

An Anthropologist Looks at Malaria

P. V. TOBIAS

SUMMARY

Regions in which malaria is hyperendemic correspond with areas of highest frequency of the genes for haemoglobin S and for the red cell enzyme lack, glucose-6-phosphate dehydrogenase deficiency. It seems that the prevalence of malaria is a major selective agent influencing the geographical distribution and incidence of these two traits. Also, malaria may be associated with the lower levels of ATP (adenosine triphosphate) in the red blood cells of Blacks. Man's cultural evolution — and especially the adoption of agriculture — may have played a big part in the establishment of areas of malarial hyperendemicity. Thus, indirectly, malaria may have helped the early Black agriculturalists to modify their own gene pool.

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Department of Anatomy, University of the Witwatersrand,
Johannesburg

P. V. TOBIAS, D.S.C., M.B. B.CH., PH.D., F.R.S. (S.A.F.), F.L.S.,
Professor of Anatomy

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SKIN COLOUR AND MALARIA

In 1813 Dr W. C. Wells read a paper before the Royal Society, being 'An account of a White female, part of whose skin resembles that of a Negro'. In that paper, Wells clearly recognised the principle of natural selection as applied to human races (although it was close on half a century before Darwin put forward the Theory of Natural Selection). Wells remarked that Blacks and mulattos enjoyed an immunity from certain tropical diseases. He tried to relate this immunity to the darker skin of Black peoples. Nature, he said, seems able to form varieties of mankind fitted for the country they inhabit. 'Of the accidental varieties of man, which occur among the first few and scattered inhabitants of the middle regions of Africa, some would be better fitted than others to bear the diseases of the country. This race would consequently multiply, while the others would decrease; not only from their inability to sustain the attacks of disease, but also from their incapacity for contending with their more vigorous neighbours. The colour of this vigorous race, I take for granted, from what has already been said, would be dark. But the same disposition to form varieties still existing, a darker and darker race would in the course of time occur: and as the darkest would be the best fitted for the climate, this would at length become the most prevalent,

if not the only race, in the particular country in which it has originated.²¹

This was half a century before Charles Darwin wrote *The Descent of Man* in 1871. But Wells was not the only early writer to hold that the relative immunity of Blacks to certain tropical diseases was related to the darker skin of Black peoples. Others before Darwin had held this view too.

DARWIN AND IMMUNITY TO DISEASE

Sixty years later, Darwin in *The Descent of Man* pointed out that the relationship of immunity to dark skin colour was a mere conjecture. It might, he suggested, be correlated with some difference in his *blood*, nervous system, or other tissues.

His suggestion about the blood was a happy choice and an interesting guess, for, although Darwin was not to know it, differences in the blood would be found 75 years later to be correlated with immunity. He was not to know that in the 40s and 50s of the present century, resistance to malaria by Blacks would be attributed to the presence of a genetic variant, haemoglobin S, which occurs frequently in Africa.

A. C. Allison, a former research student of the Anatomy Department at the University of the Witwatersrand, confirmed experimentally that blood differences are behind the immunity of some Blacks to malaria. He did this by showing that malarial infection seems to be less severe in subjects who are heterozygous for the haemoglobin S trait — that is, who possess the allele for sickling haemoglobin in single dose—than it is in those without the trait.²

HAEMOGLOBIN S AND AFRICA

The abnormal form of haemoglobin known as haemoglobin S (Hb S) is widespread in Africa. It reaches high values in populations living between the Tropics. Red blood cells which carry this form of haemoglobin readily assume the shape of a sickle under some conditions. So the character is usually called the sickle cell trait.

The frequencies of African carriers of haemoglobin S rise as high as 45% among the Amba of Uganda and 44% among the Mbangala in Angola. However, south of the Kunene and Zambezi Rivers, the frequency of sicklers is extremely low. The trait is virtually absent in South African Blacks, San (or Bushmen) and Khoikhoi (Hottentots). The variability is great. A review of all available data for Black peoples south of the Sahara in 1966 showed that the figures for Bantu-speaking tribes in Kenya varied from 0 to 35%; Uganda from 2 to 45%; the Congo (Leopoldville), now Zaire, from 4 to 36%; Mozambique from 0 to 40%; Malawi from 3 to 9%; Zambia from 0 to 22%; Angola from 11 to 44%; Rhodesia from 2 to 12%; Botswana from 0 to 5%; South Africa from 0 to 1%.³ Since the 1966 survey, several further studies have been made, using paper electrophoresis or starch gel electrophoresis. The newer studies have been made by Barclay *et al.*,⁴ Bernstein,⁵ Ashworth and Macpherson,⁶ Ezeilo,⁷ M. C. Botha and Van Zyl,⁸ Botha *et al.*⁹ and Jenkins.¹⁰

They have confirmed in greater detail what Beet showed as long ago as 1946 and 1947;^{11,12} and Brain in 1952 and 1953^{13,14}—namely, that the sickle trait was present in high frequencies in many of the populations north of the Zambezi and Kunene; but that, south of these rivers, the frequency dwindled very dramatically.

GENETICS OF SICKLE CELL HAEMOGLOBIN

Jenkins has resuscitated the important role played by E. A. Beet at Serenje in Northern Rhodesia, in unravelling the genetics of Hb S. In 1947 he showed that sickle cell anaemia occurred in homozygotes only¹² (i.e. in the same year as J. V. Neel's famous paper to the same effect).¹⁵ Indeed, as Jenkins has shown, Beet should be considered as an independent co-discoverer of the mode of inheritance of sickle cell anaemia.

As early as 1953, Brain had proposed that the abnormal Hb might offer an unfavourable environment for plasmodia.¹⁴ The sickler might thus be favoured by having an enhanced resistance to malaria.

Indian origin: Lehmann^{16,17} suggested that the trait was brought to Africa from the East, across the strait of Bab-el Mandeb at the southern end of the Red Sea. Brain¹⁴ supported this view and showed a parallel between the spread of the sickle cell trait and that of the zebu or short-horned Indian cattle in Africa. He suggested that the men who brought the cattle also brought the gene. There is a complete absence of zebu south of the Zambezi, and likewise of Hb S. Moreover, sickling occurs in very high frequency among the Achdam of Southern Arabia and the Veddoids of South India. Could the trait have reached Africa from India, along with the zebu?

Hiernaux¹⁸ and Neel¹⁹ feel that there is no evidence of substantial gene flow in either direction, between India and Africa. However, they both draw attention to the fact that, given the selective advantage attributed to the heterozygotes for haemoglobin S under the theory of balanced polymorphism, very few immigrants carrying this trait into a foreign group could serve as a focus of dissemination — and this would be true for migrants in either direction. Given the same conditions of intensive selection as exist today in tropical Africa, the frequency of the sickle cell gene could increase from 0.1% to a near equilibrium value of 20% in 35 generations.²⁰ The same reasoning would apply to the views of those who have sought to localise the origin of the sickle cell gene within Africa; for example Singer²¹ located it in the region of the Ruwenzori Mountains, where a small patch of very high frequencies is surrounded by much lower ones. This idea remains a possibility, but just as good a case could be made out for the Mozambique origin of the sickle cell trait, since Foy *et al.*²² found a patch of high frequencies (average 39%) among the Makondo-Makua. Similarly, we cannot rule out Lehmann's theory, although a case could perhaps be made for the African origin of the sickle cell trait of India.

Whatever the origin, we certainly can agree with Hiernaux¹⁸ that the sickle cell trait appeared somewhere in the ancestral stock of the living Blacks, after the dividing of the San and Negro branches, and, we may add, after

the separation and southward migration of the Southern African Blacks. Because of the intensity of the selective pressures operating on the trait, the frequency of the gene could have risen to very high levels in a relatively short time, so that the centre of origin of the gene, or the ethnic group in which it originated, cannot safely be determined from the trait's present distribution. Hiernaux counsels that physical anthropologists should be very cautious when working with a highly adaptive character, and should keep constantly in mind the implications of its value in natural selection.

HAEMOGLOBIN S AND MALARIA

When the gene-allele for Hb S is present in double dose (the homozygous state), it causes—as is well known—a severe anaemia, sickle cell anaemia. One might have thought, therefore, that because of the disadvantage entailed, there would have been strong evolutionary or selective pressures against the allele for sickling. Nevertheless, the facts do not support this notion. Despite the disadvantage caused by the homozygous state, the gene remains at a high frequency in many parts of Africa, certain areas around the eastern Mediterranean, including parts of Greece, Arabia and India. Something must be keeping the frequency of the gene high in these areas, despite the prediction that it should have been selected against and therefore disappearing. This phenomenon, by which in the same population there coexist homozygotes for normal haemoglobin alleles, homozygotes for Hb S, and heterozygotes for Hb S, is called genetic polymorphism.

Why should there be such a polymorphism? What factors are responsible for maintaining the apparently harmful gene in such high proportions? Whenever the human biologist is confronted with a polymorphism like this, he makes a search for the cause, for the selective factor which may be operating in favour of the apparently harmful gene.

This is precisely where malaria comes into the picture. The distribution of Hb S coincides very closely with those areas of Africa where malaria is endemic and especially hyperendemic. It was suggested earlier that these two facts were connected. The connexion was supposed to work in this way: while homozygotes carrying a double dose of Hb S were at a decided disadvantage, heterozygotes (who carried the Hb S gene in a single dose, together with a single dose of the gene for normal haemoglobin) were at an advantage because they offered greater resistance to the malarial parasite. The tie-up was early suggested by Beet in Central Africa,^{11,12} and followed up by the 2 Lambotte-Legrands¹³ and Brain.^{13,14}

But it was Allison's work in 1954 that provided proof for the hypothesis.² Most convincingly, he showed that children who were heterozygous for normal and sickle cell haemoglobin genes were at a decided advantage in hyperendemic malarious areas compared with either homozygote. The degree of parasitaemia and the clinical course were both diminished in the case of these heterozygotes (or genetic carriers).

This selective effect could be because of differential mortality—especially in children; or because heterozygous females were more fertile; or even because heterozygous males were more fertile. Much recent work has supported Allison's hypothesis, although it has not been without its critics. The most recent reviews of the subject by Neel,²⁰ Eaton and Mucha,²⁴ and Alciati and Caraci²⁵ have supported the idea that the geographical distribution and the incidence of the sickle cell trait are strongly influenced by the severity of malaria in any area.

The relation of malaria to Hb S remains one of the best proved examples of balanced polymorphism, that is, a genetic polymorphism in which homozygote disadvantage is counterbalanced by heterozygote advantage, so that the frequency of the deleterious trait remains high.

G-6-PD DEFICIENCY

In the same way, the frequency of an inherited sex-linked enzyme deficiency, glucose-6-phosphate dehydrogenase deficiency (G-6-PD), has been shown to be related to the prevalence of malaria. For example, the Tonga people living on the north bank of the Zambezi were intensively investigated by myself in 1957-1958^{26,27} and by 2 members of my staff, T. Jenkins and S. R. Blecher, in subsequent years. They found that the Tonga people on the north and south banks of the Zambezi, as well as on the plateau to the north, had the lowest frequencies of Hb S (below 5%) of all Blacks living in hyperendemic malarious areas.²⁸ This was probably because the Tonga and the Bantu-speaking Black tribes further south were settled in the Zambezi Valley and south of it before the arrival of the sickle cell gene. On the other hand, these same Tonga people have one of the world's highest rates of the red cell enzyme lack, that is, G-6-PD deficiency.²⁸ Thus it would seem that the gene for G-6-PD deficiency must have arisen before these southern Bantu-speaking Blacks moved southwards away from the rest of the sub-Saharan Blacks.

This deficiency occurs in South African Black populations with a frequency of 0-10%; but in Central Africa it ranges from 3 to 17% in Kenya, 4 to 28% in Zaire and 20 to 27% in Tanzania. In Central Africa, where falciparum malaria is hyperendemic, it was demonstrated by Allison and Clyde²⁹ that malaria was an important selective agent in maintaining the G-6-PD polymorphism.

Malaria is believed to be a major selective agent producing high frequencies of the sickle cell trait; probably also of the G-6-PD enzyme deficiency; and perhaps, too, malaria is responsible for the lower levels of adenosine triphosphate (ATP) found in the red blood cells of Blacks.³⁰

Yet, interestingly, it seems that man himself was at least partly responsible for making certain areas of Africa hyperendemic for malaria—and so, indirectly, for altering his own gene make-up.

The early Black peoples lived in West Africa—on the edge of the great rain forest of the Southern Cameroons and Ubangi Shari.³¹ Later, something over 2 000 years ago, they adopted a new way of life—agriculture. This meant clearing large tracts of tropical rain forest for

agricultural purposes, as the people spread across middle Africa. The new forest clearings multiplied the number of breeding places for the mosquitoes which carry malaria, especially the *Anopheles gambiae* species complex. This man-made change in the biotope led to malaria becoming hyperendemic in West Africa.²²

Under these new, intensely malarious conditions, there would be increased selection for individuals with the sickle cell trait (and perhaps with G-6-PD deficiency and with low ATP in the red blood cells). Hence, we can see how the population's gene pool would alter with time. Thus, the change to agriculture could have catalysed, or speeded up, genetic changes among the African Blacks.²³

CONCLUSION

The interaction between man and malaria in the history of this continent has been a subtle and complex one. It has provided human biologists with a model of how man's genetic polymorphisms could have been maintained, and of how the gene pool of a population could change with time. Nature works slowly and patiently, accumulating genes which help survival in malarious areas; but man cannot sit around for that long. Man has to relieve suffering or, better, prevent suffering. Man has to work faster than evolution: and he has it in his power to do so. His culture has given him the means virtually to wipe out malaria.

That is the real reason behind this Symposium: and it is to be hoped that the foresight and wisdom of the Lowveld Division of the Northern Transvaal Branch of the

Medical Association of South Africa will be amply rewarded by the putting into operation of still better steps for the control of malaria.

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