SKELETAL CHANGES IN THE HAEMOGLOBINOPATHIES

J. H. MIDDLEMISS and A. B. RAPER, BRISTOL, ENGLAND

In one sense it is surprising that there should be such a disorder as haemoglobinopathy—a potentially disease-producing variant of so important a substance as our main respiratory pigment. In another sense it seems appropriate that nature should try out, in the form of mutations, variations that might be of advantage; and that we should find variations that have proved to have some uses, though perhaps only under very special circumstances. Sickle-cell disease represents one of these variations. This condition and the many other haemoglobinopathies recently discovered have excited great interest because they offered the first complete demonstration of how disease could be based on a defined molecular lesion. For it is from this lesion, which is quite a simple one, that all the symptoms and all the intense genetic importance of the haemoglobinopathies spring.

PATHOGENESIS

An abnormality in so important a protein as haemoglobin is likely to be reflected in every system of the body. In regard to the skeleton, changes may arise in two main ways. Firstly, they may arise from chronic anaemia. Some of the haemoglobinopathies do not produce anaemia, but those that do, and they are the common ones, all do so because the life-span of red cells containing the abnormal haemoglobin is reduced, often very drastically, from an early stage of infancy. To say that red cell life-span is reduced is to give the modern definition of a haemolytic anaemia, and to indicate that the bone marrow will be called upon to replace red cells at an increased rate, which may reach six to ten times the normal rate. To do this the marrow hypertrophies, and over the years this hypertrophy declares itself clinically by enlargement especially of the frontal and parietal bones, or, if the process is less intense, by causing radiological changes. Secondly, bone changes may be caused by infarcts. These occur only when sickling of the red cells is present, and their mode of production will be explained below. At this stage it is necessary to refer to the structure of the haemoglobin molecule.

Like other protein molecules, the globin of haemoglobin consists of intertwined polypeptide chains—four in this case, a pair of a and a pair of b chains. Each chain is a coiled string of 140 to 150 amino-acids; the exact number and their order in the chains are now known. The immense variety of all the proteins in nature is achieved with only about twenty amino-acids as building blocks, by varying the number and order of those that are built into the protein chains. While haemoglobin is being made in the young red cells, the amino-acids are added on in the right order—an order prearranged by the person's genetic constitution—as if on a template. But if there is a "mutation" in the genetic template at one point, it will mean that at just one particular point in the chain the "wrong" amino-acid will be put in; and this is what makes an abnormal haemoglobin. The new amino-acid may carry a different electric charge from the normal one it has replaced, and so the net charge on the whole molecule will be different, and we can detect this by the appropriate technique, usually by electrophoresis. Further, the aberrant molecules may take longer to synthesise, or the cells that contain them may be of poor viability, and this is the basis for anaemia in some of the haemoglobinopathies.

But haemoglobin production can go wrong for other reasons than the incorporation of "wrong" amino-acids. The synthesising mechanism may be perfect, but the genetic message may not come through to the site of synthesis, so that there is a failure to produce, say, the b chains. This is the defect that underlies thalassaemia, and if the defect is inherited in a homozygous manner the result is more disastrous than if there is merely an aberrant
haemoglobin, because the red cells, lacking haemoglobin, are non-viable, and liable to be destroyed as soon as formed. The marrow hypertrophies, but its efforts at erythropoiesis are ineffective.

COMMON HAEMOGLOBINOPATHIES

Everyone inherits genes for haemoglobin production from both parents, and these genes are independently expressed—that is, each determines the formation of its own type of haemoglobin molecule. The product of two normal genes is normal adult haemoglobin (haemoglobin A) and the normal person’s genetic constitution can be written AA. If one inherited gene is abnormal (the heterozygous state) two separate haemoglobins are formed in each red cell, and the person’s constitution will be AS, AC, AE, etc.; he will be referred to as a trait carrier, and generally does not suffer from the disease. The abnormal homozygous states (e.g., SS, CC, EE) are usually associated with anaemia, as for example sickle-cell anaemia in those of SS constitution. Further, two different abnormalities may be inherited, and the person (a double heterozygote) may be anaemic; examples will be given later.

Of particular interest is the differential distribution of haemoglobin variants amongst the human races. Haemoglobin S is found all over tropical Africa, but is not equally common among the various African peoples. It is also found round the Mediterranean, in the Middle East, in South India, and wherever West African slaves were taken. Haemoglobin C is present in high frequency in West Africa, and wherever West African slaves were taken. Haemoglobin D occurs in Algeria, Turkey and parts of India. Haemoglobin E occurs in Burma, Thailand, Indonesia and Ceylon. Thalassaemia is predominantly found in Mediterranean countries, but is also present in West Africa, the Middle East, India, Burma, Thailand, Indonesia, China and very rarely in Britain.

Sickling and its effects—The shape of a protein molecule depends on the way in which the surface chemical groups of the various amino-acids react with one another. Attached to the globin of haemoglobin are the haem groups, and it so happens that in the abnormal haemoglobin (haemoglobin S) that is the cause of sickle-cell disease the new aberrant amino-acid is so placed in relation to the iron atom of haem, and is of such a nature, that it will react quite dramatically with reduced, but not with oxygenated haem. When the haem is reduced the whole molecule of haemoglobin S alters its shape, and also hitchs up with other haemoglobin S molecules to form spiral aggregates that are long and rigid, and distort the containing red cell. This is what accounts for sickling.

Any red cell with haemoglobin S in it can be made to show these long pseudo-crystals \textit{in vitro} if the oxygen tension is lowered sufficiently. Whether sickling will occur in, say, a marrow sinusoid depends upon the actual concentration of haemoglobin S in the cells. In sickle-cell anaemia (the homozygous state) nearly all the patient’s haemoglobin is haemoglobin S and sickling occurs quite readily in the capillaries, especially where the circulation is sluggish; but so long as the circulation is not blocked the cells can “unsickle” when they pass on to better oxygenated regions. In sickle trait carriers (heterozygotes) rather less than half the haemoglobin is haemoglobin S, and sickling will occur in the body only if the oxygen tension reaches quite low levels; this \textit{can} happen, but it is unknown as a cause of bone infarcts, from which carriers are free. However, in the mixed syndromes mentioned above, depending on the simultaneous inheritance of haemoglobin S and some other abnormality such as haemoglobin C or thalassaemia, the proportion of haemoglobin S in the red cells may be over 50 per cent, and sickling occurs in the body with an ease intermediate between that of SS and that of AS subjects. These intermediate states are important to the surgeon, because they may not be associated with any obvious anaemia, and yet there may be radiological changes, and even infarcts.

Infarcts occur in the red marrow, presumably because the circulation is slow and oxygen utilisation high. These two factors initiate sickling, and this leads to packing of the sinusoids
with sickled cells, further reduction of oxygen tension and more sickling; eventually there will be local thrombosis. Necrosis follows. A further complication is that wherever the typhoid-paratyphoid diseases are common, infarcts tend to become infected by these organisms, and the aseptic necrosis becomes a Salmonella osteitis. Indeed, most examples of Salmonella osteitis are in persons with abnormal haemoglobins.

**Thalassaemia and its effects**—The inheritance of a single thalassaemia gene produces only minor haematological changes (thalassaemia minor), but no clinical abnormality. In the homozygous state there is very severe interference with haemoglobin production, giving rise to Cooley’s or Mediterranean anaemia. Most patients die in infancy; in those that survive longer there is very intense, but ineffective, marrow hyperplasia. Mixed syndromes occur when thalassaemia and an abnormal haemoglobin are separately inherited. The most important of these are haemoglobin S-thalassaemia and haemoglobin E-thalassaemia. Although these patients have one normal A gene its function is impaired by the thalassaemic defect, and they can only manufacture the abnormal haemoglobin. They suffer from anaemia nearly as severe as that of thalassaemia major. Bone infarcts do not occur in thalassaemia or in the mixed syndromes, except when haemoglobin S is present.

**RADIOLOGY OF THE HAEMOGLOBINOPATHIES**

The radiological changes that may be seen in these conditions include changes from thrombosis, infection of bone, disturbance of bone growth, tendency to spontaneous fracture, and marrow hyperplasia, as well as other changes.

**Sickle-cell anaemia (homozygous SS haemoglobinopathy).**

**Changes from thrombosis**—Infarction in the small bones of the hands and feet is especially common in infancy. The metacarpals and phalanges are commonly involved. The response is an attempt at repair resulting in hyperaemia especially of the arteriolar penetrating branches from the periosteum. The hyperaemia causes a slight elevation of the periosteum, producing a local osteoblastic activity shown radiologically as a periosteal reaction (Fig. 1). The “dactylitis” that occurs clinically in this condition is thus almost certainly caused by multiple small infarcts followed by repair. Aseptic necrosis is always followed by osteoclastic resorption of necrotic bone, and this shows radiologically as a zone of translucency or resorption in the affected bone. When bone undergoes necrosis in the metaphysis of a child, growth ceases temporarily (Fig. 1). Thus if all the metacarpals were to be involved the result would be symmetrical; but if only one bone is involved it ceases to grow during the initial repair phase while others continue to grow normally, the result being an asymmetrical hand.

Infarction occurring in long bones has characteristic radiological appearances, but it is emphasised that radiological changes in bone always lag behind clinical symptoms and signs. It seems to occur more often in older children, usually in bone ends (Fig. 2) or epiphyses; for example it produces in the femoral head the clinical and radiological features of Perthes’ disease (Fig. 3). **Infection in bone**—Mention has been made of Salmonella osteitis in this condition. This may arise without an antecedent history of clinical typhoid. It is probable that small foci of necrosis are a suitable nidus for infection by a mild bacteraemia that might otherwise produce no overt disease. Radiologically the bone lesions differ little from those of pyogenic osteomyelitis.
but extension of the lesions is usually somewhat slower, and the response to specific drugs is slow. The metaphysis of a long bone is often first affected, and the process, unlike pyogenic osteomyelitis, often destroys epiphysial cartilage (Fig. 4). Osteoporosis of the medulla from hyperaemia, and destruction of trabeculae and of the cortex can be seen radiologically, and

![Figure 2](image1)

**FIG. 2**
Absorption of necrotic bone and periosteal reaction in the radius and ulna of both arms.

![Figure 3](image2)

**FIG. 3**
Figure 3—Avascular necrosis of the femoral head. Figure 4—Salmonella osteitis affecting the metaphyses of the right and left femora and the left tibia.

there is usually a periosteal reaction. The clinical expression of this is so mild that pathological fracture may occur as the first symptom, and the child may be brought because of a fracture resulting from minimal or unnoticed trauma.

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Figure 5—Medullary hyperplasia in the foot of a child showing widened intertrabecular spaces and narrowing of cortex. Figure 6—Medullary hyperplasia in the spine with typical compression deformities of the vertebral bodies.

Figure 7—Medullary hyperplasia in the frontal bone producing apparent spiculation. Figure 8—Coxa vara caused by weight bearing in the presence of medullary hyperplasia. The deformity was bilateral.
Marrow hyperplasia—This is a response of the erythroblastic elements of the marrow to the long-standing haemolytic anaemia. Rarefaction is the most notable feature, and when this is analysed it is seen to be produced by widening of the medulla and of the spaces between bony trabeculae, and also by thinning of the cortex. It may be seen in the small bones of the hands and feet (Fig. 5), in the long bones and in the pelvis. In the pelvic bones the apparent loss of bone structure may be very great.

The vertebral bodies often show intense rarefaction, loss of visible trabecular structure, and characteristic compression deformities. These may take the form of anterior wedging, or more often of a biconcavity with bulging of the nucleus pulposus into the opposing margins of the vertebral bodies (Fig. 6). The process involves the whole spine, and may occur early in life, or may not become apparent for many years.

Skull changes may also occur and have a characteristic appearance. This takes the form of widening of the diploë, and in long-standing cases there may rarely be thickening of the frontal and parietal bones with thinning of the outer tables and radial arrangement of the new trabeculae (Fig. 7). This gives a “sun-ray” appearance which must not be confused with that of neoplastic changes.

Changes from disturbance of growth—These are mainly caused by a mechanical effect on the osteoporotic skeleton and by bone infarcts in zones of growth. For example, coxa vara may occur (Fig. 8), or diminished stature or kyphosis may result from the compression of vertebrae.

Tendency to spontaneous fracture—This has been noted by several observers, and is possibly caused not only by the diminished strength of the osteoporotic bone but also by the associated malnutrition that is common in the communities under consideration. It is rare for the fractures to be through infarcts; they occur more often in the long bones (Fig. 9).

Other effects—Dilation of the heart accompanies long-standing anaemia. Visceral infarcts are known to occur, and pulmonary infarction has been described. Pigment gall-stones are being found with increasing frequency.

Haemoglobin SC disease (sickle-cell haemoglobin C disease)—The doubly heterozygous SC-haemoglobin state is compatible with survival to adult life, for the tendency to haemolysis is not so great in this condition. Its clinical features are low grade haemolytic anaemia with episodes of abdominal pain and joint pains; the anaemia is often greater in Africa than in America because of added parasitic and nutritional stresses. Sickling of red cells within the body may occur when oxygen tension is reduced, often when some physical stress such as pregnancy is added.

Changes produced by thrombosis—In childhood these are not seen as often as in haemoglobin SS disease, though in the phalanges small metaphyseal infarcts do occur, and affect bone growth. In adolescence and adult life infarction in the femoral head is relatively common. It usually does not involve the entire femoral head, and it appears, therefore, like an unusually large area of osteochondritis dissecans (Figs. 10 to 13). In adults, changes are seen in the hips.
and shoulders fairly often. By the time these patients seek advice they have often had multiple episodes of joint pain; at this stage radiographs show large areas of infarction in either the femoral or the humeral heads, often with the infarcted segment of bone lying separate. In older patients, after continued use of the damaged joints, further disorganisation of the joint ensues, particularly in the hip. Multiple infarcts in vertebral bodies with subsequent collapse and deformity sometimes occur after childbirth, presumably from the trauma caused by intense muscular contraction during labour. Occasionally the repair process may be seen in phalanges and metacarpals, producing a periosteal reaction and "dactylitis," as in sickle-cell anaemia; but this is rare.

![Fig. 10](image1)
![Fig. 11](image2)

![Fig. 12](image3)
![Fig. 13](image4)

Examples of segmental avascular necrosis in the femoral heads in individuals with haemoglobin SC disease.

Marrow hyperplasia—The hyperplastic marrow causes thinning of trabeculae, which in turn leads to osteoporotic bone. This, however, occurs at a later age than in sickle-cell anaemia, and is rarely so severe as in the latter condition (Fig. 14). One feature is of particular interest. In the phalanges of the older children large vascular channels are often seen (Fig. 15). These are ascribed to the increased blood flow required for very active haemopoiesis in a small bone that is still growing. They are more likely to be seen in SC than in SS disease, because they become apparent in the second decade and persist into later life, a period not often reached by the homozygous SS individual.

Other effects—Splenic infarction sometimes occurs in adult life. What used to be described as tropical splenic abscess is almost always a manifestation of infarction in haemoglobin SC disease. The gas comes out of solution from the blood in the usually very enlarged spleen, and a fluid level is formed by the necrotic material, which can be seen radiologically. Similarly,
Figure 14—Medullary hyperplasia in the lower end of the humerus in haemoglobin SC disease. Figure 15—Widened vascular channels in the phalanges of an adolescent with haemoglobin SC disease.

Figure 16—Medullary hyperplasia in thalassaemia. Note the scalloping of the cortex beneath the periosteum of the fourth metacarpal. Figure 17—Medullary hyperplasia in the skull in thalassaemia. Note that the paranasal sinuses have had their air spaces obliterated.
the occasional haematuria may be due to infarct of the renal pyramids with sloughing of the papillae, producing a papillitis necroticans. This again can be demonstrated radiologically. **Thalassaemia major and mixed syndromes**—The radiological changes in thalassaemia major are caused by intense marrow hyperplasia. They resemble those of sickle-cell anaemia, but are usually more marked. They are rarely seen in the first year of life. There is thinning of cortex, widening of intertrabecular spaces, usually best seen in the hands but also often very obvious in the ribs and pelvis. In the hands there is interference with the normal growth process of moulding of the bone, and individual bones may appear "swollen" (Fig. 16). Extramedullary haemopoietic tissue sometimes grows beneath the periosteum, producing a scalloped edge to the cortex; this may be seen in the hands (Fig. 16), feet, tibia and fibula, around the knee joint, or in the radius and ulna. Large intrathoracic masses, simulating paravertebral tumours but caused by extramedullary haemopoietic tissue, have also been described. Wide vascular channels are usually seen in the phalanges (Fig. 16). Growth and skeletal maturation are retarded. In the skull great thickening of the cranium may take place, and overgrowth of the facial bones may impede pneumatisation of the sinuses (Fig. 17). Anaemic dilation of the heart is common.

Haemoglobin S occasionally, and haemoglobin E more commonly, occur in the heterozygous state together with thalassaemia minor. Patients with haemoglobin S-thalassaemia may reach adult life and show in modified form some of the changes described, particularly narrow hyperplasia and the development of extramedullary haemopoietic tissue (Fig. 18): occasionally the patient may present for the first time with hip and shoulder infarcts. In haemoglobin E-thalassaemia, a disease not uncommon in Burma and Indonesia, the appearances are indistinguishable from those of thalassaemia major.

**TREATMENT**

As yet no treatment can alter the underlying genetic lesion. Doubtless we shall one day be repopulating the abnormal marrow with normal red cell precursors. But in the meantime there is something that can be done to prevent infarctive lesions in sickle-cell disease or to limit them when they are threatened.

Infections that lead to general or local anoxia (especially pneumonia) should be treated early. Anaesthesia should be flawless, and subsequent respiratory efficiency ensured. The second and third stages of labour need careful management. The tourniquet is potentially dangerous, but in practice it does not seem to have caused trouble. It is a reasonable precaution to immunise patients against the typhoid-paratyphoid group of infections.

More positive modes of attack have been aimed at reducing the amount of "sickleable" haemoglobin in the red cells, so that, in effect, the patient is made to resemble the carrier rather than the homozygote. To do this, part of the haemoglobin has to be turned into a form that cannot be de-oxygenated; it will then be useless for respiration, but neither will it participate in sickling. For example, sodium nitrite can be given in amounts sufficient to turn about 20 per cent of the haemoglobin into methaemoglobin, but patients do not tolerate this treatment...
long. It has been claimed also that sickling is impaired if about 6 per cent of the haemoglobin is turned into carbonmonoxy-haemoglobin, but the practical usefulness of this treatment is disputed. Recently some success has been claimed for the promazine drugs. It can be said, however, that drug therapy is not very successful in long-term prevention.

When local pain in a susceptible subject suggests that a thrombotic crisis is beginning it is worth while to try to limit the extent of the thrombosis. A recommended method is the intravenous injection of 50 per cent magnesium sulphate: 2 millilitres for adults; 1 millilitre for children. The injection is given slowly, and may be repeated four-hourly until improvement occurs. At the same time magnesium glutamate is given by mouth, and enough sodium bicarbonate is given to keep the urine alkaline, because sickling occurs less readily in an alkaline medium. Some success has been reported, but clearly success will depend a good deal on circumstances, such as having the patient under care at the onset or very soon thereafter.

**SUMMARY**

1. Bone changes in the haemoglobinopathies are caused by either (a) chronic haemolysis with marrow hyperplasia, or (b) infarction, when Hb S is present in the red cells in amounts sufficient to allow sickling (and therefore vascular occlusion) *in vivo*.

2. Marrow hyperplasia produces osteoporosis, widening of the medulla, and thinning of the cortex; it may lead to spontaneous fractures and disturbances of growth. Enlargement of the foramina of the nutrient arteries may be seen especially in the phalanges. Infarcts leading to aseptic necrosis occur in the long bones, and may become infected with Salmonella organisms. The range of radiological lesions caused by these processes is illustrated.