

The CENTRAL AFRICAN JOURNAL OF MEDICINE

Dr. DAVID LIVINGSTONE

Vol. 2. No. 2.

FEBRUARY, 1956

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PUBLISHED MONTHLY, ANNUAL SUBSCRIPTION £2 2s. 0d.

Registered at the General Post Office as a Newspaper.

The Sickle-cell Phenomenon

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The sickle-cell phenomenon is an inherited peculiarity of the red blood cells, by virtue of which, when oxygen is withdrawn, the cells assume elongated or crescent shapes somewhat resembling sickles. Clinically, those whose red cells show the sickling anomaly fall roughly into two classes:—

(a) Bearers of the sickle-cell trait, a symptomless condition in which no sickled cells are found in the circulating blood, but in which sickling can be produced by artificially reducing (i.e., deoxygenating) the haemoglobin.

(b) Patients with sickle-cell disease. There are two main pathological manifestations of sickling, which may appear together in the same patient or separately. These are (1) sickle-cell anaemia, a haemolytic anaemia characterised by the appearance of sickled cells in the peripheral blood; and (2) vascular complications due to the blocking of small vessels by masses of sickled erythrocytes. This may lead to infarction of various organs with results such as haematuria, hemiplegia or sudden death—the sickling crisis. It has been suggested¹ that the haemolysis in sickle-cell anaemia may be due to the disintegration of masses of sickled cells which have become impacted in small vessels, perhaps by reason of their shape. This would mean that the primary lesion in sickle-cell disease was always one of vascular occlusion, but the view is not universally accepted. Gelfand⁴⁰ has described a case of sickle-cell anaemia from Southern Rhodesia, and I shall say no more on the clinical features of this disease. The vascular manifestations of sickling will be considered later.

Sickle-cell anaemia was first recognised in 1910 by Herrick in an American negro student.² For some years sickling was sought in the ordinary smear taken from the peripheral blood, and thus the existence of the trait was not recognised. In 1921 Hahn and Gillespie³ showed that sickling occurred when the haemoglobin in susceptible cells was in the reduced state. When means of reducing the haemoglobin were applied to the cells of apparently normal American negroes, it was found that a proportion

showed sickling who did not develop the anaemia or show other signs of disease. These were the trait-bearers. The incidence of the trait in American negroes is on the average about 8 per cent.⁴

Several methods have been used to elicit sickling. In the classical one a drop of blood is sealed under a coverslip with vaseline.⁵ The slide is examined with the microscope at intervals. The activities of the white and young red cells gradually remove oxygen from the blood and sickling usually appears within 24 hours in trait-bearers: in sickle-cell anaemia it begins much sooner. More efficient methods, using chemical reducing agents, are now available. Daland and Castle⁶ use a 2 per cent. aqueous solution of sodium metabisulphite, Na₂S₂O₅. A drop of blood is mixed on a slide with a drop of this reagent, which should be freshly prepared. Sickling appears in five minutes or less.

No matter what method is used to elicit it, sickling appears far more rapidly in the blood of patients with sickle-cell anaemia than in trait-bearers. In the anaemia also the sickled cells have long filamentous processes not seen in the trait. It has been shown that the reduction of oxygen tension necessary to elicit sickling is less in the anaemia than in the trait, which accounts for the more rapid sickling in the blood of patients with the anaemia and for the appearance of sickled cells *in vivo*. In the sickle-cell trait the haemoglobin has to be deoxygenated beyond physiological limits before sickling will occur.

In 1949 Pauling and his colleagues⁷ showed that in subjects with the sickle-cell anomaly an abnormal haemoglobin is present in the red cells. This haemoglobin was identified by its electrophoretic mobility—that is, by its rate of migration in an electric field. It differs from normal haemoglobin also in being very insoluble when reduced, and it is the crystallisation of the abnormal haemoglobin inside the cell which accounts for the sickled shape when oxygen tension is reduced. It was shown that in sickle-cell anaemia all or nearly all of the haemoglobin was of the abnormal variety, now known as haemoglobin S. In bearers of the sickle-cell trait haemoglobin S represents about 40 per cent. of the total, the rest being normal.

It had been known for a long time that sickling was inherited as a Mendelian dominant character. In 1949 Neel⁸ in America and Beet⁹ in Northern Rhodesia suggested independently

that sickle-cell anaemia was a manifestation of homozygosity for the sickling gene—that is, that for a patient to develop sickle-cell anaemia he must possess a pair of sickling genes, one derived from each of his parents. Those who were heterozygous—that is, who had only a single sickling gene—would show the trait, but would not develop the anaemia. This is true as far as it goes, but the theory has required some modification. In particular it has been found that one sickling gene may combine with another gene to produce syndromes clinically resembling sickle-cell anaemia. Thus a patient who receives a sickling gene from one parent and a gene for Mediterranean anaemia from the other may show a sickle-cell-anaemia-like syndrome known as sickle-cell-thalassaemia disease.¹⁰ The sickling gene may combine in the same way with genes producing two abnormalities of the haemoglobin, known as haemoglobins C and D. The syndromes thus produced are called sickle-cell-haemoglobin-C and sickle-cell-haemoglobin-D disease.^{11, 12, 13}

We have seen that in America, where sickling was first discovered, about 8 per cent. of the Negro population possess the trait. Occasional cases of sickling have been described in white Americans.¹⁴ Where this is not due to Negro ancestry it is usually found that these subjects are of Mediterranean descent. Sickling is not uncommon in parts of Greece¹⁵ and in other Mediterranean countries. In Africa, sickling is widely but patchily distributed in the black peoples. In West Africa, the original home of the American Negro, an average incidence of 12.4 per cent. was found by Findlay *et al.*¹⁶ In the Bantu tribes of Central, East and South Africa there are all degrees of sickling incidence from less than 1 per cent., e.g., in the Karanga of Southern Rhodesia,¹⁷ to 45 per cent. in the Baamba of Ruwenzori.¹⁸ Lehmann and Raper¹⁸ showed that in Uganda the incidence of sickling in Bantu tribes was inversely proportional to the extent of their recent contact with peoples of Hamitic (non-Negro) stock. One of the most remarkable features of sickling distribution in Africa is its rarity south of the Zambesi River.^{17, 19} In Southern Rhodesia most of the sicklers found are immigrants from the north or their descendants. The tribe of highest incidence so far recorded in Southern Rhodesia is the Ndau of the Eastern Border,¹⁷ who show 3 per cent. of sicklers. In the Union of South Africa the indigenous Bantu have less than 1 per cent. of sickling,^{19, 20, 21} and the Bushmen²² none at all. At the Zambesi River the incidence rises

sharply. The Cikunda on the river have 13 per cent.¹⁷ of sicklers and the Senga of Fort Jameson 20 per cent.²³ English²⁴ found an overall incidence of 17.5 per cent. among the workers in the copper mines of Northern Rhodesia. Fig. 1 shows percentage incidences of sickling in some tribes of the Federation and adjacent territories. The general distribution of sickling in Africa was summarised, with a map, by an annotator in the *South African Medical Journal* in 1952.²⁵

We have seen that many of the African tribes have an incidence of the sickle-cell trait considerably higher than that in the American Negroes. Thus we would expect sickle-cell anaemia to be a relatively common disease in Africa. Many believe, however, that sickle-cell anaemia is by no means as common in Africa as it ought to be. South of the Zambesi its rarity is understandable, because of the very low incidence of the sickle-cell trait. Elsewhere, experienced workers such as Jelliffe²⁶ in Nigeria and Lehmann²⁷ in Uganda have expressed doubt whether the anaemia occurs at the expected frequency. Lehmann has brought forward evidence to suggest that many homozygous sicklers survive in Africa without being incapacitated by sickle-cell anaemia. In the United States those who develop sickle-cell anaemia either die young or, if they survive, do not usually reproduce. In Africa, where the incidence of sickling is in some parts five times as great as that in the United States, such a loss of homozygotes should lead to a very rapid reduction in sickling incidence. This does not appear to happen, which suggests that, as Lehmann believes, some homozygous sicklers may escape the disease. Other authors, however,^{28, 29} have shown that in some parts at any rate sickle-cell anaemia occurs at the expected frequency. The question is still undecided.

Until quite recently it was always assumed that the sickle-cell anomaly was of African origin, since the only other places in which it was found were in the New World, to which it had been conveyed by the slave trade, or in the Mediterranean countries which had been penetrated by Africans from the earliest times. When Lehmann and Cutbush³⁰ discovered the trait in India, therefore, it was clear that ideas on the origin of the sickle-cell would have to be modified. These authors investigated the aboriginal hill tribes of South India, who are the survivors of the pre-Dravidian population. They are at a very primitive stage of civilisation.

In a sample of 201 of these aborigines, 31 per cent. of sicklers were found. The question at once arose whether these Indian tribes had not received their sickle-cells from African sources, but the study of their blood groups showed that this was most unlikely. All black peoples in Africa south of the Sahara, and the Bushmen as well, possess a high incidence—everywhere over 50 per cent.—of the Rh chromosome cDe (Rho). The Indian aborigines, however, showed a very low cDe incidence. Thus, unless they

developed their sickle-cells independently of the Africans, we have to consider the possibility of a migration which brought the sickling gene from India to Africa. The presence of Vedidian peoples, related to the Indian aborigines, in Persia and South Arabia lends support to this theory, which has been put forward by Lehmann.³¹ He suggests that the route may have been through South Arabia and across the southern end of the Red Sea, introducing the sickle-cell into what is now Somaliland. I have

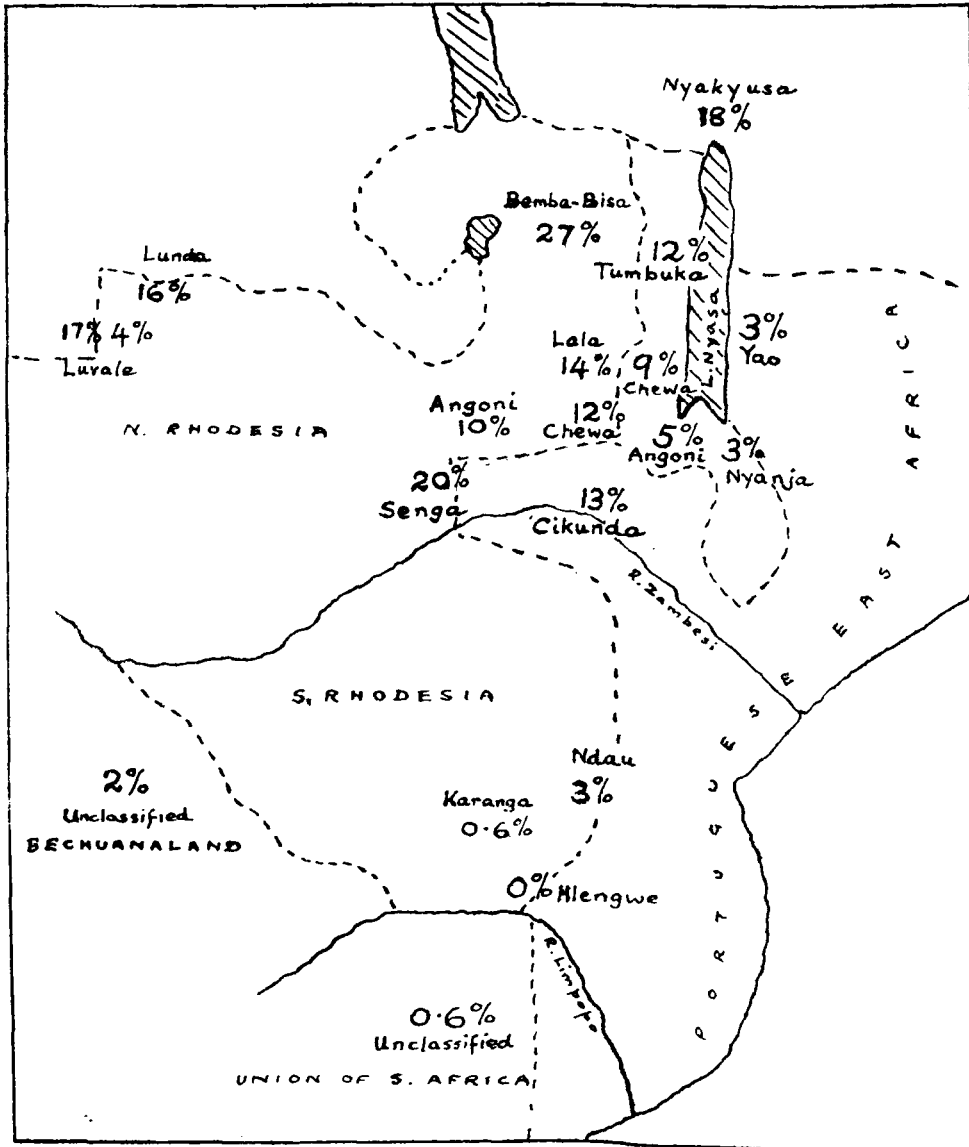


Fig. 1—Known incidence of sickling in Bantu, classified by tribe, in the Rhodesias and Nyasaland. See References for sources of information.

suggested elsewhere³² that the distribution of a certain breed of Indian cattle in Africa supports the view of Lehmann on the introduction of the sickle-cell.

When we consider the distribution of sickling in Africa from the point of view of the physician rather than that of the anthropologist, it is clear at once that it has some very peculiar features. In a tribe with a trait incidence of 40 per cent.—and such tribes are not very uncommon—we would expect about 8 per cent. of all children born to be homozygous sicklers. We have already seen that it is not agreed whether all homozygous sicklers develop the anaemia in Africa; but no one doubts that some of them do. Even if only a proportion of these children died in infancy or otherwise failed to reproduce, there would be a very considerable loss of sickling genes in each generation. Thus the frequency of sickling in populations might be expected to decline from generation to generation until it died out altogether. The sickle-cell gene has apparently existed in Africa for centuries without dying out. What mechanism compensates for the loss of homozygous sicklers?

There are several possible explanations of this phenomenon. At least one author³³ has suggested that the genes are replaced by mutation—that is, by the appearance *de novo* of sickling genes in the chromosomes of normal individuals. This would mean, however, that the mutation rate would have to be different in every tribe of different sickling incidence, and in high-incidence tribes the rate would be indeed incredible. It seems more probable that the key to the problem lies with the bearers of the trait; that is, with the heterozygotes. If trait-bearers were to enjoy a small advantage in health or fertility over normal non-sickling subjects, this might compensate for the loss of homozygous sicklers because of the fact that the heterozygotes are far more numerous. In other words, a balanced polymorphism would be set up. This question hinges on the health of trait-bearers.

In the earlier days of sickling investigations, many workers held that the sickle-cell trait was itself a cause of morbidity. These opinions were based more on clinical impressions than on statistics, and it has become clear with the passage of time that trait-bearers are not more liable to disease, generally speaking, than are normal people. To me at any rate it seems very doubtful whether intravascular sickling of red cells ever occurs to a significant degree in true

trait-bearers, i.e., in heterozygotes, except during aeroplane flights at high altitudes.^{34, 35} I think it very likely that the vascular phenomena in sickling, like the anaemia, are the prerogative of homozygous sicklers.³⁶

If it is true that trait-bearers are not unhealthy by comparison with normal subjects, this is indeed what would be expected on biological grounds, since if it were not so the survival of the gene would be very hard to explain. But to account for this survival the trait-bearer should in fact be *favoured* by selection. In 1949 Raper³⁷ had tentatively suggested that sickling might protect against tropical parasites, though he regarded it as unlikely. Beet²³ and myself¹⁷ had observed that trait-bearers in Rhodesia had a lower incidence of palpable spleens than non-sicklers, and I suggested³⁸ that the abnormal haemoglobin in sicklers might offer an unfavourable environment for plasmodia and that the sickler might thus be favoured by having a high resistance to malaria. This was conjecture, but Allison was then already working on the same lines and has produced some more convincing evidence.³⁹ He exposed sickling and non-sickling volunteers to malaria and found that the trait-bearers appeared to have a considerably higher resistance to infection with the parasite than normal subjects. It seems probable that increased resistance to malaria is at least one of the mechanisms by which selection favours the heterozygous sickler. This view gains support from the fact that sickling is seen at highest frequencies in some of the most malarious areas of Africa. Where there is no malaria the selective disadvantage of homozygosity might well prevent the establishment of the gene.

Despite the apparent fact that sickling is most common in malarious areas, it is clear that malaria will not account fully for its distribution in Africa. For example, the gene is rare south of the Zambesi River, although malaria is not. I think that this is simply because the comparatively recent migration that brought the gene to Africa did not spread further south than the Zambesi River. Thus the distribution of sickling is still of great anthropological interest. All over Africa the tribal groups are breaking up, and what work is to be done on the distribution of sickling will have to be done soon. There are large gaps in our knowledge. From Northern Rhodesia I know of no sickling investigations since the impressive work of Beet, who is no longer in the colony. The only studies of Nyasaland tribes known to me are my own, and

as these were done on emigrant miners in Southern Rhodesia they may well not be representative. In Southern Rhodesia little is known about the more northern tribes, such as the Shona-speaking Zezuru and Korekore and the Tonga of the north-west. The technique of sickling surveys is simple and they need not take up much time, and it would be most gratifying if medical officers in the Federation could contribute to our still very inadequate knowledge of sickle-cell distribution.

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SOURCES OF INFORMATION FOR FIG. 1

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- Southern Rhodesia:
Brain (17).
- Bechuanaland:
Griffiths (19).
- Union of South Africa:
Griffiths (21).



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