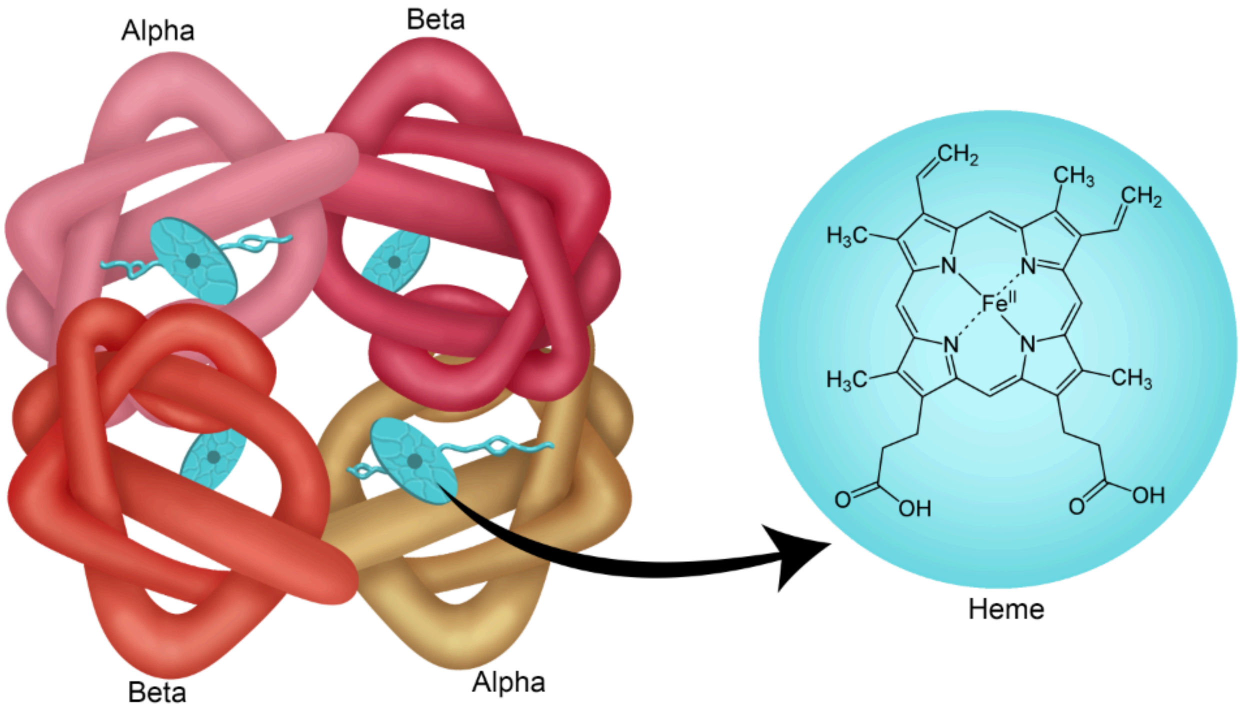
3.2.1

Hemoglobin and the Breakdown of Hemoglobin



Adult hemoglobin with 2 alpha chains and 2 beta chains. The molecular structure of heme is also shown. *Image by Becky T. BYU-I S20*

Each red blood cell contains about 270 million hemoglobin molecules. Each hemoglobin molecule has four globin chains. There are different possibilities in the types of globin chains that might be expressed depending on age. Adult hemoglobin has a pair of alpha chains and a pair of beta chains. Fetal hemoglobin has a pair of alpha chains and a pair of gamma chains. We will reference alpha, beta and gamma chains in this reading. Regardless of the specific type of globin chain, each contains a single heme molecule with iron where oxygen binds.

Please watch the video [Hemoglobin Breakdown/Metabolism]

When an old or damaged red blood cell is going to be destroyed by macrophages, lots of hemoglobin needs to be recycled. The breakdown of red blood cells mostly occurs in the spleen, but it also occurs with bruises or other bleeds. The breakdown of hemoglobin is as follows. Hemoglobin is initially broken down inside macrophages and the heme groups are separated from the globin chains. The globin chains are subsequently catabolized into amino acid residues which can be recycled to make other new proteins. Next, ferrous iron (Fe^{2+}) is removed from the heme ring and leaves the macrophage by way of the transporter **ferroportin 1**. It is then oxidized into ferric iron (Fe^{3+}) by **hephaestin** on the macrophage cell surface and enters the blood. Ferric iron binds to the protein **transferrin** in the blood and most of it is transported to the bone marrow to be used again in erythropoiesis to form new red blood cells. With iron gone, the remaining heme ring is quickly oxidized to become **biliverdin**, which is bluish-green in color. Biliverdin then goes through another biochemical transformation to become unconjugated **bilirubin**, which is yellow in color (these color changes can be seen as a bruise heals). Bilirubin folds over in a way that its polar ends form hydrogen bonds. It is then released into the blood by the macrophage to be delivered to the liver. Bilirubin is quite lipid soluble and does not dissolve well in the aqueous plasma of the blood. It is therefore carried by albumin, which acts as a bilirubin transporter.

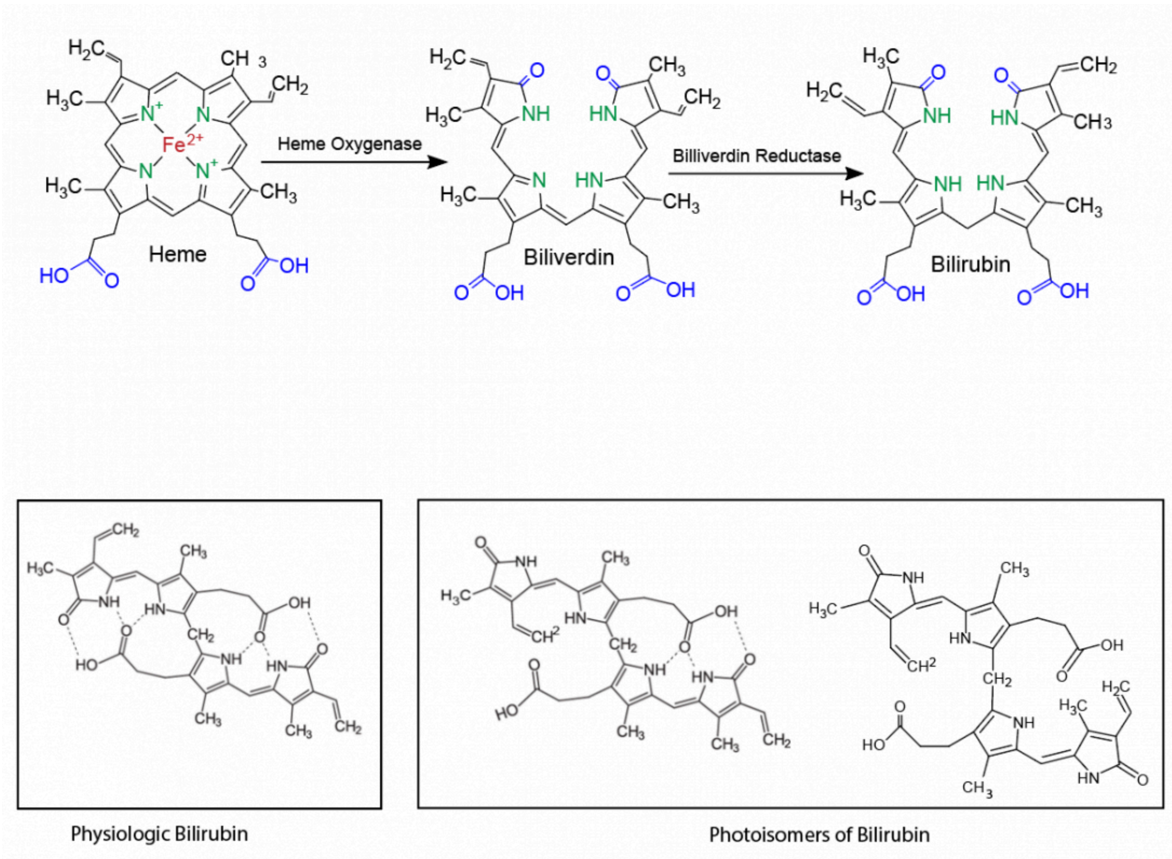
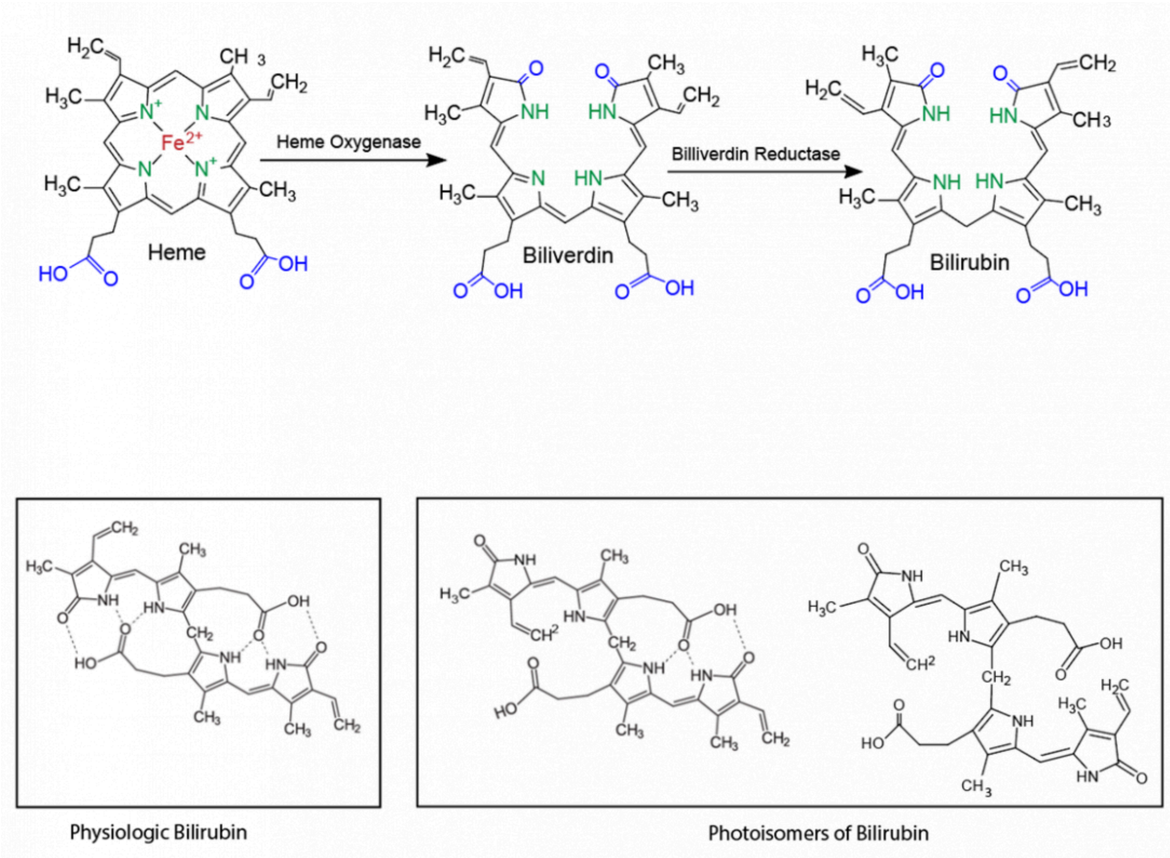


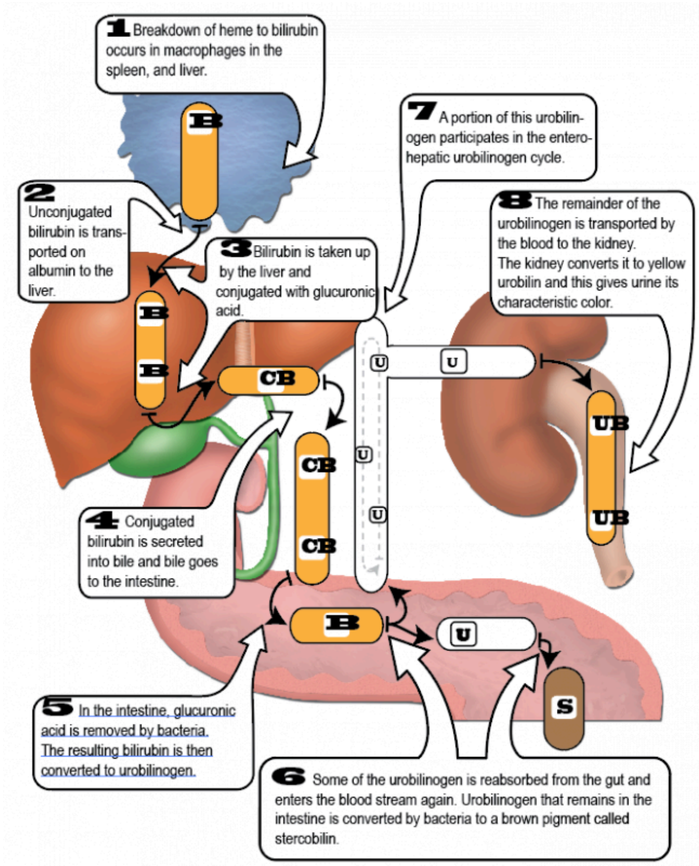
Illustration of heme breakdown to biliverdin and then bilirubin *Image by Becky Torgerson BYU-I Fall 2019*

Blue lights are often used in neonatal care to help reduce bilirubin concentrations in the blood to treat jaundice. Jaundice manifests as a yellow tint in the skin and whites of the eyes because of excess levels of bilirubin. Jaundice is a concern because high bilirubin levels can damage nerves and the brain. Infants are more at risk for this condition because their livers are immature and they have increased bilirubin levels and increased turnover of red blood cells compared to adults. Blue light is used because light in the blue wavelength range can stimulate double bonds in the bilirubin molecule to break and then reform so that polar groups are turned outward from the center part of the molecule. This gives the polar portions of the bilirubin molecule a chance to interact with water molecules in the plasma. As a result, the bilirubin becomes more water soluble. This increased water solubility allows bilirubin to be transported more efficiently through the blood and be passed out of the body more quickly by the liver and the kidney. Bilirubin that does not assume the more water soluble photoisomer form due to light exposure (which can occur from the sun as well) is called **physiologic bilirubin** or **unconjugated bilirubin (UCB)**. It continues its journey to the liver bound to albumin and is there converted to a more water-soluble form.



Comparison between structure of physiologic bilirubin and photo isomers of bilirubin *Image by Becky Torgerson BYU-I Fall 2019*

Unconjugated bilirubin in the blood is believed to enter the hepatocytes through passive diffusion, but it may also do so through currently unknown transporters. Once inside the hepatocyte, the unconjugated bilirubin has two glucuronic acid moieties added to it. This is done by the enzyme UDP glucuronosyltransferase and the bilirubin is now called by several different names including **conjugated bilirubin, bilirubin glucuronide (BC)** and direct bilirubin. This conjugated form of bilirubin is much more water soluble. Most of the newly formed bilirubin glucuronide is then secreted from the hepatocytes into the bile and exits the liver by way of the hepatic duct. Although most of the bilirubin glucuronide ends up in the bile immediately, some of it gets secreted from the upstream hepatocytes back into the blood. It travels downstream in the liver and is then taken back up into downstream hepatocytes. The bilirubin glucuronide then also exits the hepatocyte to enter the bile and go through the hepatic duct. It is believed that this reuptake and secretion loop prevents saturation of upstream hepatocytes with bilirubin. From the gallbladder and liver, bilirubin glucuronide is dumped into the small intestine. It then travels to the colon where it is deconjugated by colonic bacteria into **urobilinogen**. Some of the urobilinogen is further converted into **stercobilin** (which is darker brown) by bacteria and is responsible for the brown color of feces. The rest of the urobilinogen is reabsorbed by enterocytes back into the blood and returned to the liver to be secreted in bile again (called enterohepatic circulation) or oxidized into **urobilin** and excreted by the kidneys. Urobilin gives urine its yellow color.



Heme Breakdown *Image by Nate Shoemaker BYU-Idaho Spring 2016*