Twenty Years of Malaria*

BY

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In choosing to speak to you to-day on "Malaria" I fully realise that I am addressing a gathering of experts, because all of you must see and treat many cases of malaria daily. However, malaria is still one of our major problems and we have still much to learn about its treatment and prevention.

I saw my first case of malaria 22 years ago in Dehra Dun, in Northern India. Most of my patients suffered from *Plasmodium vivax* infection, but there were many cases of falciparum infection too, and occasionally of blackwater fever. Treatment was much simpler then because we only had one drug—quinine. This was administered as a mixture containing 10 gr. to the ounce, and was given thrice daily for a week to 10 days. Vomiting was common, but if this occurred the patient was given some sodium bicarbonate and the dose was repeated. Intramuscular quinine was not encouraged owing to a fear of abscess formation and possibly of tetanus, but intravenous quinine was considered to be more suitable, especially in seriously ill or cerebral cases. Atebrin (now called mepacrine) was discovered by the Germans in 1931, and it and plasmoquine were introduced as the standard treatment for benign tertian malaria in India about 1935. This treatment was very successful and consisted of seven days' treatment with atebrin and then two days' rest, followed by seven days' treatment with plasmoquine.

All patients were issued with mosquito nets and every case was given a curative course of treatment. This entailed 14 days in hospital. No prophylactic drugs were used, but great emphasis was laid on the prevention of mosquito breeding and much money was spent on drainage and spraying of pools with anti-mosquito oils.

Up to the outbreak of the Second World War in 1939 no major change occurred in the treatment of malaria in India, but with the loss of Java and the great quinine-producing countries, much research was undertaken to produce substitutes. This resulted in the discovery of chloroquine and camoquine. The Germans had discovered Resochin, and the Americans, after giving it clinical trials, named it chloroquine, and camoquine was just a variant of chloroquine. The most important British discovery was proguanil, or paludrine as it is commonly called. It was discovered after experimentation with sulphadiazine, from which it is derived. By the end of the Second World War there were therefore five groups of anti-malarial drugs available for clinical use:—

(1) Quinine.
(2) Mepacrine and the acridine drugs.
(3) Chloroquine and camoquine (the four aminoquinolines group).
(4) Paludrine or proguanil.
(5) Primaquine and pamaquin (the eight aminoquinolines group).

In India in 1940 we were still using quinine, mepacrine and the eight aminoquinolines only. From 1941 to 1945 I was in Malaya, and throughout this period these three groups of drugs were available in limited quantities. The Japanese had plenty of quinine, but as far as I am aware did not use mepacrine or primaquine. Malarial infection in British prisoners of war in Malaya was extremely common. Some of the worst cases were seen among British troops escaping from the siege of Singapore. Some of these troops were sunk in small ships and swam ashore on to the many small islands. When they were finally brought into the prison hospital by the Japanese they were in the final stages of malaria and almost all of them died. One party, consisting of senior officers of the R.A.F., on reaching a small island, made the great mistake of occupying the deserted huts of the local inhabitants. The hungry mosquitoes were waiting for them all full of parasites, and it was not long before all the party were infected. Only three survivors reached hospital and only one survived. The blood of the fatal cases contained enormous numbers of M.T. parasites, and more than 50 per cent. of the red cells were invaded. The party had quinine with them and took it at first, but decided that all their symptoms could not be due to malaria and many of them stopped taking it.

Malaria took a heavy toll of the prisoners, especially among those separated in smaller parties, who ran out of supplies and could not get drugs from the Japanese. In addition, beriberi and dysentery were constantly with us, and in their poor state of health the troops had practically no resistance to malaria. I have never seen so many relapses of malaria as I saw in Singapore, and many of my patients relapsed

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every 10 to 14 days. Infections were about equally divided between M.T. and B.T. types. Many re-infections occurred too, as the troops were constantly at work so long as they could stand up. If "working parties" became too small, the Japanese visited the hospital wards and beat up the doctor. It was never a question of "Is this man fit to work?" but rather "Which of these very sick men can I possibly send out to-day?"

At the end of the war and a short leave in the United Kingdom I returned to India. I well remember the visit of D. G. Davey, who was one of those who discovered paludrine. In a crowded classroom in Calcutta he told us about this wonderful new drug which prevented infection with malignant tertian malaria and suppressed, and sometimes cured, benign tertian malaria before clinical symptoms arose. One tablet a week was all that was required then. Now we use one tablet daily, and even then, owing to resistant strains of malaria, we find clinical infections breaking through. In this connection, Bishop *et al.* (1947) has produced experimentally a forty-fold increase in resistance to paludrine in avian malaria; and Chalmers, in Australia (1951), mentions the possibility of having to take 55 tablets of paludrine daily when a very resistant strain of malaria is encountered. Experts, such as Sir Gordon Covell (1951) and Davey (1951), recommend that another drug should be used when paludrine fails to prevent a "break through" in prophylaxis, and their choice of an alternative drug is chloroquine in 300 mg. doses weekly.

In 1951 I came to Africa, and the malarial picture here is very different from that of India or Malaya. The predominant type of malaria is the malignant tertian variety. Patients having violent rigors, with chattering teeth and shaking their beds in the cold stage, and flinging the bedclothes off in the hot stage, are seldom if ever seen. Malaria in the adult African seems deceptively mild, and one has to treat African children or Europeans to see severe forms of the disease. After India there is a comparative lack of mosquitoes. There is no constant hum of mosquitoes in the evenings, and presumably the few that one can see or hear do very deadly work. Widespread infection may be partly due to the uncommon use of mosquito nets, except by Europeans, and the lesser emphasis laid on preventive measures. There is a dread of interfering with the immunity of the local population, which is probably well founded, and so treatment of the adult African is the minimum necessary to tide him over his attack without causing complete cure. Benign tertian infections are not very common, probably only accounting for about 10 per cent. of cases seen in Zomba.

In a survey made in 1951, Dr. Baird found an appreciable number of quartan infections, mainly from the Domasi area. However, since then I have not had a case of quartan malaria under my care. It may be that some of these quartan cases were in fact malignant tertian. I say this because according to Shute (1951), the merozoites of acute primary cases of *P. falciparum* malaria that are seen in the peripheral blood are much smaller than those of the same strain of parasite seen in chronic cases, in which the ring forms may occupy one quarter, and sometimes nearly one half, of the red cell. These large *P. falciparum* parasites may easily be mistaken for *P. malariae* parasites.

In spite of being equipped with the most modern drugs and with laboratory facilities, patients still do not always get the best treatment. I would like to quote three examples. My first example is that of the business man from Salisbury who took a room in the Shire Highlands Hotel. He became unwell and stayed in his room. It so happened that the B.M.A. was holding its annual dinner in the hotel some days later, and Dr. Kirwan and myself went up to his room at the request of the manageress. We found the patient in a semi-conscious state and sent him to hospital. His blood revealed a 50 per cent. parasitaemia with *P. falciparum*, and in spite of urgent treatment he died next day. I do not think any blame can be put on anyone for his death, which was due to malaria which was neglected for too long.

My second example is that of a government servant in the Public Works Department. He contracted a pyrexial illness and his doctor found malarial parasites in his blood. For this he received mepacrine injections thrice daily, along with other anti-malarial drugs. When I saw him some weeks later he had enormous abscesses in his buttocks extending as far down as the knee on one side. These were incised and large quantities of pus were evacuated. Some months later Dr. Baird and myself held a board and he went back to the United Kingdom and never returned to Nyasaland. This is an example of excessive and wrong treatment. In this connection I would like to quote Manson-Bahr (1951), who stated in connection with intramuscular injections for malaria: "There are in reality no indications for more than one or at the most two injections. It should not be one's aim to

convert one's patients' buttocks into pincushions!"

My third example is that of an elderly European woman who was admitted to the Zomba European Hospital in an unconscious state. On somewhat slender grounds the medical officer decided that her symptoms were due to cerebral malaria, and he informed the husband accordingly. Blood films were negative, and soon afterwards I performed a lumbar puncture which contained almost pure blood. There was no doubt that the real diagnosis was a subarachnoid haemorrhage, and she died soon afterwards. The husband was well satisfied with the first diagnosis and was never informed of the true state of affairs.

In conclusion, I would like to mention some of the problems I have met in treating malaria in Nyasaland. The first one is that of prophylaxis. Many patients ask what is the best prophylactic drug to take. For those who live in malarious places I am sure that paludrine is the best drug to take, as it (and the eight aminoquinolines) are the only drugs which act on the early exoerythrocytic forms in the liver. Paludrine is therefore a true causal prophylactic drug for *P. falciparum* malaria. However, as *P. vivax* malaria gives rise to secondary exoerythrocytic forms, which are not affected by paludrine, it is not a causal prophylactic in this type of malaria. The alternative drug of choice is chloroquine, which acts on the asexual forms and has a high intrinsic activity and persistence which permits it to be used at intervals of one week. Toxic effects of paludrine have been reported by Cosgrove (1951) and Slater Brown (1951). These consisted of loss of appetite, lack of energy, abdominal discomfort and loss of balance. I have mentioned already the liability of certain strains of malaria to become resistant to paludrine.

Another problem is that of the chronic relapsing case. I have often been told by patients that "whenever my blood is examined for malaria, it's positive." Some of these patients are apyrexial and some have had courses of different anti-malarial drugs, including injections. One would naturally think that these patients were infected with benign tertian parasites and prescribe 7 mg. of primaquine thrice daily for 14 days, but this is not always the case. More often the parasites are reported as subtertian. This state of affairs is difficult to explain, because on the face of it subtertian infections are easily controlled in the early stages by all of the commonly used drugs, and since there are no secondary exoerythrocytic forms produced by this parasite it should be easy to eradicate.

Perhaps the explanation lies in resistant strains, but resistance to several anti-malarial drugs has not been reported as far as I am aware. Perhaps these patients are in a poor state of general health and have other concurrent infections such as I have described in prisoners of war in Malaya. To my mind none of these explanations quite fits the picture, and I suspect that parasites are seen in these films because of faulty preparation. Blood films are almost always prepared by African staff trained by the central laboratory. When they are sent away to out-stations and work on their own, I know that they do not often make fresh stains or use unscratched slides, so it is possible that parasites are carried over from case to case. Invariably, when I take blood back to Zomba with me, the films are negative.

A problem I often meet with in African patients is the seriously ill or unconscious adult in whom subtertian parasites are reported, usually in small numbers. There is a temptation to ascribe his whole condition to cerebral malaria. I know that it is possible for an adult African to suffer from cerebral malaria, especially if he comes from a distant locality and has little immunity to the local strains of malaria, but on the whole it is unlikely. It is frequently the case that he suffers from a cerebral haemorrhage, uraemia, diabetes, meningitis, poisoning, injury or even pneumonia. These patients should, I am sure, receive antimalarial treatment, but only as an adjunct to the treatment of the basic condition. I have only once diagnosed cerebral malaria in an adult African, and then I was wrong.

It so happened that I was called to see two members of the staff of the Zomba African Hospital. On examination, both had slight pyrexia, with restlessness and twitching of the face and vomiting. Both patients were semi-conscious and scanty malarial parasites were reported in one. Both of them died, and it was subsequently discovered that they had been drinking methyl alcohol.

Cerebral malaria is not uncommon in African infants, and then there is often a state of shock, the infant being cold and listless, with a sub-normal temperature. Blood films usually show enormous numbers of parasites, and death is the rule before effective treatment can be instituted.

I have endeavoured to show that the diagnosis and management of malaria in both semi-im-

mune and non-immune patients is still a matter for skill and care. It can be one of the simplest and at times one of the most dangerous and difficult diseases to treat. For these very reasons it remains a source of interest to many of us.

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