THE BONE CHANGES IN SICKLE CELL ANAEMIA AND ITS GENETIC VARIANTS*

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The presence of an abnormal haemoglobin (S) in sickle cell anaemia was demonstrated in 1949 by Pauling, Itano, Singer and Wells by means of electrophoresis. Neel (1947, 1949, 1951) showed that haemoglobin S is inherited as a Mendelian dominant, and he postulated heterozygous and homozygous states to explain the symptomless sickle cell trait and the true sickle cell anaemia. An individual receiving the haemoglobin S gene from one parent only (the heterozygous state A/S) would have the sickle cell trait, whereas if the gene should be received from both parents (the homozygous state S/S) he would have sickle cell anaemia (Fig. 1).

Sickle cell anaemia and its variants—In sickle cell anaemia the greater part of the haemoglobin is of the S type but there is a small fraction of foetal or F haemoglobin which is resistant to denaturation with alkali. Under reduced oxygen tension, the S haemoglobin comes out of solution and the resulting "crystallisation" produces the bizarre, sickle-shaped red cells. In the arterial blood, only about 5 per cent of the erythrocytes are sickle-shaped, whereas after prolonged exposure to low oxygen tension, 90 to 100 per cent become so. These cells may block capillaries, venules or even arterioles. If an area of skin affected by this process is examined, a tangled mass of these cells will be found held together in a loose fibrin mesh. In poorly vascularised areas, such as the lower leg, this may cause chronic ulceration (Murphy and Shapiro 1945).

In the sickle cell trait, less than half the haemoglobin is of the S type, the remainder being normal or type A. The sickle cell trait is usually a benign condition, but in certain circumstances (such as flight in an unpressurised aircraft) symptoms may occur. Smith and Conley (1955) described fourteen cases of splenic infarction in patients of this kind.

In 1951 Itano described a second haemoglobin variant (C), which can interact with haemoglobin S to produce sickle cell haemoglobin C disease (S/C). This condition is clinically milder than sickle cell anaemia and is less commonly associated with crises, but there is a peculiar tendency to avascular necrosis of epiphyses. Smith and Conley (1954) went so far as to suggest that avascular necrosis of bone occurred only in the variants of sickle cell disease and never in homozygous sickle cell anaemia; but Tanaka, Clifford and Axelrod (1956) and Carrington, Ferguson and Scott (1958) showed that similar changes may be found in true sickle cell anaemia and described eight cases proved by electrophoresis. We have been able to confirm and extend their findings.

The S gene is found in 10.9 per cent of Jamaicans (Went 1957). Haemoglobin C is the next commonest variant and is found in 3.1 per cent of Jamaicans.

The thalassaemia gene is also found in Jamaica. In addition to five cases of thalassaemia major, we have seen eleven cases of sickle cell thalassaemia disease. This condition needs special consideration, because with the normal haematological techniques and with paper electrophoresis it may be impossible to distinguish it from true sickle cell anaemia. Two of the cases of sickle cell thalassaemia disease which we have encountered were in Afro-Chinese

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and have been reported elsewhere (MacIver, Went and Cruickshank 1958); we have seen another similar case since. The remainder were patients of predominantly African descent (Went and MacIver 1958).

The laboratory methods which were used were described by Went and MacIver in 1956.

FIG. 1

Electrophoretic patterns of normal adult haemoglobin (AA), and of the sickle cell trait (AS), sickle cell anaemia (SS), sickle cell haemoglobin C disease (SC), the haemoglobin C trait (AC).

CLINICAL MATERIAL

In this paper we describe the bone changes that we have found in sickle cell anaemia (S/S), sickle cell haemoglobin C disease (S/C) and sickle cell thalassaemia disease (S/Thal.) (Tables I to IV).

TABLE I
DISTRIBUTION OF SERIES

Type of disease	Number of cases	Age range (years)	Average age (years)
S/S .	51	1-48	17
S/C .	19	6-47	24
S Thal.	2	22-28	25

TABLE II
ANALYSIS OF BONE CHANGES

Type of disease	Number of cases	Bone changes			
		Hyperplasia	Avascular necrosis	Impaired growth	Infection
S S .	51	36	5	47	7
S C .	19	—	13	—	—
S Thal.	2	—	1	—	1

TABLE III
INCIDENCE OF HYPERPLASTIC BONE CHANGES

Type of disease	Number of cases	Bones affected			
		Skull	Long bones	Vertebrae	Flat bones
S S .	51	42 per cent	58 per cent	64 per cent	46 per cent
S C .	19	—	—	—	—
S Thal.	2	—	—	—	—

TABLE IV
AVASCULAR NECROSIS OF FEMORAL HEAD

Type of disease	Number of cases	Number of patients with avascular necrosis of femoral head	Number of hips affected	Average age (years)
S S .	51	5	6	15
S C .	19	13	17	30
S Thal.	2	1	1	22

Since 1956 over 110 patients with sickle cell anaemia have been studied. Only fifty-one of these have been included in this series because the others were not seen in the orthopaedic clinic. Most of the patients under four years of age showed no radiographic skeletal changes other than some widening of the trabecular pattern, particularly in the hands and feet and skull, except after a crisis affecting the region.

Clinical features—The symptoms of the disease are varied. Pain in and about the joints is a prominent feature of about 80 per cent of cases of sickle cell anaemia. The patient presents himself in a state of crisis with pyrexia, malaise and pain in any part of the body where blocking of the vessels can occur. Priapism and splenic infarction are not uncommon. All the subjects of sickle cell anaemia with bone changes had suffered from crises. By contrast, crises and hyperplastic bone changes are less common and less severe in the sickle cell variants.

BONE CHANGES

The bone changes are conveniently divided into four groups (Table II).

Bone changes due to marrow hyperplasia (Table III)—In sickle cell anaemia the erythroid hyperplasia affects the bone trabeculae and causes absorption, osteoporosis, softening and change in shape (Carroll and Evans 1949). This is well illustrated in the vertebrae, which are affected in about 70 per cent of cases. The bodies of the vertebrae, particularly in the lower lumbar region, become reduced in height and the discs bulge into the bodies, causing them to become cupped (Henkin 1949). The normal height-width ratio of a lumbar vertebra is 1 to 1.8 (Diggs, Pulliam and King 1937); in this series it was found to be 1 to 2.8. We have not seen these changes in the sickle cell variants.

FIG. 2

FIG. 3

Figure 2—Radiograph of part of the skull of boy aged fourteen years with sickle cell anaemia, showing widening of trabecular pattern. Figure 3—Part of the skull of boy aged sixteen years with sickle cell anaemia showing "hair-on-end" appearance.

The most obvious radiographic changes may occur in the skull. A loss of trabecular definition, giving a "ground glass" appearance, is seen, and the outer table appears thin and partly absorbed (Cole 1955). The classical "hair on end" appearance is not in fact common in sickle cell anaemia and is more typically seen in thalassaemia major (Figs. 2 and 3). In later life the skull changes take the form of lamellated new bone, and tend to be in the parietal region and symmetrical (Hamburg 1950). Infarction is not severe or common in the skull but it does occur and may cause localised patches of osteoporosis which later may become sclerosed.

In the long bones the cortex becomes thinned on its inner surface as the medulla hypertrophies. The diaphysial trabeculae widen, and as osteoporosis proceeds the metaphyses appear relatively more dense. The bones do not actually become widened by this process as they do in thalassaemia major.

The metacarpals and metatarsals show the same type of thinning of the inner aspect of their cortices and a widened trabecular pattern.

The flat bones, pelvis, and particularly the ribs, show these changes very well. The ribs show widening of the trabecular pattern, osteoporosis, cortical thinning and sometimes a patchy sclerosis or erosion if infarction has supervened. This is a valuable finding because these changes may be visible on the chest radiograph, and, together with an enlarged heart and pulmonary vascular congestion, they are sufficient to suggest a diagnosis of sickle cell anaemia. The gross hyperplastic changes, dactylitis, and skull bossing described in Africans are not common in the West Indies and may be attributed to malaria.

FIG. 4

Figure 4—Hip of boy aged ten years with sickle cell haemoglobin C disease. Figure 5—Hip of girl aged nineteen years with sickle cell haemoglobin C disease, showing avascular necrosis of part of the upper femoral epiphysis.

FIG. 5

Bone changes due to thrombosis and infarction—The hyperplastic changes described above are mainly of diagnostic interest, because they do not cause symptoms. On the other hand, the changes that arise from thrombosis and infarction may cause severe and crippling disability. Occasionally massive infarction may cause complete collapse of a vertebral body (Legant and Ball 1948). Gradually the body will regain a blood supply and re-form if weight bearing is avoided. One case of partial collapse of a vertebra has been seen in this series.

The femoral head is most often affected by these processes, particularly in the variants of sickle cell anaemia (Table IV). These cases all resemble Perthes' disease* in their clinical features and response to rest. Nevertheless it is apparent that there are significant differences. In Perthes' disease, not only are the patients younger, but there are usually well marked changes in the metaphyses (Mindell and Sherman 1951, Goff 1954): only in one of the cases in this series was such a change present. The radiographic appearances of the hip in sickle cell haemoglobin C disease are diagnostic of the condition (Figs. 4 and 5). Avascular necrosis of the epiphysis is typically seen. This occurs just before the epiphysis has fused. The outer third of the head may be spared. The adult type of avascular necrosis may be seen (Moseley and Manley 1953).

Besides presenting the changes of avascular necrosis, in two cases a hip has been seen to be dislocated. Seemingly this was secondary to an infection of the opposite hip, which caused a sympathetic effusion and stretching of the capsule to allow dislocation.

* It has been stated that Perthes' disease probably does not occur in the negro (Smith and Conley 1956). Out of eleven cases of Perthes' disease seen here since 1954, six were in negro patients who were proved to have neither SS, AS or SC genotypes. Nevertheless the figures that we have available from our clinics suggest that, whereas there is no significant difference in the incidence of Perthes' disease between European, Indian and Chinese, the condition is about ten times less common in the negro.

Avascular necrosis is found in other regions—especially in the head of the humerus, where an area of sclerosis without symptoms or bony collapse may be seen. This was found in six of our cases of sickle cell haemoglobin C (S/C) disease and in one out of ten cases of sickle cell anaemia (S/S) in which this change was particularly looked for.

Often the femoral shafts and other long bones showed a medulla mainly filled by bone and a sclerosed thick cortex. The sclerosis may be patchy and irregular, resembling that of Paget's disease or a chronic inflammatory process.

Although avascular necrosis of a complete bone has not been seen in this series, it has been described in the wrist and in the lumbar spine. In one of our cases the whole of the calcaneum collapsed and became infected. This process may well have started with infection in a small infarct which later spread to the rest of the bone.

Death of a whole segment of shaft occurred in a child of fifteen months with sickle cell anaemia (S/S) who was admitted to hospital with a history of pain and swelling in the lower part of the buttocks which had been present for the previous three weeks. A radiograph showed that the uppermost third of each femoral shaft was expanded and that, within a shell of subperiosteal new bone, the shaft was infarcted and crumbling. The structure of the bone returned almost to normal in three months.

Growth effects—A chronic anaemia itself will cause retardation of growth. In sickle cell anaemia, in which the average content of haemoglobin is 7.5 grammes per cent, many of the changes already described will add to this retardation. The vertebral cupping and diminution of height lead to kypholordosis. If the head of the femur is affected the growth of the bone will be impaired (Macht and Roman 1948). We have seen one patient, aged twenty-three, with a bone age and size of thirteen years.

That one isolated bone can be retarded in growth is well illustrated in a girl of fourteen with sickle cell anaemia (S/S). The radiographs showed that the whole of the right side of the pelvis was deformed and much smaller than the left. The process affected particularly the ischium and pubis. The head of the femur had almost disappeared, probably because of avascular necrosis. The ribs, pelvis and skull showed hyperplastic changes. An intra-articular arthrodesis of the hip was performed, and at operation the distorted, yellowish head of the femur could be seen. The remains of the head were flattened and the overlying cartilage was fibrillated and absent over about a third of the head. The pieces of the head removed at operation were examined. The cartilage was degenerated and partly absent. In the underlying bone there were multiple small sequestra lying in fibrous tissue. In some areas there was evidence of new bone formation.

In this series there was no significant retardation of growth in the sickle cell variants, whereas forty-eight out of fifty-one patients with sickle cell anaemia (S/S) were below average size.

The crisis and secondary osteomyelitis—In a crisis there are fever and a moderate leucocytosis, and if a bone is affected the part becomes hot and swollen. This quite often occurs in the metacarpals, metatarsals and phalanges of small children; radiographs usually show osteoporosis and widened trabeculae, and the structure in general has a ground glass appearance. If an infarct occurs, a layer of subperiosteal new bone is laid down which makes it look rectangular (Carroll and Evans 1949). Within the bone the cortex loses its structure temporarily, and small areas of transradiancy may be seen. When the process is complete the affected bone may be seen to have lost the normal waist and its sides remain parallel (Fig. 6).

If a joint is affected it becomes acutely tender and a large effusion develops: the fluid is deep yellow and glairy, and it contains a few red cells, some of which are sickle-shaped.

It is not uncommon for infection to supervene, causing osteomyelitis. This complication has been seen in seven cases of sickle cell anaemia and one of sickle cell thalassaemia. In four of these cases the infection was no longer active, but there was a healed sinus over a rather

unusual site such as the shaft of the radius, the upper end of humerus, the calcaneum or the upper end of the femur. The infection seemed to have been of low grade, because the patients did not give a history of severe illness.

Two cases of salmonella osteomyelitis have been reported elsewhere (Golding 1956). Over thirty other such cases are described in the literature (Burch 1949; Wigh and Thompson 1950; Hodges, Holt, Jacox and Collins 1951; Traisman and Champlin 1951; Ehrenpreis and Schwinger 1952; Smith 1953; Ellenbogen, Raim and Grossman 1955; Roberts and Hilburg 1958). Salmonella osteomyelitis is characterised by its chronic course with little local reaction or constitutional upset. The bone affected shows patchy osteoporosis and erosion, with only slight periosteal reaction. We have seen one case of salmonella osteomyelitis with sickle cell haemoglobin D disease.

SUMMARY

1. The bone changes are described in fifty-one cases of sickle cell anaemia, nineteen cases of sickle cell haemoglobin C disease and two cases of sickle cell thalassaemia.
2. Avascular necrosis of the head of the femur has been found in all three types of sickle cell disease. These responded to treatment.
3. The changes found in six cases of Perthes' disease in the negro are compared with the changes in avascular necrosis of the head of the femur in sickle cell disease.
4. Hyperplastic bone changes are seen only in true sickle cell anaemia and not in the variants.
5. Secondary osteomyelitis appears to be fairly common in sickle cell anaemia. Organisms of the salmonella group have often been found in these cases.

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FIG. 6

Foot of boy aged five years with appearances typically seen after crisis with periosteal reaction about infarcted metatarsal shafts.

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