# BILIRUBIN METABOLISM : MOLECULAR AND METABOLIC CONSIDERATIONS

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Improvements in molecular biology has resulted in significant improvements in our understanding of bilirubin metabolism and basis of the inherited disorders thereof. Bilirubin is a metabolic degradation product of heme moiety of senescent red blood cells. It is carried in the blood in an unconjugated state, bound to albumin in a reversible, non-covalent bond, to the liver where it is conjugated with glucoronic acid primarily to make it water soluble and excreted in the bile canaliculi. Excretion is the rate limiting step in bilirubin metabolism, hence conjugated hyperbilirubinemia occurs commonly in liver diseases. A number of conditions, however, are characterized by unconjugated hyperbilirubinemia caused by defective enzymatic conjugation of bilirubin. These are due to mutations in the uridine glucoronyl transferase 1 gene. Commonest of these is Gilberts' syndrome, which is due to insertion of an additional TA sequence in the promoter region of UGTI A1 gene, reducing expression of the relevant gene. Graded increase in severity of hyperbilirubinemia is produced by mutations involving the exons in crigler najjar syndromes 2 and 1. Excretion of bilirubin from the hepatocyte to the lumen of the bile canaliculi is dependent upon membrane bound exporters. Genetic defect in them produces familial cholestatic disorders, like Dubin Johnson syndrome.