A SURVEY OF THE HAEMOGLOBIN VARIANTS AMONG NAJJDIANS

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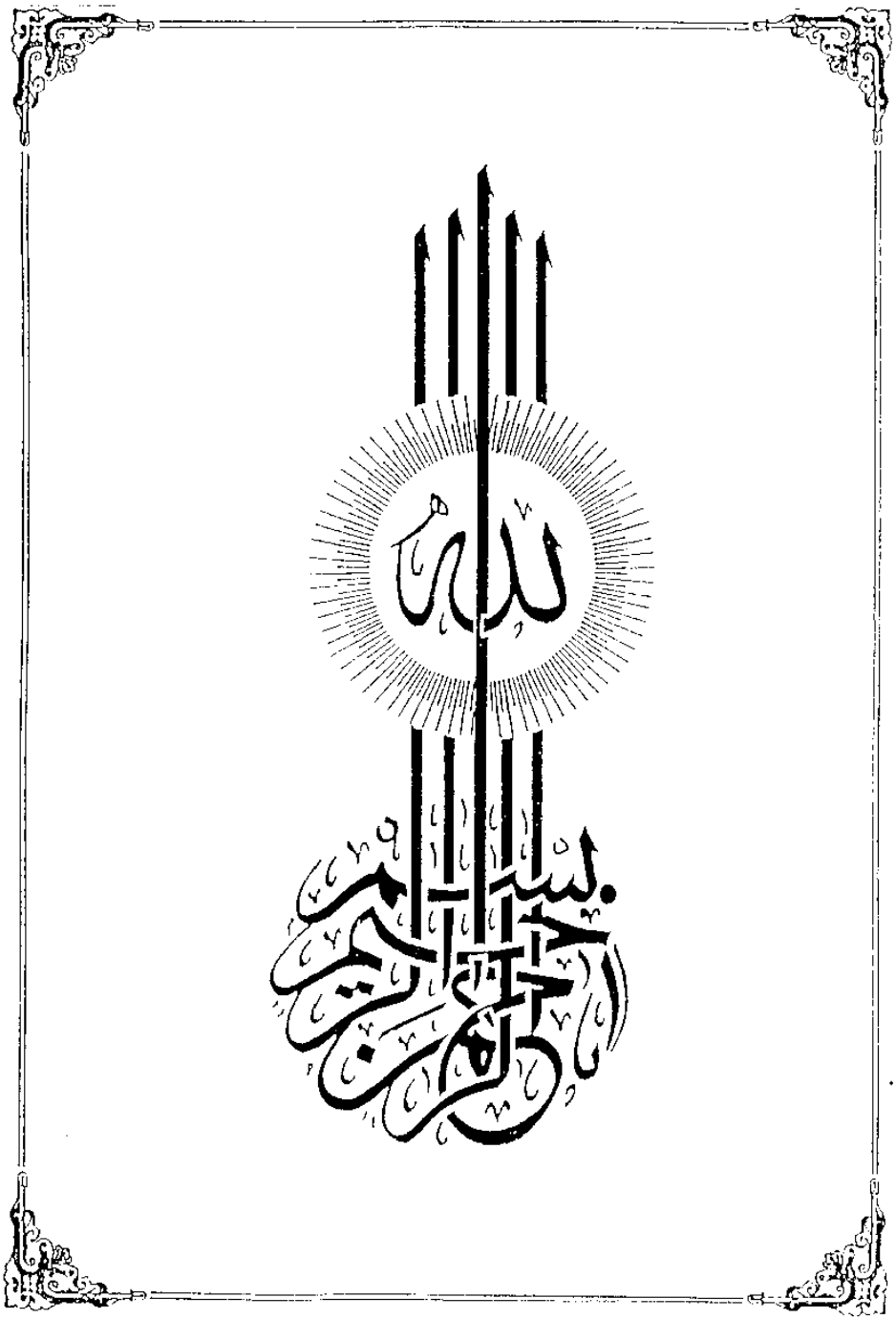
" TO THE MEMORY OF MY MOTHER"



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INTRODUCTION AND AIM OF WORK

Since the original description of the first abnormal haemoglobin variant (Hb-S) in 1910[1] and its genetic, biochemical and clinical basis, many studies have been carried out all over the world which have led to discovery of several haemoglobin variants.

It is only in the last two decades that we have begun to appreciate just how common haemoglobinopathies are and what a considerable public health problem they pose, particularly in countries where medical resources are limited. As, the haemoglobinopathies are inherited disorders, the prognosis for severely affected individuals remains bad. Research on the distribution of abnormal haemoglobin variants, an understanding of the genetics of the disorder can improve the clinical management of these potentially disabling conditions.

The study of haemoglobin variants and their distribution can also be used as an anthropological marker for ethnic groups which have been exposed to population migration. The introduction of sickle cell haemoglobin to the inhabitants of the Middle East countries from the importation of slaves from Africa is an excellent example of this.

The Arabian peninsula is one of the Middle East areas which has been influenced by African slave trade many centuries ago. It was thought desirable, therefore, to study the frequency of haemoglobin variants in Najjd area (Central province) and compare findings with those reported from the other different parts of the country.

HISTORICAL BACKGROUND

The story of the growth of knowledge of the Hb variants provides a fascinating picture illustrating the value of the pursuit of knowledge for its own sake. It reveals the fruits that can be gained if curiosity is aroused and an answer sought to questions that may at the time seem to be of no practical importance.

In 1910, James Herrick[1] reported peculiar, elongated, sickle-shaped red cell in a case of severe anaemia in a Negro boy. The sickle cells he thought, were freakish poikilocytes and suggested that they were a manifestation of a specific chemical or physical condition.

In 1917, Emmel,[2] observed the transformation of the biconcave disc to the sickle form in vitro. He also noted that sickling occured both in persons with severe anaemia and in others who were apparently healthy, thus recognising both sickle cell anaemia and sickle cell trait. In 1927 Hahn and Gillespie[3] delineated the conditions affecting sickling process in vitro, including pH, temperature, fixatives and tonicity. Among the most important of their observations was that exclusion

of oxygen was a prerequisite to sickling and that the phenomena could be reversed on re-exposure to the gas, they postulated that similar effects of oxygen could occur in vivo. Later, Hahn[4] applied the term "sickle cell trait" to the asymptomatic condition associated with in vitro sickling.

Paralleling these events was the report of Cooley and Lee in 1925,[5] who separated from the complex of disorders of infancy and childhood that had been known as Von Jaksch's anaemia a syndrome characterised by chronic, progressive anaemia commencing early in life, with erythroblastosis in the blood, a characteristic facies, splenomegaly and a familial incidence. The observation that these patients were of Mediterranean background led to the introduction of the name "thalassemia" derived from the Greek word for sea.

At this time and in the following years, descriptions appeared in the Italian literature[6] of a milder disorder, encountered in adults as well as children, which was marked by morphologic abnormalities in the red cells and evidence of increased haemolysis.

In 1938, Camino-Petros[7] noted that the parents of a child suffering from severe thalassemia had diminished red cell osmotic fragility.

In 1940 Wintrobe and his associates[8] described what was considered to be a mild form of Cooley's anaemia. These investigators also showed that the manifestations of this disorder were present in both parents of a child with classic Cooley's anaemia.

Subsequent genetic studies established that Cooley's anaemia is the homozygous state for a partially dominant autosomal gene. The patients described by Rietti and by Wintrobe and their co-workers representing the heterozygous state. In 1940 Sherman[9] confirmed the observations of Hahn and Gillespie regarding the influence of oxygen on sickling process, also he found that the cells in the sickle cell disease were birefringent, an observation which was remained unexplained for nearly a decade.

The birefringence was called to the attention of the physical chemist, Linus Pauling.[10]

In 1949 Pauling conceived the possibility that interaction between abnormal haemoglobin molecules might explain this phenomenon, with Itano, he discovered that the haemoglobin of patients with sickle-cell anaemia differed from that of normal people. Pauling

discovery was the first step in a series of investigations which greatly increased our understanding of the genetics, chemistry and physical properties of normal and abnormal haemoglobins.

As it was explained, the concept of molecular disease was formulated by Pauling who discovered the presence of abnormal haemoglobin in patients with sickle-cell anaemia, this haemoglobin was found to be electrophoretically slower than the normal haemoglobin, "Hb-A" and it was called "Hb-S", thus Hb-S was the first discovered abnormal haemoglobin.

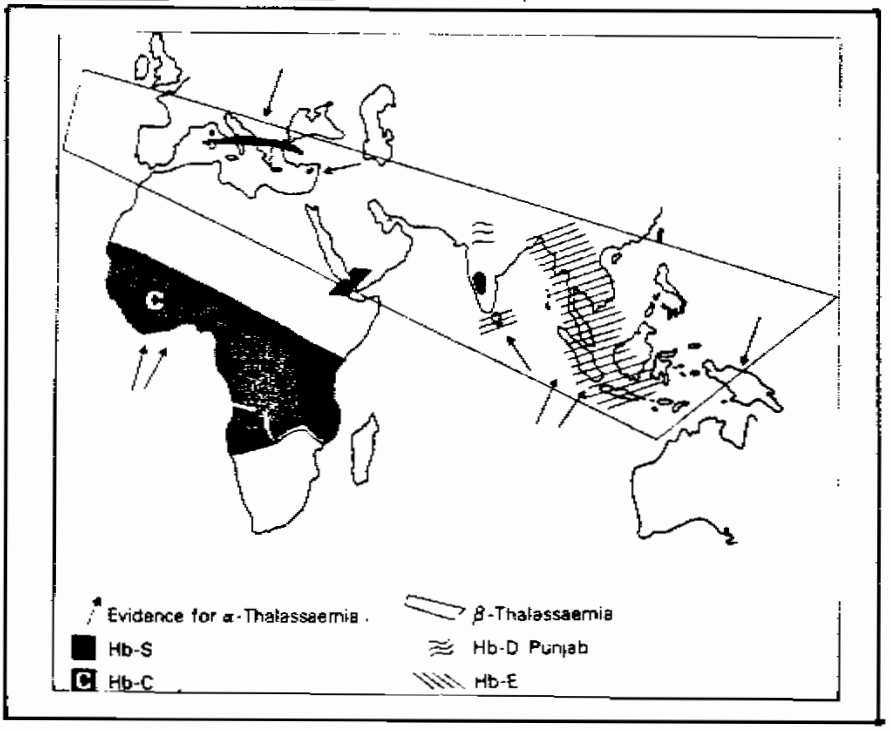
In the same year that Pauling made his discovery, Neel[11] published a report of genetic studies establishing that sickle cell trait was the heterozygous and sickle cell anaemia, the homozygous state for the same gene.

Year after year discoveries were going on, and more than 326 pathological haemoglobin variants are known at the present time,[12] among them only, four haemoglobions, S. C, D Punjab, and E, often are called the "common haemoglobins" because each affects millions of individuals. It soon became clearly evident that

the frequency of the abnormal haemoglobin varies considerably with geographic location and racial group, e.g. the maximum prevalence of thalassemia is around the Mediterranean littoral and in South-east Asia, on the other hand Hb-S and Hb-C are prevalent in tropical Africa and also seen among immigrant Negro populations in the New World. Hereditary disorders of haemoglobin are less common among people of Northern European origin, but no ethnic group is totally spared.

Haemoglobin S is by far, the most common of all abnormal haemoglobins, it is found particularly in equatorial Africa in a broad zone extending from coast to coast.(Fig.1)

Figure 1. Geographical distribution of the clinically important haemoglobin variants.



* In Western Africa, Hb-C is found, in addition to Hb-S, as indicated in the map.[13]

The gene for sickle-cell haemoglobin (Hb-S) is transmitted as an autosomal dominant, if a single gene is inherited from one parent the relatively benign heterozygous sickle-cell trait results, on the other hand the inheritance of two genes, one from each parent, produces the severe homozygous sickle-cell anaemia.

The sickle-cell gene may also be associated with a gene for another structural haemoglobin variant or with one of the thalassemia genes. Some studies in Africa[14] showed that homozygous sickle-cell disease was rare in spite of a high though variable incidence of the sickle-cell trait and it seemed surprising that the disease was commoner in the American Negro.[15]

It was soon realized however that in Africa the mortality rate of homozygous sickle-cell disease in early childhood is so high that not many cases reach adulthood falsifying its actual incidence as expected from genetic theory.[16] In spite of loss of genes at each generation its incidence remains high and it does not appear that the spontaneous mutation rate is great enough to account for this.[14]

It is suggested that individuals with the trait are endowed with some advantage so that they reproduce

more efficiently than those without it, a "balanced polymorphism".[17] A likely advantage is that heterozygotes enjoy a relative immunity to Falciparum malaria.[18]

The "malaria hypothesis" also can be applied to the other types of the common haemoglobin as well as thalassemia and G6PD deficiency. It was found that the geographic distributions of Falciparum malaria and Hb-S can coincide remarkably and the frequency of sickle trait is correlated with the endemicity of malaria in many tribes, furthermore a lower rate of parasitization of the blood is found in subjects with sickle trait, even when they are deliberately inoculated with the parasite, and the mortality rate from cerebral malaria is much lower in children with the trait than in those free of Hb-S.[19]

The mechanism of malarial resistance has not been established, but the most likely hypothesis is that the invaded cells adhere to vessel walls where they become deoxygenated and assume the sickled shape, which in turn leads to their destruction by phagocytosis. When red cells are used in in vitro culture systems, growth occurs as well in Hb-S cells as in normal cells.[18]