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OBSERVATIONS ON THE LONGEVITY OF PLASMODIUM FALCIPARUM

by

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Introduction

It is generally admitted that in P. falciparum infections, relapses are fairly common but as a rule do not occur more than a year after infection. But undoubtedly, whether because of strain or some other difference from the typical, P. falciparum relapses may occur for several years after infection.

Eyles & Young (1951) found that a United States' strain from Carolina, the Santee Cooper strain, lasted an average of 222 days  $\pm$  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, Jeffery & Eyles (1954), 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 (1955) fed mosquitos at all stages of infection on 88 patients with the Panama and South Carolina strain of P. falciparum malaria. Infection frequently occurred with densities of less than 10 per  $\text{mm}^3$  of blood and occurred as late as the 321st day of patent parasitaemia in the South Carolina strain and the 410th day in 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.

Recently P. falciparum trophozoites were found in the blood of a Nigerian woman in London after she had left exposure for 19 months (Walters, 1960). Logan (1953) mentions the case of an adult American who continued to show P. falciparum four years after having left the Congo. Ciuca et al. (1955) on the perhaps unique experience of induced falciparum malaria that they had in Romania, estimated the maximum duration of infection with these strains as 27 months. James et al. (1952) cites 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 (WHO, 1962) 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. (1963) 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 was 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, Pennsylvania, and Durango, Colorado, in 1931 and 1932 and in Boston in 1933, he had several typical 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 United States in 1930 and the positive blood findings in 1934 had this man been exposed to malaria infection. A prolonged course of quinine medication finally cured this infection. (As pointed out by Macdonald (1957), it must not be taken that these limited series include the extremes which may be found in nature.)

The following observations, and at least the first two examples, suggest that P. falciparum in Mauritius can survive in the human host up to three years. After this period of time the infections become asymptomatic and subpatent (parasitaemias submicroscopic and/or short-lasting). Their epidemiological importance in the continuation of transmission in old residual foci need further investigation.

## 1. 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, A. funestus, which apparently was 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 Eradicated Project was launched. This project, based on adequate surveillance with both active and passive case-detection, revealed an over-all incidence of two per 1000, which dropped to 0.3 per 1000 in 1962. (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.

In 1963, interruption of transmission had been achieved throughout the country, except in three neighbouring small villages (population 1200) on the western coast where ten 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.

The area, where practically all the P. falciparum cases are detected, is the warmest and driest part of the island.

## 2. Long-lasting infection detected by epidemiological investigation of a case of cerebral malaria after blood transfusion<sup>1</sup>

This case was discovered during epidemiological investigation of a case of cerebral malaria which occurred after blood transfusion. The recipient was in a coma for two days with 15% of the red cells parasitized by P. falciparum, but recovered with classical treatment (chloroquine). The routine blood examination of the donor was negative. However, the donor was considered suspect because of a history of previous fever attacks and was kept under close follow-up.

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<sup>1</sup> A full account of this observation is given in another paper, A case of Cerebral Malaria after Blood Transfusion (in preparation).

It was only on the seventh follow-up, three-and-a-half months after the transfusion, that this blood donor was found with an extremely low P. falciparum parasitaemia. In checking one of the slides considered negative, the malariologist found one female crescent on a thick film and a ring on the other one. 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 method was also unsuccessful.

Epidemiological investigation of the donor, a goat keeper of Indian origin, aged 49, was very difficult, but revealed that he was asymptomatic the day on which the positive slide was taken. The donor showed, 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 cases, the donor was looked for but could not be found at that time. According to these two positive members of his family, they all three had their first fever attack at the same time. 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.

### 3. 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, a female aged 21 years was found positive with scanty rings and crescents (10 per mm<sup>3</sup>). She was complaining of headache (a symptom found in 95% of P. falciparum infections in Mauritius) but not of fever and denied having ever had any previous attack of fever.

This shows the unreliability of some inquiries as on her positive record card, No. 1301, it was noted that she was found positive on 5 April 1960 and was at that time complaining of fever, rigor, and sweating, since 28 February 1960, and was given

chloroquine tablets for a 3-dose treatment which was probably not entirely taken. During the recent treatment difficulties were encountered when vomiting occurred after the first 600 mg chloroquine dose.

The patient was detected in 1960 in the same locality and there is no evidence that she moved from this village during this period. It is probable that in this focus (Tamarin) interruption was obtained since 1961 and that therefore no reinfection could occur either in 1961, 1962 or 1963.

Proof of interruption of transmission in this focus is three-fold:

- (a) no positive cases have been detected in this focus since the transmission season 1960 in spite of fortnightly visits (ACD) and a dispensary located in this village (PCD);
- (b) this focus was considered as a special demonstration area and sprayed twice a year since April 1960;
- (c) this coastal village is a residential place for many Europeans who spend their weekends in "campements" and it is probable that if transmission occurred positive cases would have been detected among these Europeans.

Moreover, an analysis of symptoms of the positive cases detected in 1962 has shown that all these cases, detected by active case-detection, passive case-detection, epidemiological investigation and also mass surveys, were all 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 a relapse of the primary infection detected three years ago, on 5 April 1960.

### 3.1 Suspect cases

Amongst the ten positive P. falciparum cases detected in the three active residual foci, 1963, were two P. falciparum cases already detected in 1960. The first reaction was to classify these cases as indigenous (reinfection) because it is generally admitted that P. falciparum infections do not usually last more than one year. However, the history of these cases was somewhat puzzling.

The first case is a labourer, aged 50, who was already found positive on 16 May 1960, with trophozoites and gametocytes of P. falciparum. He was complaining of fever, rigor, sweating and vomiting. He was found again positive on 25 February 1963, during

epidemiological investigation of the foci. He had fever for approximately two weeks and the symptoms were again fever, rigor, sweating, vomiting, headache and backache. Blood examination showed the presence of trophozoites and immature gametocytes of P. falciparum. The patient reported that every year, since 1960, he had repeated attacks lasting approximately a fortnight and presenting the same symptoms. These attacks were rapidly brought to an end by combined tablets given by the surveillance agent (chloroquine 600 mg + pyrimethamine 50 mg).

The second case is a girl, aged nine, who was found positive on 6 June 1960, with trophozoites and gametocytes of P. falciparum. She was complaining of fever, rigor, sweating and vomiting. She was found again positive on 4 February 1963, when she complained of fever, rigor, sweating, vomiting headache and backache, from a few days previously. The blood smear was taken by the surveillance agent during his house-to-house visits. According to her parents and herself, the girl had the same symptoms in April 1962, but apparently not in 1961. This attack was stopped by a suppressive treatment (combined tablets) given by the surveillance agent. There was another positive case in her family in 1960.

There is a striking similarity in the history of these two cases:

(a) They were detected the first time during the beginning of the surveillance project in 1960. At that time, due to the high number of cases detected, part of the radical treatment had to be left with the patients. Subsequent experience has shown that doses left with the patient are usually not absorbed. It is therefore not known if these patients have taken the full radical treatment. For the same reasons these cases were seen only once by the follow-up units.

(b) These patients had repeated attacks of fever with the same symptoms. They were seen again by the surveillance agents (house-to-house visits), received combined tablets, after which the symptoms rapidly disappeared but for some reason the smears were reported negative. In the family of one patient, there was another case in 1960, but since that time no other cases were detected in these families. Now if we admit that these cases are reinfections, it would mean that these cases were probably reinfected during the transmission season 1961, 1962, or at least during the transmission season 1963. In this case, it is most surprising that no other members of their families were infected.

The above facts, clinical history, parasitological findings, therapeutic effect and absence of infection in their families, might suggest that these cases are clinical relapses and parasitological recrudescences of previous infections, rather than re-infections. Of course, the possibility of reinfection is not excluded.

These suspected long-lasting P. falciparum infections were all detected in Mauritians of Indian origin.<sup>1</sup>

#### 4. Conclusions

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. However, if the course of the disease has been altered by repeated suppressive treatment, which probably stops the process of immunization, the infection may still be symptomatic and patent.

From the epidemiological point of view, it is not impossible that these subsymptomatic and subpatent cases (hidden reservoir) may play an important role in the continuation of transmission, but would be extremely difficult to detect. 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 the duration of survival of P. falciparum in the human host may sometimes be equal to P. vivax but its infectivity may last longer (in terminal infections of P. falciparum gametocytes are frequently present while in terminal infections of P. vivax they are frequently absent).

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

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<sup>1</sup> While the suggestion of the author as to the probability of these cases being recrudescences or relapses of previous infections is plausible, nevertheless this must be assessed with caution. Some of these cases were found in the remaining active foci of transmission; the fact that members of their families were not infected is of limited significance in the conditions of Mauritius. (Editor's remark)

In areas where conditions were equally favourable for the transmission of P. falciparum and P. vivax, the following may therefore be expected: (a) Transmission has been completely interrupted. In this case, P. falciparum will apparently disappear first, its clinical relapses being much rarer usually than P. vivax and its terminal infections submicroscopic. (b) Transmission has been sharply reduced but not completely interrupted.

The terminal "hidden" or "invisible" P. falciparum reservoir constituted by asymptomatic and apparently subpatent cases (parasitaemias either short-lasting and/or submicroscopic) will escape detection but continue to infect the Anopheles and produce new cases both symptomatic and parasitic.

In other words, in residual active foci, the greater difficulty to detect P. falciparum infections should result in the earlier eradication of P. vivax. At the beginning of 1961 on purely theoretical deductions, the earlier eradication of P. vivax was foreseen in Mauritius. Recent happenings in Mauritius seem to confirm this prediction and similar happenings are also reported from other parts of the world (America).

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