HAEMOGLOBINOPATHIES IN NEWBORN

An Essay

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of Master Degree in *Paediatrics*

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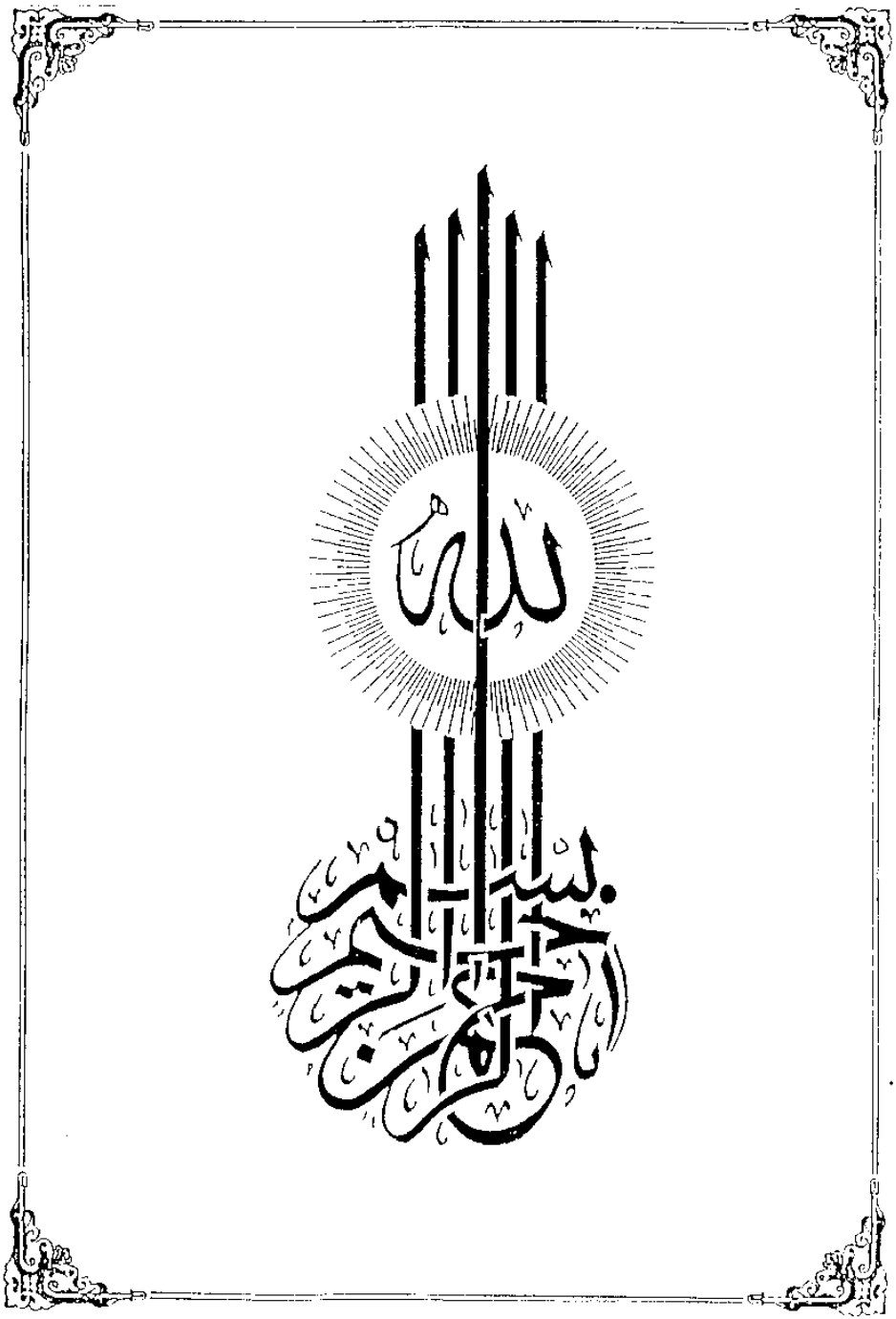
بسم الله الرحمن الرحيم

" سبحانك لا علم لنا إلا ما علمتنا ، إنك أنت العليم الحكيم "

صدق الله العظيم

سورة البقرة
الآية ٣٢



To My Dear Family:
My Father, My Mother, My Brother,
My Husband and My Lovable Daughters

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LIST OF ABBREVIATIONS

Hb	: Haemoglobin
α	: Alpha
β	: Beta
γ	: Gamma
δ	: Delta
ϵ	: Epsilon
ζ	: Zeta
RBC	: Reticulocytic blood corpuscle
Thal.	: Thalassaemia

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INTRODUCTION

INTRODUCTION

Haemoglobin has been described once by the American biochemist L.J. Henderson as "The second most interesting substance in the world *(Barcroft, 1928)*.

In the eighteenth and nineteenth centuries, the ideas about the importantce of oxygen for life, and the production of animal heat by controlled combustion or respiration developed slowly. It was not shown until 1864 by the english mathematician and physicist *George Stokes* that haemoglobin, reversibly binds and releases oxygen, changing colour as it does so. It was one of the first proteins to be purified to the point where its molecular weight and amino acid composition could be established accurately *(Dickerson and Gleis, 1983.*

The main role of Hb is to bind molecular O_2 to its haem irons at the lungs and to deliver it to the tissues. A second task is to bring the CO_2 by product of oxidation to the lungs to get ride of it *(Stryer, 1981)*.

The concentration of Hb within human red cells is high (34 gm/dl) and its efficiency as an oxygen carrier is enhanced by its packaging in flexible (red) cells of optimal shape for the diffusion of gases *(Bunn et al., 1977)*.

The molecular and biochemical characteristics of the haemoglobins are remarkably well known now. The genes of

their component polypeptide chains have been located on chromosomes number 11, 16 and the actual genes have been isolated and their DNA sequences determined *(Nelson, 1983)*.

The Alpha Chains

A pair of polypeptide chains present in each molecule of all haemoglobin variants in the normal human blood.

Each chain contains 141 aminoacids. It has an N-terminal sequence, valine-leucine. The amino acid sequence of alpha polypeptide chain is shown in Fig. (1).

The Non Alpha Chains

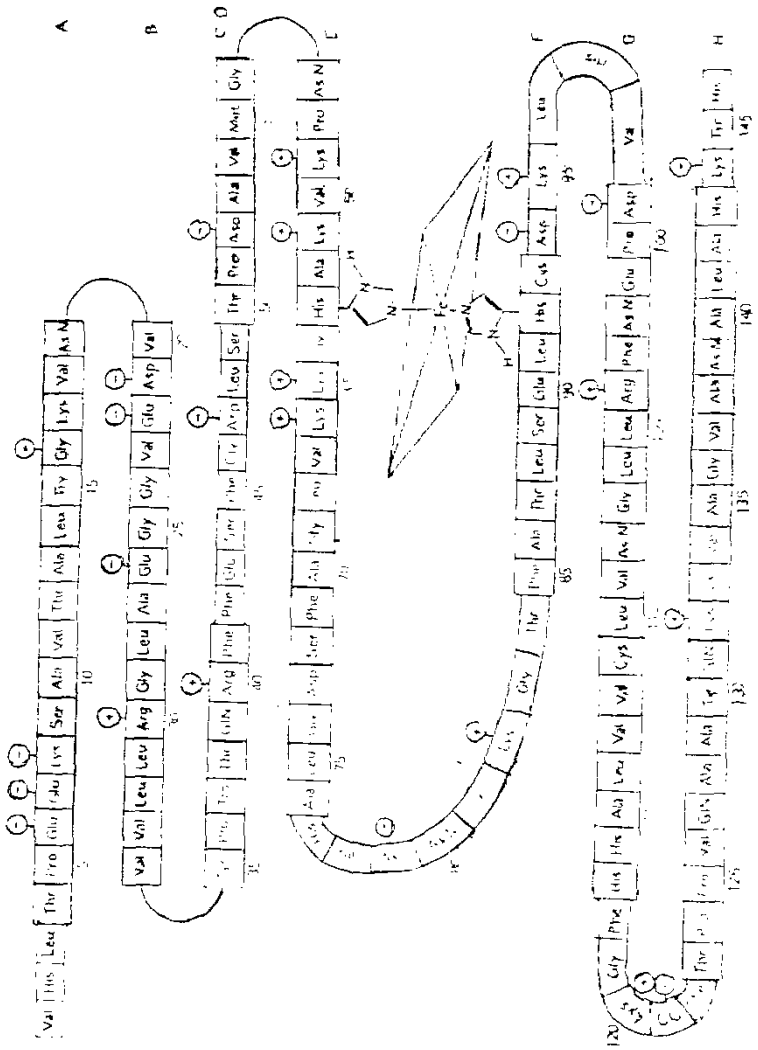
There are 3 types of non alpha chains in normal human blood: Beta (β gamma (γ) and delta (δ).

The β Chain

A pair of β polypeptide chains are normally present in each molecule of the major adult Hb A_1. Each β chain contains 146 amino acids. The β chain has an N-terminal sequence Valine-Histidine. The amino acid sequence of β polypeptide chain is shown in Fig. (2).

The Delta Chain

Each molecule of the minor adult component HbA_2, contains a pair of delta chain besides the pair of alpha chain. Each delta chain contains 202 amino acids residues and differs from β chain and γ chain.



ig. 2: The sequence of 146 amino acid residues in the β chain of haemoglobin From *Murayama (1971)*.

The Gamma Chain

Each molecule of foetal Hb contains a pair of gamma chain. Each gamma chain contains 146 aminoacids, the same number as the β chains *(Jukes, 1966)*.

During the last 20 years, knowledge of molecular defects underlying the group of haematologic disorders called haemoglobinopathies has burgeoned at tremendous pace. Techniques for peptide and amino acid analysis, following enzymatic degradation of the large haemoglobin polypeptide chains, have led to the discovery of 154 variants due to a single point mutations in the α chain.

In the β chain, 250 due to a single point mutation and 4 with 2 point mutations. Ten due to point mutations in the δ chain, and 19 due to point mutations in the γ chains *(Virgil, 1983)*.

Most haemoglobin variants have no clinical effect, even though they may be found to have some malfunction when scrutinized in the research laboratory. Most patients in whom they are detected are heterozygotes. Homozygotes may have abnormal red cell morphology without anaemia. Unstable variants, those with high or low oxygen affinity or those causing methaemoglobinaemia, are expressed in heterozygotes, and there is always the chance of a double heterozygote for an abnormal haemoglobin and thalassaemia.

HbS and rare sickling variants are unique in that they are relatively harmless in the heterozygote but may produce a severe disease in the homozygote and in some double heterozygotes such as Hb S/C, S/O Arab and S/D Panjab *(Bunn et al., 1977)*.

Several new substitutions have been discovered in the past few years and are listed in table (1) *(Chalaby et al., 1985)*.

AIM OF THE ESSAY

Review of the haemoglobinopathies in newborn including:

1. Genetic control of haemoglobin synthesis.
2. Normal human haemoglobins.
3. The different haemoglobin variants and haemoglobinopathies.
4. Prenatal diagnosis and neonatal screening for haemoglobinopathies.

Table 1: New Abnormal Haemoglobins

Residue	Substitution	Name	Electrophoretic Mobility pH 8.4	Clinical Effect
α chain				
α6(A4)	Asp-deleted	Hb Boyle Heights	Between Hb f&5	None
α6(A4)	Asp-Val	Hb Ferndown	Behind Hb A	None
α11(A9)	Lys-Cln	Hb J-Wenchang-Wuming	In front of Hb A	None
α20(B1)	His-Tyr	Hb Necker Enfants Malades	Like Hb A°	None
α27 (B8)	Glu-Lys	Hb Shuangfeng	In front of Hb A_2	Haemolytic anaemia
α44(CE2)	Pro-Arg	Hb Kawachi	Like Hb A	Erythrocytosis
α45(CE3)	His-Gln	Hb Bari	Like Hb A	None
α49(CE7)	Ser-Arg	Hb Savaria	Like Hb S	None
α56(E5)	Lys-Glu	Hb Shaare Zedek	Like Hb H	None
α60(E9)	Lys-Glu	Hb Dagestan	Like Hb I	None
α75(EF4)	Asp-Gly	Hb Mizushi	Like Hb S	None
α8(F2)	Ser-Cys	Hb Migeria	Like Hb A⁻	α-Thalassaemia trail
α8(F8)	His-Arg	Hb M-Iwate	Behind Hb A	Mathaemo-globinemia
α122(H5)	His-Gln	Hb Westmead	Like Hb A	α-thalassaemia trail
α125(H8)	Leu-Pro	Hb Quong Sze	Like Hb A	α-Thalassaemia trail
β chain				
β13(A10)	Als-Asp	Hb J-Lene	Like Hb 3	None
β21(B3)	Asp-Asn	Hb Cocody	Like Hb S	None
β21(B3)	Asp-Tyr	Hb Connecticut	?	Low O_2 affinity
β21(B3)	Asp-Tyr	Hb Yusa	Like Hb S	None
β23(B5)	Val-Cly	Hb Miyashiro	Like Hb A	None
β31(B13)	Leu-pro	Hb Yokohama	Like Hb A	Compensated haemolytic anaemia
β34(B16)	Val-Phs	Hb Pitie-Salatriere	Like Hb A°	Erythrocytosis
β45(CD4)	Pha-Ser	Hb Cheverly	Like Hb A	Erythrocytosis cyanosis
β52(D3)	Asp-His	Hb Summer Hill	Like Hb S	None
β75(E19)	Leu-Arg	Hb Pasadena	Like Hb S	Compensated haemolytic anaemia
β75(E19)	Leu-deleted	Hb Vickaburg	Like Hb A	β-Thalassaemia
β79(EF3)	Asp-Tyr	Hb Tampa	Between Hb F and S	Normal homo- and Hetero-zygotes