SICKLE-CELL ANAEMIA

A MAJOR DISEASE IN WEST AFRICA*

BY

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The first case of sickle-cell anaemia to be described was that of J. B. Herrick, of Chicago, in 1910. Emmel (1917) described the sickling phenomenon in a father and son. Taliaferro and Huck (1923) formed the opinion that a Mendelian factor responsible for sickling produced sickle-cell anaemia in some persons and in others only sicklaemia. It was not until 1947 that Neel put forward the hypothesis that when this factor was inherited from one parent the individual presented as a sicklaemic subject, and when from both parents, as a sickle-cell anaemia victim.

It is now recognized that both the sickling phenomenon and the disease are inherited; that both types of manifestation have been found in communities in which sickling has been detected; that the conditions are found in Africans or people who must have had blood connexions with Africans; and that the sickling phenomenon is connected with the chemical and physical properties of the haemoglobin in the red cells.

Beyond this there are unexplained facts about sickling and the disease. For example, it is generally believed that while the sickle-cell trait is common on the African continent the actual disease is uncommon. In contrast, it is said that the incidence of the disease is much higher in the U.S.A., where the calculated percentage of the trait among the negro population is comparatively low. The object of this paper is to examine some facts hitherto presented and to show that sickle-cell anaemia is common in Lagos and, most probably, in West Africa generally.

Characteristics of the Disease

Sickle-cell anaemia is a hereditary and familial disease characterized by persistent anaemia, often resulting in retarded growth; by recurrent crises marked by fever, headache, and bone and joint pains; and by signs of haemolysis (jaundice-leucocytosis) and of blood regeneration—for example, nucleated red cells and active marrow. It mostly starts early in life (at about 2½ years). The usual story is that the child has never been really well, is smaller than children of the same age, and is backward in general development. He is subject to attacks of joint pains, bone pains, abdominal pains, and headache. The presenting symptoms, however, may vary; and here it may be emphasized that this is where medicine, surgery, and midwifery meet. On examination the child is usually underdeveloped, often very poorly nourished. The conjunctivae are pale to varying degrees, and the sclerae lemon yellow. The anxious expression on the mother's face, and the victim's shiny face, underdeveloped appearance, and protuberant abdomen with compensatory lumbar lordosis, are striking, and make one suspect the disease as the patient walks into the consulting-room. The story told is that this is the third or fourth attack. The liver (almost invariably) and the spleen (less frequently) are enlarged.

Blood Picture.—Red cells, 3,000,000 to less than 1,000,000; leucocytosis of 12,000–40,000 during a crisis; reticulocytosis of 5–25%; normoblasts; target cells; raised serum bilirubin; absolute values usually normal, and the E.S.R. may be retarded. Sickle-cells may be found in the fresh preparation or after 24 hours' incubation, or after reduction of the haemoglobin.

For diagnosis, the finding of sickle-cells is not enough. It should be clinched by demonstration of the characteristic electrophoretic pattern of sickle-cell anaemia. This test is seldom possible in West Africa to-day, and may not be available in many hospitals for some years. But the disease should be suspected by every doctor practising in West Africa whenever a young subject presents with jaundice and multiple joint or bone pains, a severe anaemia with or without jaundice, pyrexia of unknown origin with leucocytosis, cirrhosis of the liver, bossing of the skull, retarded growth, signs suggestive of Perthes's disease, the acute abdomen, or hemiplegia. If one laboratory report shows no "sickling" in suspicious cases, the test should be repeated. In any event, laboratories should be encouraged to carry out carefully the more modern chemical methods of demonstrating sickling.

The Literature

Raper (1950) advanced the view that "the sickling aberration is much less to be regarded as a cause of morbidity among Africans than among negroes in the U.S.A." From a comprehensive review of the literature, he quotes the following figures: for sicklaemia, the average figure among U.S.A. negroes was 7%, with the highest, 14%, in South Carolina (Switzer and Fouche). On the African continent the trait incidence varies from 12 to 27%. Lehmann and Raper found the incidence varied considerably in various ethnological groups in Uganda—Hamitic, 2.9%; Pygmoids, 46%; Bantu, 19–27%. A. E. Beet found similar variations in Northern Rhodesia (average 12.9%); Mackey in Tanganyika, 23.3%; Abbott in Southern Sudan, 21.2%; Texeira in Angola, 27%; Evans in Nigeria (males only), 18.75%; Findlay in the Gold Coast, 12.4%; Gordon and Reid in Sierra Leone, average 27%.

Raper concluded, taking an average of 20% from the above figures, that nearly 40 million people "sickled" in Africa among an estimated population of 200 million. Hence the trait (sicklaemia) is thrice as common on the African continent as among the American negroes.

On the contrary, only 106 cases of the disease had up to that date been described south of the Sahara. Texeira said the disease was extremely rare in Angola. Beet found only two cases in 2,000 people in Northern Rhodesia. Lehmann and Milne saw only two cases out of several hundred people with sicklaemia. Russell and Taylor found one case in Accra in 1932; E. C. Smith described six necropsy cases in Lagos in 1943. Trowell found 35 cases in Uganda; Robertson and Findlay reported 46, or possibly 58, in West Africa; Raper reported two post-mortem cases in Uganda. In more recent years, workers in West Africa have found more cases. Foy and his associates (1951) in Kenya, and J. and C. Lambotte-Legrand (1951) in the Congo, reported a high incidence. Jelliffe found 22 cases in 18 months at Ibadan.

We have, however, encountered 63 cases in the General Hospital, Lagos, in the last three years (April, 1952, to March, 1955). Of these, 13 are described because of their more peculiar features.

Case Reports

Case 48.—A boy aged 6 presented as a case of right-sided hemiplegia with aphasia. The only other abnormality found was that he was in a typical sickle-cell crisis. He had mild fever and lost the use of the right side of the body and of speech 48 hours before admission. He was well developed. Apart from fevers (which might have been malarial) there was no history suggestive of previous crisis. Blood picture: R.B.C., 2,730,000; Hb, 62% (9.15 g.); C.I., 1.14; W.B.C., 13,000; reticulocytes, 5%; 85 normoblasts per 200 W.B.C.; target cells, + + +; occasional sickle cells. Sickling + + + after 24 hours' incubation, with a preponderance of bizarre-shaped forms. Marrow: normoblastic hyperplasia; no megaloblasts.

Case 47.—A boy aged 12, quite small for his age, had been known to have crises for several years. He died in

*Read at the Annual General Meeting of the Nigeria Branch of the British Medical Association, March, 1955.

anaemic cardiac failure. Blood picture: R.B.C., 1,460,000; Hb, 7.5 g.; W.B.C., 23,700; reticulocytes, 4%; a few target cells. Sickle cells present after 24 hours' incubation.

Case 56.—A boy aged 8 was admitted in a severe crisis. He was poorly developed. There was a severe and intractable epistaxis. The marrow showed evidence of active regeneration. Megaloblasts were present.

Case 14.—A boy aged 3½ had megaloblasts present in the marrow.

Case 49.—This boy, aged 14, was well developed and showed signs of a mild crisis. His only complaint was of intractable pain in the right thigh for several years. *X*-ray examination of both femora, knees, and hips revealed no abnormality. He had to stay away from school when the pain was severe. The marrow showed atypical megaloblasts.

Case 8.—A girl of 17 (a niece of mine) was treated for "catarrhal jaundice" in 1940 in a provincial hospital. She has had regular recurrent crises since. From an initially precocious child, she came gradually to lag behind children of her own age, and puberty has been delayed. Diagnosis was first made in 1943. Laparotomy was performed during a crisis in 1948, and she was put in a plaster cast for tuberculosis of the hip in 1949. Blood picture: R.B.C., 2,390,000; Hb, 7.1 g.; W.B.C., 14,000; reticulocytes, 14%; sickle cells, + + + in stained preparation. Sternal marrow: active normoblastic erythropoiesis; no megaloblasts.

Case 50.—A woman aged 25, first encountered in 1944 in a surgical unit as a case of multiple joint tuberculosis; had her left knee-joint excised and arthrodesed. In 1952 she was sent to the medical unit from the maternity hospital, seven months pregnant and in a crisis from which she never recovered.

Case 51.—A baby whose first crisis occurred at 8 months. Sickling was severe, and was demonstrated in fresh preparations.

Case 45.—A normal healthy male baby aged 18 months suddenly had a severe crisis with rapid loss of weight: jaundice, an enlarged tender liver, and severe sickling in fresh preparation. He was irritable and resented passive movements in all limbs.

Case 46.—A boy aged 9 was known to have had sickle-cell anaemia for several years. He was well developed and was described as brilliant at school. A laparotomy was performed during a crisis two or three years previously. In February, 1954, he had a severe crisis in which the abdominal pain appeared unusually severe and definitely paroxysmal. Gall-stones were confirmed by cholecystography. The problem arose whether cholecystotomy or cholecystectomy should be done. In view of the fact that large quantities of bile were likely to be formed continually, it was decided to do the former and leave the gall-bladder alone if it was healthy.

Case 52.—A man aged over 40 had been in the Army for several years and was quite fit. There was no history of previous crises. He was admitted to hospital as a case of severe pyrexia of unknown origin which persisted for several weeks. Investigation revealed no cause for the pyrexia. The picture was typical for a sickle-cell anaemia crisis. This diagnosis was at first dismissed in view of his age and of the fact that he had been in the Army. The blood, however, was sent for electrophoresis, and the report stated that it showed a sickle-cell anaemia pattern.

Cases 19 and 61.—These are of interest because of the *x*-ray appearances of the skull ("hair-on-end" appearance) (Figs. 1 and 2).

Commentary

These 13 cases show the protean nature of sickle-cell anaemia. Several cases, like Nos. 56 and 14, showed megaloblasts in the marrow. These patients often came from the poorer class. The megaloblastic portion of the anaemia was considered to be nutritional in origin or due to severe liver damage. The Hb went up on vitamin B_{12} and folic acid, but was never normal. No case from the higher, well-fed section of the community showed megaloblasts. It might here be mentioned also that the prognosis is worse in the poorer class. A superadded malnutritional state brought on a more speedy end. Cases 8, 50, and 56 illustrate the hazards to which these children are liable. Case 50 might have had multiple joint tuberculosis, but it is probable that she did not have it. Differential diagnosis could be difficult, especially in early cases.

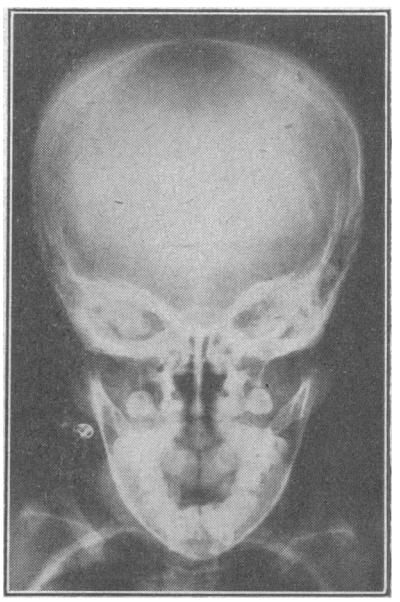

FIG. 1.—Typical changes in sickle-cell anaemia, showing hair-on-end appearance.

Case 46 is of great interest. A crisis led to an apparently needless laparotomy. Yet two or three years later gall-stones were demonstrated during a crisis. An unusual deepening of the jaundice should make one look for signs of biliary obstruction. The highest clinical judgment may be needed. Colleagues in other departments of the hospital are usually most helpful under such circumstances. The two infants described (Cases 51 and 45) are being followed up. Case 52 is an isolated case. Patients with sickle-cell anaemia seldom live beyond the age of 30. This may be a new disease in which part

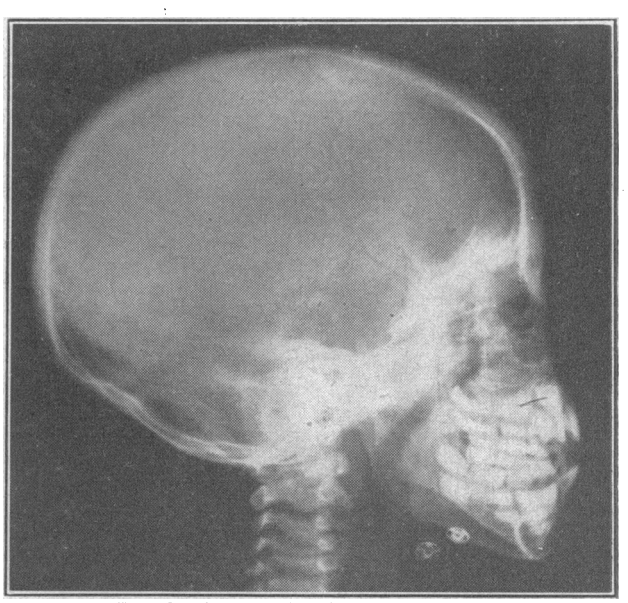

FIG. 2.—Same as in Fig. 1, lateral view.

or all of the haemoglobin is not of the sickle-cell variety but of another kind which shows the same electrophoretic behaviour—for example, haemoglobin D. If sickling is present part of the haemoglobin is, however, presumably of the sickle-cell variety. Subtertian rings were demonstrated in two cases during a crisis. Two cases were fatal during pregnancy. A third patient (Case 44) (very ill in crisis) was removed from the hospital at the seventh month and could not be followed up. The high mortality among pregnant cases may be attributed to the high

incidence of pregnancy anaemia in Lagos. Despite the high incidence of tropical ulcers among the ordinary population here, only three of our cases had chronic leg ulcers.

It is our firm opinion that sickle-cell anaemia is common on the West Coast of Africa. We have had as many as five cases in the wards at the same time, and three new patients walked into the medical out-patient department in the course of one morning clinic. The 63 cases here presented are the severest. In the last nine months we have had the advantage of having the blood of our cases examined electrophoretically. All cases clinically diagnosed have been confirmed. All cases here presented were most probably correctly diagnosed. On the other hand, many cases have not been included because they could not be well covered by our criteria for diagnosis—namely, clinical features, history of recurrent crises, family history, the finding of signs of haemolysis and of blood regeneration, and the demonstration of sickling. The greatest stress is laid on the history of recurrent crises and on the fact that the anaemia is never cured.

No attempt has been made to relate our figures to general population figures. Many sick people have no easy access to the hospital in West Africa to-day, and the great load on the doctor and laboratory where these are available makes frequent blood examination impossible. Figures may be grossly misleading at the present stage of our development. Moreover, Choremis *et al.* (1951) found small foci of sickle-cell anaemia in villages in Greece. It is probable that there are scattered areas of dense foci in villages and towns of West Africa. These can be discovered only as medical facilities expand.

Raper (1950) suggested admixture of African and Caucasian genes as responsible for the higher incidence of sickle-cell anaemia in American negroes. He also stated: "This essay has been directed to showing that the disease is of more importance to the negro [sic] than to the African." It is gratifying to note that he has since revised his opinion, at least so far as Uganda is concerned (Welbourn and Raper, 1954). But this statement requires correction in something more than a letter to the *British Medical Journal*. One has seen several instances in which the diagnosis of sickle-cell anaemia was dismissed merely on the grounds that it was "uncommon on the continent of Africa." It is also of interest to note that J. and C. Lambotte-Legrand have found the disease to be frequent in the Belgian Congo. In the Gold Coast the frequency of the disease appears to be not inconsiderable. The racial admixture theory would therefore appear not to be the answer to the comparative frequency of the condition in the American negro.

The truth appears to be that sickle-cell anaemia is common in American negroes because it is common on the West Coast of Africa. West Africa is the original home of the American negro. Literature on the exact parts of the world from which the negro originated appears to be scanty. But the Rev. J. Leighton Wilson (1850), of the American Mission established on the Gaboon River, wrote: "Take as an illustration the history of the slave trade in the Bight of Biafra. All who have investigated the subject know that the Rivers Benin, Bonny, Brass, Calabar, and Cameroon were once the chief seats of this trade. It is through these rivers that the Niger discharges itself into the ocean; and as the factories near the mouth of these different branches had a great facility of access to the heart of Africa, it is probable that the slave trade was carried on more vigorously here than anywhere else on the coast."

The Rev. Henry Venn (1865) honorary secretary to the Church Missionary Society, wrote: "Until 1840, the Slave Trade had been carried out to its full extent along the greater part of the sea-board of Western Africa from the River Gambia in the North to Little Fish Bay in Latitude 15° South. . . . "

Hodges (1950) quotes from Frazier (1949): "Negroes continued to be brought from Guinea, Gambia, Calabar (Niger Delta region), Angola (the lower Congo) and a few from Madagascar." He (Hodges) goes on to say: "Most authorities agree that the slave traders sailed in the majority of cases from W. African ports. . . . There is no knowledge concerning how far from the coast slaves were acquired, but it is known that some of the overland treks from the inland to the sea coast required many months of travel on foot."

The areas covered by these three authors correspond roughly to the areas occupied by the true negro. It is seen that this covers the whole of British and French West Africa, extends into the Sudan, Abyssinia, portions of Kenya and Uganda, and probably into the Congo (Seligman, 1930).

Severe cases of sickle-cell anaemia are so obvious and so easy to diagnose that workers interested in the condition would have had no difficulty in recognizing such cases if they occurred with any frequency. There is no doubt that the disease is rare in South and in parts of East Africa. It is suggested that we are dealing with two areas of Africa in which the sickle-cell gene behaves differently. In West Africa and surrounding negroid zones, sickle-cell anaemia occurs with considerable frequency. In places like Southern Rhodesia the disease is infrequent even though the *trait* is frequent. The negro in the U.S.A. and the coloured West Indian are outflows from the former areas.

The genetic theory of Neel and Pauling does not seem to explain fully the relationship between sickle-cell disease and sicklaemia. It is here suggested that there is a third factor (or the lack of a protective factor) present in West Africa but absent in those various ethnic groups in East and South Africa which show a high incidence of sicklaemia but a low incidence of sickle-cell disease. It is difficult to believe that in places like Southern Rhodesia marriages in which husband and wife are both heterozygous for the sickle-cell trait do not occur frequently.

Sickle-cell anaemia is a major disease of West Africa. It is a cause of distress in many families. It is, in view of its protean mode of presentation, a diagnostic problem in every department of a general hospital. It therefore deserves much better recognition than it gets at present. It should be treated as a major disease in schools of tropical medicine, in textbooks on tropical medicine, and in all medical schools in tropical Africa.

Summary

Sixty-three cases of sickle-cell anaemia have been diagnosed in the Lagos General Hospital in three years.

Thirteen of these cases, illustrating the protean mode of presentation and some special diagnostic problems, are described.

It is pointed out that the disease is a major problem in West Africa and should be given greater prominence.

It is suggested (*a*) that the disease is common in the U.S.A. because West Africa is the home of the American negro, and (*b*) that there is an unknown "protective" factor that would explain why the disease is comparatively uncommon in certain parts of Africa though the trait exists.

I thank my friend Colonel J. H. Walters, of the West African Council for Medical Research, Lagos, who helped to clinch the diagnosis by electrophoretic analysis in the later cases, and Dr. S. L. A. Manuwa, the Chief Medical Adviser to the Federation of Nigeria, for his helpful criticism and for permission to publish this paper.

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