Editorial: The background to sickling

Sickle cell haemoglobin is an abnormal haemoglobin found mainly but not exclusively in people of negro origin. This particular abnormal haemoglobin has an unusual property in that, when it is deoxygenated, it becomes insoluble and distorts the normally discoid red cell into a characteristic sickle shape. Such sickled red cells tend to obstruct capillaries and this leads to infarction, especially in areas of vascular stasis such as the spleen and the bone marrow. The periphery of the retina may also be affected and the ophthalmic manifestations resulting from the presence of sickle cell haemoglobin are considered in two articles appearing in this number of the Journal.

STRUCTURE OF NORMAL ADULT HAEMOGLOBIN

Protein (e.g. the globin of haemoglobin) consists of an assortment of twenty chemically distinct amino-acids linked together to form a polypeptide chain. The order in which these different amino-acids occur in the polypeptide chain of any particular protein is determined by the gene responsible for the production of that specific polypeptide chain. An alteration in the deoxyribonucleic acid (DNA) of which that gene is composed (i.e. a mutation) will result in an alteration in the amino-acid composition of the polypeptide chain and the production, in the case of globin, of an abnormal haemoglobin.

Normal adult haemoglobin is a tetrramer constructed from four haem/globin units, each of the four globin units being a polypeptide chain of approximately 140 amino-acid units long. Two of the four globin units of the haemoglobin molecule are similar to each other and are called \( \alpha \), whereas the other two are composed of amino-acids arranged in a different order and are called \( \beta \). Normal adult haemoglobin is called \( \alpha_2 \beta_2 \), different genes being responsible for the production of the \( \alpha \) polypeptide chains and the \( \beta \) polypeptide chains.

ABNORMAL HAEMOGLOBINS

The great majority of the abnormal haemoglobins differ from normal adult haemoglobin in that, in one position of either the \( \alpha \) or the \( \beta \) polypeptide chain, a different amino-acid has been substituted for the one that is present in normal adult haemoglobin. Over one hundred abnormal haemoglobins have now been described, and of these only four different types are common, all having abnormalities in the \( \beta \) half of the haemoglobin molecule. A polypeptide chain may be likened to a paper chain composed of 140 links and made up from paper strips of twenty different colours, each colour representing a different amino-acid. In the case of sickle cell haemoglobin, the haemoglobin molecule will be identical to the normal except that, in the 6th position in the \( \beta \) polypeptide chains, the paper link will be of a different colour. The two paper chains representing the two \( \alpha \) polypeptide chains in each haemoglobin molecule will be normal. It can thus be seen that, structurally speaking, the abnormality in an abnormal haemoglobin is remarkably small. Nevertheless, the functional effect of such a minute structural change can be remarkably devastating.
(1) **Haemoglobin S** (Sickle cell haemoglobin)

The main reservoir for this abnormal haemoglobin is Central Africa and the New World negroes originating from this area. Small pockets are found in the Mediterranean area (e.g. Greece), the Middle East, and some tribal groups in India. In the case of Haemoglobin S, the amino-acid valine has been substituted for glutamic acid, the amino-acid normally present in the 6th position of the \( \beta \) polypeptide chain.

(2) **Haemoglobin C**

The reservoir for this abnormal haemoglobin is West Africa, it being therefore also found in the New World negro. In the case of Haemoglobin C, the amino-acid lysine has been substituted for the glutamic acid normally present in the sixth position of the \( \beta \) polypeptide chain.

(3) **Haemoglobin D (Punjab)**

The main reservoir of Haemoglobin D is North West India and Pakistan.

(4) **Haemoglobin E**

This abnormal haemoglobin is found in South East Asia.

**Thalassaemia**

In the case of thalassaemia there is a depression of either \( \alpha \) polypeptide chain production (\( \alpha \) thalassaemia) or \( \beta \) polypeptide chain production (\( \beta \) thalassaemia). In some instances, the depression of polypeptide chain production by the thalassaemic gene is total, and in others it is only partial. The geographical distribution of thalassaemia is widespread, through the Mediterranean area and the Middle and the Far East. It is also found to some extent in negro populations of West Africa and the New World.

**The sickle cell syndromes**

There are two \( \beta \) polypeptide chain genes, one inherited from each parent. As either one or both may be abnormal, a number of related clinical states are thus possible.

**Normal**

Genetic State = \( \beta^A - \beta^A \)

The normal \( \beta \) polypeptide chain gene is labelled \( \beta^A \), the A symbolizing normal adult haemoglobin.

This normal \( \beta^A \) gene produces normal \( \beta \) polypeptide chains as found in normal adult haemoglobin.

**Sickle cell carrier**

Genetic State = \( \beta^A - \beta^S \)

In many parts of Central Africa, 20% of the population are sickle cell carriers, the carrier rate in the New World negro being approximately 8%. It is convenient to consider that 10% of negro immigrants in the United Kingdom are sickle cell trait carriers. Because only about half of the haemoglobin present in the red cells is sickle cell haemoglobin (the other half being normal adult haemoglobin), the red cells of a sickle cell carrier require severe deoxygenation to sickle. Unless the subject is submitted to extremely low and unphysiological Po\(_2\) levels (e.g. an anaesthetic accident), the sickle cell trait can be
considered to be harmless; indeed its presence may be beneficial because it results in an increased resistance to malignant malaria.

**Sickle cell anaemia**

Genetic State = $\beta^4 - \beta^s$

The patient with homozygous sickle cell disease (SS) will be born at a frequency of one in one hundred births when the carrier rate is 20% and one in four hundred births when the carrier rate is 10%. A patient with sickle cell anaemia produces no normal adult haemoglobin—virtually all the haemoglobin present in the red cells being sickle cell haemoglobin. Patients with sickle cell anaemia have a chronic haemolytic anaemia interspersed with crises, mainly of the infarctive type.

**Sickle cell Haemoglobin C disease (SC disease)**

Genetic State = $\beta^4 - \beta^C$

Patients with sickle cell Haemoglobin C disease also lack a normal $\beta^A$ gene capable of producing normal $\beta$ polypeptide chain genes. They therefore have no normal adult haemoglobin, their haemoglobin consisting of Haemoglobin S and Haemoglobin C produced by the $\beta^s$ and $\beta^C$ polypeptide chain genes respectively. Patients with sickle cell Haemoglobin C disease suffer little if at all from anaemia, the main clinical problem being infrequent, but on occasions, severe infarctive crises.

**Sickle-cell $\beta$ thalassaemia**

Genetic State = $\beta^s - \beta^{Thal}$

Because the $\beta$ thalassaemia gene results in a depression of normal $\beta$ polypeptide chain production, the majority of the $\beta$ polypeptide chains produced will be from the $\beta^s$ gene and will carry the amino-acid substitution characteristic of sickle cell haemoglobin. Whether a minority of normal adult haemoglobin or none is found will depend upon whether a few normal $\beta$ polypeptide chains or none are produced by the $\beta$ thalassaemia gene.

It is customary to include under the term “sickle cell disease”, sickle cell anaemia, sickle cell Haemoglobin C disease, and sickle cell $\beta$ thalassaemia, all conditions commonly associated with clinical disability. The simple sickle cell trait carrier is so rarely associated with symptoms that it is not considered to be a sickle cell disease. This classification is not universally acceptable, some authors considering that sickle cell disease is an interchangeable synonym for sickle cell anaemia.

**Bibliography**

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