WHO'S AFRAID OF MALARIA?

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Malaria is a disease that derives its name from the ancient belief that it was caused by "bad air" emanating from rotten vegetation. The disease was endemic in marshy areas of Europe such as the English fens and the estuaries of the Solway, Thames and Medway. We know now that the disease is caused by parasites injected into the blood by a blood-sucking mosquito.

Much has been written about the mosquito as having saved West Africa from European settler occupation. In parts of Africa where malaria was not such a serious scourge (Algeria, Kenya, Zimbabwe, South Africa) large numbers of Europeans settled permanently. To free themselves from colonial rule and regain their lands, Africans in those countries had to fight terrible wars of liberation. Our freedom from colonial rule was handed to us on a platter of gold.

Many Europeans died of malaria and other tropical maladies in West Africa; thus the region earned the epitaph of "the white man's grave". But that did not deter Europeans from coming here. Those who survived, and that included the founding fathers of the Nigerian Field Society, relied on shear physical toughness, ingenuity, grim determination and quinine. The tonic in the gin was always generously laced with quinine. Chloroquine and related drugs did not emerge until after World War Two; during the war, Germany's allies, the Japanese had over run British and French cinchona plantations in Java in South East Asia. The Allied Forces deployed in Africa and other malarious zones were in danger of being defeated by malaria. This was when American scientists rediscovered chloroquine, which, ironically, had originally been synthesised by German chemists. Thus European fear of malaria gave rise to the world's most effective, safest and cheapest anti-malarial drug. We in Africa have benefited from the drug too.

The other strategy that enabled the brave Europeans in West Africa to survive was to separate their living quarters from those of the Africans. In many parts of Africa, separate quarters for Africans and Europeans evolved out of the fear of malaria. Colonial science had a theory: that Africans were immune to malaria, but that each African, especially the children carried a load of parasites. Africans were therefore carriers of the disease. This so-called mosquito theory had widespread impact on colonial urban planning and architecture

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[1]Being the text of a lecture given on the occasion of the 75th anniversary of the founding of the Nigerian Field Society by Frank Bridges in 1930, at the Drapers Hall, Institute of African Studies, University of Ibadan, on 12 March, 2005.

through out Africa.

The parasite causing human malaria had been discovered by a French Algerian, called Laveran in 1880; a Scottish army surgeon called Ross discovered later that the parasite can be transferred through the bite of the female *anopheles* mosquito (the male *anopheles* is harmless!). Before the female sucks blood, she first injects saliva that contains an anti-coagulant so that the blood does not clot in her syringe! The saliva also contains the parasite which causes malaria if the mosquito is infected.

Separate living quarters simply ensured that the Africans with their load of parasites and the Europeans did not live within the flight range of the female anopheles. That is how European Quarters came into being in many West African towns. These were usually on high ground (e. g. Hill Station in Jos); the exceptions are below-sea-level places like Ikoyi.

However Europeans living in European Quarters also needed African servants to be nearby day and night. Hence the characteristic servants' quarters in West Africa were invented. Separation of living quarters was called *sanitary segregation* despite protests from some élite Africans that it amounted to *racial segregation.* Sanitary segregation was justified on the *mosquito theory* propounded by scientists from the Liverpool School of Hygiene and Tropical Medicine. Based on the belief that "native children" were the source of malarial infection, here is what they said:

> Destruction of mosquitoes and other measures were all very well, but segregation of Europeans at a distance from all natives offers itself now as the only measure by which absolute freedom from the disease can be guaranteed (Curtin, 1985),

The domestic servants (cook, steward, and gardener) were always male. Though they might have been old, middle-aged and married, they were always referred to as "boys", hence the servants quarters became known as "Boys' Quarters" (popularly known as BQ). Now, the standard BQ was built at a specified regulation distance from the main house and facing away from it. This was not, as some people have suggested, because Master did not want to have constantly in his view his servants and their numerous wives and their naked children quarrelling, fighting, playing or making love. No, it was because colonial science had determined the maximum flight distance of the female anopheles mosquito. So the BQ like the EQ evolved in West Africa out of the fear of malaria.

In some parts of Africa where racial segregation operated, such as South Africa or Zimbabwe, there are no BQs; instead they have black townships. The reason is that black domestic servants in Southern Africa are women employed to work for the European Madame of the house. This might have been a problem for some husbands as miscegenation was a serious crime under apartheid law! In West Africa the male servant was hired to work for the Master. The Colonial European male usually left his wife behind in Europe, because of the fear of malaria.

The new inhabitants of the former European Quarters, now renamed GRAs or Housing Estates are Africans. But the BQs continue to be built at specified regulation distances from the main house, facing away from it, not out of the fear of malaria but because that is how the original European designers did it! These new African segregationists justify the practice, not by sanitation, nor by race, but by socio-economic imperatives. This has resulted in a gross distortion of urban development in African cities. The élite Nigerian lives in quarters (*GRAs, Iyaganku, Bodija or Idi-Ape*) separate from the masses in *Bere, Mapo, Apata Ganga*. In general, we can say that patterns of behaviour that Europeans adopted to survive in the tropics have been copied by the Nigerian élite without justification and perpetuated to the detriment of even urban development.

I must also mention the research institutes built by colonial governments, called Schools of Hygiene and Tropical Medicine; there is one in London and another in Liverpool. Contrary to what is generally believed to be the case, these schools were built to ensure the survival of the European in tropical climates. In these schools, research is conducted on a variety of tropical diseases, but the greatest concern in setting up these schools was the fear of malaria. Undoubtedly, Africans have also benefited from some of the research. It is not surprising that not much attention is paid in those schools to the nature of the African immunity to malaria and how to strengthen that immunity.

More recently, the medical press and daily newspapers have been highlighting the dangers to humanity that malaria now poses. The WHO statistics are quite frightening: 300 million people suffer from malaria every year mostly in black sub-Saharan Africa. Malaria affects five times as many people as TB, AIDS, measles and leprosy combined and kills one person every 30 seconds. Mind you, a recent *Lancet*, (a British medical journal) has reported that dirty water and lack of proper hygiene kills 4000 people every day, mostly in Africa, equivalent to 3 persons every 30 seconds! One does not know what to believe! Those who live far away from Africa must wonder if there will be any people left there soon! Malaria is reputed to have huge negative impact on economic productivity also. Quite expectedly therefore, malaria and AIDS are currently serious weapons in the appeal by African countries begging the West for aid and debt forgiveness. They are trying to exploit the fear of malaria.

The bad news from WHO is that the incidence of malaria is rising and has been doing so during the past decade; this is worrisome because in the past twenty years, WHO has devoted more money and brains to malaria research than at any other time in history. This it has done through the WHO special programme called TDR. Malaria is not a complex disease like cancer or hypertension or diabetes where the cause of the disease is often difficult to pinpoint. In the case of malaria we know precisely that it is caused by a microscopic parasite called *Plasmodium*. This organism can be easily detected by technology in the blood of a person suffering from malaria. There are many drugs that can kill the parasite and cure malaria.

So why is the incidence of malaria rising? There are two areas of concern. One is the occurrence of chloroquine resistance. The parasite that causes most of the malaria in Nigeria, *Plasmodium falciparum*, has evolved, during millions of years, the capacity to resist virtually any chemical poison to which it has been exposed. The news that Nigeria's Minister of Health intends to phase out the drug "chloroquine" has caught the newspaper headlines. The experts who have been following the spread of chloroquine resistance from Cambodia/Thailand to India, from there to East Africa and Eastern Nigeria, and now virtually everywhere in Nigeria, are not surprised at the Minister's warning. Once resistance to chloroquine has developed in the population of *Plasmodium falciparum* parasites, the proportion of resistant parasites in that population rapidly increases. What is more, the parasite that is resistant to chloroquine usually also becomes resistant to many common antimalarial drugs. So it is sensible to reduce the use of chloroquine once resistance to it has been detected. Phasing out chloroquine creates two problems: one is that alternative drugs are more expensive. One consequence of expense is that not enough of the new drug may be used, leading to exposure of the parasite to sub-lethal concentrations of the drug and hence rapid appearance of resistant parasites. Secondly, there is strong evidence (Oduola et al, 1991) that *Plasmodium falciparum* has an inherent capacity to develop resistance to any drug, provided that the parasite is exposed to sub-lethal amounts of that drug for a sufficient length of time. Therefore, switching from chloroquine to more expensive drugs is not a satisfactory long-term solution.

The other area of concern is that malaria may spread to places where it was formerly not endemic or to places from where the disease had been successfully eradicated; and, disease intensity seems to be increasing in endemic areas. The appearance of malaria in new places can be due to population movement caused by wars and natural disasters, global warming and environmental degradation. A major European/American fear is that with Africans carrying the parasite in their blood or the *anopheles* mosquito itself in the folds of their *agbada* to non-malaria endemic regions, malaria may become re-established in those parts of Europe or America from which it had been successfully eradicated. In the United Kingdom and the rest of non-malarious Europe, imported malaria is now a serious health problem. Most of the malaria is coming from Africa. The number has increased from a few thousand cases in the 1970s to 15 000 in the year 2000 (Ranford-Cartwright, 2004).

Increase in chloroquine resistance has coincided with a doubling of malaria mortality in some parts of Africa (Ranford-Cartwright, 2004). This is due either to lack of alternative effective drug therapy or to the fact that the resistant parasite is more lethal, more virulent. Whatever may be the reason, the availability of drugs has not improved the over all hope of successful malaria control in Africa. If anything it has worsened it.

My aim in this lecture is to do two things: (1) to draw attention to the fact that we Africans who have lived with the malaria parasite for nearly a million years have, like the parasite itself, evolved effective defences against it. (2) to urge, not only the scientists but also the

general public who are potential victims of malaria, to take advantage of this armoury in our war against malaria. In all of these, I want to say that our fight against malaria may not be won until we integrate what African ancients knew and did about malaria with the new scientific methods. The scientific methods must always be applied with the knowledge that Africans have innate resistance to malaria.

It is well known that in host parasite relationships, it is in the interest of the parasite that the host survives the presence of the parasite (Ukoli, 1974). The parasite needs the host to survive. But if every time the parasite enters the host the latter dies, the parasite itself would soon cease to exist. In the case of *Plasmodium falciparum* this general principle seems to have been developed to the highest level of sophistication. The parasite has induced its human host to develop not one, but several mechanisms that protect the host from the parasite's potentially lethal presence. What I have done in the following pages is to describe a few of these adaptive mechanisms to show that the African child born even in an environment of the most intense parasite transmission has very little to fear from malaria if she is otherwise well looked after.

Natural acquired immunity (hypergammaglobinaemia)

After hundreds of thousands of years of being exposed to malaria, the African has acquired the capacity to produce antibodies to the various antigens of the parasite, resulting in varying degrees of natural immunity. Joseph Edozien (University of Ibadan nutritional biochemist) recorded in 1957 that the concentration of gammaglobulins (the plasma protein fraction that constitutes antibodies) is higher in black Africans than in Caucasians (Edozien, 1957.) He showed that this hypergammaglobinaemia is a genetic adaptation in the African as a result of frequent exposure to the *Plasmodium* parasite over evolutionary time. Thus, African Americans have a higher concentration of this protein than whites of similar socio-economic status. West African blacks resident in London, even after several years in the malaria-free environment, have higher values than their Caucasian counterparts. But it is the West Africans living in the malaria endemic environment that have the highest values. Nigerians returning home from Europe after a long stay are more susceptible to malaria infection than those who are continuously resident in the region. These observations prove that continued repeated exposure to infection is necessary for the maintenance of very high concentrations of gammaglobulin and therefore of natural immunity.

The proof that high gammaglobulin concentration protects from malaria infection comes from an interesting observation. If children are given pyrimethamine (Daraprim)—Sunday-Sunday medicine—for some weeks, the gammaglobulin concentration (the natural immunity) of those children falls, and when they are taken off Daraprim, they are can have severe malaria. This also shows that drugs interfere with the natural immunity with which people in the endemic areas are endowed. It is incomprehensible that WHO should be recommending the use of insecticide-impregnated mosquito nets for Africans in Africa!

Sickle cell haemoglobin – Sickle cell disease

The blood protein, called haemoglobin, is one of the miracles of evolution, or creation, if you prefer. This protein extracts oxygen (O2) from the air in the lungs carries the O2 to the tissues where the O2 is downloaded. It then takes up the carbon dioxide (CO2) produced by the tissues and returns to the lungs where it expels its load of CO2 and begins the whole cycle again with its load of O2. Breathing in and out is taking in oxygen and giving out carbon dioxide, and the agent that enables us to do this is haemoglobin.

An abnormal form of the haemoglobin (HB-S) that causes the disease sickle cell anaemia, occurs at high frequency in regions of the world where *Plasmodium falciparum* is or has been endemic. HB-S is found in Saudi Arabia, Iran, the Mediterranean basin (Turkey, Greece, Italy, Sicily) and on the Indian continent. But the highest frequency of occurrence of the sickle gene is now in tropical Africa and in people of African descent in Europe and the Americas. HB-S differs from the normal haemoglobin (HB-A) only in a small molecular detail; this is enough to cause sickle cell disease if the person's haemoglobin is predominantly HB-S.

The gene for the abnormal haemoglobin is transmitted by simple Mendelian inheritance. Those who are born with the normal haemoglobin are of the genotype HB-AA while those with the abnormal haemoglobin are HB-SS. HB-AS are individuals whose haemoglobin consists of a mixture of normal and abnormal haemoglobin. They have inherited an abnormal gene from one parent and a normal gene from the other. HB-AS is a carrier of the sickle cell trait, but does not suffer from sickle cell disease.

The sickle cell gene is a device by the *plasmodium* to protect the human vector from its deadly presence. The person with the HB-AS genotype is partly protected from malaria (the trait carrier has on average a 29% advantage over those with normal or HB-SS haemoglobin). Very importantly, Fleming observed a complete absence of HB-AS children among those dying of cerebral malaria—the killer form of the disease. The mechanism by which the trait carrier is protected from malaria has been a subject of investigation for many decades. There is no point going into it here. The HB-SS individual is not protected. The reason for this is not known, but the question would not have arisen since under normal circumstances that person dies of sickle cell disease at a very early age.

From theories of population genetics it is possible to calculate the proportion of infants who would be born to each genotype if we know the incidence of HB-AS in the adult population (Fleming, 1982). From such calculations it is known that in parts of Africa where there is intense exposure to *Plasmodium falciparum* up to a third of the children are HB-AS and these are partially protected from malaria.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency.

The enzyme, glucose-6-phosphate dehydrogenase, is a red cell glycolytic enzyme. It is used in the process that converts glucose to energy. Normally, the *Plasmodium* parasite does not have the enzyme but uses the host enzyme to make its own energy from glucose. A person whose red blood cells are deficient in G6PD is protected from malaria; the deficiency, like the sickle cell trait, is found in regions of the world where *Plasmodium falciparum* is, or has been, endemic. This includes Africa, parts of the Middle East, Southern Italy and people of African descent in Europe and America. The gene responsible for the deficiency is inherited from the male. In the hemizygote where all the red blood cells are deficient in G6PD there is no protection from malaria. On the other hand, in the heterozygote where only 50% of the red blood cells are G6PD deficient there is protection. This shows that it is not the G6PD deficiency *per se* that gives the protection. Luzzatto and his colleagues over a period of many years tried to discover the mechanism by which G6PD deficiency protects against malaria. The work constituted a brilliant body of research that made Luzzatto a world acclaimed haematologist and geneticist. What he and his colleagues in Ibadan found out led to the following proposition. In the absence of red cell G6PD, the parasite can adapt by making its own variant of the enzyme. In the heterozygote where there is a mozaic of normal and deficient red cells in the same environment, such an adaptation cannot take place and therefore the parasite does not develop. The presence of normal and deficient red cells in the same individual confuses the parasite, and the heterozygote is protected.

An important function of this enzyme is to protect the red cell membrane from oxidative stress that can be caused by poisonous chemicals in food or drugs. More than 20% of West Africans are deficient in this enzyme (Luzzatto, 1986). This means that when such people take certain types of drugs e.g. sulphonamides, their red blood cells can break up releasing haemoglobin which may appear in the urine. The urine turns dark. Many Nigerians who took the popular M & B tablets and saw their urine turn black attributed this to the power of the drug in cleansing the blood of impurities!

Breast Milk

Infants fed wholly on breast milk are protected from malaria and other infections. Among other reasons, this is because human breast milk lacks para-aminobenzoic acid (PABA) which is an essential metabolite for the parasite to use in making folic acid. The parasite cannot develop without folic acid and it cannot use ready-made folic acid as humans can. This is a well-known fact that is exploited in developing drugs like sulphadoxine, dapsone, pyrimethamine and proguanil that are used as antimalarials. All these drugs prevent the parasite from using PABA to make folic acid. So feeding an infant only on human breast milk is the natural malaria prophylaxis. Before feeding bottles, infant formulae and antimalarial drugs were invented, breast feeding in many African societies extended to several years after birth. The first couple of years are the most crucial by which time natural

immunity is beginning to kick in.

To summarise, we can say that all things considered, West African children come into this world equipped to meet the challenges posed by *Plasmodium falciparum.* Up to one third are born with HB-AS. Greater than one fifth have G6PD deficiency. The African child has a genetically programmed natural immunity and neonates can acquire antibodies from their mothers *in utero.* If the infant is fed solely on human breast milk, its chances of getting malaria are negligible.

Unfortunately, these protective adaptations will not help if the child's resistance is weakened by characteristically African diseases of poverty such as malnutrition, gastro-enteritis, infections, vitamin deficiency and degraded environment against which the child has no immunity. Deaths caused by these major diseases can neither be ignored nor simply blamed on malaria. These maladies could be wiped out if governments invested heavily in the welfare of the child. It is misleading to give the impression to those in authority, as the WHO usually tends to do, that the solution to high rates of infant mortality in tropical Africa lies in technical programmes to find drugs that kill the malaria parasite. A lot can be done to reduce child and mother mortality by improving the living conditions of both.

When African children die, what kills them?

Here is what Olikoye Ransome-Kuti said in his 1985 inaugural lecture: *That our children will not die: Part II*

> The county's infant mortality is now rated as 178 per 1000; still one of the highest in the world, and the child mortality rate (0-5 years) as 322 (per 1000) for males and 306 for females in the rural areas. That is, 40% of children... will die before the age of five years, the majority of these deaths occurring in the first two years.

Although malaria is clearly an important factor contributing to the death of African children, several other factors have been identified. These include poor hygiene at delivery causing infections such as tetanus; gastro-enteritis (due mainly to dirty water, bottle–instead of breast–feeding), malnutrition of mother and child, vitamin deficiency and generally degraded environments. Ransome-Kuti ranked gastro-enteritis and bronchopneumonia ahead of malaria as major causes of child mortality.

Sickle cell disease as a major cause of death of African children

Let us now consider how sickle cell disease may complicate the overall statistics of mortality in African children, especially in the rural areas. From theories of population genetics, it is possible to calculate the proportion of infants that will be born HB-SS if we know the incidence of HB-AS in that population. The distribution of genotypes in the new-born in a population is said to follow the Hardy-Weinberg law (Knox-Macaulay, 1982).

Such calculations show that in some endemic areas of intense transmission, up to 4% (40/1000) of the population of new born infants are HB-SS, and therefore have sickle cell disease which is invariably fatal. It is known that severe sickle-cell crisis can be touched off by any kind of stress—infections including malaria; starvation, malnutrition, emotional upheaval. Since the HB-SS child is as prone to malaria as the normal child it must be difficult to separate death due to malaria per se from death due to sickle cell disease in a rural setting. There is indirect evidence that traditional societies recognised sickle cell deaths: *Abiku* described by Wole Soyinka as a spirit child destined to a cycle of birth and rebirth to the same mother, *Ogbanje* (Igbo) and *Omoesiso* (Urhobo) are now considered to be references to sickle cell deaths. Where there are no proper health facilities and where the people do not recognise it, it is estimated that more than 95% of HB-SS children die before the age of 5. It is interesting that this is the age range (0-5) when mortality from malaria is said to be highest. We can say that significant sickle cell deaths are enclosed in the malaria mortality statistics.

Why then does the WHO not talk about sickle cell mortality as they do about AIDS and malaria? I suggest that those who decide on research priorities, those who decide where the research money should go, those who pay the piper and dictate the tune are afraid of malaria and AIDS, but not of sickle cell disease. They cannot catch sickle cell disease as they can malaria or AIDS.

How African ancients, our ancestors handled malaria

Our ancestors may not have known that malaria is caused by microscopic parasites injected into the blood by a mosquito. But they had practical knowledge of the most consistent symptoms of the disease namely, fever, aches and pains. Can we learn anything from the ancients? I think there is a lot we can learn from the way our ancestors used plant concoctions (*agbo, uhunvwun*) to treat fever aches and pains (FAP). FAP are a manifestation of inflammation. The presence of the malaria parasite in the body causes the body to secrete fever and pain-producing substances that are directly responsible for these symptoms. When Nigerian scientists have subjected African medicinal plants to scientific analysis, the plants that yield the most consistent evidence of efficacy are those used by traditional people to treat FAP. If a traditional healer tells you he can use plant medicine to cure hypertension or diabetes permanently, you should be careful; almost certainly, he does not know how to identify hypertension. But if he shows you a plant-derived fever remedy, better believe it. He knows what fever is. Scientific analysis of the plants used to treat FAP show that many of them contain anti-inflammatory principles, but very little direct evidence of chemicals that actually kill the parasite. What we can say, therefore, is that our ancestors tackled the symptoms of malaria, but did little that confronted the parasite directly. For the African with natural immunity to malaria, all that is needed, the ancients seem to be saying, is take care of the symptoms and the body will take care of the parasite. In doing so the body reinforces its natural immunity against malaria.

Thus our ancestors were not afraid of malaria and neither should we be. It is interesting that medical science now recognises malaria as an inflammatory disease; certain classes of anti-inflammatory drugs will be used to treat malaria in the future. Our scientists should be provided with facilities now to study in detail the complex anti-inflammatory profile of the anti-fever remedies that are abundant in Nigerian communities.

This also suggests that a realistic policy on malaria management must recognise the need to develop different strategies for the treatment of three categories of people:

- the semi-immune African, that is the generality of adult West Africans living continuously in contact with the parasite,
- children under the age of 5 and pregnant women and
- non-immune expatriates.

To try and kill the parasite as we do with drugs in modern medicine is to provoke the ancient parasite into developing resistance. The evidence is that the resistant parasite is more dangerous, more virulent and more deadly. That is why the incidence of malaria disease is rising. It is time to think of a different strategy.

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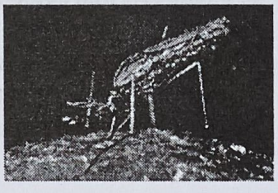

Members present at the 2005 ABM.
Top: Ibadan, Abeokuta, Ife
Bottom: Benin, Asaba