PARENTRAL IRON THERAPY IN THE TREATMENT OF ANAEMIA DUE TO CHRONIC RENAL FAILURE

THESIS

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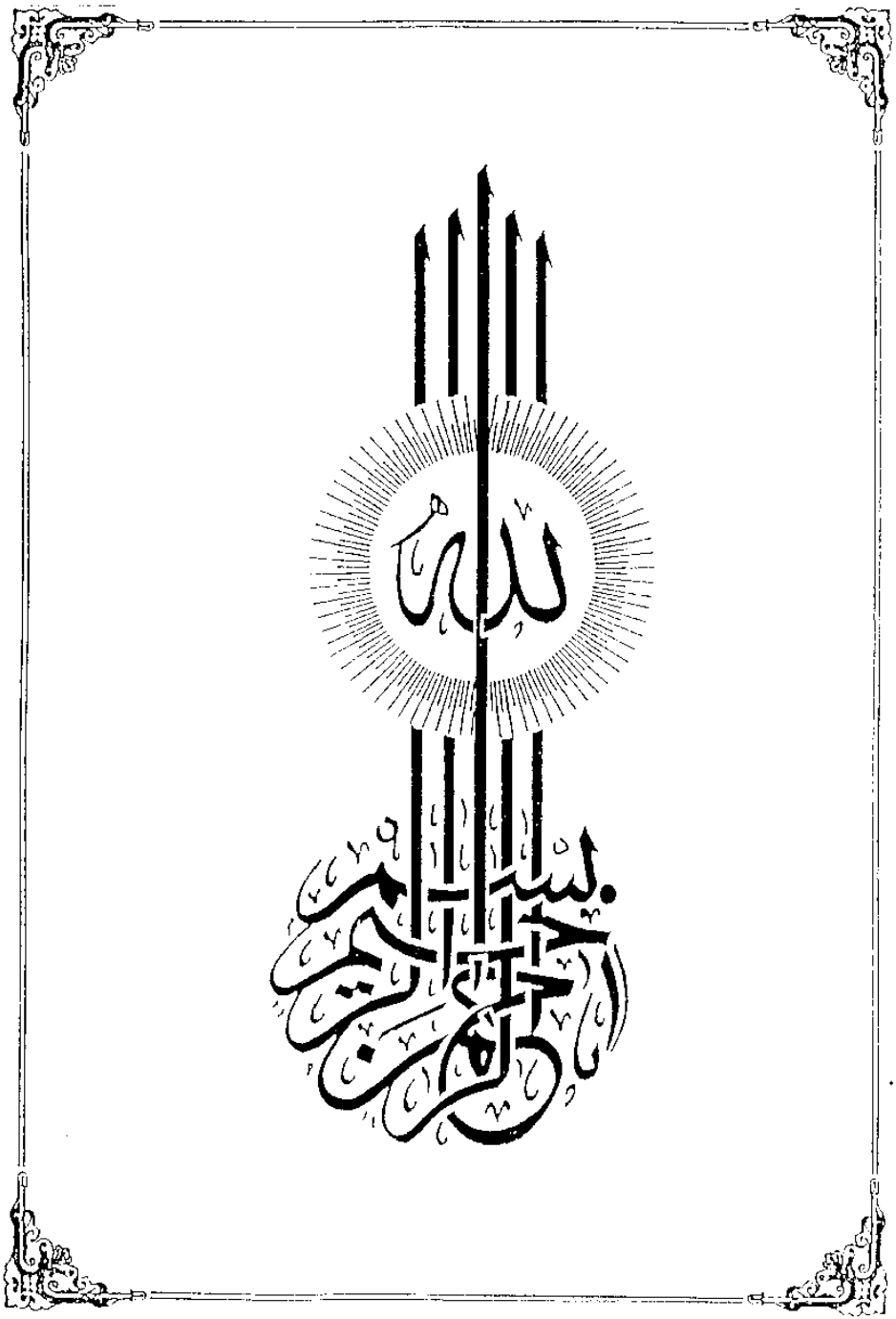

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INTRODUCTION AND AIM OF WORK

INTRODUCTION AND AIM OF THE WORK

Among the many symptoms of chronic renal failure anaemia stands as a hallmark and is one of the diagnostic clues. It is as good a hallmark of chronic renal failure as the blood urea level.

Anaemia is almost invariably present and its severity is usually quantitatively related to the extent of uraemia (Erslev, 1969).

Whatever the underlying cause of renal failure, the anaemia of uraemia appears to have a common pathogenesis and microscopical picture. It is usually normocytic normachromic reflecting the hypoproliferative nature of the erythroid activity.

Yet, other causes share in the pathogenesis of this anaemia, as iron deficiency that can occur through chronic blood loss in the gastro intestinal tract or after the institution of regular haemodialysis.

Kurtides et al (1964) reported immediate improvement in the erythropoiesis following correction of uraemia by haemodialysis and this was attributed to either removal of marrow inhibition by toxic metabolites

or improvement in threshold of secretion of erythropoietin by extrarenal sources (Brown et al, 1980).

Other lines of treatment were tried with some benifit, but non proved to be ideal.

The aim of this work is to use a simple method of treatment and to evaluate its benifit in anaemia of chronic renal failure.

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REVIEW OF LITERATURE

ERYTHOPOIESIS AND ITS REGULATION

A number of tissues in the mammalian species can support red cell production, but apparantly the environment inside the bone marrow is optimal for cellular proliferation and maturation. However bone cavities do not develop until the fifth foetal month and presumably less favourable sites, are responsible for red cell production during early embryonic life.(Erslev, 1977).

In the human being blood cells are first formed outside the embryo in the yolk sac (Bloom and Bartelmez 1940). During the next foetal months the liver is the main site for red cell production.

For normal erythopoiesis to be established and maintained three main sets of requirements must be satisfied. Firstly, there must be an adequate supply of stem cells established in a favourable environment and sensitive to the various influences ordering their maturation until they eventually emerge into the circulation as erythrocytes. Secondly, there must be an adequate supply of materials necessary for the normal growth and development of these erythroid cells at all stages, as well as the existence of normal regulatory mechanisms. Thirdly, the circulating erthrocytes must not suffer such a degree of premature destruction that the blood

forming tissues are unable to maintain normal numbers of cells in the circulation (Thompson 1977).

One of the most important influences at several stages of erythropoiesis, is the regulatory substance erythropoietin. Also, essential materials as iron, vitamin B_{12} and folic acid are required.

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E R Y T H R O P O I E T I N

AND THE KIDNEY

Paul Bert, in 1878, predicted that as a harmonious compensation of nature, an increase in the red cell count and haemoglobin concentration would be found in the blood of men and animals living at high altitudes. In 1893, Miescher suggested that the ultimate stimulus to erythropoiesis, was tissue hypoxia, while, in 1906, Carnot and Deflandre postulated that hypoxia might not exert its effects on the marrow directly, but by stimulating the production of hormone "haemopoietin" which, they believed was present in the circulating blood.

The existance of a humoral agent, erythropoietin as the sole or prime regulator of erythropoiesis was established in the first instance by the study of Erslev (1953). The determination of the properties & chemical constitution of erythropoietin have been hampered by difficulties of obtaining adequate supplies of pure material. Attempts to obtain pure material from the urine of anaemic patients had not been satisfactory (Lowy and Keighley 1968), but plasma of anaemic sheep (Goldwasser and Kung, 1972) was possible source of it. Pure material, which has now been obtained, is a glycoprotein ; its molecular weight was

estimated to be about 60000 by Lukowsky and Painter (1968) and 46000 by Goldwasser and Kung (1972). It contains sialic acid, hexosamine and hexoses and consists of 70 per cent protein and 30 per cent carbohydrate of which 10 per cent is sialic acid, possibly the sialic acid moiety is required for attachment to a carrier. Desialation of erythropoietin renders it biologically inactive in vivo, but it retains an effect on haem-synthesis by marrow cells cultured in vitro (Gordon, 1971).

It is not clear what proportion of erythropoietin is utilized, how much is metabolised and how much is excreted (Kuratowska, 1968). There is evidence to suggest increased utilization in situations where there is increased erythropoiesis (Stohlman and Brecher, 1959). An inverse relationship between haematocrit levels and urinary erythropoietin levels has been established. Erythropoietin is excreted in the urine in amounts which closely parallel those in the plasma (Alexanian 1966)

Site of Erythropoietin Production :-

Jacobson et al (1957) reported that the plasma erythropoietin levels of anephric rats do not rise on exposure to hypoxia, cobalt or anaemia as do those of

intact rats,uraemic rats with ligated ureters, or rats with other organs than kidney removed. Accordingly these authers postulated that erythropoietin is produced in the kidneys. This hypothesis was subsequently supported both by the observations of Naets(1958) that erythropoiesis ceases in anephric dogs and can be restored by injection of erythropoietin, and by demonstration of erythropoietin in the perfusate after perfusing isolated rabbit or dog kidneys (Reissman and Nomura, 1962). The kidneys are considered essential for production of erythropoietin in humans as evidenced by the absence of detectable erythropoietin in the plasma of most severely uraemic patients(Gallagher et al., 1959), in contrast to elevated erythropoietin Levels in non uraemic patients who are comparably anaemic.

Attempts at extracting erythropoietin from the kidneys of normal, hypoxic, or anaemic animals were unsuccessful (Gordon et al., 1956). Also, Kuratowska et al. (1964) observed that perfusion of isolated rabbit kidneys with saline did not yield erythropoietin in the perfusate, whereas infusion with plasma, serum or plasma α - globulin did. These investigators postulated that the kidneys produce an inactive erythropoietin precursor which requires a plasma α- globulin for either activation or stabilization.

An alternative theory had been postulated by Contrera et al 1966) and Gordon et al (1967). They have separated a factor from the light mitochondrial fraction of kidney extracts, which was capable of generating erythropoietin when incubated with plasma from a normal animal. Zanjani et al (1967) concluded that the kidneys produces a substance that reacts enzymatically with a plasma substrate. Katz et al (1968) have implicated the liver as a probable site for synthesis of the substrate for erythrogenin.

Recently, another theory was postulated by Erslev et al (1971). They proposed that the kidneys produce erythropoietin, but that it is in an inactive storage form while in the kidney, because of an inhibiting effect of the lipid extractable renal factor. When this complex comes into contact with a plasma born protein, biologically, active erythropoietin is released. Recently, Zanjani et al (1972) have confirmed the presence of a lipid soluble inhibitor for erythropoietin in the kidney and have reported that kidney extracts contain both biologically active erythropoietin and erythrogenin.

Considerable controversy still exists regarding the specific sites within the kidney which are responsible for erythropoietin production. The juxta

glomerular apparatus was logically one of the first to be implicated because of its well recognised endocrine function (Naetes, 1958). Mitus et al (1962), suggested that the site of erythropoietin production is likely to be located in the renal medulla. Fisher et al (1971), have reported on the other hand that radioactively labelled anti-bodies to erythropoietin localize in the glomeruli. The work of Zanjani et al., (1967 , 1972) showed that erythrogenin is apparently present through out the kidney and possibly the glomerulus is the site at which erythrogenin reacts with its substrate erythropoietinogen.

Extra-renal erythropoietin :-

In man the kidney is not the exclusive source of erythropoietin, since anephric man is still capable of responding to anoxia with a reticulocytosis, and erythropoietin may still be demonstrable in the plasma (Davis , 1975). The sites of extrarenal erythropoietin production are not definitely known nor it is clear whether extra-renal erythropoietin is identical with renal.

Most of the evidence points to the liver as the primary site of extra-renal erythropoietin production