THE BONE CHANGES IN SICKLE CELL ANAEMIA

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by

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ALTHOUGH THIS LECTURE is primarily concerned with the effects of sickle cell anaemia on the bony skeleton, it is desirable to commence by briefly discussing the clinical manifestations of the condition because its widespread effects on every organ are a vital concern in the treatment of any case.

Sickle cell anaemia can be defined as a chronic, familial, haemolytic anaemia usually confined to negroes. The red blood cells of such a patient will under certain conditions change from round bi-concave discs to pointed elipses or sickle cells.

The sickle cell trait can be defined as a non-anaemic condition in which a proportion of the circulating cells can be made to sickle in vitro. This does not happen spontaneously in the body and there are no symptoms associated with the trait. Patients with the trait carry one sickle gene and can pass this to their offspring. Those with sickle cell anaemia carry the double gene.

The first clinical description of the disease was by Herrick in 1910. The vast majority of the work on this condition has been done in the United States and only recently has the condition been investigated in this country or in Africa. With the influx of Jamaicans into this country, its importance will increase. Five years ago the condition was hardly recognised in Jamaica while now it is a common diagnosis. In Africa a great deal of work has been done by Raper on the distribution and frequency of the trait. In 1950 he reported that the incidence varied from tribe to tribe between 45 and $\frac{1}{4}$ per cent. with an overall incidence of about 20 per cent., yet sickle cell anaemia was a rare diagnosis. However, in 1954 he reported that his own work and the reports from other centres throughout the continent made it quite clear that the incidence was as common as genetically it should be (Welbourne and Raper, 1954; Mabayoje, 1956). This suggests that there are about one million Africans south of the Sahara with sickle cell anaemia. When it is considered that the vast majority of Africans are treated by doctors trained in this country, the importance of the condition becomes obvious.

Clinical description

The clinical picture presented by the patient is usually clear cut, but in spite of this the diagnosis is not easy because of the super-added acute symptoms which will be described later and are most misleading. The patients are usually small with a short trunk and comparatively long thin limbs and "spider" fingers. There is often a mild kyphosis and

lordosis. The chest tends to be hoop-shaped. In children the abdomen is protuberant. There is a peculiar greenish yellow tinge to the conjunctivae. Chronic ulcers over the lower third of the legs are quite frequent (Margolies, M.P., 1951).

On examination the heart will be found to be enlarged. This enlargement involves the ventricles and pulmonary conus but spares the left auricle. An apical systolic murmur is usual and there is evidence of pulmonary congestion.

The liver is often enlarged and its actual size may be found to vary over the course of a few days. The spleen, in children particularly, may be very big but as time goes on it tends to shrink and becomes impalpable. Gall stones may be found in about a third of cases. As cholelithiasis is rare in the Negro, sickle cell anaemia may be suspected when it is found. The stones are composed of calcium bilirubinate and are soft, dark green in colour. They are radio-opaque.

There is frequently a low grade fever and lymphadenopathy is common.

The main difficulty in diagnosis occurs because the patient rarely presents as a chronic anaemia but in a state of crisis caused by one of the thrombotic episodes which characterises the condition. This crisis is accompanied by fever and leucocytosis which tends to mislead the clinician. According to the particular organ mainly involved, this crisis will vary in the picture it presents.

An abdominal crisis can exactly mimic practically any acute abdominal emergency. Many unnecessary laparotomies have been performed even in clinics where the condition is well recognised. Thus in 350 cases collected from the literature, there were thirty-five unnecessary operations (McGavack and Nussbaum, 1942).

When the central nervous system is involved the clinical picture may resemble a hemiplegia or meningitis. Drowsiness, stupor, coma or various transient nerve palsies are common complaints.

However, the commonest form for the crisis to take is to simulate some bone or joint disease. This type of pain occurs, often in conjunction with other symptoms, in over 80 per cent. of cases (Patterson *et al.*, 1950). With cardiac enlargement which is commonly present as a result of the anaemia, the resemblance to rheumatic heart disease or rheumatic fever is very close. If a bone is the main site of thrombosis, acute osteomyelitis is mimicked and if a joint, an acute arthritis.

It is most unusual for a child under six months to have a crisis for reasons which will be explained later. However, a crisis has been described as early as nineteen days.

Abnormal haemoglobin

The disease can only be understood after considering the peculiarities of the abnormal haemoglobin which is present. In 1949 Paulling separated out the abnormal haemoglobin. Neel (1949) and Beet (1949) next worked out the genetics of the condition. From this time great strides have been

made because it is now possible to separate the cases of trait from those of the anaemia by studying the blood in the laboratory.

Paulling used the electrical properties of the haemoglobins to differentiate sickle from normal adult haemoglobin. It is possible to separate these two haemoglobins by passing a current through a drop of the haemoglobin solution on absorbent paper. The adult normal haemoglobin moves from negative to positive more rapidly than the sickle, so that it is possible to estimate not only what is present but also the proportions. In sickle cell anaemia practically all the haemoglobin is of the sickle type although there may be a certain amount of foetal haemoglobin and rarely a small amount of the normal. In the sickle trait 60 to 75 per cent. of the haemoglobin is normal, the rest being sickle (Bergren *et al.*, 1954) (see Fig. 1).

Reticulocytes	Sickling	Blood Condition	Zone — Electrophoresis			Pattern +
			Origin	III	II	I
Normal 0·5–1·5%	—	Normal A/A	●			●
Normal	+	Sickle Trait A/S	●		●	●
+ + + 5–25%	+ + +	Sickle Anaemia S/S	●		●	

Fig. 1. Diagram showing the electrophoretic pattern and principal blood changes in sickle cell trait and sickle cell anaemia.

Sickle cell haemoglobin is only one of a series of abnormal haemoglobins which have been discovered and each of these appear to be genetically controlled. If one parent has the gene of such an abnormal haemoglobin and the other has the gene of sickling, the offspring will be liable to suffer a haemolytic anaemia giving symptoms and having a clinical course similar to that found in pure sickle cell anaemia.

There are some other properties of the sickle haemoglobin which may be of clinical importance. Oxyhaemoglobin is of equal solubility to oxy-sickle haemoglobin (in phosphate buffer solution); however, the reduced form of the sickle cell haemoglobin is about a hundred times less soluble (White and Beaven, 1954).

If sickle cell anemia erythrocytes are haemolysed and a cell free solution of haemoglobin is obtained, it will form a gel at low oxygen tensions. Small crystal like formations can be seen under the phase contrast microscope. These resemble the shape of the sickled cell and are known as tactoids (Harris, J. W., 1950). The presence of foetal haemoglobin does not accelerate this process. This may be one of the factors that accounts for the difficulty in a sickle cell anaemia infant with which sickling is

demonstrated. In the cord blood, very little sickle haemoglobin can ever be detected.

By transfusing sickle cells into a normal, it is possible to show that such cells survive for about forty days while those of a normal survive about 120 days (Singer *et al.*, 1948).

The parents of a patient with sickle cell anaemia must both contain the gene which carries the condition. These parents will usually have only the trait and will carry one gene of sickling and the allele will be normal (Harris, H., 1953). They will have no symptoms from this abnormality but one in four of their children will get a double sickling gene and will have the anaemia. Thus in Africa where the sickle trait is found in about 20 per cent. of the population, one in twenty-five marriages will result in two persons with the trait producing children with sickle cell anaemia at a rate of one in a hundred in the general population.

When the two sickle genes are found in one patient, the haemoglobin in that patient is virtually all abnormal. The red blood cells will become pointed and sickle shaped. They become longer ; up to four times the diameter of the original red blood corpuscle. This occurs when the oxygen tension is low and can be made to occur in vitro. These sickled cells block capillaries, venules and even arterioles. If an area of skin affected by this process is examined it will be seen that there are masses of these cells blocking the small vessels as a tangled mass which appears to be held together by a loose fibrin mesh. In areas of poor vascularity such as the lower leg, this may result in the development of a chronic ulcer (Murphy and Shapiro, 1945).

Although it is not possible to examine directly all the processes that occur actually during a crisis it is possible to gain some idea of the state of the vessels and the blood itself.

The fundus can be examined and it will be seen that the veins are tortuous and dilated (Hardin, 1937). The arteries also show these signs but to a much less marked extent. Haemorrhages and exudates are seldom seen although they have been described. The venous dilation has the effect of slowing the blood flow but at the same time, the vessels will more easily pass the elongated sickled erythrocytes if they do form. Crises do not seem to occur in the eyes so that one cannot observe the process there.

Priapism is quite a frequent occurrence in sickle cell anaemia. The blood is dark red, almost black in colour. If the blood is aspirated and examined it is found to be not clotted but rather glairy and under the microscope sickled cells can be clearly seen. However, the blood is not truly clotted and the jelly like substance is found to contain the loose crystals or tactoids previously described. It is interesting that in a case that came to autopsy no true thrombosis was found. Also it is found that various vaso-dilating agents such as Etamon will sometimes give marked but temporary relief. In spite of this, the final result of the process is fibrosis and impotence (Rosokoff and Brodie, 1946). It would

seem likely that in the bone also it is the capillary block which causes the damage rather than the venous thrombosis which occurs later.

When the lungs are affected by this process, the blocked vessels will result in a diffuse pneumonitis, or an actual infarct. It is the less well oxygenated pulmonary arterial system which is affected and pulmonary congestion is usual.

The liver is often enlarged and the small vessels are clogged with sickle cells. Many of these are found in the histiocytes and macrophages which take up the débris. Haemosiderin deposits can be seen and these changes result in hepato-cellular damage, sometimes cholangiolar damage may be marked but this is rather unusual.

The spleen is often markedly enlarged in the early years of life. The capillaries around the Malpighian bodies are distended to form large pools and the veins are varicose and enormously dilated. These spaces are full of sickled cells. Multiple infarcts appear and these areas fibrose and contract until the spleen may shrink to a very small size and all the pulp is destroyed. This process is called auto-splenectomy. In a spleen which has been removed for massive enlargement, the pulp will be seen to be purplish and engorged. There are masses of haemosiderin deposits and sometimes diffuse calcification may be apparent (Macht and Roman, 1948).

The brain may show rather similar changes with blocked vessels surrounded by an area of cortical necrosis in the grey matter. The venous sinuses and, in fatal cases, even the middle cerebral artery may be blocked.

The kidneys show progressive damage and become scarred and puckered. Occasionally the infarction may be so severe as to cause a massive necrosis (Bauer, J., 1940). The urine contains red blood cells and sometimes there may be a frank haematuria. Hyaline casts are usual and where the kidneys are severely damaged, the specific gravity may become fixed at 1010 (Henderson, 1950).

The bone marrow is purplish and congested. Even in the adult, red marrow can be found in all the bones of the skeleton except the distal arm bones and the fore-foot. This marrow is extremely cellular and congested. The capillaries and tissue spaces are full of sickled erythrocytes, which with the erythrogenic hyperplasia gives the marrow its characteristic appearance. The nucleated cells are predominantly primitive in type. Islands of these cells and megaloblasts are scattered about in the pulp. Large mononuclear cells can be seen carrying the débris of old sickled erythrocytes. Fat necrosis may be found and areas of fibrosis, thrombosis, and haemorrhage are usual (Wade and Stephenson, 1941).

Due to these changes in the marrow, the medullary cavities of the long bones are expanded with cortical thinning. As the process of thrombosis and infarction proceeds, the bones show the same processes that we have seen in other organs modified by the peculiar structure of the tissue (Diggs, Pulliam and King, 1937).

Sickle tests

In the laboratory the usual method of testing for sickling is to transfer a drop of the patient's blood to a slide. A cover slip is put on and sealed with grease to keep the blood moist. As the blood loses oxygen, the erythrocytes begin to sickle and can be seen under a microscope. This process takes up to 48 hours. It is possible to speed the process by introducing a reducing substance such as sodium bisulphite or a preparation of B. Subtilis or by passing carbon dioxide through a preparation of the cells. In these ways it is possible to get a result in fifteen minutes. If specimens of venous and arterial blood are obtained and immediately fixed with formalin, it is found that in sickle cell anaemia there are about 5 per cent. sickled cells circulating in arterial blood and 15 per cent. in the venous blood. The trait will show no circulating sickled erythrocytes.

Laboratory findings

The blood in sickle cell anaemia shows a normocytic normochromic anaemia. If the anaemia is very profound, there may be a macrocytic anaemia. The degree of anisocytosis and poikilocytosis also varies with the severity of the anaemia. Nucleated red cells, target cells and reticulocytes are seen, the latter may reach 20 per cent. of the total erythrocytes. The white cell count usually lies between 10 and 20,000/cu. mm. However, during the first days of a crisis the count may be higher.

The erythrocyte sedimentation rate, depending on rouleaux formation, is low and if a tourniquet is applied before taking the blood, this lowers the E.S.R. by producing more sickled cells.

Cell resistance is high and even distilled water will often not lyse all the cells. The cells are, however, particularly liable to physical damage.

In addition to the changes mentioned previously, one finds that the albumen globulin ratio is reversed, the icterus index is consistently raised and if renal damage is marked, the blood urea is high. The Van den Burgh reaction is negative direct but usually positive to the indirect test. The serum potassium level is raised. Haemoglobinuria may be found.

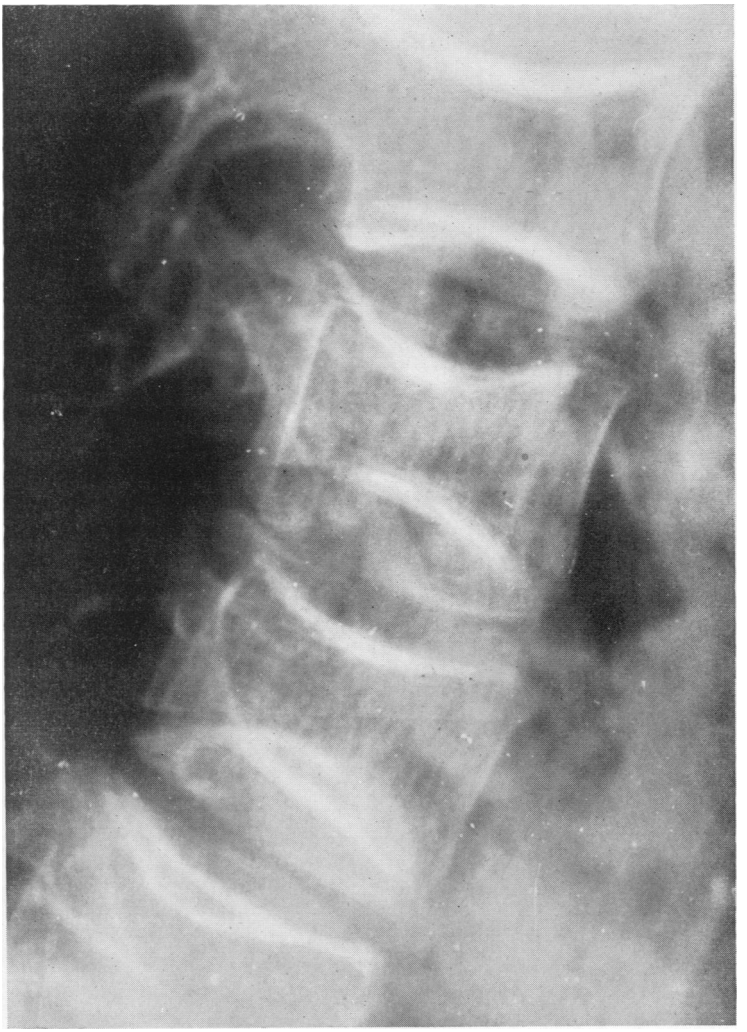
BONE DISEASE

We have already considered the clinical form the crisis takes, bringing the patient to the doctor. Often symptoms are multiple, but in about 80 per cent. of cases, pain in and around the bones or joints will be one complaint. Before discussing the lesions that occur in bone, it is important to stress that the basic pathological changes are the same as elsewhere in the body. They will be grouped into those secondary to hyperplasia of the bone marrow, those due to changes in blood supply, disorders of growth and finally the changes that accompany secondary infection. It must be realised that any or all these groups may be present in one and the same bone.

(a) **Changes due to marrow hyperplasia**

The erythroid hyperplasia effects the bone trabeculae and causes absorption, osteoporosis, softening and change in shape (Carroll, D. S.,

and Evans, J. W., 1949). This is well illustrated in the vertebrae which show these changes in about 70 per cent. of cases. The body 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). This change may be seen in other conditions such as senile osteo-porosis. If the height and width of the vertebral bodies are measured, it will be found that there is usually a marked decrease in height and increase in width. The normal height to width ratio in the



Figs. 2*a* and *b*. Antero-posterior and lateral radiographs of lumbar vertebrae showing "cupping," diminution of height and increase of width. (See facing page.)

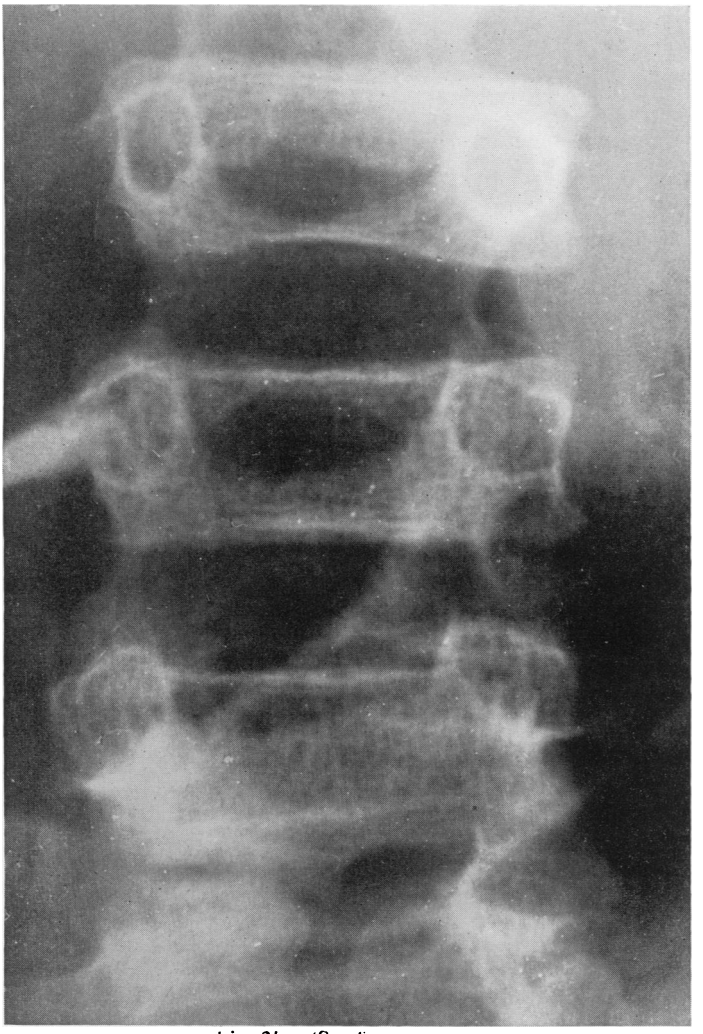
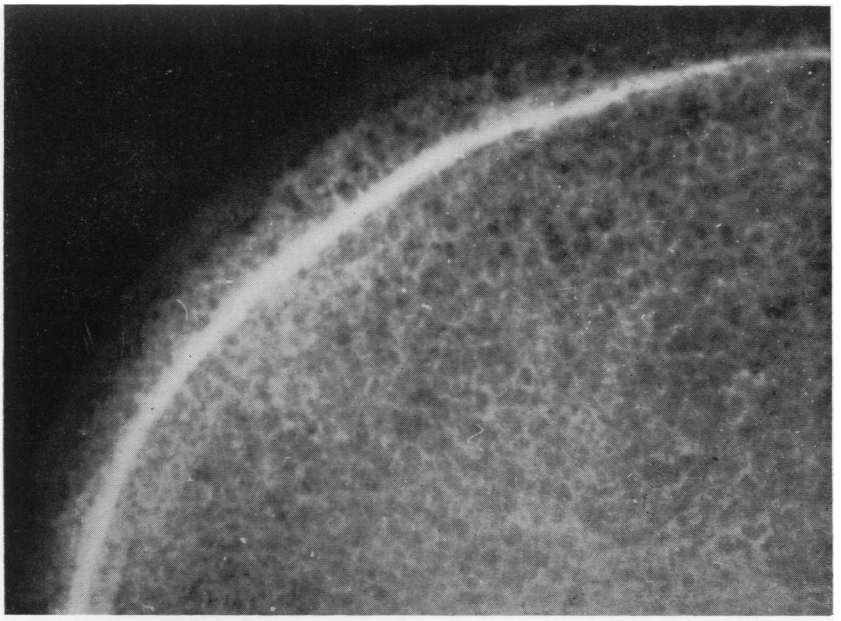


Fig. 2*b*. (See facing page.)

negro is 1 : 1·8 (Diggs, Pulliam and King, 1937). In this series it was 1 : 2·8 on the antero-posterior view, the greatest being 1 : 3·9 (see Fig. 2 (*a*) and (*b*)).

The change of thrombosis and infarction may also be seen in the vertebral bodies leading to sclerosis. This change is probably pathognomic for sickle cell anaemia (Ehrenpreis and Schwinger, 1952). In the early stages of medullary hyperplasia, the vertebrae resemble on the radiograph the appearance of a haemangioma (De Lorimer, 1949). Later irregular sclerosis appears as infarcts organise and become calcified.



Figs. 3*a* and *b*. Portion of the parietal region of the skull showing the usual reticular pattern compared with the rare " hair-on-end " appearance.

Fig. 3*b*.

This process may become so severe that the vertebrae may resemble the changes of severe Paget's disease or the sclerosing metastases of prostatic carcinoma.

Occasionally massive infarction may occur causing complete collapse of a vertebral body (Legant and Ball, 1948). Gradually the body will revascularise and reform if weight bearing is avoided.

The skull like the vertebrae shows mainly hyperplastic changes. Obvious changes may be seen on the radiograph in about 25 per cent. of cases but a further 25 per cent. mild changes are observed. The twenty skull radiographs in this series showed marked changes in six cases and mild but definite changes in a further six cases.

The most common radiographic change is usually a loss of trabecular definition giving a ground-glass appearance to the skull. The outer table appears thin and partly absorbed (Cole, 1955). The classical " hair-on-end " appearance is in fact not common in sickle cell anaemia and is more likely to be seen in Thalassaemia. The perpendicular striations will be seen radiating out vertically from the inner table. This peculiar result of erythroid hypertrophy in the diploic marrow, accounts for the tower skull deformity which is characteristic. The parietal bones are usually symmetrically affected (Hamburg, 1950). This condition causes no symptoms. Two of these cases have been encountered (see Fig. 3 (*a*) and (*b*)).

In later life the skull changes tend to be also in the parietal region and symmetrical. They take the form of lamellated new bone formation. Although infarction is not severe or common in the skull, it does occur and gives patches of localised osteoporosis which later may become sclerosed. We have not seen a case of this type.

In the long bones, as the medulla hypertrophies, so the cortex is thinned on its inner surface. The diaphyseal extremities widen and as osteoporosis proceeds the metaphyses appear relatively denser. The bones never actually widen by this process as they do in erythroblastic anaemia.

The flat bones, pelvis, scapula and particularly the ribs, show these changes very well. Thus the ribs show wide trabeculae, osteoporosis, a thin cortex and sometimes patchy erosion or sclerosis if the process of infarction has been super-added. This is a most useful finding for these changes are often visible on the chest film. With the presence of an enlarged heart and pulmonary congestion, it is often enough to suggest the true diagnosis. The pelvis usually demonstrates the same changes as the other flat bones, but in this site sclerosis may be so severe that with similar changes in the lumbar spine, Paget's disease is suggested.

(*b*) Bone changes from thrombosis and infarction

To the clinician, these hyperplastic changes are more of interest in making the diagnosis than anything else for they do not cause symptoms. The next group of conditions due to changes in blood supply are of the greatest clinical significance, for thrombosis and infarction causes severe

and crippling disability. In this respect, sickle cell anaemia resembles haemophilia in that the patient having survived early danger, may become permanently incapacitated.

Having already described the general skeletal changes, I will confine my remarks to the usual types of lesion caused by thrombosis and infarction in bone. The hip is commonly affected by these processes and in this series there were fourteen patients with avascular necrosis of the head of the femur. These cases can be grouped according to age. The younger age group showed changes resembling those of Perthes' disease. Six of these cases varied in age from eight to fifteen years with an average of eleven years. In addition, there was one man of twenty-one years who had bilateral hip disease and was virtually bedridden due to the effects of this condition on both hips many years before. They resembled Perthes' disease in their clinical signs and response to treatment. However, there is one significant difference between the two conditions, for whereas in a severe Perthes' disease, there are usually well marked changes of widening and a cystic appearance in the metaphyseal region, this does not seem to occur in those due to sickle cell anaemia (Mindell and Sherman, 1951). However, one case did show an area in the centre of the metaphysis which might have been a small cyst. In one case associated with sickle cell anaemia, the whole head of the femur had subluxated. This case will be described in more detail when the problems of growth disturbance are considered as there was a marked lack of growth of the whole side of the pelvis which may well have been a factor in the process of subluxation (see Fig. 4).

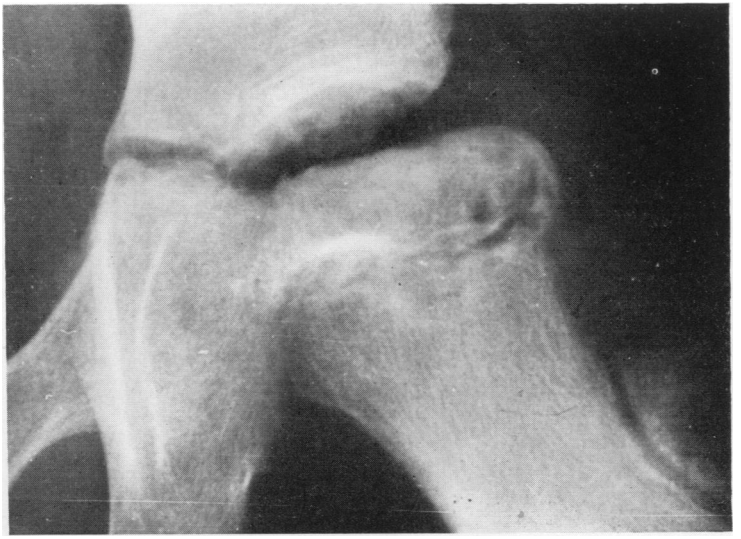


Fig. 4. Radiograph of the left hip showing the Perthes' type of lesion.

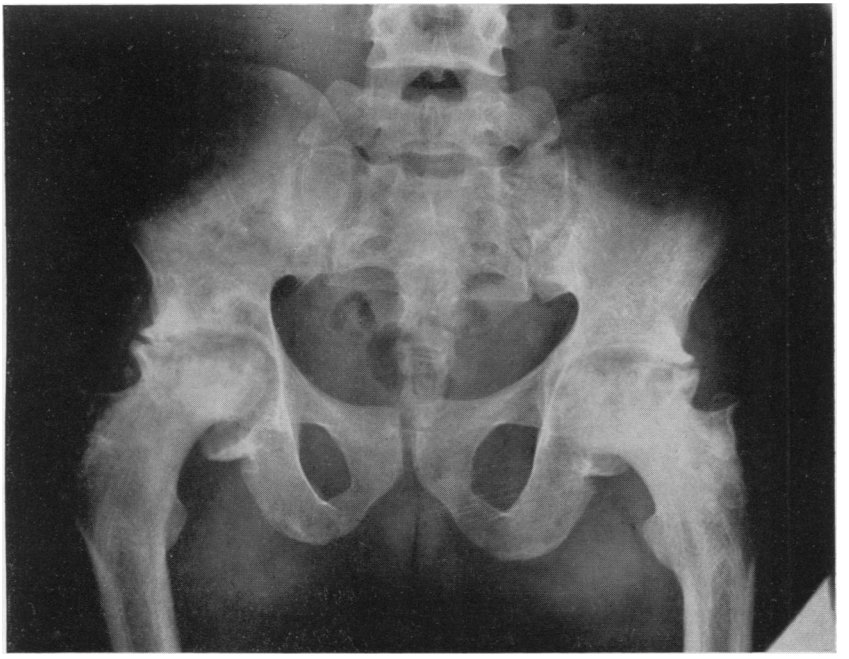


Fig. 5. Pelvis of male aged 57 years showing typical avascular changes in the heads of both femora.

These six cases suggest that the changes in the head were a primary phenomenon and not secondary to thrombosis or changed vascularity in the metaphyseal region.

The adult type of avascular necrosis may be seen (Moseley and Manly, 1953). The number of cases reported in the literature is small and it is remarkable that in this series there were seven cases of avascular necrosis. In four of these cases the changes were bilateral and quite characteristic. These cases occurred in patients between the ages of twenty-four and fifty-seven years of age. The three older patients in this group stated that they had trouble with their hips for between fifteen and twenty years suggesting that the condition usually starts between twenty and forty-five years of age. However it would also seem that in the earlier onset cases, the whole head of the femur may collapse, while in the older age group the collapse involves the inner three-quarters of the femoral head so that a projecting portion is above the superior lip of the acetabulum and forms a bar to abduction. This condition was bilateral in all four cases so that it was seen in eight hips (see Fig. 5).

Most of the patients in whom the head of the femur had borne the brunt of the disease showed changes of widened trabeculation and sometimes patchy sclerosis in the pelvis. They all showed changes somewhere else in the skeleton. None of these lesions was an isolated abnormality.

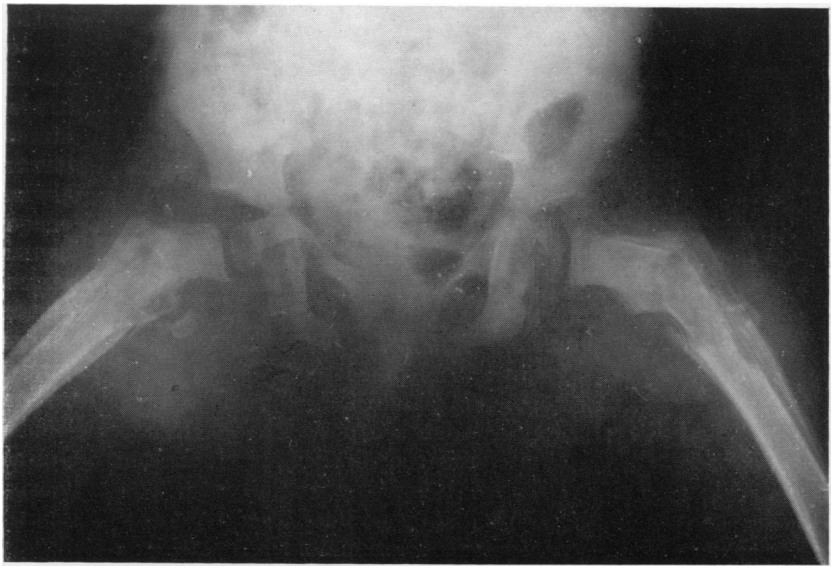


Fig. 6. Femoral shafts of child aged 15 months showing symmetrical infarction with bilateral pathological fractures.

Frequently, the femoral shafts and other long bones showed a medulla mainly filled by bone and a sclerosed thick cortex. The medullary canal may be completely obliterated by this process. The sclerosis may be patchy and irregular, resembling Paget's disease or a chronic inflammatory process.

Although avascular necrosis causing death of a complete bone has not been seen in this series, it has been described in the wrist and tarsal navicular as well as the case previously described in the lumbar spine. However we have seen one case where the whole of the os calcis collapsed and became infected. This process may well have started with the infection of a small infarct which later spread to the rest of the bone.

Death of a whole segment of shaft has been seen in a child of fifteen months 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. The patient was shown to have sickle cell anaemia and both parents had the trait. The child was uncooperative and miserable, there was a slight pyrexia. The upper part of both thighs was intensely painful and there was a pseudo-paralysis of both legs. A radiograph showed that the upper one-third of both femoral shafts were symmetrically expanded and that, within a shell of sub-periosteal new bone formation, the shaft was infarcted and crumbling. On the right side there was an obvious pathological fracture and possibly a healing fracture on the left accounting for the new bone formation. This was at first thought to be an unusual type of osteomyelitis, but as there was a negative blood culture

and the fever rapidly settled, this diagnosis was revised. In four weeks the structure of the bone could be seen to be returning to normal and the tenderness had completely disappeared. Five weeks after admission the patient again became miserable and the temperature rose to 102deg. The spleen and liver became temporarily enlarged but this settled in a few days. Six months after discharge from hospital the patient again had tenderness and swelling of the left ankle which settled without trouble. There were no X-ray changes in the ankle. At this time, the femoral shafts were seen to be enlarged but the bone structure had returned to normal. A rather similar case in the lower third of the femur has been described in a twenty-one-months-old child (Almklov, *et al.*, 1950) (see Fig. 6).

Growth effects

A chronic anaemia itself will cause retardation of growth. In sickle cell anaemia, many of the changes already described will add to this retardation. The vertebral cupping and height diminution results in some degree of kypho-lordosis, and if the head of the femur is affected this may interfere with the growth of the femoral neck (Macht and Roman, 1948).

That one isolated bone can be retarded in growth is well illustrated in the following case :

V. G., aged fourteen years, attended complaining of pain in the right hip which had become severe during the previous seven months. There was a severe limp. The hip was found clinically to be practically ankylosed in marked flexion and adduction resulting in a lordosis. She had had attacks of pain in various joints for as long as she could remember. The radiographs showed that the whole right side of the pelvis was deformed and much smaller than on the left. The head of the femur had practically disappeared, probably due to the effects of a severe Perthes' type of lesion some years previously, and the joint was subluxated. The ribs, pelvis and skull showed hyperplastic changes. It was decided to perform an intra-articular arthrodesis of the hip, 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 portions of the head removed at operation were examined. The cartilage was degenerated and partially absent. In the underlying bone there were multiple small sequestrae lying in fibrous tissue. In some areas there was evidence of new bone formation (see Fig. 7).

The crisis and secondary osteomyelitis.

When a bone is affected in a crisis, the part becomes hot and swollen. There is a fever and a moderate leucocytosis. This quite often occurs in the hands or feet of small children. Usually these bones show osteoporosis, widened trabeculae and the structure in general has a ground-glass appearance. However, if an infarct occurs, a layer of sub-periosteal new bone is laid down which makes it look rectangular in

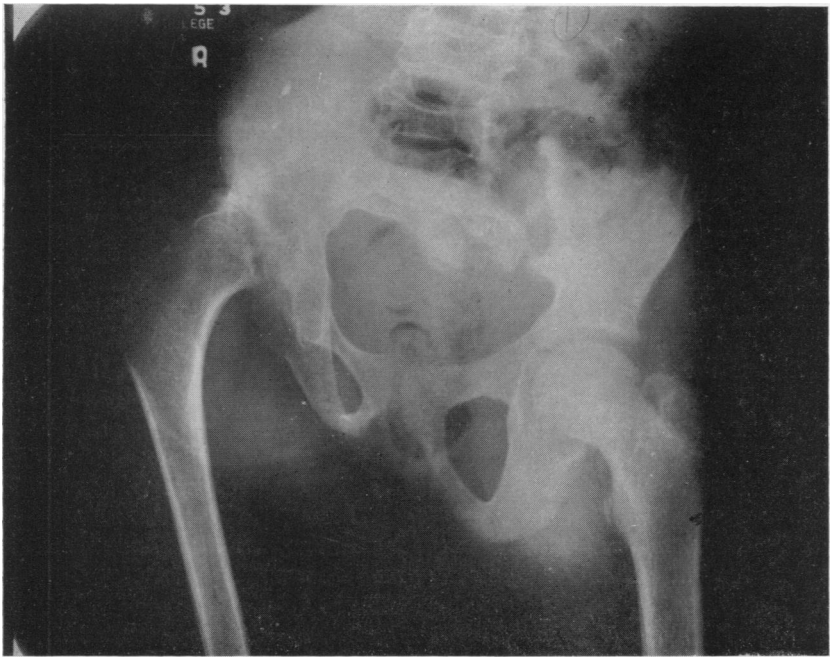


Fig. 7. Pelvis of girl aged 12 years showing agenesis of the right side and destruction of the right hip.

shape (Carrol and Evans, 1949). Within the bone the cortex loses its structure temporarily and small areas of transradiancy may be seen. The affected bone when the process is complete may be seen to have lost its normal waist and remains with parallel sides.

If a joint is affected, a large acutely tender effusion develops which is a deep yellow in colour and of glairy consistence. There are a few red cells in the effusion and some of these will be seen to have sickled.

The first case of sickle cell bone crisis that I encountered so exactly mimicked an attack of acute osteomyelitis that it was decided to try and find out from the literature if the theoretically ideal conditions of avascular bone did actually lead to an increased incidence of osteomyelitis. It was not possible to get an answer to this problem because though all considerable series did include some where infection occurred, there was no indication of the frequency in the non-anaemic patient. It was decided to carry out a survey on all cases attending orthopaedic out-patient clinics for two years, and in the 4,237 cases seen there were thirty-eight cases of osteomyelitis and ten cases where osteomyelitis was a complication of sickle cell disease. The sickle cell trait rate in Jamaica is 5·7 per cent. (Jelliffe, 1954), which would give an anaemia rate of about 1 in 1,500 of the population; so that it is about thirty to one against any one of the

forty-eight cases of osteomyelitis having sickle cell anaemia if the two conditions were quite unrelated. This would suggest that osteomyelitis is several hundred times more common in the sickle cell anaemia patient than in the rest of the community. It would be most interesting to do a similar study in Africans who have a much higher incidence of sickling. It would seem that the sickle cell anaemia patient who survives infancy has at least a one in twenty chance of getting bone infection.

Out of the seventy-two cases of tuberculosis of bone and joint seen in the two-year period, two were found to have sickle cell anaemia. In one the lesion was in the hip and in the other it was in a thoracic pedicle.

The actual form that the infection takes tends to the bizarre so that one comes to suspect any acute or chronic osteomyelitis which is found in an unusual site or in an unusual situation (see Fig. 8).

Salmonella osteomyelitis

In this series there were two cases of secondary osteomyelitis due to a salmonella infection. This is a very rare bone infection and it is remarkable that it is reported by other authors to accompany sickle cell anaemia in seven cases (Smith, 1953 ; Burch, J. E., 1949). Recently at the Children's Hospital, Los Angeles, three such cases (previously unreported) were demonstrated (and also two cases of osteomyelitis due to haemophilus influenza B). All these cases were of a low grade osteomyelitis occurring in children who very often had no history of intestinal infection. All were in debilitated children usually living in squalor. This remarkable association of two rather rare conditions, so far as the United States is concerned, is not understood. Two factors would seem to play a part in this association. Certainly before the advent of the antibiotics and possibly still, a number of sickle cell children must succumb to the overwhelming force of an attack of staphyloccoccal osteomyelitis. Most of the literature was written in these pre-penicillin days. Even if they reach hospital a patient already debilitated may die in the stage of septicaemia. This will have an effect in reducing the number of sickle cell patients with osteomyelitis from the usual organisms. Salmonella cholerae suis, the usual cause of the osteomyelitis infection, may apparently exist in the intestine of a pig and cause no disease unless the animal's resistance is lowered by intercurrent infection. If this occurs in children in poor surroundings it is possible that the lowering of resistance caused by a sickle cell crisis allows the organism to enter the body. It then settles in an infarcted area.

The first case of salmonella osteomyelitis which occurred in this series was in a boy of seven who presented with a low grade osteomyelitis of the right ulna. He stated that he had injured the elbow three weeks before the pain and swelling began. There was a low grade pyrexia and a fluctuant abscess was incised over the middle third of the forearm. The pus grew organisms of the salmonella group. These were sensitive to chloromyecetin and the condition slowly settled and healed when this drug was administered. This boy had skull changes. His mother had sickle cell anaemia and the father had the trait.

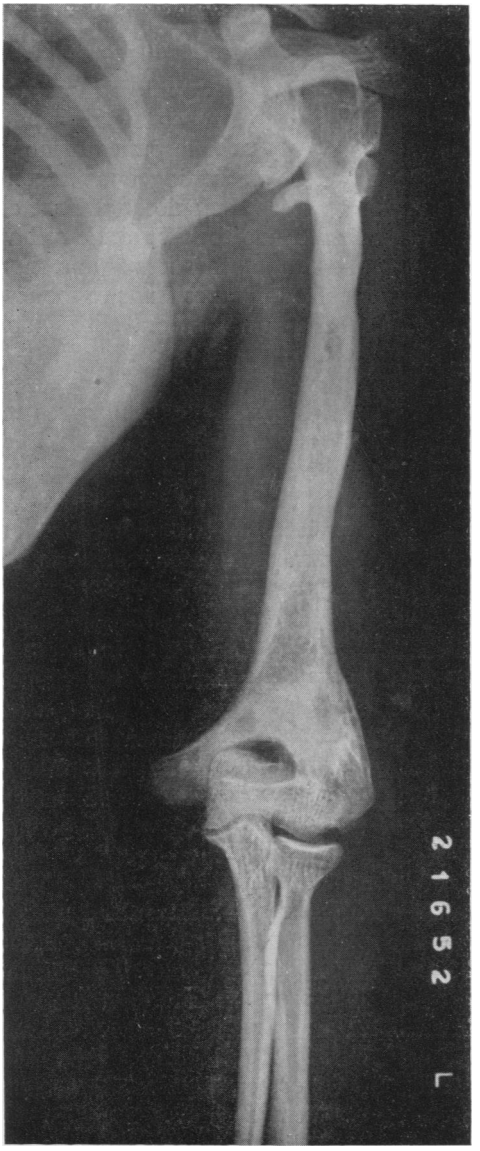


Fig. 8. Upper left humeral shaft of a girl aged 21 years showing loss of the epiphysis and evidence of old osteomyelitis.

The second case occurred in a man of twenty-one years who was admitted in a state of stupor. He had been ill for four days prior to admission with joint pains and severe lassitude. He had been unable to walk for many years. He had had many crises. There were ulcers on both lower legs.

The heart was enlarged and there were typical changes in the ribs and most of the other bones of the skeleton. The haemoglobin was 5·2gm./100ml. the albumen was 2·4gms per cent. and the globulin 5·4gms per cent., the blood urea was 448gms per cent. denoting severe renal damage. He was shown to have homozygous sickle cell anaemia. His general condition slowly improved and then an abscess appeared over the right upper medial aspect of the tibia. This was incised and found to have originated in bone. The pus grew organisms of the Salmonella group. The agglutination reaction was strongly positive for S. Paratyphosum CH at 1 in 3,200. He was treated with Achromycin in which the organism was sensitive in vitro. In spite of this he developed another lesion in the lower end of the left tibia and later in the lower end of the right femur. All these lesions were low grade and the bony changes were those of erosion and absorption rather than sequestration.

TREATMENT

Although there is no known cure for sickle cell anaemia much information is available about the measures that can be used to ameliorate the results. It has been found that the patients get along very well with a haemoglobin around 8 gms. per cent., and that above this figure transfusion is not needed. Repeated transfusions are not without danger and in sickle cell anaemia they are particularly liable to give rise to severe transfusion reactions and to result in a smaller rise in haemoglobin than one would expect. In spite of this it is advised by some workers that small transfusions should be given regularly. The sickle erythrocyte has been shown to live only a third as long as the normal. The transfusion is thought to give better results if 500 ml. of blood is removed from the patient while 1,000 ml. is being administered. There is some evidence that regular transfusions four times a year lessen the frequency of the crises and also their severity. Blood from those with the trait lasts as well as that from a normal subject.

In attempts to help these patients, many drugs have been used without benefit including dicumarol and heparin (Henderson, 1951). The vasodilating drugs may be of temporary benefit. Sympathectomy has been used for the leg ulcers with benefit (Klinefelter, 1942). Oxygen has been administered over long periods without success either in ameliorating the crises or raising the haemoglobin level ; indeed, there is evidence that oxygen actually does harm by inhibiting haematopoiesis.

There is little doubt that an anoxic period under anaesthesia can initiate a severe crisis as was shown in one of my cases in which death occurred thirty hours after a spinal fusion. This patient went into a series of convulsions. The brain showed blocked vessels throughout the cortex and to a lesser extent in the brain stem. Since recognising this fact, we have experienced no further trouble of this sort.

Splenectomy should be advised if the spleen is considerably enlarged. It has no benefit if the spleen is not readily palpable. It appears to benefit

the patient by raising the haemoglobin slightly and at the same time reducing the number of crises ; the number of transfusions needed subsequently is also reduced (Shotton, *et al.,* 1951).

The bone lesions that one may be called upon to treat are those associated with the crisis, avascular necrosis and secondary infection.

The patient who presents in a state of crisis affecting a bone or a joint is likely to develop secondary infection unless antibiotics are used to cover this period. It is very difficult to be positive in the early stages of a crisis that one is not dealing with an infection which may spread disastrously while a positive diagnosis is being made.

The Perthes' type of lesion in the child can be satisfactorily treated by rest and the avoidance of weight bearing. However, as the condition seems to affect a slightly older age group, it is likely that the final result in those due to sickle cell anaemia will be rather poor, in the same way as one finds that the late onset Perthes' disease heals badly.

The adult type of hip lesion will usually require surgery and when the condition is bilateral, a high femoral osteotomy of the McMurray type gives satisfactory results. If the avascular necrosis affects one hip, an arthrodesis is advisable and the bone will be found to heal satisfactorily and at a normal rate.

When the whole of the bone or part of the shaft of a long bone is affected by avascular necrosis, the lesion will heal provided that the region is protected from weight bearing while the dead bone is being absorbed and healing is taking place.

The principles in the treatment of a case of established osteomyelitis by large doses of an appropriate antibiotic, by drainage of an abscess and by sequestrectomy are as applicable to the patient with sickle cell anaemia as in any other patient.

Finally, by the early recognition of the condition and by the scheme of treatment that has been described, one can save these patients from much permanent and increasing disability. It may be many years before we find the answer to this type of molecular hereditary disease, but by studying its natural history the treatment of its complications will become increasingly more effective.

REFERENCES

ALMKLOV, J. R., HANSEN, A. E., and SCHNEIDER, M. (1950) *Pediatrics* **5**, 204.
BAUER, J. (1940) *Arch. Surg. (Chicago)* **41**, 1344.
BEET, E. A. (1949) *Ann. Eugen. (Camb.)* **14**, 279.
BERGREN, W. R., STURGEON, P., and ITANO, H. A. (1954) *Acta haemat. (Basel)* **12**, 160.
BURCH, J. E. (1949) *Sth. med. J. (Bgham, Ala.)* **42**, 135.
CARROLL, D. S., and EVANS, J. W. (1949) *Radiology* **53**, 834.
COLE, W. R. (1955) *British Surgical Practice, Surgical Progress* **5**, 126.
DE LORIMER, A. A. (1949) *The Arthropathies.* Year Book Publishers, Chicago p. 295.
DIGGS, L. W., PULLIAM, H. M., and KING, J. C. (1937) *Sth. med. J. (Bgham, Ala)* **30**, 249.
EHRENPREIS, B., and SCHWINGER, H. N. (1952) *Amer. J. Roentgenol.* **68**, 28.
HAMBURG, A. E. (1950) *J. Bone Jt. Surg.* **32A**, 893.
HARDIN, A. S. (1937) *Amer. J. Dis. Child.* **54**, 1045.
HARRIS, H. (1953) *Eugenics Laboratory Memoirs* **37**.

HARRIS, J. W. (1950) *Proc. Soc. exp. Biol. (N.Y.)* **75**, 197.
HENDERSON, A. B. (1950) *Amer. J. Med.* **9**, 757.
——————— (1951) *Amer. J. med. Sci.* **221**, 628.
HENKIN, W. A. (1949) *Amer. J. Roentgenol.* **62**, 395.
HERRICK, J. B. (1910) *Arch. intern. Med.* **6**, 517.
JELLIFE, D. B., STUART, K. L., and WILLS, V. G. (1954) *J. Haematol.* **9**, 144.
KLINEFELTER, H. P. (1942) *Amer. J. med. Sci.* **203**, 34.
LEGANT, O., and BALL, R. P. (1948) *Radiology*, **51**, 665.
MABAYOJE, J. O. (1956) *Brit. med. J.* **1**, 194.
MACHT, S. H., and ROMAN, P. W. (1948) *Radiology* **51**, 697.
MARGOLIES, M. P. (1951) *Medicine* **30**, 357.
MCGAVACK, T. H., and NUSSBAUM, C. C. (1942) *Urol. cutan. Rev.* **46**, 199.
MINDELL, E. R., and SHERMAN, M. S. (1951) *J. Bone Jt. Surg.* **33A**, 1.
MOSELEY, J. E., and MANLY, J. B. (1953) *Radiology* **60**, 656.
MURPHY, R. C., and SHAPIRO, S. (1946) *Ann. intern. Med.* **23**, 376.
NEEL, J. V. (1949). *Science*, 110, 64.
PATTERSON, R. H., WILSON, H., and DIGGS, L. W. (1950) *Surgery* **28**, 393.
PAULLING, L., ITANO, H. A., SINGER, S. J., and WELLS, I. C. (1949) *Science* **110**, 543.
RAPER, A. B. (1950) *J. trop. Med. Hyg.* **53**, 59.
ROSOKOFF, J., and BRODIE, E. L. (1946) *J. Urol. (Baltimore)* **56**, 544.
SHOTTON, D., CROCKET, C. L., and LEAVELL, B. S. (1951) *Blood* **6**, 365.
SINGER, K., ROBIN, S., KING, J. C., and JEFFERSON, R. N. (1948) *J. Lab. clin. Med.* **33**, 975.
SMITH, W. S. (1953) *Ohio St. med. J.* **49**, 692.
WADE, L. J., and STEPHENSON, L. D. (1941) *Amer. J. Path.* **17**, 47.
WELBOURNE, H., and RAPER, A. B. (1954) *Brit. med. J.* **1**, 1440.
WHITE, J. C., and BEAVEN, G. H. (1954) *J. clin. Path.* **7**, 175.

OVERSEAS VISITORS TO THE COLLEGE

OVERSEAS GUESTS AT the Monthly Dinner in October included Sir Henry Newland, Past President of the Royal Australasian College of Surgeons; Dr. C. P. Rhoads, Director of the Sloan Kettering Institute of Cancer Research, New York, and Mrs. Rhoads; Lt.-Gen. B. Chaudhuri, the D.G.M.S. of India; Lt.-Col. S. Prakash, the A.D.M.S. at the Office of the High Commissioner for India, and Mrs. Prakash; Lt.-Gen. W. A. Burki, the D.G.M.S. of Pakistan; Lt.-Col. T. M. Niaz, the A.D.M.S., Pakistan Liaison Staff, and Mrs. Niaz.

APPOINTMENT OF FELLOWS AND MEMBERS TO CONSULTANT POSTS

T. G. BARLOW, F.R.C.S.	Orthopaedic and Traumatic Surgeon to the Ashton, Hyde and Glossop Group of Hospitals.
P. J. CARTER, F.R.C.S., D.L.O., L.D.S.	E.N.T. Surgeon to St. Charles' Hospital.
J. G. FAIRER, M.R.C.S., F.F.A.R.C.S.	Anaesthetist to Mount Vernon Hospital and the Royal National Orthopaedic Hospital.
T. O. GARLAND, M.D., M.R.C.S., D.P.H.	Physician in Industrial Medicine to Central Middlesex Hospital.
D. C. HARLAND, F.R.C.S.	Surgeon to Luton Group of Hospitals.
A. F. ROBINSON, F.R.C.S.	Surgeon to the Burnley and District Group of Hospitals.
I. SUTTON, M.D., M.R.C.S., D.P.M.	Psychiatrist and Superintendent to Friern Hospital.
H. T. H. WILSON, M.D., M.R.C.P., M.R.C.S., D.T.M.	Dermatologist to Mount Vernon Hospital.
MISS B. M. L. UNDERHILL	Surgeon to the Government Hospital, Bahrain, Persian Gulf.