EFFECT OF PHOTOTHERAPY ON PLATELET COUNTS IN JAUNDICED NEONATES

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THESIS

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By

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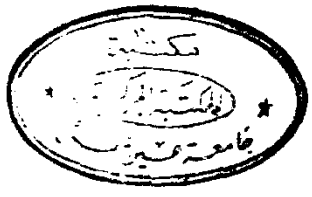

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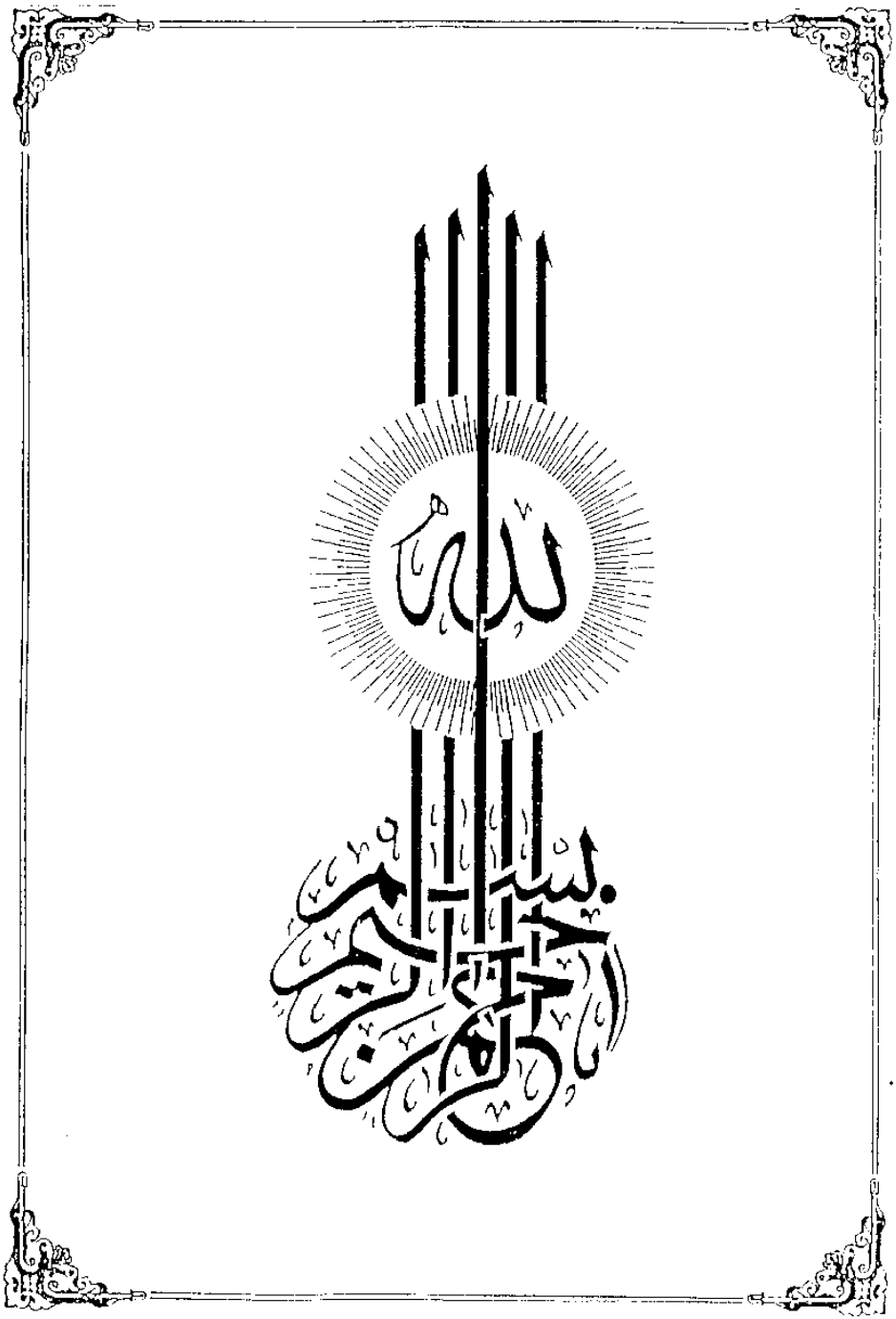

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INTRODUCTION & AIM OF THE WORK

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Phototherapy with blue fluorescent light is widely employed for treatment of neonatal hyperbilirubinemia. Functional, biochemical and morphologic changes produced by blue fluorescent light in human platelet were identified and characterized in vitro.

The present work was carried out to evaluate the action of phototherapy on platelet counts in jaundiced neonates.

Bilirubin Metabolism

Chemical hyperbilirubinemia can be defined as a serum concentration of bilirubin that exceeds 1.5 mg/100 ml, and is probably universal in all newborns during their first week of extrauterine life. In 10 to 15% of normal term births, their neonatal hyperbilirubinemia becomes sufficiently elevated to be visible as jaundice to the clinical examiner (Hardy et al., 1971). The formation of bilirubin results from the catabolism of heme proteins that include primarily hemoglobin and, to a lesser but not insignificant degree, muscle myoglobin, and heme containing enzymes derived mostly from the liver e.g. cytochromes, catalases, and tryptophan pyrrolase.

Sources	Sites of conversion	Products
1. Hemoglobin	R-E system	carbon monoxide increase
2. Non-erythroid heme-protein	Gut mucosa	Bilirubin
3. Myoglobin	Tissue macrophages	Iron

Bilirubin Formation (Odell, 1980)

The metabolic pathway by which bilirubin is formed from heme containing protein has been clarified to a considerable extent by (Schmid et al., 1975).

The protoheme molecule is catabolised by microsomal heme-oxygenase localized primarily in reticuloendothelial tissues (Tenhunen et al., 1969), but also present in tissue macrophages and intestinal epithelium (Raffin et al., 1974).

The protoheme becomes bound within the microsomes by what is thought to be an apoprotein of cytochrome P450. The electron transport system of the microsomes, in turn reduces the porphyrin iron (Fe^{+++} to Fe^{++}) within the intact cyclic tetrapyrrole, and an oxygen radicle is simultaneously generated. The latter radicle reacts with the methene carbon of the tetrapyrrole at its α-bridge position forming an intermediate hydroxyle derivative. Subsequent oxidation opens the pyrrole ring at the α- position and oxygenation of two position carbons of the A and D pyrrole nuclei occurs. The resulting linear tetrapyrrole is biliverdin IX . Coincident with the latter oxygenation, the iron is lost from the tetrapyrrole and the methene carbon is released as carbon monoxide the iron is reutilized by the body, but the carbon monoxide requires eventual excretion by way of the lung. The action of the microsomal hemeoxygenase is known as a coupled oxidation because it involves a reduction and oxidation in tandem. This reaction is NADPH specific and dependent (Tanhunen et al., 1969) and the source of the oxygen has been demonstrated to come from dissolved molecular oxygen (Brown et al., 1978). Hemeprotein is almost exclusively metabolised to biliverdin IXα. Then the biliverdin IXα undergoes further reduction after its release from the microsomes to bilirubin IXα. This conversion is catalysed by the cytosol enzyme biliverdin reductase which is also NADPH dependant and highly specific for biliverdin

IXα, the latter enzyme is found in the same tissue that contains the hemeoxygenase system. Consequently little biliverdin is ever found in the circulation. Bilirubin IXα is yellow, poorly soluble in aqueous medium, toxic and can not be excreted without energy consuming biotransformation. In aqueous media bilirubin IXα is internally hydrogen bonded and as shown by crystallography it is in its ZZ form which is the thermodynamically more stable structure (Bonnett et al., 1976). The insolubility of bilirubin IXα due to its unique configuration imposes two additional requirements for its hepatic excretion: 1. A carrier molecule is necessary to transport it from its sites of formation to the liver for excretion. 2. The hepatocyte must render bilirubin more water soluble by biotransformation to its glucoronide derivatives before it can be excreted by the liver into bile. Plasma albumin serves as the vehicle for the transport of the bilirubin in the circulating extra-cellular fluid (Jacobsen , 1972). For the liver to efficiently clean bilirubin from the blood circulating through its sinusoids, the hepatocytes must have receptors of ever greater affinity for bilirubin to be competitive with the binding of bilirubin to albumin. There is no evidence that albumin enters the cytosol of the liver with bilirubin attached to it. The plasma membrane of the hepatocyte contains receptor carrier molecules (Y and Z) that bind bilirubin. The biotransformation of bilirubin to more water soluble

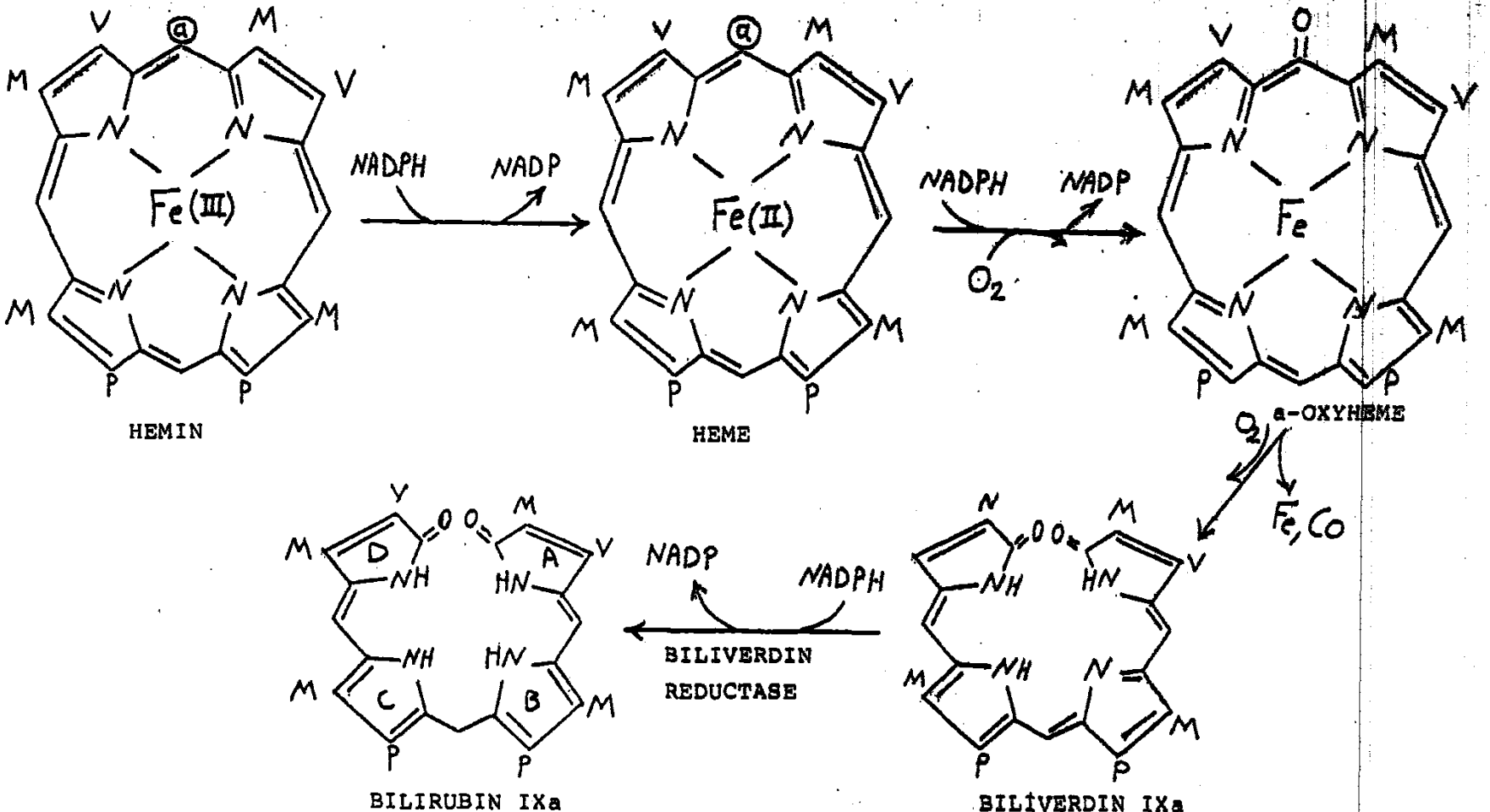

Figure I: Formation of bilirubin IX a from heme. The initial reactions are catalyzed by microsomal heme oxygenase and require NADPH as a cofactor. The reaction has a high specificity for the α-methene bridge, and α-oxyheme is a probable intermediate that is oxidized by molecular oxygen to biliverdin In mammals biliverdin is converted to bilirubim by biliverdin reductase. (From Wintrobe, 1981) P 181

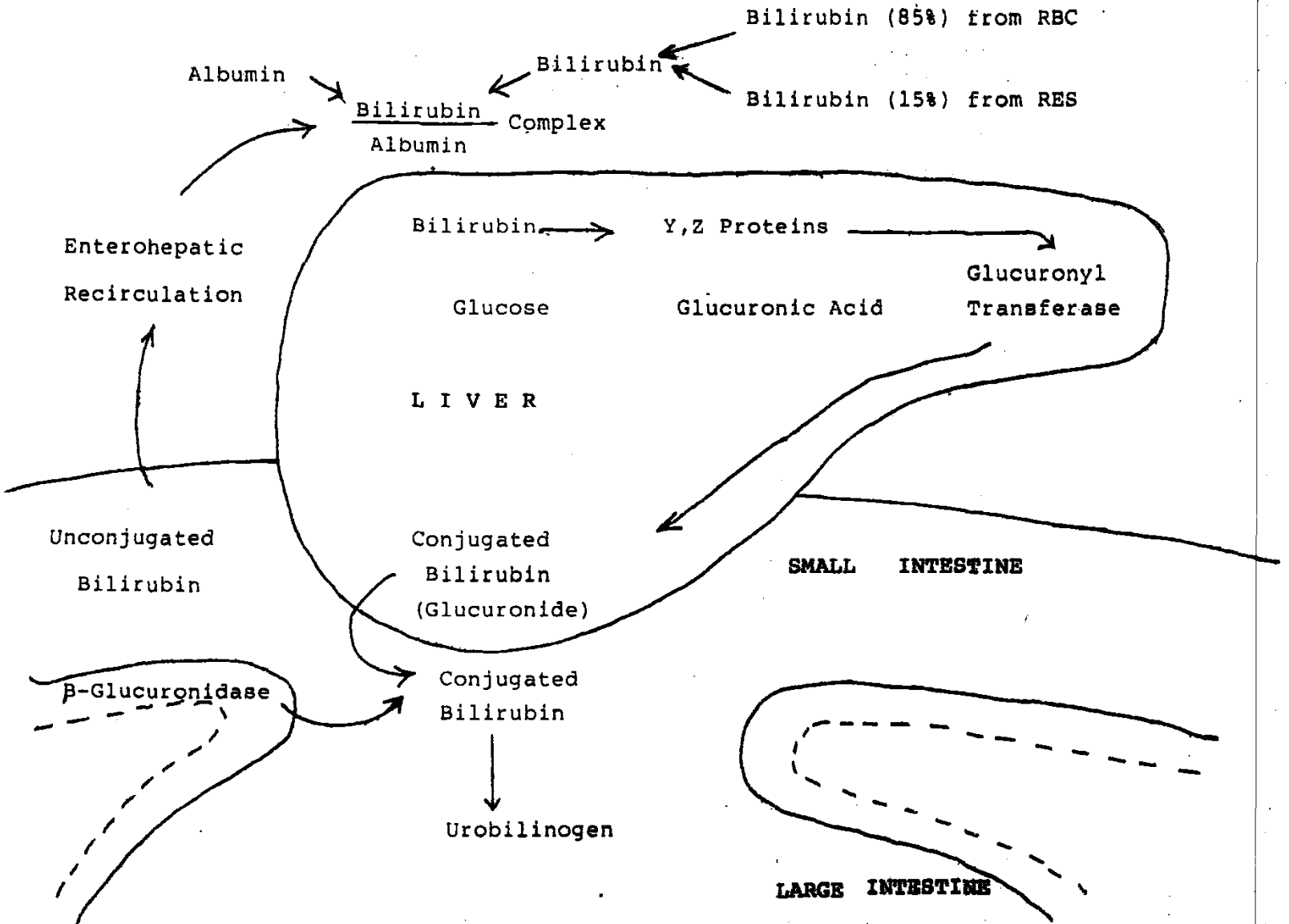

Figure II: Scheme of bilirubin metabolism
(Gartner and Lee, 1983 P352)

derivatives occurs within the endoplasmic reticulum of the microsomes. In man, it is initially conjugated to an acyl-monoglucuronide. The reaction is catalysed by a bilirubin glucuronyl transferase that is specific for bilirubin.
A second glucoronidation of bilirubin is necessary to form diglucuronide which represents 85% of the excreted pigment, whereas 15% can be excreted as a monoglucuronide. The excretion of mono and diglucuronide is a secretory transport process that occurs at the canaliculus of the hepatocyte. After excretion into the gut it may be acted upon by a beta-glucoronidase, which releases unconjugated bilirubin and this may be reabsorbed via the entero-hepatic circulation (Alistair, 1980).

Causes of indirect hyperbilirubinemia:

I. Increased bilirubin load:

1. Haemolytic disease:

a. Fetomaternal blood group incompatibility, particularly Rh and ABO and others.

b. Hereditary spherocytosis.

c. Non spherocytic haemolytic anaemias.

d. G-6-P-D deficiency.

e. Pyruvate kinase deficiency.

f. Other red cell enzyme deficiency.

g. Thalassemia.

2. Extravascular bleeding:

Cephalhaematomas, Cerebral or pulmonary haemorrhage, or any occult bleeding.

3. Polycythemia:

Twin-twin transformation, maternofetal transfusion, or anything which will produce an elevated hemoglobin level or an increase in the red cell mass.

4. Increased enterohepatic circulation:

As in case of pyloric stenosis, intestinal atresia, oral fasting, in these cases more time is allowed for bilirubin deconjugation and reabsorption and delayed meconium expulsion.

5. Induced delivery with oxytocin.

II. Decreased bilirubin clearance:

1. Inborn errors of metabolism
   a. Familial non hemolytic jaundice type I and II and Gilbert's syndrome.
   b. Dubin Johnson syndrome.
   c. Rotor's syndrome.
   d. Galactosemia.
   e. Thyrotoxicosis.
2. Transient familial neonatal hyperbilirubinemia (Lucey Driscoll syndrome).
3. Drugs e.g. Benzoate.
4. Prematurity.
5. Infants of diabetic mothers.
6. Breast feeding jaundice (Sims, 1975 and Nelson,1983).

Hyperbilirubinemia in the premature and low birth weight infants:

Biluribin concentrations rise higher in premature infants than in full term infants because of impaired ability to conjugate bilirubin in the liver. This functional defect is manifested in equal degree among premature infants of all gestational ages until 37 weeks of gestation, beyond which much lower bilirubin concentrations develop (Saigal et al., 1972, Odell et al., 1980). They reported that the reasons for frequent hyperbilirubinemia seen in the prematures are multiple for the metabolic and circulatory hemostatic mechanism for extrauterine life are often deficient. There is deficiency of uptake, conjugation and secretion of bilirubin. Approximately 10% of low birth weight infants will develop serum bilirubin concentration of over 20 mg/100ml. during the neonatal period (Lucey, 1960). Kernicterus may occur in these infants especially if ill, at levels of bilirubin well below 20 mg/100 ml. (Gartner et al., 1970). Kernicterus has been observed in premature infants who died after having unconjugated bilirubin levels which did not exceed 12 mg/100ml. Total protein rises with advancing gestational age. Also premature infants (indeed all low birth weight infants) are more likely to be subjected to cold stress, with release of free fatty acids in large quantities. These compete for binding sites on albumin and may displace bilirubin. Acidosis is more likely to be seen in association

with sepsis and respiratory disorders seen in premature infants. The associated drop in pH may affect the affinity of bilirubin to bind to albumin. This problem may be further compounded by the tendency of cooling to produce acidosis. Physiologic mechanisms are exaggerated in the premature. It may take longer to stimulate glucoronyl transferase to turn on (Tsao et al., 1972 and Zamet et al., 1975). The acceptor proteins (Y and Z) are porbably in smaller quantities. Beta-glucoronidase seem to be in greater quantities in premature infants and in addition such infants may not be fed enterally for several days. Total body fat particularly subcutaneous fat may act as a sort of reservoir into which bilirubin flows. When the reservoir is full, the risk of kernicterus increases (Alistair, 1980). Most of the reported cases of kernicterus have occured in critically ill low birth weight infants with serum indirect bilirubin levels lower than those formerly associated with kernicterus in Rh sensitised infants. An association was noted between severe respiratory distress, acidosis, and kernicterus in low birth weight infants during the late 1960's (Gartner et al., 1970). With more aggressive treatment of both acidosis and jaundice and with improve outcome in low birth weight infants the number of cases of kernicterus seen at one institution during the 1970's was lower than in 1960's (Pearlman et al., 1978) and kernicterus tended to occur mainly in infants with neonatal sepsis (Pearlman