Notes

Observations on the Longevity of *Plasmodium falciparum*: with Special Reference to Findings in Mauritius

by J. VERDRAGER, M.D., *WHO Epidemiologist, Malaria Eradication Programme, Philippines; formerly, WHO Malariologist, Malaria Eradication Project, Mauritius*

It is generally admitted that in *P. falciparum* infections, recrudescences (short-term relapses) are fairly common but as a rule do not occur more than a year after infection. Undoubtedly, however, whether because of strain or some other difference from the typical, *P. falciparum* "relapses" may occur for several years after infection.

Eyles & Young[a] found that a United States strain from South Carolina, the Santee Cooper strain, lasted an average of 222 days ± 25 in 22 artificially inoculated subjects, but in one case the infection lasted 480 days, i.e., 16 months. It was concluded that an infection contracted towards the end of one malaria transmission season might persist through the following season and the one after that.

Utilizing a Panamanian strain, Jeffrey & Eyles,[b] in 39 artificially inoculated subjects, observed a duration ranging from 114 to 503 days. Five cases persisted for more than one year. The same authors[c] fed mosquitos at all stages of infection on 88 patients with the Panama or South Carolina strain of *P. falciparum* malaria. Infection frequently occurred with densities of less than 10 per mm^3 of blood and occurred as late as the 321st day of patent parasitaemia with the South Carolina strain and the 410th day with the Panama strain. It was concluded that the long duration of parasitaemia of these strains of *P. falciparum* may be of considerable epidemiological importance in certain endemic areas.

Ciuca et al.[d] on the basis of one, perhaps unique, experience of induced *P. falciparum* malaria that they had in Romania, estimated the maximum duration of infection with these strains as 27 months. As pointed out by Macdonald,[e] it must not be taken that these limited series include the extremes which may be found in nature.

Recently *P. falciparum* trophozoites were found in the blood of a Nigerian woman in London after she had ceased to be exposed for 19 months.[f] *P. falciparum* trophozoites were also found in the blood of an Australian seaman in Sydney after he had ceased to be exposed for 14 months.[g] James et al.[h] cite the case of Ziemann, who had an attack of *P. falciparum* malaria 18 months after leaving the Cameroons, during which period he had not been exposed to reinfection.

Recent observations[i] made in Bechuanaland showed that *P. falciparum* can survive in the human host for at least 18 months. Parasite rates among imported labour remaining in the non-endemic mining areas of South Africa were still of 6.5% after 16-18 months.

Russell et al.[j] also report one case, that of a student at Harvard Medical School, who, in 1934, was able to demonstrate repeatedly during his course of clinical pathology crescents of *P. falciparum* in his blood smears, although his last exposure to infection had been in Africa in 1930. He had been repeatedly infected between 1926 and 1930 while running a medical dispensary in the Belgian Congo and had returned to the United States of America in 1930. During residence in Pittsburgh and Meadville, Pa., and Durango, Colo., in 1931 and 1932 and in Boston, Mass., in 1933, he had several typical

[a] Eyles, D. E. & Young, M. D. (1951) *J. nat. Malar. Soc.*, **10**, 327.

[b] Jeffery, G. M. & Eyles, D. E. (1954) *Amer. J. trop. Med. Hyg.*, **3**, 219.

[c] Jeffery, G. M. & Eyles, D. E. (1955) *Amer. J. trop. Med. Hyg.*, **4**, 781.

[d] Ciuca, M. et al. (1955) *Bul. sti. Sect. Şti. med. (Bucureşti)*, **7**, 61.

[e] Macdonald, G. (1957) *The epidemiology and control of malaria*, London.

[f] Walters, J. (1960) *Brit. med. J.*, **1**, 1206.

[g] Black, R. H. (1960) *Med. J. Australia*, **2**, 446.

[h] James, S. P., Nicol, W. D. & Shute, P. G. (1932) *Proc. roy. Soc. Med.*, **25**, 1153.

[i] *Report of the Third African Malaria Conference*, 1962 (unpublished working document WHO/Mal/376; AFR/Mal/9/62).

[j] Russell, P. F. et al. (1963) *Practical malariology*, London.

relapses of malaria with occasional blood smears positive for *P. falciparum*. The attacks were relieved by quinine. At no time between his return to the USA in 1930 and the positive blood findings in 1934 had this man been exposed to malaria infection.

Infections produced by strains of *P. falciparum* from different geographical areas may show wide variations in pathogenicity, ability to develop in the mosquito host and response to the action of a particular drug. It is not surprising, therefore, that differences in their longevity may be encountered.

The following observations suggest that *P. falciparum* in Mauritius can survive in the human host for up to three years. After this period of time the infections become asymptomatic and subpatent (parasitaemia being submicroscopic, short-lasting or both). Their epidemiological importance in the continuation of transmission in old residual foci needs further investigation.

Epidemiological background

Mauritius was struck by wide and devastating malaria epidemics which culminated in 1867, when a quarter of the inhabitants of the capital, Port Louis, died, and the general death-rate for the island rose to 120 per 1000. The island remained severely affected until 1950, when a comprehensive DDT spraying scheme brought malaria to a " virtual end ". The main vector, *Anopheles funestus*, which was apparently wholly endophilic and anthropophilic, was eradicated. On the other hand, *A. gambiae*, highly exophilic and zoophilic, remained in high density.

In 1960, a WHO-assisted malaria eradication project was launched. This project, based on adequate surveillance with both active and passive case-detection, revealed an over-all incidence of 2 per 1000, which dropped to 0.3 per 1000 in 1962 and to 0.04 per 1000 in 1963 (present population, 670 000). It was also shown that, transmission being maintained by a vector which bites man relatively infrequently and the temperature being unfavourable to the rapid completion of the extrinsic cycle for a part of the year, the resulting type of malaria was an unstable one, with anophelism without malaria occurring over large areas.

P. vivax and *P. falciparum* were the two parasites commonly found ; *P. malariae* was rare. For the period 1960-61 the following proportions were observed : *P. vivax*, 61.7% ; *P. falciparum*, 36.9% ; *P. malariae*, 1.4%.

In 1963, interruption of transmission had been achieved throughout the country, except in three neighbouring small villages (population, 1200) on the western coast, where 10 *P. falciparum* cases were detected. The investigation included a mass blood survey in addition to the usual active case-detection, passive case-detection and epidemiological follow-up.

Long-lasting infection detected by epidemiological investigation of a case of cerebral malaria after blood transfusion

On 19 July 1962, an assistant driver of Euro-African origin, aged 30, was severely injured in a road accident resulting in a dislocation of his left shoulder with rupture of the brachial plexus and massive haematoma.

On admission to hospital he received two pints of blood from two different donors. On 25 July, he had a slight rise in temperature, and on 28 July started a quotidian type of fever not exceeding 38.5°C, which was attributed to infection of the left arm and treated with antibiotics.

On 16 August, the patient became unconscious, and then lapsed into a comatose state with symptoms simulating cerebrospinal meningitis or tetanus (neck rigidity, trismus). The cerebrospinal fluid was normal.

On 17 August, blood examination for malaria revealed hyperinfection with *P. falciparum* and thin films showed that 15% of the erythrocytes were infested. In addition numerous crescents were detected.

A five-day treatment was immediately started which included 2500 mg of chloroquine (of which 300 mg chloroquine sulfate by intramuscular injection) and 83 mg of pyrimethamine. In addition the patient received intravenous glucose and saline and intramuscular vitamin B_1.

The patient soon recovered both clinically and parasitologically. Only 1% of the erythrocytes were infested 24 hours after the beginning of the treatment, and after 72 hours rings had completely disappeared (gametocytes disappeared only 3 weeks after the beginning of the treatment).

A few days later, however, fever recurred but was obviously due to the gangrene of the left arm and stopped with the amputation of the limb on the 28 August.

July coincides with the non-transmission season, and therefore the possibility of the patient having received an infective bite a week before the injury could be disregarded. In fact two origins were possible : (*a*) a recrudescence of a latent infection

brought out by injury and shock, or (*b*) an induced infection.

Epidemiological evidence seemed to be against the first alternative because of the absence of previous attacks of fever in the patient (no primary asymptomatic cases had been demonstrated in Mauritius since 1960) and the absence of cases in the locality.

As to the possibility of an induced infection, the systematic routine blood examination of the two blood donors before transfusion had been negative. Repeated thick films and examination after centrifugation were made again during the epidemiological investigation but were also negative. However, one of the blood donors was considered suspect because of a history of previous fever attacks, and he was therefore closely followed up.

It was only on the seventh follow-up, three-and-a-half months after the transfusion, that this blood donor was found to have an extremely low *P. falciparum* parasitaemia. In checking one of the slides considered negative, the malariologist found one female crescent in a thick film and a ring in another. The laboratory technician subsequently found another crescent. Prolonged examination failed to reveal any other parasite. Ten other thick films taken three days after the positive day were again negative and centrifugation was also unsuccessful.

Epidemiological investigation of this donor, a 49-year-old goat-keeper of Indian origin, was very difficult, but revealed that he was asymptomatic the day on which the positive slide was taken. He had, however, a very mild attack of fever with headache the following day. He was unable to state exactly when the primary fever attack occurred, but it was found that during the beginning of the surveillance project (April 1960) two other persons living in the same house were found positive (*P. falciparum*). During the epidemiological investigation of these two positive persons, the donor was sought but could not be found. According to these two positive members of his family, they all three had their first attack at the same time. No positive cases having been detected in this focus since 1960, it is therefore probable that the primary attack occurred in April 1960.

This case suggests that *P. falciparum* infections may last two-and-a-half years but are extremely difficult to detect by the standard thick film method.

Long-lasting asymptomatic infection detected by follow-up investigation

In the course of epidemiological investigation in 1963 follow-ups of all *P. falciparum* cases detected in 1960 and 1961 were carried out.

On 29 March 1963, an Indian female aged 21 years was found positive with scanty rings and crescents (10 per mm^3). She complained of headache (a symptom found in 95% of *P. falciparum* infections in Mauritius) but not of fever and denied ever having had any previous attack of fever.

This shows the unreliability of some inquiries, as on her positive record card it was noted that she was found positive on 5 April 1960 and had complained at that time of fever, rigor, and sweating since 28 February 1960 ; she was given chloroquine tablets for a three-dose treatment, but she probably did not take them all. During the 1963 treatment, difficulties were encountered when vomiting occurred after the first 600-mg chloroquine dose.

The patient had been detected in 1960 in the same locality as in 1963 and there is no evidence that she moved from this village during this period. It is probable that in this focus (Tamarin) interruption had been achieved since 1961 and that therefore no reinfection could have occurred in 1961, 1962 or 1963.

Proof of interruption of transmission in this focus is threefold: (*a*) no positive cases have been detected in this focus since the 1960 transmission season either by the fortnightly visits or by the dispensary located in this village ; (*b*) the focus was treated as a special demonstration area and sprayed twice a year from April 1960 onwards ; (*c*) the focus is in a coastal village which is a residential area for many Europeans who spend their weekends there in *campements*, and it is probable that, had transmission occurred, positive cases would have been detected among these Europeans.

Moreover, an analysis of symptoms of the positive patients found in 1962 by active and passive case-detection, epidemiological investigation and mass surveys showed that all were symptomatic with at least a recent history of fever attacks. Only old relapsing cases detected by follow-up were sometimes asymptomatic or at least subsymptomatic (secondary asymptomatic parasitaemias).

It is therefore considered that this asymptomatic and submicroscopic case is probably one of recrudescence of the primary infection detected three years previously on 5 April 1960.

Infectivity of the " hidden reservoir "

No attempt was made to study the infectivity of these *P. falciparum* cases to the local vector,

A. gambiae. However, it is well known that patients without symptoms and with low gametocyte density may just be as infective as those obviously ill and with gametocyte density.

Robertson,[k] working with *A. gambiae* in West Africa, recorded infections at a threshold below 3 crescents per 1000 leucocytes. In one batch of 13 *A. gambiae*, one specimen became infected when the crescent density was 0.7 per 1000 leucocytes (less than 5 per mm^3 of the blood).

Muirhead-Thomson,[l] also in West Africa, found that 25% of human carriers were infective to mosquitos at a time when crescents were so scanty as to be scarcely detectable in thick blood film. On the other hand, about 10% of crescent carriers were non-infective at a time when crescents were abundant in the blood.

Young and his colleagues [m] in the USA have also studied intensively the infectivity of *P. falciparum* to mosquitos. Batches of *A. quadrimaculatus* were induced to take blood-meals from Negroes in South Carolina who were known to have had malarial attacks in recent months, irrespective of whether gametocytes, or, indeed, parasites of any sort, had been detected in the peripheral blood. Of 124 patients with *P. falciparum* infections 25 showed gametocytes, all in low density, and 16 of these infected mosquitos. Some patients showed no parasites at all, yet four of these proved infective. Patients without symptoms were just as infective as those obviously ill. It was concluded that the patient with asymptomatic parasitaemia, usually with a relatively low gametocyte density, is the important factor in the transmission and maintenance of *P. falciparum* in the area studied.

Conclusions and discussion

There is some evidence that in Mauritius, *P. falciparum* infections may last up to three years. After this period of time they are usually sub- or asymptomatic and submicroscopic (terminal infections) and extremely difficult to detect by the standard thick film method.

From the epidemiological point of view, it is not impossible that these subsymptomatic and subpatent cases which are so hard to detect may play an important role in the continuation of transmission, acting as a hidden reservoir. This might explain why it is usually impossible to find, even by repeated mass surveys, the source of new infections occurring at the beginning of the transmission season in residual active foci.

Not only may the duration of survival of *P. falciparum* in the human host sometimes be equal to that of *P. vivax*, but its infectivity may last longer (in terminal infections with *P. falciparum* gametocytes are frequently present, while in terminal infections with *P. vivax* they are frequently absent).

Moreover, *P. vivax* infections are easier to detect. The primary attack is usually longer and more typical and repeated clinical relapses occur in the course of the disease, while with *P. falciparum* there is a far greater potentiality of secondary asymptomatic parasitaemias.

In areas where conditions were equally favourable for the transmission of *P. falciparum* and *P. vivax* and malaria eradication campaigns have been carried out, either of two things may therefore be expected. First transmission may have been completely interrupted; in this case, *P. falciparum* will apparently disappear first, its clinical relapses being much rarer usually than those with *P. vivax* and its terminal infections submicroscopic. Secondly transmission may have been sharply reduced but not completely interrupted; in this case, the terminal "hidden" or "invisible" *P. falciparum* reservoir constituted by asymptomatic and apparently subpatent cases (parasitaemias being short-lasting, submicroscopic or both) will escape detection but continue to infect the *Anopheles* and produce both symptomatic and parasitic new cases,

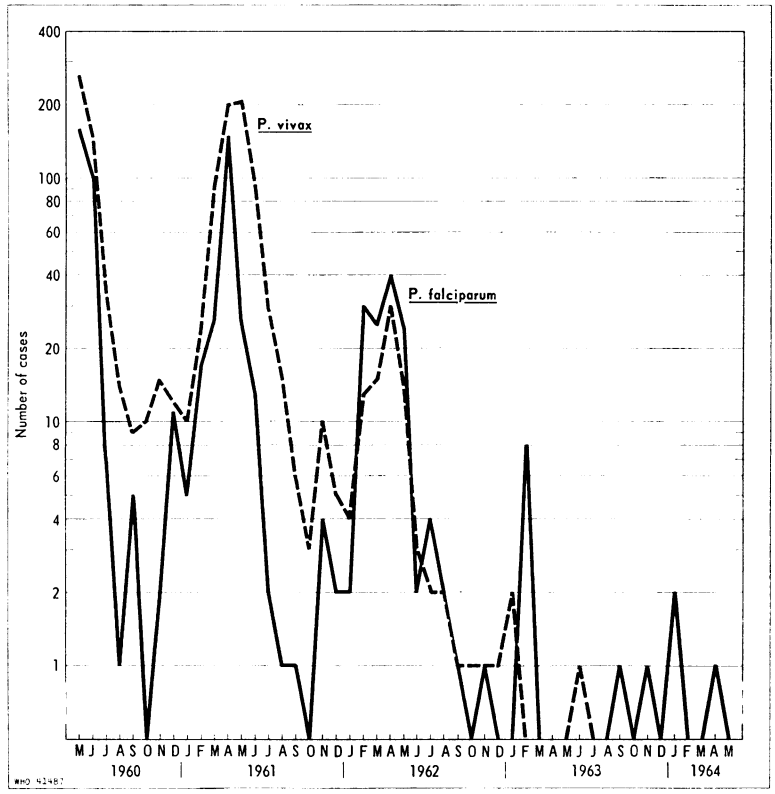
In other words, in residual active foci, the greater difficulty of detecting *P. falciparum* infections should result in the earlier eradication of *P. vivax*. At the beginning of 1962, on purely theoretical deductions, the earlier eradication of *P. vivax* was foreseen in Mauritius. Recent happenings in Mauritius seem to confirm this prediction. The accompanying figure illustrates the order of disappearance of *P. falciparum* and *P. vivax* in Mauritius. Not only did residual spraying and surveillance cause *P. vivax* to disappear at the same rate as *P. falciparum*, but from mid-1963 onwards only *P. falciparum* cases have been detected in the island. Moreover, it should be pointed out that the three *P. vivax* cases detected in 1963 were relapses while the two *P. falciparum* cases detected during the first quarter of 1964 were indigenous.

[k] Robertson, J. D. (1945) *Ann. trop. Med. Parasit.*, **39**, 8.

[l] Muirhead-Thomson, R. C. (1954) *Trans. roy. Soc. trop. Med. Hyg.*, **48**, 208.

[m] Young, M. D., Hardman, N. F., Burgess, R. W., Frohne, W. C. & Sabrowski, G. W. (1948) *Amer. J. trop. Med.*, **28**, 303.

ORDER OF DISAPPEARANCE OF *P. FALCIPARUM* AND *P. VIVAX* FROM MAURITIUS



The classical view that " during malaria eradication campaigns *P. falciparum* is the first species to disappear "[n] does not, therefore, apply to Mauritius. Similar happenings have also been reported from other parts of the world (e.g., America).

As far as *P. malariae* is concerned, there has been recently a relative increase in the number of cases detected in Mauritius, the majority of which are induced by blood transfusion.

[n] Pampana, E. (1963) *A textbook of malaria eradication*, London.