FOLLOW UP STUDY OF PHOTOTHERAPY IN THE NEWBORN

A THESIS

Submitted for the Partial Fulfilment
of Master Degree of Pediatrics

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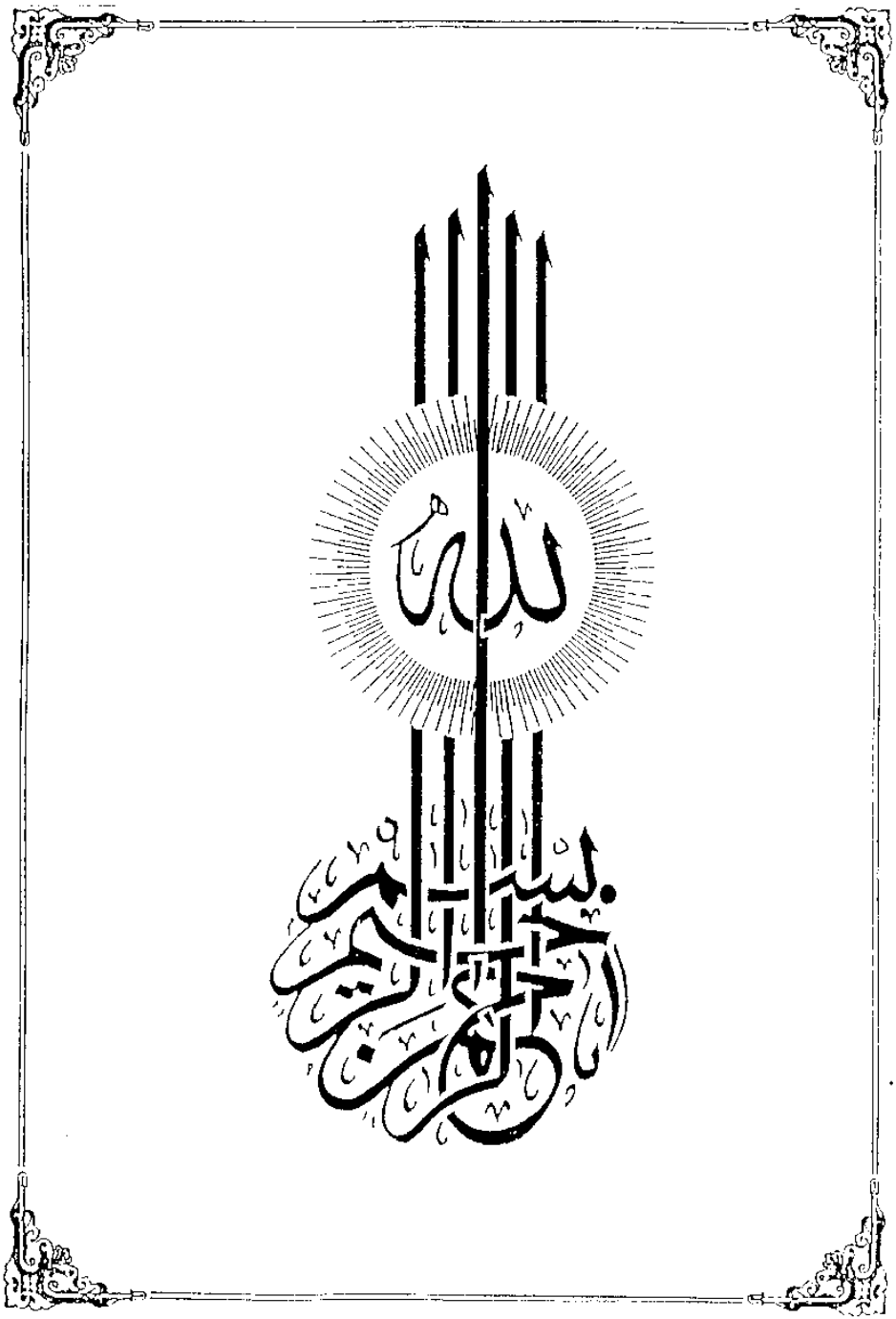
To My Parents



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Introduction & Aim Of The Work

Introduction and Aim of Work

Jaundice may be encountered with a wide variety of cilinical disorders, and with the exception of the physiologic jaundice, it is one of the most serious signs to find. Excessive hyperbilirubinemia during neonatal life may produce functional impairment ranging from severe cerebral palsy to the syndrome of "minimal brain danage" (Odell et al., 1970).

Management of hyperbilirubinemia is directed at keeping the serum bilirubin levels below 20 mg/dl., thus lowering the incidence of kernicterus (Boggs et al., 1967).

Nowadays, phototherapy is extensively used in many premature units to treat a large number of newborn infants with hyperbilirubinemia. Reports of complications during usage are few. (Lucey 1970; 1972).

Romagnoli et al., in 1979 and Bergstrom in 1981 demonstrated a greater incidence of decreased serum calcium with phototherapy. Hypoglycemia was also found in 20 % of preterm infants treated with phototherapy. (Romagnoli et al., 1979).

The aim of this work is to show the efficiency of phototherapy in lowering serum bilirubin level and to detect some of its possible complications. Estimation

of serum bilirubin, serum calcium and blood glucose were done in low-birth weight jaundiced infants before and after phototherapy and were compared with healthy low-birth-weight infants.

Review Of Literature

BILIRUBIN METABOLISM

Definition:

Bilirubin is a linear tetrapyrrole formed by cleavage of cyclic tetrapyrrole protoporphyrin. Protoporphyrin and iron form a complex "heme" which is the prosthetic group of hemoglobin and other heme proteins (Nelson, et al., 1975).

Sources of Bilirubin:

Bilirubin results from the catabolism of heme proteins in the body which include:-

1. Hemoglobin:

About 80-90 % of the total daily production of bilirubin in adults and 75 % in newborn infants is derived from the normal destruction of the circulating red cells. The catabolism of 1 gm of hemoglobin yields 34 mg. bilirubin.

2. Other heme-containing proteins:

These form about 10-20 % of the total daily production of bilirubin. It is a small but a significant source of bile pigments which is derived from extra-erythrocytic sources (Robinson, 1968). These extra-erythrocytic sources are:-

a. Muscle myoglobin.

b. Heme-containing enzymes derived mainly from the liver e.g. cytochromes, catalases, peroxidases and tryptophan pyrrolase. (Israel et al., 1963).

Among the hepatic heme proteins, the cytochromes of the endoplasmic reticulum appear to play a major role because of their relatively high concentration (Schmid et al., 1968). A significant proportion of bilirubin derived from the hepatic hemes passes through the plasma in the unconjugated form before conjugation and secretion into bile (Jones et al., 1972).

The source of bilirubin has been studied in humans by using radioisotope N^{15} labeled glycine which is incorporated into newly formed hemoglobin and can be followed until it appears in bile. Erythrocytes which contain N^{15} labeled hemoglobin survive for an average of 120 days in adults and 90 days in the newborn before degradation (Vest et al., 1965). After their destruction, there is a large increase in the excretion of labeled stercobilin which is an intestinal oxidation product of bilirubin. This is known as the late peak of bilirubin synthesis. Two earlier peaks of bilirubin synthesis appear before incorporation of N^{15} glycine into erythrocytes. These correspond to:-

1. Hepatic heme turnover at 0 - 3½ hours.

2. Ineffective erythropoiesis at 3-5 days after labeling of heme (Robinson et al., 1966).

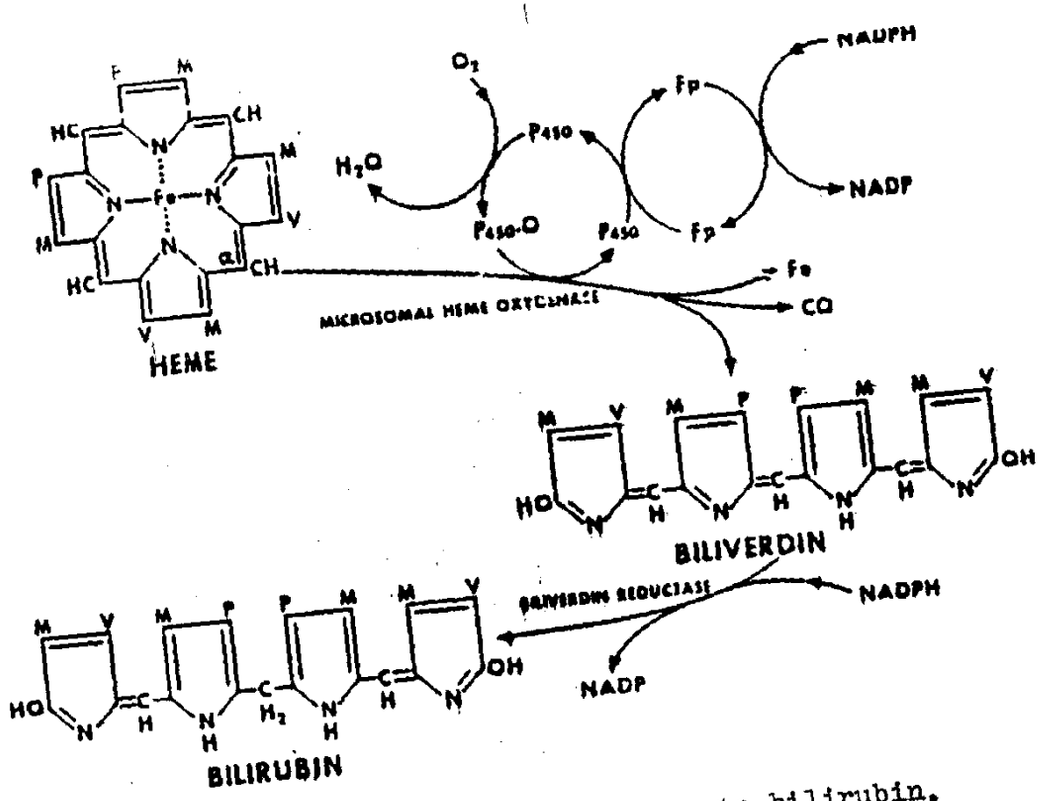
Bone marrow stimulation due to hypoxia, erythropoietin or hemorrhage increases the second early peak (3 - 5 days) (Robinson et al., 1966), while bone marrow aplasia due to irradiation results in suppression of this peak (Israel et al., 1970).

However, under pathological conditions, bilirubin may be derived from hematin, the trivalent iron-hydroxide of protoporphyrin. This may be found in hematomas and collection of blood in serosal cavities. Thus in severe hemolytic states such as erythroblastosis fetalis and clostridium perfringens sepsis, intra-vascular hemolysis occurs with the release of free hematin. The latter combines with serum albumin to form met-hemalbumin (Robinson, 1968).

Mechanism of Bilirubin formation:

Metabolism of bilirubin occurs primarily in the reticulo-endothelial tissues but also present in tissue macrophages and intestinal epithelium. These contain microsomal heme oxygenase and cytosol biliverdir reductase, the 2 enzymes necessary for the degradation of heme to bilirubin (Tenhunen et al., 1969).

The initial reaction in the formation of bilirubin



Metabolic pathway of heme degradation to bilirubin.
(Estabilished by Tenhunen R, Marver HS and Schind R "1969"
J. Biol. Chem. 244 : 6388).

is the oxidation of the iron atom of hemoglobin to trivalent state forming met-hemoglobin. Next the linkage between heme and globin is strengthened yielding hematin which is the trivalent iron-hydroxide of protoporphyrin. Opening of the heme porphyrin ring is accomplished by oxidative removal of carbon atom in the alpha-methane bridge producing carbon monoxide and biliverdin IX a (Ludwig et al., 1957). The cleavage is catalysed by microsomal heme oxygenase enzyme (Tenhunen et al., 1970). The reaction is NADPH specific and dependant. The source of oxygen has been demonstrated to come from dissolved molecular oxygen (Tenhunen et al., 1969). Therefore heme protein is almost exclusively metabolized to biliverdin IX a which is a water-soluble green pigment. Biliverdin IX a then undergoes further reduction after its release from the microsomes to bilirubin IX a. This conversion is catalysed by the cytosol enzyme biliverdin reductase which is present in the same tissues that contain the heme oxygenase enzyme and is also NADPH dependant and is highly specific for biliverdin IX a (Schmid, 1978).

Thus for each molecule of heme degraded, one molecule of carbon monoxide, ferric iron and bilirubin are formed (Landow et al., 1970). The iron is reutelized by the body but the carbon monoxide requires eventual excretion by the way of the lungs without any change. This is the main reaction in the human body in which

carbon monoxide is produced. Thus determination of the rate of carbon monoxide production, which was once considered a reliable measure of heme degradation has been questioned recently because of evidence that the peroxidation of microsomal lipids may also result in the formation of carbon monoxide (Walff and Bidlack, 1976).

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

Bilirubin formation
(Odell, 1980)

The predominant isomer, bilirubin IX a (ZZ) exists as a charged molecule (dianion) which has hydrophilic (polar) properties in eight locations. Bilirubin molecule folds up establishing intramolecular hydrogen bonds to form bilirubin IX a (ZZ) acid. These bonds saturate the hydrophilic (polar) groups of the molecule leaving no affinities for the attachment of water. The molecule therefore becomes hydrophobic and insoluble in water (Bonnett et al., 1976). It is no longer able to bind to albumin but has a pronounced tendency for aggregation and binding to tissues. Under these conditions, it may be potentially toxic (Brodersen, 1978).