

ERYTHROPOIETIN IN HEALTH
AND DISEASE: AN OVERVIEW
ESSAY

رسالة

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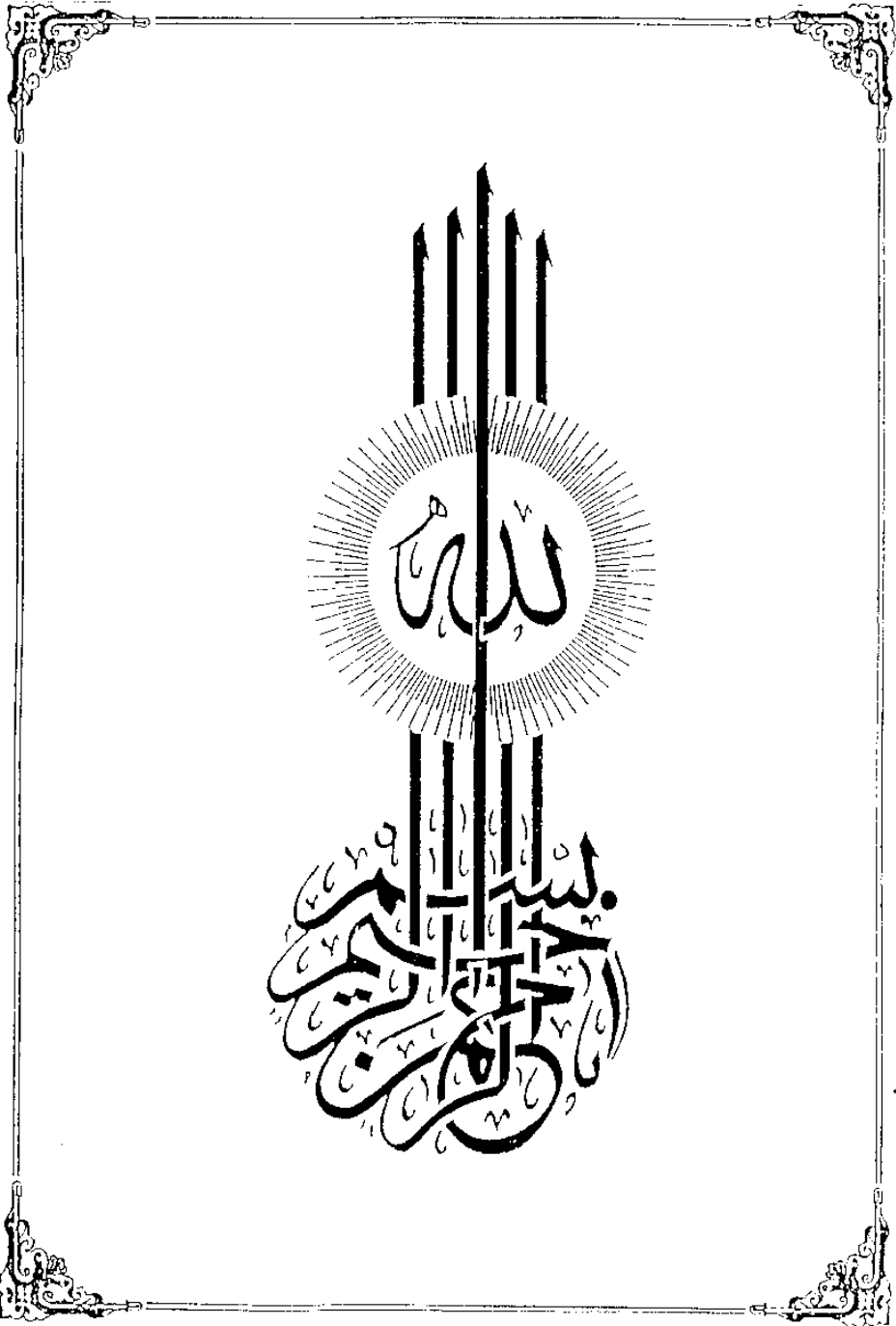
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ABBREVIATIONS

| | |
|----------|--|
| ABD | autologous blood donation |
| ADPKD | autosomal dominant polycystic kidney disease |
| AIDS | acquired immunodeficiency syndrome |
| Ara-C | cytosine arabinoside |
| AmB | Amphotericin B |
| BFU-E | Burst-forming units-erythroid |
| cdNA | complementary DNA |
| CFU-C | colony-forming units ⁱⁿ culture |
| CFU-E | colony-forming units erythroid |
| CFU-G | colony-forming units granulocyte |
| CFU-GEMM | colony forming units-granulocyte erythrocyte macrophage megakaryocyte |
| CFU-GM | colony-forming units granulocyte-macrophage |
| CFU-Meg | colony forming units-megakaryocytes |
| DNA | deoxyribonucleic acid |
| EEG | Electroencephalogram |
| E/M | erythroid/myeloid ratio |
| EPO | Erythropoietin |
| FSH | folllitropin |
| g | gram |
| GARG | goat anti-rabbit IgG |
| G-CSF | granulocyte-colony stimulating factor |
| GM-CSF | granulocyte-macrophage colony stimulating factor |
| G-6Pd | Glucose 6 phosphate dehydrogenase |
| Hb | Haemoglobin |
| HbF | Haemoglobin F |

| | |
|---------|---|
| HIV | human immunodeficiency virus |
| HLA | human leucocyte antigen |
| IL-1 | Interleukin-1 |
| IL-3 | Interleukin-3 |
| IL-4 | Interleukin-4 |
| Kg | Kilogram |
| LH | lutropin |
| MDS | myelodysplastic syndromes |
| mg | milligram |
| MRI | Magnetic resonance imaging |
| mRNA | messenger RNA |
| Na | Sodium |
| PNH | paroxysmal nocturnal haemoglobinuria |
| PW-CM | Pokeweed-stimulated T-lymphocyte-conditioned medium |
| RIA | radioimmunoassay |
| R-HuEPO | recombinant human erythropoietin |
| RNA | ribonucleic acid |
| TE | testosterone |
| TSF | thrombopoiesis-stimulating factor |
| WEHI-CM | a mouse leukaemic cell-conditioned medium |
| | English Pound |

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Introduction and

Aim of work

INTRODUCTION AND AIM OF WORK

The existence of an erythropoietic feedback system responsive to the tissue tension of oxygen was first suspected by Dennis Jourdanet, a French physician who in the 1860's practiced medicine in the highlands of Mexico. He observed that the dark blood of his surgical patients was thick and flowed slowly, and he suggested that there was a connection between a low arterial content of oxygen and thick blood. Subsequent studies by the famous Parisian physiologist, Paul Bert (1878), on the physiologic effect of low barometric pressure led to the hypothesis that decreased arterial oxygen tension stimulated red cell production. Supporting evidence came from the fact that many patients with chronic pulmonary disorders or with right-to-left shunts were polycythaemic (Erslev and Gabuzda, 1979). Since anaemia, despite normal arterial oxygen tension, is also associated with increased red cell production, it was concluded that erythropoietic stimulation is caused by tissue hypoxia due to either a decreased oxygen tension or a decreased oxygen content of arterial blood (Erslev and Gabuzda, 1979).

hormonal mediator of erythropoiesis (erythropoietin) was first suggested by Jacobson et al. (1957), but final proof came only recently with the finding within renal cells of mRNA for erythropoietin (Schuster et al., 1987).

Erythropoietin has been purified to homogeneity and the gene which regulates its structure has been cloned. These remarkable advances have allowed the development of an accurate radioimmunoassay and production of erythropoietin for therapeutic purposes.

Recombinant human erythropoietin has been used successfully in several clinical settings.

Trials in patients with end stage renal failure are consistent (Winearls et al., 1986; Eschbach et al., 1987 and Adamson, 1989).

Other conditions in which erythropoietin is being used include anaemia of prematurity, myelodysplastic syndromes and anaemia associated with HIV infections.

It has also been used for short term stimulation of bone marrow prior to venesection for elective autologous transfusion (Surgenor, 1987).

Review of Literature

Chapter I

Physicochemical Properties of EPO

I. PHYSICOCHEMICAL PROPERTIES OF EPO

Chemistry of EPO

Erythropoietin is a glycoprotein of molecular weight 34,000 to 39,000. Both human and murine erythropoietin cDNA have been isolated. The human erythropoietin coding sequence encodes a hydrophobic 27 amino acid leader peptide followed by the 165-amino acid mature protein. The messenger mRNA is encoded by at least 5 exons, and the protein backbone has a relative molecular mass of 18,398. The terminal sialic acid of erythropoietin is required for full in vivo, but not in vitro, biologic activity. The human erythropoietin gene resides on chromosome 7 (Powell et al., 1986).

Site of Production of EPO

In 1957, Jacobson and Co-workers (Jacobson et al., 1957) provided indirect evidence for the kidney being the site of production of erythropoietin. However, it took almost 20 years of experimental work and debate to show that this was indeed true and that hypoxic kidneys produce and contain erythropoietin (Erslev, 1974 and Fried et al., 1981).

Using molecular probes for erythropoietin mRNA, several investigators have pinpointed the synthesis in cortical interstitial, perhaps endothelial cells (Lacombe et al., 1988 and Koury et al., 1988). Other investigators have found some synthetic activity in tubular (Caro and Erslev, 1984) and even glomerular cells (Jelkman et al., 1983). It is also possible that several cellular elements are involved in an integrated process of oxygen sensing and erythropoietin synthesis (Jelkman et al., 1983).

A reduction in the amount of functioning renal tissue gradually leads to a decrease in the capacity of the kidneys to respond to anaemia with the production of erythropoietin. However, it does not cease altogether, even in the anephric individual (Nathan et al., 1964 and Erslev et al., 1968), because extrarenal tissues, especially and perhaps exclusively the liver, have some capacity for erythropoietin synthesis in response to severe hypoxia (Fried, 1972).

This production, whether originating from hepatocytes, kupffer cells, or endothelial cells, is responsible for about 5 to 10% of total erythropoietin titres in plasma. During foetal life however, hepatic erythropoietin production is of major importance for red cell production.