MAINTENANCE OF HIGH SICKLING RATE IN AN AFRICAN COMMUNITY

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It is accepted that the sickle-cell gene can cause early death if it is inherited in the homozygous state, yet in spite of this constant depletion it still exists at remarkably high frequencies in tropical Africa. Several attempts have been made to explain this. Neel (1953) gives a review of population dynamics in this connexion, and Edington and Lehmann (1956) trace the opinions that led up to Allison's (1954a, 1954b) formulations of the two hypotheses that at present hold the field. Firstly, Allison postulated greater fitness of sickle-cell heterozygotes (AS) as compared with normal homozygotes (AA) in respect of malaria, a higher death rate amongst the latter balancing the loss of S genes by deaths from sickle-cell anaemia. Secondly, he deduced from his own observations, and from reports in the literature, that about 25% of sickle-cell homozygotes (SS) survived and procreated. Each of these explanations raises problems that are briefly outlined below.

Differential Malarial Morbidity

The questions whether malarial infection is less easy to establish in sicklers as originally claimed by Allison (1954a), and whether malarial parasitaemia is less common in them than in non-sicklers, have been investigated by several workers. The evidence, some of which is contradictory, has been recently reviewed (*British Medical Journal*, 1955; Edington and Lehmann, 1956). In our opinion there is no reason to believe that the mere establishment of a *P. falciparum* infection is any more difficult in a sickling subject than in a normal person.

But from a genetic point of view these matters are of negligible importance. The crucial question is whether more non-sickling than sickling children die, directly or indirectly, from malaria. A relatively lower direct mortality from malaria in sickling children has recently been demonstrated (Raper, 1956), thus establishing that malaria is quite capable of acting as a selective agent. However, there has been a reluctance to believe that its effect could be powerful enough to account for the maintenance of some of the highest sickling rates observed.

For example, if the sickling gene (S) had no lethal effect, a population showing 36% of the phenotype S can be calculated to consist of 4% of the genotype SS, 32% of the genotype AS, and 64% of normal persons of genotype AA. One-fifth of the S genes are therefore carried by the sickle-cell homozygotes. If the latter were all to die before reproducing, the original S gene frequency could be restored only by the removal of one-fifth of the A genes, none from the heterozygotes, but all from the normal homozygotes. This would mean the death of 25% of the normal homozygotes from the selective agent alone. It has been difficult to imagine how malaria could account for this, especially when the total deaths may only slightly exceed this figure. We shall show below that the above calculation does not take account of all the facts; but we note here that it has contributed to the need for the second hypothesis, the survival of a proportion of the SS homozygotes.

Survival of Sickle-cell Homozygotes

There is no reliable information concerning how far the survival of sickling homozygotes contributes to the maintenance of high frequencies of the gene. It is difficult to accept statements asserting their survival to adult life unless the claim is supported by analysis of the haemoglobin. This criterion has become important since the recognition of haemolytic syndromes caused by the inheritance of certain other genes together with that for sickling, where both are in the heterozygous state; for such syndromes are generally compatible with longer life than is sickle-cell anaemia. For example, in West Africa sickle-cell-haemoglobin C disease (SC) in adults is not uncommon.

Only two published investigations refer to adult homozygous sicklers in Africa, and support the claim by haemoglobin analysis; those by Allison (1954b) and Edington and Lehmann (1955a). The latter found, in two healthy adults, a composition of haemoglobin indistinguishable from that seen in sickle-cell anaemia. Subsequent family studies showed, however, that these persons were in fact heterozygous for the sickling gene, and that they carried a thalassaemia (or thalassaemia-like) gene which suppressed the formation of haemoglobin A to such an extent that it could no longer be revealed by electrophoresis (Edington and Lehmann, 1955b). Allison's two examples showed "significant amounts of haemoglobin F together with more than 50% haemoglobin S," and he at that time reasonably accepted them as homozygotes; but in view of Edington and Lehmann's later experience his claim cannot be accepted as proved.

Nevertheless we thought it unlikely that every sickle-cell homozygote in Africa should necessarily exhibit a severe form of the disease, and die prematurely. In Uganda we have observed adolescents and young adults suffering from sickle-cell anaemia of no great severity, in whose cases haematological, chemical, and genetic studies were consistent with the view that they were homozygotes. But we have no knowledge of what proportion of such people succeed in reproducing and contribute to the stock of S genes in the next generation.

To obtain more evidence on these subjects we decided to examine a population showing a very high incidence of the sickling gene. The Baamba tribe shows the highest sickling rate in Uganda, and for this reason was chosen. Of this tribe it had been stated that "the incidence of sickling among the pygmoid Baamba is 45%; this percentage must include homozygotes" (Lehmann, 1951). Even if only 25% of homozygotes survived to adult life there would still remain a good numerical chance of discovering them. Finally, if it could be shown that the survival of homozygotes made no contribution to the high sickling rate we should be able to observe the effect of any selective agent at its most intense.

The Baamba Tribe

The Baamba live in a region bounded on the south-east by the spurs of the Ruwenzori range, and on the north and north-west by the Semiliki river and its tributaries. The altitude is around 2,500 feet (760 metres). Baamba is a largely forested country, and the dense vegetation near the river is continuous with the Ituri forest in the Belgian Congo to the west. The people living here were effectively isolated by forest and mountain until 1938, when the completion of a mountain road from Fort Portal connected Bwamba with the rest of Uganda.

The Baamba consist of two linguistically different groups. The Babulibuli speak a language allied to some spoken in the neighbouring Congo; it is claimed that they have always occupied Bwamba, and were certainly there when the other group, the Babwizi, began to invade the country peacefully from the east, perhaps under pressure from more advanced pastoral peoples. For our present purposes, we may regard the two groups as having fused, over several centuries, into a fairly homogeneous tribe in a fixed habitat. The

neighbours of this tribe are the Bakonjo, who lead a separate existence on the mountain slopes above Bwamba; and in the forest are scattered groups of pygmies. Doubtless the Baamba miscegenate with both, but only to a very small extent.

Procedure

Blood was obtained by finger-prick from 623 Baamba. Each sample was distributed as follows: One drop was mixed immediately on a slide with a broth culture of *Bact. coli*, covered, and inspected for sickling after one to four hours (method of Singer and Robin, 1948). On another slide thick and thin blood films were made, except in the case of some of the adult subjects. The thick films were stained by Field's rapid method, and the thin films were fixed in alcohol for future reference. Finally, several drops of blood were collected in a small test-tube to be available for electrophoresis later in the day.

In all cases where the sickle-cell test proved positive, and in addition in about half of the negative samples, the haemoglobin was examined by paper electrophoresis. The method of Smith and Conley (1953) was used, electricity being provided by dry batteries.

Random samples were obtained by examining out-patients attending the Government Dispensary, catechumens attending a mission, and schoolchildren at a mission school near Bundibugyo, the main centre of population. People from a wide area came to these institutions. In this way we obtained samples of blood from 574 persons, 490 of them over the age of 5 years. To obtain more children we collected at two localities in the field, realizing that we should not obtain true random samples by this means. In fact, in one place the sickling rate was considerably higher, and in the other considerably lower, than that of the people examined at random.

In all cases location, name, sex, and, where applicable, family relationship were recorded. If the age was not known, a near estimate was made. In 463 instances we asked whether the people belonged to the Bwizi or Bulibuli section of the Baamba. It may be stated here that there was no apparent difference in sickling rate between the two.

Results

1. Sickling Rate

Table I summarizes our findings in subjects of different ages and at different localities.

TABLE I

Age Group	Locality	Total Examined	Sicklers
Adults (15 years and over)	Dispensary ..	162	56
	School and mission ..	117	47
Children (5 to 14 years)	Dispensary ..	20	8
	School and mission ..	191	72
	In the field ..	13	8
Infants (Under 5 years)	Dispensary ..	84	20
	In the field ..	36	16
Total ..		623	227

To arrive at a sickling rate for the adult population based on a random sample, certain data have to be excluded: (a) all children under 5 years, because among them it is assumed that equilibrium has not been reached; (b) those collected in the field, because the subjects consisted of families; and (c) the first-degree relations of any one subject—mostly the children of mothers at the dispensary.

Having excluded these groups, we were left with 277 adults, of whom 102 were sicklers, and 201 children aged 5 to 14, of whom 75 were sicklers; a total of 478 subjects with a sickling rate of 37.0%.

Two previous estimates of the sickling rate of the Baamba have been made. These had drawn their subjects from similar sources; Lehmann and Raper (1949) found 63 sicklers amongst 140 subjects (45%), and Allison (1954c) found 86 amongst 220 (39.1%). Calculation of χ^2 shows that each of

these three samples might, with a probability of more than 0.1, have been drawn from populations of identical sickling rate. For the purposes of calculation below, the three series have been added, giving an incidence of 39% (38.9%).

2. Electrophoretic Analysis

Altogether 435 blood samples, including those from all the 227 sicklers, were examined by paper electrophoresis. No variants of adult haemoglobin other than haemoglobin S were found.

Of the 227 sicklers, 223 were shown to possess both haemoglobin A and haemoglobin S, hence they were sickle-cell heterozygotes. These included all the adults and children, and all but four of the infants. In two sickling babies, aged 2 and 4 weeks respectively, no resolution of the haemoglobin was seen; a single spot was present in the position of foetal haemoglobin, indicating that the proportion of any other haemoglobin present was too small to allow it to be revealed by electrophoresis. Such a finding is quite usual in babies if there is a high proportion of foetal haemoglobin, and it is only at a later age, when the foetal haemoglobin has fallen, that the composition of the adult fraction of the haemoglobin can be determined. It is impossible to say whether these two babies were homozygotes or heterozygotes. In two instances (Cases 571 and 605, aged respectively 14 and 18 months) electrophoresis revealed only one component with the mobility of haemoglobin S. We concluded that these children were homozygous for the sickling gene. At the time of examination, neither had shown any clinical signs suggesting the diagnosis of sickle-cell anaemia. Examination of their thick and thin blood films gave the following results:

Case 571.—Thick film: Scanty *P. falciparum*, including gametocytes. *Thin film:* No leucocytosis; erythrocytes showed mild anisocytosis and a slight degree of polychromasia, a few macrocytes, no normoblasts. These findings needed no other explanation than the malaria which was present, and we cannot therefore conclude that this child was suffering from sickle-cell anaemia at the time of examination.

Case 605.—Thick film: No parasites. *Thin film:* There was a fully developed leuco-erythroblastic picture—numerous normoblasts and many irreversibly sickled erythrocytes were seen. There could be no doubt that this represented sickle-cell anaemia.

As we have pointed out above, analysis of the haemoglobin cannot prove beyond doubt that a subject is homozygous for the sickling gene. However, we did not think it necessary to test our diagnosis in these cases by family studies, as we should have done if the subjects had been adults.

3. Malaria

It is known that Bwamba is a highly malarious district. Its entomology and climate have been intensively studied by the staff of the Yellow Fever Institute of the Rockefeller Foundation; we are indebted to Dr. A. J. Haddow for the information that malarial transmission occurs throughout the year. We examined thick blood films from 166 children and 186 adults. The only species found were *P. falciparum* and *P. malariae*. The crude malarial incidence at different ages is given in Table II, and will be seen to be characteristic of a hyperendemic area.

TABLE II.—Incidence of Malaria (All Species) at Various Ages in Bwamba

Years:	$\frac{1}{2}$	$\frac{1}{2}$ –1	1–2	2–5	5–10	10–15	15+
Total cases ..	30	22	25	38	22	29	186
Malarial ..	16	13	19	28	18	6	9
Malaria rate ..	53%	60%	76%	73%	81%	21%	5%

A large proportion of this high incidence, however, was due to *P. malariae*. Taking all ages, the incidence of *P. falciparum* was 15% and of *P. malariae* 13%. In the 77 children under the age of 2 years (before the acquisition of immunity is well advanced) *P. falciparum* was present in 32.5% and *P. malariae* in 35%. But malarial transmission was probably less than the average for Bwamba at the time

of our study, which was just before the "long rains," and examination at such a time would tend to minimize especially the falciparum infection rate.

Discussion

Adult Sick-cell Homozygotes

The sickling rate in Bwamba is 39%. If we assume for the moment that the previous generation had contained no sickling homozygotes, and had consisted of 39% heterozygotes and 61% normal homozygotes, the present generation must have contained at birth 3.8% sickling homozygotes. If only 25% of these survived to adult life, and if at the same time sufficient normal homozygotes died to restore the sickling rate to 39%, it can be calculated that the incidence of sickling homozygotes would become 0.98%. But this percentage would be exceeded if, instead of our original assumption, the previous generation had also contained 25% of adult homozygotes. Thus our random sample of 478 adults should have contained at the very least five sickling homozygotes. Surprisingly, none were found. From the Table for Poisson distribution of Pearson and Hartley (1954) an observed value 0 corresponds to an expected value between 0 and 3.69, with probability (confidence coefficient) 0.95, and to an expected value between 0 and 5.30 with probability 0.99. A survival rate of 25% of homozygotes is thus unlikely, and we conclude that the survival of sickle-cell homozygotes plays no significant part in the maintenance of the high sickling rate in the Baamba.

Balanced Polymorphism

Having established that selection against sickle-cell homozygotes is virtually complete, we can calculate the degree of selection against the normal homozygotes necessary to maintain a stable sickling rate of 39%. An adult population consisting of 61% normal homozygotes and 39% heterozygotes will give rise in the following generation to one consisting at birth of: normal homozygotes, 64.8%; heterozygotes, 31.4%; sickle-cell homozygotes, 3.8%. The death of all the last-named involves the loss of 7.6 S genes out of 39, or 19.5% of all the S genes. A counterbalancing loss of 19.5% of the A genes, through the death of normal homozygotes only, would involve the death of 24.2% of the latter. From this it can be calculated that the "fitness" of the normal homozygotes compared with the heterozygotes is 1:1.32. This ratio, however, is one which merely expresses the relative viability of these two elements of the population, or the final genetic equilibrium between them at the end of the process of selection that occurs between the moment of conception and the time of procreation. It gives no information concerning precisely how or when the equilibrium is brought about, and some further analysis of this is necessary.

We have no reason to believe that any selection operates in respect of mating, fertility, or foetal viability, and can assume that selection occurs between birth and reproductive age. It is postulated that the main reason why the normal homozygotes are less viable than the heterozygotes is that the former are more likely to die from falciparum malaria. But this may not be the only factor. Quite possibly the balance is a complex of several factors, some of which may actually be to advantage of the homozygotes; for instance, there have been suggestions (Lambotte-Legrand, 1951; Raper, 1956) that typhoid is a more serious disease in sicklers. However, the only effect of this kind that has been proved to exist is that exerted by malaria. So far as we can tell at present, malaria distinguishes between sicklers and non-sicklers only in that the former escape the heaviest infections and rarely if ever succumb to cerebral malaria or the other serious forms of the disease (Raper, 1955, 1956). This distinction vanishes when immunity is acquired, a process that our observations suggest is completed soon after the fifth year in Baamba children. Before this age, malaria undoubtedly leads to ill-health, and perhaps contributes to mortality from other diseases, but we have little reason to suppose that this effect is significantly more important in

normal homozygotes than in sicklers. As a hypothesis, therefore, we may suppose that the whole process of selection in Bwamba is attributable to falciparum malaria in childhood, and that it is manifested by deaths directly due to this disease in normal homozygotes, none (or an insignificant number) occurring in heterozygotes. We have to consider whether this is a tenable hypothesis.

The question cannot be answered directly without a full knowledge of the vital statistics of Bwamba, which we do not possess. This information is difficult to obtain even in much more developed parts of Africa, and it then refers to deaths from malaria in the whole community. We must therefore examine the implications of the selective process in terms of the loss of life from malaria in the whole child population. One of the facts we shall have to take into consideration is the total loss of life from all causes in childhood, or, more accurately, before puberty; and fortunately we have a reliable estimate of this. Dr. J. McFie conducted a survey in the district in 1954, during which he carefully questioned all the women in one location about the number of live births claimed by each, and the number of their children who had died before the time of questioning. With his permission we are able to quote that 45 women of all ages claimed 189 live births, and recorded 111 deaths of their children. Thus at the time of the survey 58.8% of the children born to these mothers had died, and it is evident that to obtain the true wastage of life before puberty this percentage will have to be increased to take account of the fact that not all the children of the mothers questioned had yet reached puberty, and that some of these might still die. A conservative estimate of the loss of life before puberty in this location would be about 65%.

Accepting this estimate of the loss of life, we may envisage balanced polymorphism being achieved in Bwamba in two extreme ways. Suppose first that selection takes place before any other deaths occur; the process then is as shown

TABLE III.—*Balanced Polymorphism in Bwamba: Selection Acting First*

Population at Birth* (1,000)	Selective Mortality		Undifferentiated Mortality	
	Malaria Deaths	Survivors (805, AS being 39%)	Deaths (AS = AA = 56.5%)	Survivors (350)
AS 314 ..	0	314	177	137
AA 648 ..	157	491	278	213

* This includes 38 sickle-cell homozygotes (SS).

in Table III. If we had been able to observe the deaths recorded in this table, we should have registered 157 deaths from malaria amongst the 648 normal homozygotes, or 24.2%, but for the whole community the loss of life from malaria would appear as 15.7%. But suppose, secondly, that selection takes place after all other causes of death have taken their toll; we should then find the results given in Table IV.

TABLE IV.—*Balanced Polymorphism in Bwamba; Selection Acting After Other Causes of Death*

Population at Birth* (1,000)	Undifferentiated Mortality		Selective Mortality	
	Deaths (56.5%)	Survivors (419; 33% AS)	Malaria Deaths	Survivors (350; 39% AS)
AS 314 ..	177	137	0	137
AA 648 ..	366	282	69	213

* This includes 38 sickle-cell homozygotes (SS).

Selection, now acting on a smaller population, still causes the death of 69 out of 232, or 24.2%, of the normal homozygotes at risk, but the observable loss of life from malaria for the whole community is only 6.9% of the children born. If malaria is imagined as causing deaths concurrently with other diseases, as would in fact be the case, the figures observed would lie somewhere between the limits assigned by Tables III and IV, and malaria would be credited with the removal of from 6.9 to 15.7% of the whole child popula-

tion, or of 10.6 to 24.2% of all normal homozygotes born. Since malarial deaths are likely to follow what must be a considerable proportion of the loss of child life—that in the first month or two—we may surmise that the observed figures would approximate to the lower rather than to the higher of these limits.

These considerations reduce the difficulty mentioned above, of requiring an excessively high malaria death rate to account for the maintenance of sickling rates as high as 39%; we find that no very high malaria death rate need be recorded if the loss of life from other diseases is high, and especially if a large proportion of that loss consists of neonatal deaths. These are the conditions that prevail in Bwamba and many other parts of Africa.

Although, as we have said, we have no mortality statistics for Bwamba, we may compare it with large parts of the Belgian Congo. Duren (1951) reviewed the sources of information on malaria mortality in the Congo, and after taking due account of their inadequacy he concluded that below the age of 3 years deaths directly from malaria amounted to 14 to 22 per 1,000 per annum. Colbourne and Edington (1954) obtained a roughly similar figure, 17 per 1,000 for children under 1 year in Accra, and 10 per 1,000 for children from 1 to 5 years. The mortality in Bwamba is unlikely to be less than these estimates, which amount to a cumulative loss during childhood of about 5 to 10% of children born. This is very close to the figure, 6.9% or more, which we have shown to be required for preserving a state of balanced polymorphism in Bwamba, and we may therefore conclude that malaria could act as an effective selective agent under the primitive conditions of Bwamba, to maintain a sickling rate as high as 39%. It follows from our consideration of the mechanics of balanced polymorphism that the malaria situation in two regions might be the same in the sense that it caused the same loss of life before the age of, say, 3 or 5 years, yet in these two regions it might be the factor in maintaining two entirely different sickling rates. This could come about if the two populations differed in their mortality before the age at which the malaria mortality in each was at its greatest. Hence no simple measure of malaria morbidity or mortality even if it were the malarial mortality in normal homozygotes that could be measured, could enable one to predict accurately the sickling rate that might be maintained. The situation cannot be defined without reference to the whole infant mortality, and its relation in time to the malarial deaths.

Summary

The Baamba, an African tribe showing a high sickling rate (39%) has been examined to determine how this high rate can be maintained.

Of the 623 subjects examined, 227 were sicklers. No genetic variants of normal adult haemoglobin other than haemoglobin S were found. Amongst 191 sickling subjects over the age of 5 no homozygotes were detected; and it is concluded that the survival of sickle-cell homozygotes plays no significant part in maintaining the sickling rate of this tribe at its high level.

If selective death of non-sicklers from malaria was responsible for the maintenance of the 39% sickling rate in Bwamba, 10.6–24.2% of all normal homozygotes (or 6.9–15.7% of the whole child population) would have to die from malaria. Reasons are given for supposing that the actual death rate to be observed would approximate to the lower rather than the higher of the two limits, and that such a death rate from malaria is to be expected in Bwamba.

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FAMILIAL AGAMMAGLOBULINAEMIA

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Absence of serum gammaglobulin causing lowered resistance to infection was discovered by Bruton (1952) in a boy suffering from recurrent septic infections. More cases in boys were described by Janeway, Apt, and Gitlin (1953). The condition as it occurred in boys was thought to be primary, familial, and sex-linked.

The primary disorder was subsequently described in males and females of all ages; of 38 case histories that we have been able to obtain, 18 have been those of boys. Kulneff, Pedersen, and Waldenström (1955) describe the disease in two brothers aged 9 and 7, and in a distant male relative aged 5.

The important features of the disease are repeated septic respiratory and non-respiratory infections, lack of cutaneous responses to antigens, almost complete absence of circulatory antibodies and of gammaglobulin from the blood serum and connective tissues, diminution in the number of plasma cells in the tissues, and failure of lymphatic nodes to respond to antigenic stimuli (Janeway, 1954). In most cases isohaemagglutinins have been entirely absent from the blood. Virus exanthems usually run their normal course, but in some children they recur. Infants suffering from agammaglobulinaemia may die of intractable infections (Keidan, McCarthy, and Haworth 1953; Janeway, 1954; Hutchison, 1955). Most of the female patients have had bronchiectasis, and in most of the adults the spleen has been enlarged.

Patients who have been given repeated injections of gammaglobulin (0.1 g. per kg. body weight per month) have usually responded well. Treatment with antibiotics has been found essential to control acute infections (Janeway, 1954), and has sometimes been given continuously with good effect.

The cases here described are those of two brothers who are suffering from familial agammaglobulinaemia in its classical form.