Malaria in the African

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The first axiom of malariology, that lessons learnt in one part of the world may not be applied to other parts of the world, without local verification, is as true as ever; it is unfortunately as often neglected as ever. And while this axiom refers to the general picture of malaria transmission, it has great relevance to the variation in parasite strains that occurs within comparatively short distances, to the physiopathological responses of the human body, and to the reactions between drugs and parasites in human bodies. I would therefore desire to make clear that although the experience on which this article is based has been obtained in the eastern side of Africa, I am ignorant of Africa south of the Zambesi. On the other hand, conclusions based on African experience are likely to be truer for Central Africa than some current generalisations that claim to be true of the world as a whole.

Apart from the differences due to such factors as climate or physiography, the situation is further complicated to-day by the changing degree of malaria hazard to which people are exposed and the increasing amount of treatment that Africans receive. These changes may arise from the action of the individual, as by the use of mosquito nets or drugs purchased; or they may be due to the protection offered by governmental or commercial agencies, as in towns, or now even in wide rural areas by the use of residual insecticides.

It is not therefore often possible to make general rules as to the handling of cases of malaria in Africans of a mixed group, such as appears, for example, at a district hospital. Yet it is still true that, in order to avoid the Scylla of over-treatment and the Charybdis of too little or too late treatment, it is necessary to take note of the background, of the malaria history of the individual. And in order to assess this history at its true significance a fundamental knowledge of the epidemiology of malaria is then still required. Such knowledge will of course be valueless without knowledge also of the country and peoples to which it is to be applied, and the medical officer should be provided, or provide himself, with as far ranging a knowledge of the surrounding country as it is possible for him to acquire.

In attempting a summary description of the types of malaria endemicity that are to be found in tropical Africa, it is necessary to evaluate not only the human variations, but also the circumstances from which they arise. Characteristic groups will be described and one or two examples of the variations that occur will be given, but it is emphasised that there occurs in nature, and especially on the eastern side of tropical Africa, every intermediate stage between the groups so described.

As in other parts of the world, *epidemic* malaria may be found, but only when the transmission season is always very brief, as in very dry tropical areas, or in those that are so high that the prevailing temperatures are too low for the normal existence of the vector anopheles, and for the development of the parasite, during the greater part of the year. It is also found in areas that are outside the central tropics. As elsewhere also, *endemic* malaria may be found, but it is more descriptive to call this *seasonal* malaria, since, although there are rare exceptions, this type of malaria occurs in Africa because of a malaria season of short duration and not because of a low rate of transmission occurring throughout the year. Characteristic of this region, and rarely found in other continents, is the fully *hyperendemic* type of malaria (for which the term *holoendemic* was suggested at the Kampala W.H.O. Malaria Conference), that depends on a high rate of transmission, spread over the greater part of the year. Of these three types of malaria, the first connotes no more immunity than that possessed by, for example, the northern European; the second a sufficient resistance to protect the typical individual from dangerous attacks; the third such a high degree of tolerance that malarial attacks in adult life are apparently no more than an inconvenience.

The underlying causes of differences in endemicity are to be found in the first place in variations of climate and topography; any given anopheline vector can thrive only within a certain range of temperature and humidity, and the shape of the country, the nature of the soil and the rainfall distribution must be such as to allow the formation of its breeding places. For example, if the slopes of stream beds are so steep that there are neither sluggish margins nor the possibility of pooling during the drier weather, such a species as *Anopheles gambiae* is unlikely to find any opportunities of breeding. Altitude by itself does not give an indication of the probable endemicity, since it is the main-

tenance of a temperature of something above 60° F. that is the essential factor for parasite development in the mosquito. Therefore latitude and the rapidity of rise in the country have also to be taken into consideration. In this respect, as in many others, human activity is of great importance, since road and rail communications have unquestionably led to the invasion by anopheles of higher areas than those occupied by them in the past. Although on the whole development and closer cultivation are reducing, in the tropics as they have already done in temperate climates, the opportunities of anopheline breeding, there are many notable exceptions, and human activity in the way of poor road and rail construction or neglected dams is unquestionably increasing the malarial endemicity in various regions.

In essence, however, all these basic factors affect the malariousness of an area by their influence on the frequency of infective bites over the year. This frequency depends in turn on the vector density, the proportion feeding on man (as compared with animals), anopheline longevity and perhaps the uncertain factor of species susceptibility. The range of frequency of infective bites is very wide. In the most intensely hyperendemic areas the frequency may be of the order of 200 dropping down to, say, 20 times a year. In areas of seasonal malaria the frequency is not more than one-twentieth of the foregoing group, ranging down to less than once a year; while in epidemic areas there may of course be quite a high biting frequency for a short period, with a complete absence of transmission for perhaps years at a time.

Three examples of differing levels of endemicity, obtained in the course of recent work at the East African Institute of Malaria, are given below; other East African examples have been given in earlier publications (Wilson, 1936; Wilson *et al.*, 1950; Wilson, 1939). While it is not as yet possible to match the human indices with accurately recorded frequencies of infection, it should be noted that the characteristic features of these differing groups are to be found in the parasite rates, the spleen rates and the gametocyte rates, and that it is necessary to take note of all these rates, not only in childhood, but at all ages, if a true appreciation of the endemic situation is to be made.

A quite different factor that may be of importance in the development of the human reaction to malaria is that of race. The work on Malays in Indonesia by Schuffner (1919), considered in relation to that of others, conveyed this suggestion; but there was no quantitative anopheline background to these human observations, and it has appeared to the writer that the range of differences to be found among Bantu, often between communities that were tribally indistinguishable, provided presumptive evidence against a racial origin of the divergences found, while a comparison of primitive tribes from very malarious areas in India and in Africa showed a close similarity (Wilson and Wilson, 1937). However, Black (1954) and others have more recently again shown how different is the human reaction in New Guinea in response to a high frequency of malarial infection, and there is clearly room for a further critical study of this matter.

As an example of the striking differences that may be found within a comparatively small area, and quite likely to be encountered in one district, Table I gives endemic indices from Uganda. The first, Jinja, is in a damp area close to the shores of Lake Victoria. The second, Butolo, is in apparently similar conditions close to Lake Victoria, but the anopheline vector population is in fact a small fraction of that found at Jinja. The third, Luwero, is from a much drier area

Table I, Giving Endemic Indices from Uganda.

Ages	JINJA			BUTOLO			LUWERO		
	Exam.	*Parasite Rate*	*Parasite Infestation*	*Exam.*	*Parasite Rate*	*Parasite Infestation*	*Exam.*	*Parasite Rate*	*Parasite Infestation*
1— 4	393	92	64	86	44	34	96	84	87
5— 9	543	85	20	140	44	23	295	75	24
10—19	248	72	14	408	35	20	669	59	16
Over	195	42	10	875	20	8	353	18	11

The figures for parasite infestation are the geometric means of counts per 500 leucocytes.

some 40 miles from the lake; but the vector house population is about six times that of the Butolo area and about one-third of that found at Jinja. The differences between these several groups of people are to be explained by the opportunities for vector breeding in the three areas in which they live. In the first there is breeding on the lake shore, in swampy valleys and elsewhere. In the second, water is confined for the most part to heavily covered swamps that offer little opportunity for vector breeding. In the third there are swamps that are less heavily covered and a good deal of less well-drained land on which many opportunities for *Anopheles gambiae* breeding may occur. It may be remarked that the physico-chemical basis of these larval breeding differences is far from being explained.

The second of these Uganda groups represents the results of a low rate of infection carrying on through the greater part of the year. Although in this case infection in man showed little seasonal change, the more usual circumstance that gives rise to this picture is that of a seasonal transmission.

Clinical Effects of Varying Rates of Transmission

There still remains a good deal of doubt concerning the nett effect on human health of the different frequencies of infection at the several stages of life, but the effect in terms of the probability of actual attacks, and on their severity, is clear enough. In infants there occurs some time during the first year or two of life the first infection; in the most malarious areas this will occur during the first six months. At this period of life there appears to be an unexplained protective mechanism that modifies the severity of the attack; but in spite of this the early attacks are a hazard to life and even more a hindrance to health, so that intercurrent infections carry a greater potential danger to the infant. In less highly malarious or seasonal areas the first attack may be postponed to the second year of life, and then there is always a direct danger to life from the malaria attack itself.

During childhood the early attacks experienced in fully hyperendemic areas have by now conferred some powers of resistance to the human body, and although sharp attacks may continue to occur, they will not be dangerous to life, and spontaneous recovery may be expected, although withholding all treatment should not perhaps be the desirable course of management in such cases. On the other hand, in the areas of seasonal transmission the attacks will have lost little of their severity and full, or nearly full, therapeutic courses of treatment are needed. This continued severity of attack will be prolonged into later periods of life as the average frequency of transmission falls until, in areas of epidemic malaria, the stage is reached at which there is little perceptible difference between the child and the adult. This is the state of affairs found in highland areas and in the very dry zones such as Somaliland or the Central Province of Tanganyika Territory, where epidemics form the characteristic manifestation of malaria, even in the central tropics. This is in marked contrast to the adult malaria experienced in the most malarious areas. In these adults, parasites may often enough be found, but they rarely suffer recognisable attacks, and more than a single day's treatment is neither necessary nor desirable for such people.

While there are wide areas in Nyasaland, and probably in western Northern Rhodesia, that come into this last group, there is very little of Southern Rhodesia that does.

Pathology

Although the pathology of fatal attacks has been described in some detail, the changes arising in various organs, and in particular the liver and spleen, during the much more common successfully treated attack are in effect unknown. Still less known is the pathological basis of the immune state in man. The cellular changes must be deduced from those seen in experimental animals at various stages of infection.

The basic changes that are responsible for the more serious effects of malaria are dependent on tissue anoxia. This state is caused by destruction of red cells, destruction of haemoglobin within parasitised red cells, and intravascular agglutination of red cells. The anoxia in turn leads to an increased permeability of the capillaries and to those changes in blood flow that have been described most vividly by Knisely *et al.* (1945) as the "sludging" of the blood. The resulting condition differs little from that of "shock."

This process is reflected in changes of a low order in liver function tests that are not in any way diagnostic, and in more serious changes in the terminal capillaries of the brain that produce the dramatic effect of cerebral malaria.

In more chronic malaria the essential change, so far demonstrated only in animals (Taliaferro, 1949), is the lympho-macrophage proliferation that occurs in the reticulo-endothelial system.

Here there is not only a proliferation of the phagocytic cells, but also an increased activity and a facilitation of their proliferation in response to reinfection, and it is on these processes that acquired immunity to resistance basically depends. Whether at the same time there occurs any permanent damage, for example, in the liver, it has so far proved impossible to determine.

Diagnosis

There is a real danger of over-simplification in the interpretation of blood film examinations. It cannot too often be repeated that the mere finding of parasites in the blood of an African from a highly malarious area does not mean that the major cause of his illness, whether it be accompanied by pyrexia or not, is malaria.

A few fine rings seen in the blood of a person who has not suffered from malaria before, whether he be an infant or a recent immigrant, may well indicate that he is in grave danger from malaria. On the other hand, a few parasites, especially if they be well developed trophozoites, may merely be incidental to another more or less serious illness that is attributable to quite other causes; these parasites will disappear, without specific anti-malarial treatment, if the major infection, such as pneumonia or enteric, be cured.

The distinction between parasites that may be insignificant and those that unquestionably are indicative of acute or dangerous malaria is difficult and must depend both on experience and on technique, for without the clean slides and good staining that give clear films the distinction is impossible. The greatest difficulty lies in the differentiation of the well developed trophozoites, seen as a thickened ring, so commonly seen in the immune or partially immune person, from the compact schizont of *P. falciparum*, indicative of grave or cerebral malaria. The latter is more solid and compact, it does not stretch across the corpuscle and the pigment, usually discernible, is clumped in its centre. The presence of dividing forms of *falciparum* must be regarded as a danger sign that demands immediate intravenous therapy, although even this is not always so among those who have some immunity. The presence of fine hair-like rings, *occurring alone*, is almost certainly indicative of a significant infection. It is not possible to gauge from the number of parasites present the probable severity of an attack. On the one hand it may be possible to find parasites only with the greatest difficulty in a possibly fatal attack; on the other hand, counts of 10 or even more per 500 leucocytes may be incidental in the blood of a person with some immunity.

Parasite Strains and Treatment

While very little is known about the variation of strains that may be encountered in different countries, the work of James and Ciuca (James and Ciuca, 1938) demonstrated quite clearly how different strains could vary the results to be expected from a given course of drug therapy. The existence of variation within a given region is less clearly demonstrated, and the emphasis must for the present lie on regional differences.

Those who have had to deal with an African military population, drawn from widely scattered districts, will require no conviction of the variability of tribal responses to treatment.

If the foregoing general conclusions are justified it must be recognised that a critical assessment of the response to treatment of local strains of parasite is still required in each area, and the individual physician is called to make this assessment of individual drugs and combinations of drugs for himself.

Far too little work has been carried out in the eastern half of tropical Africa on the reaction of parasite strains to the more recent drugs, and any attempt to define their effectiveness has to be based mainly on opinion. Tentatively, therefore, it may be suggested that East Africa parasites do not respond very readily to mepacrine alone, even if given in high dosage; that the 4-amino-quinolines (chloroquine, camoquine, nivaquine) are very effective, but rather slower in their action than is the general experience in other parts of the world; and that the biguanides (paludrine, daraprim) are comparatively ineffective in the treatment of attacks.

The ultimate effect of treatment depends greatly on the amount of drug given. Thus it is quite possible to treat an attack, with a dosage that is adequate to control pyrexia and to eliminate parasitaemia, without diminishing the development of immunity to an extent that will leave the subject liable to severe attacks in the future. On the other hand, the repeated administration of even small amounts of anti-malarial drugs (as is so often done for pyrexial attacks that have nothing to do with malaria) will unquestionably reduce the titre of immunity or interfere with its development. Very often, however, the increase of treatment and protection from attacks are found to be coincidental in a community, especially an urban one, and it is then of course impossible to evaluate the effect of either.

But from the results of experimental infections in animals it is clear that the level of immunity is directly proportional to the degree of antigenic stimulation. So that if treatment is limited to the cure of symptoms it is improbable that the evocation of immunity, with all the advantages that this implies to those repeatedly exposed to infection, will be hindered.

The choice of treatment is in general therefore dependent upon the striking of a balance between two main considerations. On the one hand the chance of reinfection; if this is high, then radical cure is not worth while and may be a disservice to the patient, as he is likely to need the assistance of all the immunity he can develop or retain; but if the chance of reinfection is small, then radical cure must be the aim. The other consideration is the state of premunition or immunity. If this is already present to a considerable extent in an individual, then he is at no serious risk, he will require little treatment to recover from his infection and the response of the lymphoid-macrophage system is all-important; but if there is little or no immunity, then drug treatment is essential, may be life-saving and can only be relaxed during later attacks. For an adequate judgment between these conflicting factors the background knowledge, referred to earlier in this paper, is essential. As regards the first factor, a knowledge of the localities in which the people are living, and for the second the previous history of the patient in relation to his surroundings. It should not be a counsel of perfection that, even in the case of malaria, the physician should treat the patient rather than the parasite.

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