms involved in the production of jaundice requires knowledge of bilirubin metabolism.
Bilirubin is primarily a breakdown product of haemoglobin.
The production of bilirubin from haem occurs mainly in the spleen (macrophages) and liver (Kupfer cells), but also all over the body by macrophages, and in renal tubular cells. The cells that perform this job are known collectively as the reticuloendothelial system.
1. Bilirubin-forming molecules (i.e. haem) are taken up by reticuloendothelial cells.

2. Inside these cells, **Haem oxygenase enzymes** break down the haem, removing iron (which is **recycled**) and carbon monoxide, leaving **biliverdin**.
The detection of carbon monoxide in breath can be used to determine how much haem is being turned into biliverdin.

Biliverdin is very water soluble, whilst bilirubin is not.
3. Biliverdin is then converted to bilirubin, whilst still in the reticuloendothelial cell. This is done by the enzyme **biliverdin reductase**.

6. **Bilirubin is not just a waste product. It takes up free radicals, and thus is an antioxidant. This is perhaps the benefit of not directly secreting biliverdin, but converting it to bilirubin first.**
4. After bilirubin is released from reticuloendothelial cells, it travels in the blood, bound to albumin. This ensures no bilirubin is excreted in the urine. At very high concentrations, bilirubin can slowly diffuse into the peripheral tissues where it is toxic.
Normal bilirubin level is:

- Conjugated: 0.0-0.4 mg/dl
- Unconjugated: 0.2-0.8 mg/dl
- Total: 0.2-1 mg/dl

It is usually detectable when bilirubin concentrations reach 2mg/dl
5. Bilirubin is then removed from circulation in the **sinusoids** by hepatocytes. This is a passive process, which occurs down a concentration gradient. The fact that hepatocytes are in direct contact with the sinusoidal fluid helps this process.
6. As soon as bilirubin enters the hepatocyte, it will become bound to glucuronyl transferase which conjugates the bilirubin ready for excretion. Bilirubin is joined with glucuronic acid in the conjugation process. Very small amounts of bilirubin will somehow evade this process and end up in bile as unconjugated bilirubin.
7. It requires energy to secrete conjugated bilirubin into the canniculi.

The process of conjugation makes the bilirubin water soluble, and thus easier to excrete.
Bilirubin that is deconjugated by bacteria in the gut will be **reabsorbed in the colon**. This process is more likely in the presence of increased bile-acids.

Bile acid malabsorption occurs in cases of **intestinal disease and resection**.

In these patients, as a compensatory mechanism, the body excretes **higher concentrations of bile salts**, and this increases the risk of **gallstones**.
More bilirubin is also re-absorbed during fasting.

Some of the urobilogen will be absorbed and enter the circulation, where they will be removed mainly by the liver, but also by the kidney.
Much of the bilirubin in the colon will also be turned into *stercobilogens* and *urobilogens*. Generally, urobilogens is colourless, and stercobilogens give faeces its colour.

In liver disease and excessive haemolysis, the liver may not be able to remove all excess urobilogens, and so more is removed by the kidney.

Note that bilirubin will oxidise back to biliverdin after excretion – hence the green colour of bile.
BILIRUBIN METABOLISM

Heme

Heme oxygenase

Biliverdin

Biliverdin reductase

Unconjugated bilirubin

UDP GT

Conjugated bilirubin

Intestinal bacteria

Urobilinogen

Stercobilin

Liver

Kidney

Urineary
Urobilinogen
Elimination of haem is accomplished in a series of steps catalyzed by different enzymes:

1. Haem (e.g., from Hb, myoglobin and cytochromes)
2. Iron, Carbon Dioxide → Haem Oxygenase → Biliverdin
3. Biliverdin → Biliverdin Reductase → Bilirubin
4. Bilirubin → Glucoronyl Transferase → Conjugated Bilirubin
The inherited hyperbilirubinemia

Unconjugated hyperbilirubinemia

- Gilbert's Disease

Conjugated hyperbilirubinemia

- Crigler-Najjar Syndrome
**Crigler-Najjar Syndrome:**
UDP-glucuronyltransferase activity is absent in the liver cell

**Type I**
- serum bilirubin levels exceed 20 mg/100 ml and
- fatal in the first 15 months of life

**Type II**
- less severe and bilirubin monoglucuronide is present in the bile.
- The enzyme defect seems to involve only the addition of the second glucuronate.
- shows improvement with phenobarbital
Gilbert's Disease

This is the name given to a group of diseases where there is excessive hemolysis and unconjugated hyperbilirubinemia.

There is some lowering of UDP-glucuronyl transferase activity. But the main defect is in the uptake of bilirubin by the liver cell.
Conjugated hyperbilirubinemia:

- Chronic Idiopathic Jaundice (Dubin-Johnson Syndrome): The urine contains bile pigments. The hyperbilirubinemia may occur in childhood or in adult life and is due to a defect in the liver cell in the secretion of conjugated bilirubin into bile. The excretion of conjugated hormones (like estrogens) and dyes (like sulfobromopthalein) is also impaired.

- Dyes which do not require conjugation before excretion (e.g. Rose Bengal) are excreted without any difficulty.
Conclusions:

1. Bilirubin is primarily a breakdown product of haemoglobin
2. Much of the bilirubin in the colon will also be turned into stercobilogens and urobilogens
3. Conjugated bilirubin is secreted into the bile, which are ultimately eliminated either in feces or, after reabsorption, in urine. The major metabolite of bilirubin in feces is sterobilin, which gives feces their characteristic brown color.
4. Present in the text