BILIRUBIN METABOLISM

Bilirubin is produced by the catabolism of hemoglobin. (Fig. 1). Hemoglobin is degraded by heme oxygenase, resulting in the release of iron and the formation of carbon monoxide and biliverdin. Biliverdin is then converted to bilirubin by biliverdin reductase. Unconjugated bilirubin (also known as indirect bilirubin) is initially only soluble in lipids, not water, and is subsequently bound by albumin in the blood stream. Any substance competing for binding sites, such as organic acids or drugs, can increase the levels of free bilirubin. In this unconjugated state, bilirubin is difficult to excrete (because it is lipid soluble), and it can easily pass into the central nervous system where it is neurotoxic and can produce kernicterus ***(Shapiro, 2003).***

On reaching the liver, albumin-bound bilirubin passes to the space of Disse, between the endothelium and hepatocytes ***(Gourley, 2004).*** Bilirubin crosses the hepatocyte membrane through a specific carrier protein, and binds to glutathione-S-transferase B (ligandin). On reaching the microsomes, bilirubin is covalently conjugated to glucuronic acid by bilirubin uridine diphosphate glucuronosyl transferase (UDPGT) forming mono and diglucuronides (β and γ bilirubin), collectively known as conjugated bilirubin. Different mutations in (UDPGT) result in the inherited unconjugated hyperbilirubinaemias, Gilbert's syndrome and the rarer Crigler-Najjar type I and II syndromes ***(Kadakol et al., 2000).***

The water-soluble bilirubin glucuronides are excreted through bile canaliculi and the bile duct system into the duodenum. The process requires an export pump transporter and carrier proteins. The export transporter is defective in Dubin Johnson syndrome ***(Gourley, 2004).*** Bilirubin may be reabsorbed from the gut, and this enterohepatic circulation is increased in breast-fed infants ***(Gartner, 2001).***

Conjugated bilirubin (direct bilirubin) is water soluble, non-toxic, and unable to cross the blood-brain barrier. It also binds to albumin and can compete with unconjugated bilirubin for binding sites. It is excretable into the biliary or intestinal tract. Once conjugated bilirubin enters the intestinal tract, it is either excreted in stool or deconjugated by bacteria, where it may reenter the circulation (enterohepatic circulation). Total bilirubin is bound to protein (mainly albumin) in the blood and is a combination of unconjugated and conjugated bilirubin ***(Gowen, 2006).***

During intrauterine life, the developing infant requires a high haemoglobin concentration to extract oxygen effectively from maternal blood and deliver it to fetal tissues. Immediately after birth, with a plentiful supply of oxygen from its own lungs, this requirement drops dramatically. The neonate’s reduced red cell lifespan (70-90 days) compared with adults means that all newborns have a considerable excess load of haemoglobin to convert into bilirubin and excrete in the immediate postnatal period ***(Soldin et al., 2003).***

Following delivery, a significant proportion of neonates may have additional haemoglobin to dispose of as a result of bruising or other losses. Haem oxygenase-1 is induced by inflammatory mediators, leading to a further increase in haem breakdown in premature infants with co-morbidities, such as respiratory distress syndrome and bronchopulmonary dysplasia. With such an exceptional load on an immature system, it is therefore not surprising that approximately half of all infants become jaundiced in the first week of life ***(May et al., 2007).***

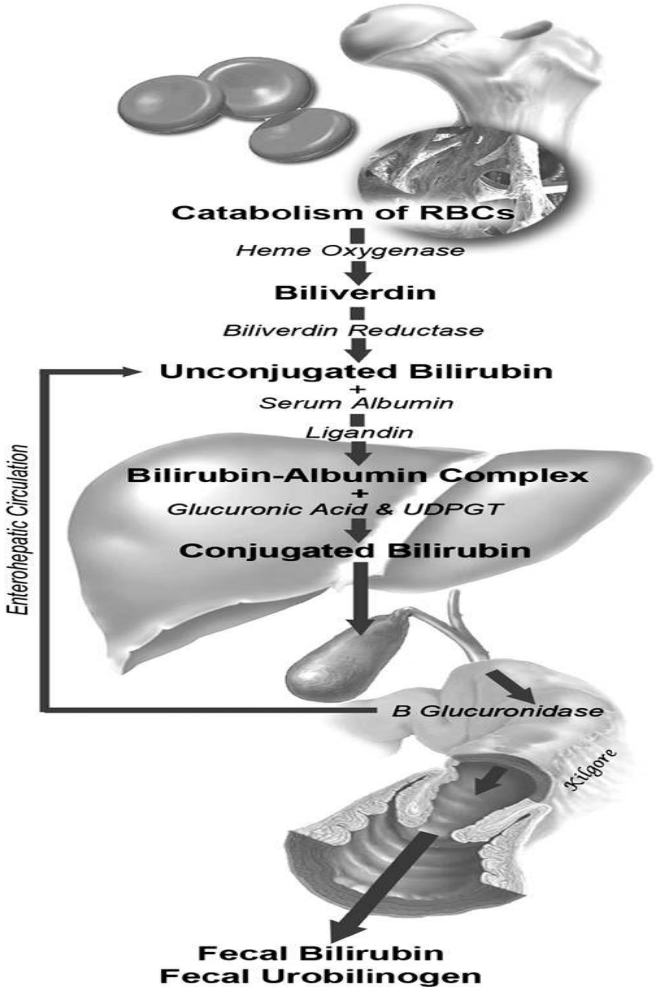

Fig. 1. Bilirubin Metabolism