RECOVERY OF SOME HEPATIC FUNCTIONS AFTER SURGERY FOR OBSTRUCTIVE JAUNDICE

Thesis Submitted for Partial Fulfilment of the Requirements
For Master Degree in General Surgery

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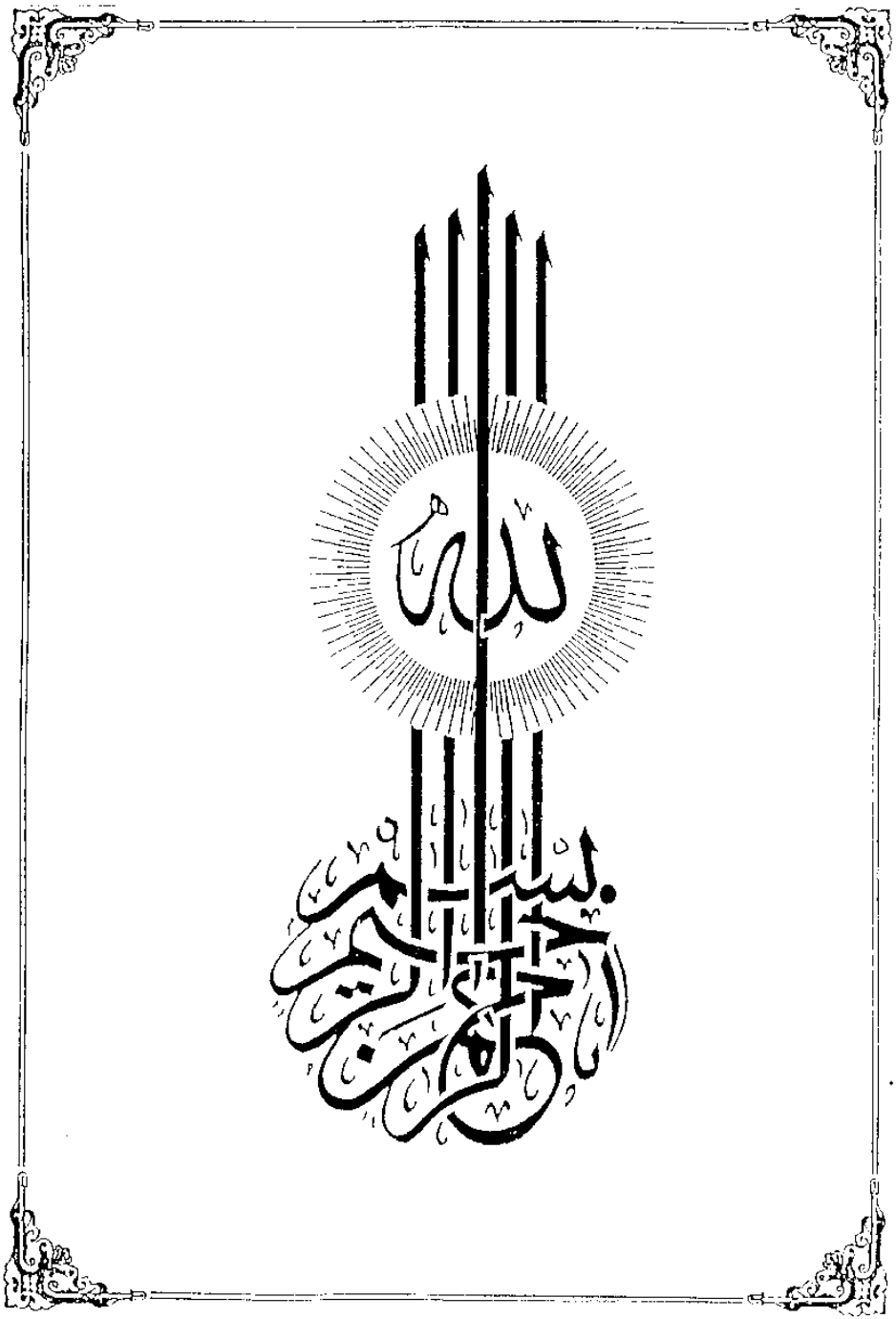

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REVIEW OF LITERATURE

Chapter 1

Pathophysiology of Jaundice

Jaundice is a generic term for the yellow pigmentation of the skin, mucous membranes, or sclera caused by a heterogeneous group of disorders. The predilection for the scleral icterus is due to abundance of scleral elastin, which has a high affinity for bilirubin. The clinical manifestations of jaundice are the direct result of increased serum levels of bilirubin. Normal serum bilirubin concentration ranges from 0.2 to 1.0mg/dl. Jaundice is clinically apparent when the serum bilirubin level exceeds 2.5mg/dl. The normal direct serum bilirubin is less than 0.35mg/dl. [Kabng&Roslyn;1997].

Bilirubin metabolism.

Breakdown product of haem coming from haemoglobin and many respiratory enzymes is excreted almost in the bile. Approximately 35 g haemoglobin are broken down daily and 300 mg bilirubin are formed. Production takes places in reticuloendothelial cells namely the spleen and bone marrow. [***Myers, 1985;Sherlock, 1996***].

About 20% of circulating bilirubin is not formed from mature erythrocytes, a small proportion comes from immature cells in spleen and bone marrow. The remainder is formed in the liver

from haemoprotein such as myoglobin, cytochromes and unknown sources. [***Sherlock, 1996***].

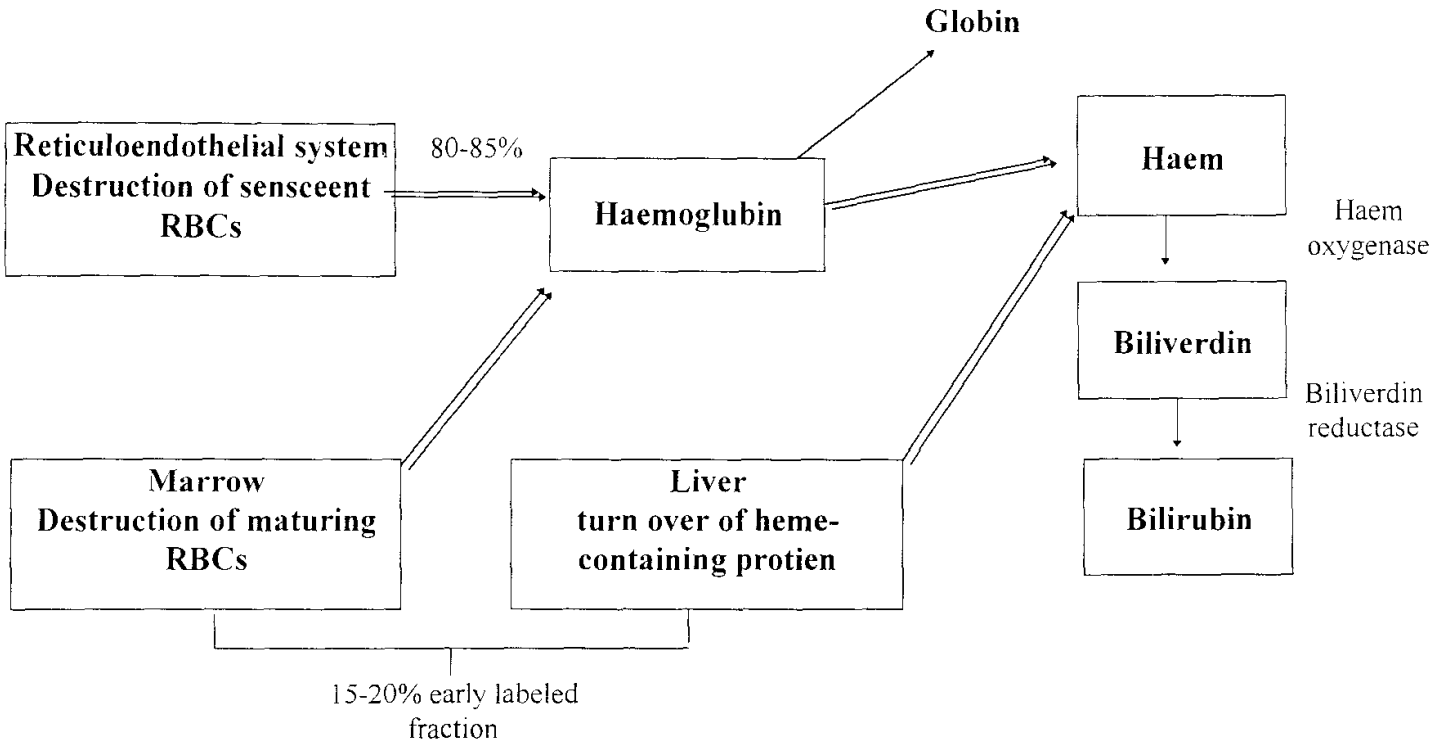
The cytochrome P-450 is quantitatively the most important non-haemoglobin haemoprotein mainly present in the liver [***Scharschmidt and Way, 1987***].

The enzyme which convert haem to bilirubin is microsomal haem oxygenase which has absolute requirement for oxygen and NADPH.

Cleavage of porphyrin ring yields carbon monoxide, ferric ion & a linear tetrapyrrole having the structure of the 1X alphabiliverdin. This is further converted to 1X alphabilirubin by an enzyme biliverdin reductase. Such linear tetrapyrrole should be water soluble whereas bilirubin is lipid soluble. The lipid solubility is explained by the structure of 1X alphabilirubin which has six intramolecular stable hydrogen bonds-this bonding can be broken by alcohol in diazo [***Vanden Bergh***] reaction converting unconjugated bilirubin to conjugated bilirubin [***Scherlock, 1996***].

Hepatic uptake of bilirubin:

Bilirubin is transported in the plasma primarily bound to serum albumin. Human serum albumin contains a single high affinity and two lower affinity binding sites for bilirubin



Sources of Bilirubin (Kabng & Roslyn;1977)

[*Zucker &Gollan; 1995].*

Drugs and other compounds that compete for albumin binding may cause an increase of the normally minute amount of unbound bilirubin in the plasma. This is of considerable clinical significance in jaundiced neonates who are at risk of developing kernickterus as result of bilirubin neurotoxicity [***Brodersen, 1980***].

Hepatic uptake of circulating bilirubin is extremely efficient despite the low concentrations of unbound bilirubin(<0.1%)[***Wolkof ; 1987***].

Dissociation of bilirubin from albumin at the hepatocellular surface is accelerated, the precise mechanism responsible for this "albumin receptor" phenomenon remains conjectural [***Wolkoff ;1981***]. No hepatocyte membrane with high affinity from albumin has been identified [***Stermmel , et al, 1983***] and approximately 40% of the bilirubin taken up by hepatocytes in a single pass through the liver refluxes unchanged into plasma [***Berk , et al; 1969***].

Hepatic uptake of bilirubin exhibits characteristics of a carrier-mediated process including saturation, competitive inhibition and counter transport [***Tiribelli, et al; 1986.]*** Unconjugated bilirubin , BSP, and indocyanine green share a sodium-independent multispecific organic anion transport

system distinct from the sodium dependent bile acid transporter. Three separate organic anion membrane transporters were isolated :

- Organic anion -binding protein [***Wolkoff, et al; 1985***]
- BSP- bilirubin-binding protein [***Berk , et al;1987***]
- Bili translocase [***Tiribelli et al; 1986***]

The first two transport proteins consist of 540 KDa subunits that form dimers of 105 DKda [***Wolkoff, et al; 1985***]. Bilitranslocase is a 100-KDa protein (α_2B) composed of 35-KDa subunits [***Teribelli, et al; 1986***]. Monospecific antibody to these transport proteins inhibit BSP uptake [***Berk , et al;1987***]. Immuniflourescence techniques localize each of these transport proteins to the sinusoidal domain of the hepatocyte plasma membrane [***Berk, et al; 1981***]. Organic anion binding protein was adetected in extrahepatic tissue as well as intracellularly, perhaps because of its structural similarity with that beta-subunit of mitochondrial F1-ATPase [***Wolkoff et al; 1989***].

Bilitranslocase reconstituted in proteoliposomes facilitates BSP transport in presence of a negative membrane potential [***Sottocasa et al; 1982***]. The driving force for hepatocellular organic anion uptake is unknown although a link with chloride transport is postulated [***wolkoff et al; 1987***].

Intracellular transport and metabolism of bilirubin:

After uptake from the plasma, unconjugated bilirubin binds to cytosolic binding proteins, like glutathions transferase B , and is then transported by these soluble transpo proteins to intracellular sites of metabolism [***Ballatori & Toug; 1989***]. However, the intracellular movement of bilirubin and other small hydrophobic organic anions may be mediated by direct inter membrane transfer and lateral diffusion within the plane of the membrane bilayer to the site of glucoronidation in endoplasmic reticulum [***Crawford , et al; 1988***]. Glucoronidation occurs more efficiently when bilirubin is presented to hepatic microsomal UDP glucuronosyl transferase associated with phospholipid vesicles rather than bound to cytosolic binding proteins [***Ntemeyer, et al; 1965***].

Furthermore, unconjugated bilirubin can transfer rapidly between unilamelar phospholipid vesicles in the absence of soluble binding proteins [***Zucker, et al; 1992***]. The precise role of cytosolic binding proteins, such as glutathion S-transferase B[ligandin], which constitute up to 5% of the intracellular protein in rat hepatocyte, remain speculative. These proteins may be important in minimizing the reflux of bilirubin across the sinusoid membrane back into the systemic circulation and in maintaining a low intracellular free bilirubin concentration [***Boyer, 1989***]. The