ANAESTHESIA AND SICKLE-CELL HAEMOGLOBIN

With a Case Report

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The problem of anaesthetizing patients who possess sickle-cell haemoglobin in their red cells has been widely discussed (Gilbertson, 1965 and 1967; Browne, 1965; Oduro, 1969; Oduntan and Isaacs, 1971).

Caution has been urged when dealing with patients suffering from sickle-cell disease (sickle-cell anaemia, sickle-cell haemoglobin C disease and sickle-cell thalassaemia). By comparison, the anaesthetic risk for patients with the virtually asymptomatic and common sickle-cell trait or carrier state must be much less. Konotey-Ahulu (1969), however, has highlighted the need to consider the anaesthetic problems associated with sickle-cell haemoglobin, irrespective of whether the patient has sickle-cell disease or the sickle-cell trait. He warned that West Africans are presenting for anaesthesia in the United Kingdom and stressed that all peoples of African descent should be screened to detect sickle-cell haemoglobin before being subjected to anaesthesia.

The following case report gives support for this view and emphasizes the need for awareness in the management of anaesthesia even for the sickle-cell trait carrier.

CASE REPORT

A 39-year-old Ghanaian was seen as an out-patient for manipulation of his left knee under general anaesthesia. The anaesthetist found that, although a sickling test had never been carried out, the patient's record showed normal haemoglobin levels on several occasions and that he had been anaesthetized previously without complications. It was, therefore, thought justifiable to proceed with anaesthesia without further tests. Propanidid 500 mg. was injected intravenously and the manipulation was completed within two minutes without event. Following propanidid, the patient hyperventilated characteristically and subsequently maintained an adequate ventilation as judged by clinical observation.

After about four minutes following the onset of anaesthesia, the patient opened his eyes on command and coincident with this arousal, started to retch. He was turned on his side and tilted into the Trendelenberg position. At this point he began to produce copious watery vomit to a total amount estimated at about one litre. The episode was accompanied by a complaint of severe pain in the left hypochondrium which was clearly described by the patient in between his vomiting episodes. Cyanosis had already been observed and oxygen therapy was provided as carefully as was possible during the episodic vomiting.

When the vomiting was finished the patient was restored to the supine Trendelenberg position and at this time examination found the patient to be without recordable blood pressure; a thready pulse and cyanosis still persisting despite 100 per cent oxygen and good spontaneous ventilation. An intravenous infusion of dextrose-saline was begun and the patient recovered a normal blood pressure, pulse and colour within about fifteen minutes, and subsequently made a good recovery. Oxygen therapy was continued for two hours.

Investigation revealed a normal e.c.g., Hb. 20.5 g/100 ml and haemoglobin electrophoresis showed the presence of both normal adult and sickle-cell haemoglobin in approximately equal proportions.

Quantitation of haemoglobin fractions by column chromatography:

<table>
<thead>
<tr>
<th>Haemoglobin Fraction</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Adult Haemoglobin</td>
<td>52.1%</td>
</tr>
<tr>
<td>Sickle-cell Haemoglobin</td>
<td>44.0%</td>
</tr>
<tr>
<td>Haemoglobin A_2</td>
<td>2.7%</td>
</tr>
<tr>
<td>Foetal Haemoglobin</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

Haemoglobin solubility studies were compatible with the sickle-cell trait. The next day the haemoglobin level had fallen to 15.6 g/100 ml. Subsequently the patient made a good recovery.

It is presumed that this sickle-cell trait carrier suffered a splenic infarction following a vomiting attack on recovery from anaesthesia. The combination of the hypoxia and a transient polycythaemia presumably caused by dehydration, seems to have precipitated the infarctive crisis.

THE STRUCTURE OF HAEMOGLOBIN

The basic oxygen carrying unit consists of a haem group deeply inserted into a globin molecule. The globin is composed of a total of about 140 amino acids joined together in a fixed order which has been predetermined by the gene responsible for the production of that particular polypeptide chain. One can liken the globin polypeptide chain to a paper chain of about 140 links. There are 20 different amino acids (colours) to choose from and each individual gene produces a characteristic paper (polypeptide) chain, i.e., the inherited genetic information exactly controls the constituents of a polypeptide chain.

Myoglobin functions as a single haem-globin unit but haemoglobin consists of four myoglobin-like...
monomers joined together to form a tetramer. The advantage that results from this union are considered when the oxygen dissociation curve of haemoglobin is discussed.

A normal adult haemoglobin molecule (Hb.A) contains two polypeptide chains called α and two polypeptide chains, different from the α chains and called β. The normal adult haemoglobin molecule (Hb.A) can therefore be labelled ααββ. α and β polypeptide chains have a different amino acid constitution, different genes being responsible for their production. It is therefore possible to have a disease process involving only the β chain, leaving the α chain production normal. Again, it is possible to have a disease process involving only the α polypeptide chains in which the β chain production is unaffected. All the states referred to in this article result from abnormalities of β polypeptide chain production, the genes responsible for the α polypeptide chain being quite normal. Diseases resulting from abnormal production of α polypeptide chain genes exist but they are relatively uncommon.

Foetal haemoglobin (Hb.F) is present at a level of about 70 per cent in the newborn and is almost completely replaced by adult haemoglobin within the first few months of life. A foetal haemoglobin molecule also contains two α chains but differs from an adult haemoglobin molecule because it has two γ chains instead of two β chains. Foetal haemoglobin can, therefore, be labelled ααγγ and may persist in adults with such conditions as sickle-cell anaemia and β thalassaemia. Other physiological haemoglobins such as haemoglobin A_2 (ααγγ), which is present in the normal adult at a level below 3 per cent, also exist.

THE ABNORMAL HAEMOGLOBINS AND THALASSAEMIA

There are two basic types of disease process which result in the faulty manufacture of a haemoglobin polypeptide chain. In one of these (the abnormal haemoglobins) the polypeptide chain produced is abnormal, and in the other (the thalassaemias) the polypeptide chain is normal but produced in insufficient quantity. Because of the sickle-cell disease called sickle-cell thalassaemia an understanding of thalassaemia is necessary.

(1) Abnormal haemoglobins.

The very great majority of the over one hundred abnormal haemoglobin molecules described, differ from normal haemoglobin in that there has been a substitution of one amino acid for another at a single position in either the α or the β polypeptide chain. For example, in sickle-cell haemoglobin (Hb.S) there has been a substitution of glutamic acid in the 6th position of the normal β polypeptide chain by valine, the α polypeptide chains being normal. In other words, the paper chains representing the two α chains in a sickle-cell haemoglobin molecule will be absolutely identical to the two α paper chains found in the normal adult haemoglobin molecule. The two paper chains representing the β polypeptide chains in the sickle-cell haemoglobin molecule will be identical to the normal except at the sixth position, where a different “colour” will be found. Imagined this way, it will be apparent that the “molecular lesion” responsible for such a devastating disease is surprisingly small.

A pair of genes, one derived from each parent, carries the genetic information necessary for the manufacture of the β polypeptide chains. Quite independent genes (whether one or two pairs is not yet certain) are responsible for the α polypeptide chain production.

A sickle-cell carrier will have inherited from one parent the abnormal sickle-cell β polypeptide chain gene. The paired (allelic) gene inherited from the other parent will be normal. The abnormal β polypeptide chain gene responsible for the production of sickle-cell haemoglobin is codominant, i.e., both the normal and the abnormal genes produce an end product, although the amount of normal haemoglobin present is always greater than the sickle-cell haemoglobin, the latter amounting to between 22 and 45 per cent of the total (Neel, Wells and Itano, 1951).

In contrast, the patient with sickle-cell anaemia will have inherited (one from each parent) the two abnormal sickle-cell polypeptide chain genes that he possesses. Because he has no normal β polypeptide chain gene, he cannot produce a normal β polypeptide chain and as a result cannot produce normal adult haemoglobin.

The three other common haemoglobin variants, haemoglobin C, D. Punjab and E also have abnormal β polypeptide chains. The carriers (heterozygotes) of haemoglobin C, D. Punjab and E are perfectly fit. The abnormal homozygotes who have haemoglobin C disease and E disease, have chronic haemolytic anaemia with splenomegaly. There is little information about haemoglobin D disease.

It is also possible for a patient to possess one gene which produces the β polypeptide chain gene characteristic of sickle-cell haemoglobin and another β polypeptide chain gene, which produces for
example, the β polypeptide chain characteristic of haemoglobin C. Such a patient would produce sickle-cell haemoglobin and haemoglobin C in approximately equal quantities and would suffer from sickle-cell haemoglobin C disease.

(2) Thalassaemia.
There is a depression of either the α (α thalassaemia) or the β (β thalassaemia) polypeptide chain production. The common type of severe thalassaemia, usually resulting in childhood death, (Cooley's anaemia or Mediterranean anaemia) is β thalassaemia major, the patient having two β thalassaemia genes and therefore no normal β polypeptide chain gene. In contrast, the relatively little incapacitated carrier of β thalassaemia (who has β thalassaemia minor) carries one β thalassaemia gene and one normal β polypeptide chain gene. It is possible for a patient to possess one β thalassaemia gene and one sickle-cell β polypeptide chain gene. Such a person has sickle-cell-thalassaemia and would produce mainly sickle-cell haemoglobin, the output of normal β polypeptide chains from the β thalassaemia gene being greatly reduced. Whilst many such patients suffer from a moderately severe clinical illness, others may be virtually asymptomatic and only detected by chance in old age.

A genetic background of α thalassaemia is complicated but fortunately is irrelevant to the problems discussed in this article.

(3) The inheritance of sickle-cell haemoglobin.
The inheritance of the haemoglobinopathies can be calculated using basic Mendelian principles. For a patient to suffer from sickle-cell anaemia, each parent (usually a sickle-cell trait carrier) must contribute an abnormal sickle-cell β polypeptide chain gene. An average of one in four children from the mating of a sickle-cell trait carrier with a sickle-cell trait carrier will have sickle-cell anaemia (fig. 1).

The family study of the patient described in the case is illustrative. He has married a woman with haemoglobin C disease (she possesses two abnormal genes each producing the β polypeptide chain with the amino acid substitution characteristic of Hb.C). He has informed us that their only child has sickle-cell haemoglobin C disease, an outcome one would expect in 50 per cent of the children of such a marriage. The other 50 per cent would be carriers of haemoglobin C (fig. 2).

The inheritance of β thalassaemia is similar to these illustrated examples. One in four children from a mating of two parents with the carrier state, β thalassaemia minor, will suffer from β thalassaemia major. It is apparent that, with genetic counselling, both sickle-cell anaemia and β thalassaemia major are preventable diseases.

THE WORLD DISTRIBUTION OF THE ABNORMAL HAEMOGLOBINS AND β THALASSAEMIA

(1) Sickle-cell haemoglobin.
The Negro population in a large area of Central Africa has a sickle-cell haemoglobin carrier rate of about 20 per cent. The Negro population of the West Indies (and the North American Negro) has a sickle-cell carrier rate of only about 8 per cent. In this country, allowing for the large preponderance of West Indian immigrants, one can reasonably assume an overall Negro sickle-cell carrier rate of 10 per cent.

Sickle-cell haemoglobin is found in much reduced quantities amongst the Mediterranean population (e.g., Greece) and also in the Middle East and hill tribes of India.

Any advice concerning the management of the sickle-cell trait carrier must allow for the fact that hundreds of millions of people carry this abnormal gene and any recommendations made would involve
20 per cent of patients in an average Central African hospital.

(2) Haemoglobin C.

Haemoglobin C, like haemoglobin S, is also predominantly a Negro variant, although much more localized in its distribution occurring in Northern Ghana at a level of about 15 per cent. It is also found in the Negro population of this country and in the New World at a level of about 2 per cent.

(3) Haemoglobin D.Punjab and E.

The two other common haemoglobin variants are haemoglobin D (Punjab), which is found mainly in North-West India and Pakistan, and Hb.E found in the Far East. These last two are unlikely to be present in the pure African Negro but could well be found combined with sickle-cell haemoglobin in countries such as Jamaica where racial admixture has occurred.

(4) $\beta$ Thalassaemia.

$\beta$ thalassaemia is spread in a broad band running through the Mediterranean, Middle East, India and into China. It occurs to a lesser extent in the West African and the West Indian.

The West African (and Negroes originating in this area, e.g., the West Indian) are likely to carry the sickle-cell gene, either paired with another sickle-cell gene or in combination with a gene for normal adult haemoglobin, haemoglobin C or $\beta$ thalassaemia.

"SICKLE-CELL SYNDROMES"

The sickling phenomenon is characteristic of sickle-cell haemoglobin. When sickle-cell haemoglobin is in the oxygenated form it is a soluble protein. However, when the pigment is in the reduced form it becomes, compared with normal adult haemoglobin, highly insoluble, crystalizing out of solution as rod-like structures. When this phenomenon occurs within the red cell, the erythrocyte becomes distorted into its characteristic sickle form. If a red cell has sickled and desickled on a number of occasions there is a risk that the cell membrane will become damaged. Such cells may become irreversibly sickled cells and are cleared rapidly from the circulation.

Sickle-cells may entwine within capillaries and venules obstructing the flow of the nutrient vessels, giving rise to scattered areas of infarction. Of all the factors which exacerbate the sickling phenomenon, the most important is a reduction of the oxygen tension. This phenomenon of insolubility in the reduced form is not possessed by the other common haemoglobin variants C, D.Punjab and E.

The term "sickle-cell syndromes" covers a number of genetically determined conditions which have in common the presence within the red cell of a variable quantity of sickle-cell haemoglobin (Hb.S). These conditions vary in clinical severity from, at one end of the clinical spectrum, the almost completely benign sickle-cell trait to—at the other end—the patient with the potentially lethal sickle-cell anaemia.

"Sickle-cell disease" is confined to the varieties of the sickle-cell syndromes commonly associated with symptoms (e.g., sickle-cell anaemia, sickle-cell haemoglobin C disease and sickle-cell thalassaemia). In order not to alarm the virtually asymptomatic sickle-cell trait carrier, it is customary not to consider the sickle-cell trait carrier as a sickle-cell disease, although even these fit carriers are liable on very rare occasions to haematuria and also infarctive crises when oxygen tension is greatly reduced (e.g., during an anaesthetic accident and high altitude flying in unpressurized planes).

(1) Sickle-cell trait carrier.

**Genetic state.**

\[
\begin{array}{c}
A \\
S
\end{array}
\]

A = normal $\beta$ chain gene

S = sickle-cell $\beta$ chain gene

**Haemoglobin production pattern.**

Whilst this carrier will possess both normal and sickle-cell haemoglobin, the amount of sickle-cell haemoglobin will always be in the minority.

**Clinical state.**

Normal.

**Haemoglobin level.**

Normal in uncomplicated cases.

**Blood film.**

Normal in uncomplicated cases.

(2) Sickle-cell anaemia.

**Genetic state.**

\[
\begin{array}{c}
S \\
S
\end{array}
\]
Haemoglobin production pattern.
Such a patient usually has about 90-95 per cent sickle-cell haemoglobin and 5-10 per cent foetal haemoglobin.

Clinical state.
Such patients are liable to periodic infarctive crises. The spleen is usually impalpable after five years of age because of scarring, which follows multiple previous splenic infarcts. Occasional patients with sickle-cell anaemia have an unusually high level of foetal haemoglobin and run a more benign clinical course having—even as an adult—a palpable spleen.

Haemoglobin level.
This usually lies between 5-10 g/100 ml.

Blood film.
Poikilocytes, target cells with polychromasia and hypochromia and often circulating sickle-cells are found. An alert technician will often diagnose an infarctive sickling crisis in a patient with sickle-cell anaemia from the blood film alone.

(3) Sickle-cell haemoglobin C disease.

Genetic state.

\[
\begin{array}{c}
S \\
C
\end{array}
\]

C = Haemoglobin C \( \beta \) chain gene

Haemoglobin production pattern.
This doubly abnormal heterozygote possesses sickle-cell haemoglobin and haemoglobin C in approximately equal proportions.

Clinical state.
These patients are often well. They are, however, liable to occasional severe and sometimes fatal infarctive crises. Splenomegaly is present in the majority of cases.

Haemoglobin level.
Commonly lies between 10-14 g/100 ml being on occasions within the normal range.

Blood film.
Target cells predominate. Circulating sickle-cells are unusual.

(4) Sickle-cell \( \beta \) thalassaemia.

Thal = \( \beta \) Thalassaemia gene

Haemoglobin production pattern.
Commonly these patients produce little or no normal adult haemoglobin and they have a haemoglobin electrophoretic pattern indistinguishable from that of sickle-cell anaemia. However, on occasion production of up to about 30 per cent of normal adult haemoglobin (produced by the \( \beta \) thalassaemia gene) may give a haemoglobin electrophoretic pattern liable to be confused with the sickle-cell trait.

Clinical state.
These patients present usually with a comparatively benign form of sickle-cell anaemia, some cases even being asymptomatic and discovered purely by chance. As with the cases of a sickle-cell anaemia, associated with high foetal haemoglobin, splenomegaly is usual and this merely reflects the fact that there have been less splenic infarcts and therefore "autosplenectomy", characteristic of sickle-cell anaemia, has not occurred.

Haemoglobin level.
Although it commonly lies between 8-12 g/100 ml, on occasions the haemoglobin level may be within the normal range.

Blood film.
The abnormal features are less marked than those described in sickle-cell anaemia, circulating sickle-cells being less common.

In this country, with a sickle-cell carrier rate of about 10 per cent one would expect about one in four hundred Negro immigrant babies to be born with sickle-cell anaemia. Sickle-cell haemoglobin C disease and sickle-cell thalassaemia would be expected, in about one in every one to two thousand children of Negro parentage.

THE PATHOGENESIS OF CRISEx ASSOCIATED WITH SICKLING HAEMOGLOBINOPATHIES
A patient with sickle-cell disease usually maintains a haematological and clinical condition which, for that individual, can be recognized as the steady state. A deterioration (crisis) in this "normal" state may have an alarmingly sudden onset and on occasion, a fatal outcome.
Infections, bacterial, viral and malarial are, in particular, liable to precipitate crisis. Such complications should be vigorously treated.

**Infarctive crisis.**

The commonest form of crisis in patients with sickle-cell anaemia is the infarctive crisis. This is caused by tangled sickled red cells obstructing blood flow which leads to tissue anoxia and ultimately tissue death. Apart from the spleen, infarctive crises in bones, chest and abdomen are particularly common. Other sites are legion—the patient may present with diagnoses as divergent as meningitis and priapism.

The major factors liable to provoke infarctive crises are: (1) Low blood oxygen tension. (2) Stasis, promoted by circulatory collapse, cooling, shock and prolonged applications of tourniquets. Increase in blood viscosity, caused for example by dehydration, can also provoke an infarctive crisis. (3) Low blood pH.

The slowing of the local circulation caused by the blockage due to the sickled cells itself causes further hypoxia, acidosis and stasis. A vicious circle is thus set up, encouraging further sickling to occur at that site.

It will be apparent that the anaesthetist may do much to prevent the infarctive crisis and indeed current emphasis is laid on the prevention of a sickle-cell crisis and not its cure.

Once established, a crisis is difficult to arrest, hence the importance of prophylaxis. No treatment is likely to unblock a vessel obstructed by sickled cells. In addition to keeping the patient warm, treating infections and maintaining oxygenation, hydration and alkalosis, the following have been suggested: (1) magnesium sulphate because of its anticoagulative and vasodilatory actions. One to two ml of 50 per cent solution (or less in small children) given over 10 minutes intravenously, 4-hourly until symptoms abate (Hugh-Jones, Lehmann and McAlister, 1964); (2) heparin, to reduce the risk of a fatal marrow embolus. It might be therefore especially indicated when severe bone pain is a presenting feature.

When treating pain, addictive drugs should be avoided if possible. Indeed, patients may mimic a sickling crisis merely to obtain the drug of their addiction.

**Aplastic crisis.**

The aplastic crisis, caused by marrow depression, is associated with infections, especially of viral type. Because of the short red cell life, even a short-lived depression of marrow activity can, in sickle-cell anaemia, cause a catastrophic fall in haemoglobin level and transfusion is then needed to maintain life. Marrow output failure may also result from a deficiency of folic acid. Prophylactic administration of folic acid is desirable in all patients with sickle-cell disease and is imperative during pregnancy.

**Sequestration crisis.**

This crisis particularly affects infants and young children. There is sudden massive pooling of red cells, especially in the spleen and immediate transfusion is needed to maintain life.

**Haemolytic crisis.**

The red cell life span varies according to the variety of sickle-cell disease. It is greatly shortened to about 17 days in sickle-cell anaemia. Any given figure will vary from patient to patient and in any particular patient the red cell life span may, perhaps as a result of infection, be suddenly reduced (the haemolytic crisis) below the "normal" for that particular person. The life span of the red cell in the sickle-cell trait is normal.

It must be remembered that ethnic groups liable to carry the sickle-cell gene may also be deficient in glucose 6-phosphate dehydrogenase. Untoward haemolytic reactions may occur in such patients on receiving many commonly used drugs (e.g., sulphonamides).

**SICKLING AND THE OXYGEN DISSOCIATION CURVE**

The sigmoid oxygen dissociation curve characteristic of haemoglobin is functionally advantageous and depends upon the fact that the presence of oxygen on one of the haems in the tetramer is able to influence the oxygen avidity of the other haem groups in the same haemoglobin molecule. The completely deoxygenated haemoglobin molecule has a low avidity for oxygen but the oxygenation of the first haem group increases the oxygen avidity of the other haem groups.

This variability of the avidity of haem for oxygen is caused by the re-adjustment of the four haem-polypeptide chains relative to each other, when oxygen molecules arrive at or depart from the tetramer.

In an oxygen dissociation curve, the percentage of oxyhaemoglobin in a sample is plotted against the Po2 (mm Hg). Increased avidity of haemoglobin for oxygen causes a shift to the left and decreased avidity, a shift to the right.

It is well known, for example, that a shift to the
right (the Bohr effect) can result from a drop in pH and the beneficial result of the decreased avidity for oxygen is an additional release of oxygen molecules towards the venous end of the capillary.

**Po2 levels and sickling.**

The ease of sickling of any red cell is roughly proportional to the concentration of sickle-cell haemoglobin within it. One would therefore find that a red cell from a case of sickle-cell anaemia will sickle more readily than a red cell from a sickle-cell trait carrier. The former commonly possesses over 90 per cent sickle-cell haemoglobin and the latter only some 30—40 per cent.

A particular red cell sickles not at a particular Po2 level but at a particular percentage deoxygenation of the haemoglobin within that red cell. The critical level of deoxygenation of the red cell that produces sickling will therefore be reached, at somewhat variable Po2 levels, depending entirely upon the position of the oxygen dissociation curve at that particular time. In other words, if through acidosis the curve is shifted to the right, the critical degree of deoxygenation that promotes sickling will be reached at a higher Po2 level and sickling will be facilitated.

For the reason stated above, it is impossible accurately to relate sickling with Po2 levels. However, in vitro work suggests that the red cells of patients with sickle-cell anaemia and sickle-cell haemoglobin C disease will be sickling in considerable numbers at Po2 levels of about 40 and 30 mm Hg respectively. The Po2 level at which the red cells of a sickle-cell trait carrier is usually about 20 mm Hg but the figure must depend upon the percentage of sickle-cell haemoglobin that a particular carrier possesses. The sickle-cell trait carrier described in this case report had an unusually high percentage of sickle-cell haemoglobin (44%) in his red cells. In vitro studies demonstrated sickling at a Po2 of 30 mm Hg, a level similar to that for sickle-cell haemoglobin C disease, which has an accepted anaesthetic risk.

Infarctive incidents during anaesthesia occurring in sickle-cell trait carriers must be extremely rare. The experimental findings explain why this particular patient would be especially liable to suffer such a complication.

Some indication of the degree of hypoxia needed in vivo to precipitate an infarctive crisis may be obtained from the reaction of people with sickle-cell haemoglobin to altitude. Patients with sickle-cell disease—especially sickle-cell haemoglobin C disease—are at some risk of, in particular, splenic infarction in pressurized aircraft, i.e. at an altitude equivalent of 5—8,000 ft. At this altitude one would expect the arterial Po2 to be between 70 and 60 mm Hg. (It is of interest that the patient with sickle-cell anaemia although suffering from the most severe form of sickle-cell disease is, presumably because of the usual lack of an enlarged spleen, relatively resistant to infarctive incidents during flight.) It appears particularly important not to underestimate the anaesthetic hazards in the often clinically benign and even undiagnosed case of sickle-cell haemoglobin C disease. At any rate, during aeroplane flight limited experience suggests these may be at greatest risk.

No incidents are known of a sickle-cell trait carrier suffering from a splenic infarction in a pressurised aeroplane but a few have been recorded in unpressurised aeroplanes flying at altitudes of above 10,000 ft where the arterial Po2 level (with considerable individual variation) would probably be below 55 mm Hg. An additional factor precipitating splenic infarction during flight might also be immobilization, together with splenic compression caused by a seat belt.

When assessing the clinical significance of figures such as those quoted above, it is important to realize that neither arterial nor mixed venous Po2 levels would accurately reflect the likely Po2 levels at a probable site of sickling—for example the splenic sinusoids. In any case it would be unwise during an anaesthetic procedure solely to attach importance to blood oxygen levels when there are other equally significant precipitating factors such as circulatory stasis.

**The oxygen dissociation curve in sickle-cell haemoglobin.**

Provided that the alveolar oxygen tension is not drastically reduced, haemoglobin with an oxygen dissociation curve moderately shifted to the right is a more efficient carrier of oxygen. Whilst, under these conditions, it will still depart fully loaded from the lungs, such a molecule will unload more oxygen in the tissue capillaries. Under normal circumstances, therefore, a circulating haemoglobin with a somewhat reduced avidity for oxygen is an advantage because it improves peripheral tissue oxygenation.

The oxygen dissociation curve in sickle-cell anaemia is shifted to the right of the normal position.
and from the point of view of oxygen delivery this is an efficient arrangement. It will be apparent that such a haemoglobin will unload more oxygen than normal during the drop from arterial to venous Po₂ levels (Huehns and Bellingham, 1969).

The anaesthetist, accustomed by necessity to assessing the patient’s haemoglobin purely by quantitation (g/100 ml) may be misled by the well-meaning efforts of his Pathology Department. The report that states a patient’s haemoglobin is, perhaps, 8g/100 ml, does not distinguish the patient who has shifted his curve to the right from the patient who has not. The patient with sickle-cell anaemia with his curve shifted to the right, will be an example of a “compensated” anaemia, his haemoglobin functioning more effectively than the low figure suggests. In order not to raise blood viscosity, such patients should not be needlessly transfused. The anaesthetist must, in the interest of the patient, accustom himself to accept haemoglobin levels which previously might have resulted in the immediate cancellation of the operation.

The oxygen dissociation curve in stored blood.

One of the other factors which effects the position of an oxygen dissociation curve of haemoglobin is the combination of the haemoglobin molecule with the cellular metabolite 2:3 disphosphoglycerate (2:3 DPG). This metabolite is a by-product of glucose breakdown in the red cell, and is able to combine with reduced haemoglobin, the combination being broken whenever complete oxygenation of the haemoglobin molecule occurs. 2:3 DPG reacts solely with reduced haemoglobin and its presence “wedges” the haemoglobin tetramer in the reduced conformation. Reduced haemoglobin combined with 2:3 DPG therefore has a low avidity for oxygen (the curve being to the right). In contrast, reduced haemoglobin uncombined with 2:3 DPG has a higher avidity for oxygen (the curve being to the left).

2:3 DPG falls in concentration especially in blood stored in the blood bank for more than two weeks. Because of this reduction in 2:3 DPG concentration, such blood has a greatly increased avidity for oxygen; stored blood partially recovers its 2:3 DPG level within a few hours of transfusion but full recovery may take longer.

There is an obvious danger therefore, in massively transfusing any patient with blood over two weeks old—it is pointless raising the haemoglobin concentration and the blood viscosity if the donated red cells are reluctant to release their oxygen to the tissues.

Certainly, if, through an aplastic or sequestration crisis, a life saving blood transfusion of a patient with sickle-cell disease becomes necessary, it is highly desirable that fresh blood should be given. Fortunately, for the great majority of routine transfusions, the immediate oxygen carrying capacity of the red cells is not a critical factor. Requests for fresh blood must be limited to the rare occasions when the patient’s welfare depends upon the instantaneous perfect functioning of the haemoglobin within the donated red cell.

Anti-sickling drugs and the oxygen dissociation curve.

Cyanate, which reacts directly with the haemoglobin molecule and makes it more avid for oxygen has been proposed as an anti-sickling reagent. (Cerami and Manning, 1971; Ranney, 1972). The Po₂ required to reach the critical percentage de-oxygenation for sickling to occur in a cyanated red cell will be lower because the oxygen dissociation curve has been displaced to the left. Unfortunately, such an avid haemoglobin being reluctant to release oxygen, functions inefficiently. There will be a tendency for such patients to compensate by developing a polycythaemia and the resultant increase in blood viscosity might prove disastrous to a patient with sickle-cell anaemia. At the present time the use of antisickling drugs such as cyanate and urea (Nalbandian, 1971) are still in the experimental stage. Nevertheless, their introduction has demonstrated the possibility that the molecular lesion carried by the sickle-cell haemoglobin molecule may, one day, be neutralized by a further chemical modification of the haemoglobin.

The diagnosis of sickle-cell disease

It is sometimes argued that the pre-operative recognition of Hb.S is not obligatory because all suspect patients can be managed as cases of sickle-cell anaemia. However, we believe it is essential to screen the blood of all Negro patients for the presence of sickle-cell haemoglobin prior to anaesthesia for the following reasons:

(1) The information that sickle-cell disease is present is a crucial factor in reaching a surgical diagnosis and assessing the necessity for surgical interference.
The absence of sickle-cell haemoglobin allows the anaesthetist to employ his usual method of anaesthesia without anxiety. It is not in the patient’s best interests to be subjected to a management regime which is unnecessary and to which the anaesthetist may be unaccustomed.

The diagnosis of postoperative complications must take into account the sickling status of the patient.

Medicolegal implications. Forensic pathologists are aware of sickling as a cause of unexpected anaesthetic deaths in Negro patients. The known presence of foci of sickle-cell haemoglobin in people of Mediterranean origin probably makes the routine screening of such patients desirable, although the yield of positive cases will be very small. This would be even more true for patients originating in the Middle East and India.

It is important to carry out the necessary laboratory investigations as soon as surgery appears indicated and this should in most cases be possible prior to admission. Inevitably some cases will come to surgery as emergencies and in these circumstances a presumptive diagnosis may have to be reached on simple rapid techniques outlined below which are suitable for an emergency pathology service.

The most important initial step is to establish, by a simple test whether a patient has or has not sickle-cell haemoglobin within his red cells. Approximately 90 per cent of Negro immigrants will give a negative result and only if sickle-cell haemoglobin is found will the blood sample require further investigation to differentiate the common sickle-cell trait carrier from the rarer case of sickle-cell disease.

The Detection of Sickle-Cell Haemoglobin.

Sickling test.

All red cells containing sickle-cell haemoglobin can be made to sickle under conditions of extreme hypoxia. This can be achieved in vitro by observing the red cells after suspension in a fluid containing a reducing agent such as sodium metabisulphite. Interpretation of the classical sickling test is more difficult than is usually appreciated and false positive and negative results are not uncommon.

Sickledex.

A proprietary preparation Sickledex (Ortho) detects sickle haemoglobin by precipitation and is therefore positive in all patients with sickle-cell haemoglobin within their red cells. Although cases of dysproteinaemia (such as myeloma) may rarely give false positive results, in practice this test has proved simple and reliable. False negative results are virtually non-existent.

The only disadvantage of Sickledex is that it would prove expensive if large numbers of patients were to be screened. It would appear of particular value in situations, such as emergency diagnosis, where only occasional tests are likely to be performed.

Non-proprietary solubility tests.

Reduced sickle-cell haemoglobin precipitates in concentrated phosphate buffer. Rapid whole blood solubility tests to detect sickle-cell haemoglobin, based upon this principle have been described. One of these tests will, in addition, assist in the differentiation of the sickle-cell trait from sickle-cell anaemia (Huntsman et al., 1970; Serjeant and Serjeant, 1972).

The Emergency Investigation of a Blood Sample Known to Contain Sickle-Cell Haemoglobin.

If sickle-cell haemoglobin has been detected by any of the above three tests and the patient’s condition permits, surgery should be delayed to elucidate the exact genotype by other tests including haemoglobin electrophoresis. Whilst a rapid cellulose acetate electrophoretic technique is possible, it is unreasonable to expect this service as an emergency procedure.

On occasions delay is not feasible. The clinician will then require rapid guidance from the laboratory in order to divide the patient who possesses sickle-cell haemoglobin into two categories:

(1) Sickle-cell trait carrier
(2) Sickle-cell disease
   - sickle-cell anaemia
   - sickle-cell haemoglobin C disease
   - sickle-cell thalassaemia

Carriers of the sickle-cell trait on rare occasions are liable to haematuria. However, unless they have been previously subjected to unphysiological hypoxia, they do not present with a painful infarctive crisis. The presence of the sickle-cell trait can be ignored when the surgeon is arriving at his diagnosis and only simple precautions are needed during the anaesthetic procedure.

The situation with patients who have sickle-cell disease is quite different. Indeed, knowledge that a
patient suffers from sickle-cell disease should make
the surgeon review a diagnosis, particularly one of
abdominal pain. The authors are aware of two
examples of children, both with sickle-cell haemo-
globin C disease, who were operated on unneces-
sarily for abdominal pain, attributable to a sickling
infarctive crisis. In each case the correct diagnosis
was made on the post-mortem table by the forensic
pathologist.

An anaesthetic procedure in patients with sickle-
cell disease is, in many cases, hazardous and sur-
gery should not therefore be lightly undertaken.
The differentiation of the sickle-cell trait from
sickle-cell disease can usually be achieved utilizing
the information that the haemoglobin level and
blood film in the uncomplicated sickle-cell trait
carrier are normal. In contrast, the blood films from
cases of sickle-cell disease (sickle-cell anaemia,
sickle-cell haemoglobin C disease and sickle-cell
thalassaemia) are abnormal and the haemoglobin
level usually reduced. An absolute distinction
between the sickle-cell trait and sickle-cell disease
on the haemoglobin level alone is not possible
because some cases of sickle-cell thalassaemia and
sickle-cell haemoglobin C disease may have haemo-
globin levels within the normal range.

Some cases of sickle-cell thalassaemia with un-
usually large amounts of normal adult haemoglobin,
may have in addition a blood film sufficiently close
to the normal picture to possibly result in confusion.
Fortunately, such patients probably present, like
the sickle-cell trait carrier, a small anaesthetic risk
only and therefore such an error resulting from the
blood film examination is unlikely to be clinically
significant.

Conversely, exceptional cases of the sickle-cell
trait with, for example, a superimposed iron defi-
ciency will have low haemoglobin levels and abnor-
mal blood films, which might well result in a false
emergency diagnosis of sickle-cell disease. Never-
theless, within the limitations mentioned above, a
knowledge of the haemoglobin level combined with
the examination of a blood film should enable a
patient to be rapidly categorized, with a reasonable
degree of certainty, into either sickle-cell trait or
sickle-cell disease. Confirmation by routine exami-
nation, including electrophoresis should be obtained
as soon as practicable.

ANAESTHETIC MANAGEMENT OF THE SICKLE-CELL
TRAIT CARRIER

An infarctive sickling crisis during the administra-
tion of an anaesthetic to a sickle-cell trait carrier
must be extremely uncommon. Nevertheless the
case reported here, where there is strong presum-
tive evidence of a splenic infarction, demonstrates
that this can occur. It appears reasonable, despite
the large number of patients involved, that some
simple precautions should be taken with the carrier.

The anaesthetic management should include:

1) Preoxygenation with 100 per cent oxygen for
about five minutes to minimize possible hypoxia during induction manoeuvres.

2) Maintenance of anaesthesia with a gas mix-
ture containing at least 30 per cent oxygen
(F1O2 of 0.3); a figure that most anaesthetists
accept as a minimum for all anaesthetics.

3) Continuous post-anaesthetic oxygen therapy
under skilled supervision until full clinical
recovery occurs. The dark complexion of the
patient may make cyanosis difficult to recog-
nize.

4) Keeping the patient hydrated and warm
throughout the anaesthetic procedure.

It appears reasonable to avoid the lengthy appli-
cation of tourniquets and if blood transfusion is
required, it would be desirable to give at least
reasonably fresh blood. These recommendations
may preclude outpatient and domiciliary manage-
ment. It has been said that the precautions men-
tioned above, whilst suggested here for the sickle-cell
trait carrier, are equally desirable for any patient.
Indeed, this line of thought has been carried further,
some believing that an anaesthetic unsuitable for a
sickle-cell trait carrier is an inadequate anaesthetic
for any member of the public. The point worth
stressing is that while the management outlined here
may well be desirable for all patients, it should be
regarded as obligatory for the sickle-cell trait carrier.

Major thoracic surgery represents a special risk
to patients with the sickle-cell trait (Huehns, 1972).
In these circumstances it would be wise to consider
a preoperative replacement transfusion regime, as
outlined for patients with sickle-cell disease.

ANAESTHETIC MANAGEMENT OF THE PATIENT WITH
SICKLE-CELL DISEASE

(Sickle-cell anaemia, sickle-cell thalassaemia and
sickle-cell haemoglobin C disease.)

Preoperative management.

If possible, operation should be carried out only
when the patient is in the "steady state". If this is
not feasible, it is essential to treat any infections, particularly those affecting the respiratory system. Prophylactic folic acid therapy is in any case advisable.

(1) Blood transfusion should not be given merely because the haemoglobin is at a level which would normally be unacceptable to the anaesthetist. If the patient's "steady state" haemoglobin level is known, this may give a clinical indication as to whether transfusion is indicated. If such guidance is not available, transfusion should be considered if the haemoglobin level is below 7 g/100 ml. If transfusion is indicated, fresh normal blood should be used and the requirement kept to the minimum. Stored blood is cold, of low pH and low oxygen tension. In addition stored red cells are extremely avid for oxygen and such a transfusion could well precipitate rather than prevent a crisis. Because of multiple previous transfusions, some of these patients have a high incidence of transfusion reactions.

An alternative approach to keeping the operative transfusion requirements to the minimum is to attempt by large scale preoperative transfusion to reduce the patient's own sickle-cell haemoglobin containing red cells to about half of the total number. The amount of blood required to achieve this figure may be approximately estimated for each patient. A single transfusion of 3 or 4 pints of packed cells given 1 week before operation may suffice in an anaemic adult. A preoperative exchange transfusion may be carried out if time does not permit a more lengthy preparation.

It is not possible to assess whether a routine large scale preoperative transfusion is necessary or even, as fresh blood is desirable, practical for all patients with sickle-cell disease undergoing routine surgery. Transfusion, is in any case not without risk. At the present time it appears reasonable to reserve such a regime for situations where either the nature of the operation or the state of the patient makes the anaesthetic especially hazardous.

For example, if a patient with sickle-cell disease is to be subjected to major thoracic surgery, an even more thorough transfusion preparation commencing 4 to 6 weeks prior to the operation, would be justified.

(2) While the value of systemic alkalization is currently being challenged, we feel inclined to support the traditional view on this matter at this time. We therefore recommend giving oral sodium bicarbonate before operation (0.5–1 g/kg/day) in divided doses in order to attain an alkaline urine (Nwokolo, 1960; Lehmann, 1963; Hugh-Jones, Lehmann and McAlister, 1964). The dose of alkali is subsequently adjusted to maintain a urine alkaline to litmus.

(3) Ensure good hydration by encouraging drinking up to the time of elective preoperative fasting, which should be kept to the minimum length of time. Dehydration increases blood viscosity and sickle-cell anaemia is associated with impaired renal concentrating power.

(4) Avoid respiratory and circulatory depressant premedication.

Operative management.

Local infiltration or nerve blocks should be used as a matter of preference. Some authorities recommend that epidural and subarachnoid block should be avoided because they allege that the resulting hypotension may lead to impaired tissue perfusion.

Tourniquets should be employed only where the success or safety of the surgical procedure will be seriously jeopardized by their omission. In such cases exsanguination of the extremity should be ensured by an Esmarch bandage prior to any lengthy application of the tourniquet (Browne, 1965). It should be noted that complete tissue exsanguination is in any case impossible. The management should include the following:

(1) Keep the patient at an equable temperature. Cold encourages vasoconstriction and excessive warmth sweating and dehydration.

(2) Set up an intravenous infusion to maintain hydration and alkalization. If blood loss is minimal, blood volume is probably best maintained by Hartmann's solution or dextran. If blood is given, it must be fresh.

(3) It appears reasonable to carry out intravenous alkalization if the pre-anaesthetic oral regime has had to be omitted. Administer 3.3 m.equiv./kg/hr of sodium bicarbonate over 90 minutes (Greenberg and Kass, 1958).

(4) Pre-oxygenate with 100 per cent oxygen for five minutes.

(5) After induction, intubate and hyperventilate (with a gas mixture containing between 30–50 per cent oxygen) to promote respiratory alkalosis. A high FiO2 will not necessarily reflect beneficially on the capillary oxygen tension which may be more dependent on the local state of circulation. Further-
more, raising the Fio₂ inevitably reduces the FiN₂ and requires increased supplements of other agents which may result in undesirable side effects (e.g., post-anaesthetic halothane shivering which creates high oxygen demand).

(6) A judicious concentration of a volatile agent will minimize hypocapnic vasoconstriction and promote good tissue perfusion.

(7) Avoid cardiac depression, peripheral vasodilation and vasoconstriction and diminished blood volume, all of which will result in impairment of tissue blood flow. It will be evident that a balance must be struck between a raised Fio₂ and the associated increase of volatile or other supplements.

(8) Give 100 per cent oxygen prior to extubation.

Postoperative management.

Anaesthetic “accidents” often occur during the recovery period when skilled supervision may be minimal.

(1) Continue oxygen therapy administration under skilled supervision until full clinical recovery occurs. Prolonging the oxygen therapy for 24–48 hours (Nunn and Payne, 1962; Conway and Payne, 1964) at a Fio₂ of 0.3–0.5 would be desirable, provided this is practicable and free from additional hazard. Because of depression of erythropoiesis by prolonged inhalation of oxygen (e.g., 4 days) there is a theoretical disadvantage in overlong administration of oxygen therapy.

(2) Maintain adequate hydration.

(3) Provided postoperative haemostasis permits, heparin administration is indicated if severe bone pain occurs, heralding a marrow infarct, which may be followed by a pulmonary embolus. Alternatively, magnesium sulphate injections (see treatment of infarctive crisis) may be used.

(4) Early mobilization should be encouraged to promote optimal tissue circulation.

(5) Prophylactic antibiotic therapy is advisable in all major operative procedures to minimize pulmonary infections.

CONCLUSION

Patients possessing sickle-cell haemoglobin are certain to present in increasing numbers for surgery in this country. The anaesthetic management must be divided into two categories:

(a) the low risk patient—the sickle-cell trait carrier. The great majority of patients with sickle-cell haemoglobin are in this category. Anaesthetic mishaps are rare and only a few simple precautions are indicated.

(b) the rarer high risk patient with sickle-cell disease

sickle-cell anaemia
sickle-cell haemoglobin C disease
sickle-cell thalassaemia

The anaesthetist should be fully aware of the diagnostic problems that must be faced as well as the course of action to follow if surgery is subsequently considered to be unavoidable. Even if every precaution is taken, anaesthesia for a patient with sickle-cell disease may prove a hazardous and at times, a fatal undertaking.

REFERENCES


BOOK REVIEW


Although this book deals with the effects on the liver of anaesthesia in general, its readers will naturally be thinking of halothane. It is therefore a refreshing change to find here a careful, impartial, and cool review of all that has been reported about the effects of not only anaesthetics in general but of halothane in particular on liver functions. Here is no impassioned condemnation of any one anaesthetic, such as some anaesthetists and hepatologists have indulged in, nor, on the other hand, is there much discussion of the sin of certitude so grossly displayed by some enthusiastic colleagues at the other end of the scale, to whom even a "suspicion" is anathema when it concerns jaundice after halothane. Dr Dykes and thirteen other Americans, all expert in this field, have collected all that is known about this subject. After a historical review of pre-first-world-war knowledge they discuss the value of hepatic function tests in general. The American National Halothane Study is naturally treated in some detail and both its strong and its weak points are exposed. The whole question of the risk of multiple halothane administration is expertly and elegantly treated. Dykes is at his best in this chapter and presents all the available evidence up to 1970 both for and against the evidence of harm. In his concluding remarks he says, and these are probably as true today as when they were written:

"The 11 positive halothane anesthetic challenges and the 2 positive true halothane challenges therefore strongly suggest and essentially prove the existence of halothane hepatitis. The 11 negative halothane anesthetic challenges, however, serve only to confirm that all the episodes of jaundice that develop after the administration of halothane are not necessarily related to the presence of the drug per se.

"We can perhaps sum up best by stating that at present it is impossible to measure either the incidence of fatal or non-fatal halothane hepatitis—although it is now certain that the entity exists—or the safety features associated with multiple administrations of the drug, to the extent that the highly desirable state of affairs in which "the greatest strides are made when numerical relationships are uncovered", still unfortunately eludes us."

The physiology of liver function is adequately covered, particularly in regard to hepatic blood flow. The general subject of drug-induced hepatitis is also included because of the number of the drugs implicated which form part of the anaesthetic mixture. There are chapters, too, on unsuspected preoperative hepatic dysfunction, the effect of swallowing halogenated hydrocarbons, and of course on postoperative hepatic dysfunction. The many contributory factors to hepatic disturbance after anaesthesia are listed and discussed very fully. The book concludes with a chapter on the medico-legal aspects of halothane, dealing in particular with the legal importance of manufacturers' "package insert". Finally, Dykes reviews the whole subject in perspective and re-emphasizes the very small risk of postanaesthetic hepatic dysfunction. He is in favour of prospective trials with halothane, particularly with multiple exposures. Whether this would receive the unqualified ethical support of anaesthetists in this country is another matter. A prospective clinical trial is ethical only when the matter is of direct clinical benefit to the individual patient and the question to be answered is in reasonable doubt. There is little consensus of opinion yet whether, in regard to halothane hepatitis and the risk of multiple exposure, that moment has been reached or whether it may ever have passed. The book is warmly recommended to all anaesthetists and hepatologists.

W. W. Mushin