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Modern Views on the Biology of the Malaria Parasites.

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Research on the biology of the malarial parasites, begun after LAVERAN's discovery and continued for almost twenty years with exceptional fervour, seemed to have reached a conclusion with the demonstration by SCHAUDINN in 1902 of the mechanism of penetration of the sporozoites into the red blood corpuscles. After this, no one paid any particular attention to the biology of the parasites, which seemed to be perfectly clear to every one, and every effort was made instead in fighting an antimalarial campaign which seemed to be an easy matter, as a result of the discoveries made. But what seemed so simple in theory was to become a very difficult thing in practice, and large scale quininisation among malaria patients did not produce the results expected. Undoubtedly, some benefits were thereby derived, but malaria persisted, and even today it must be said that its diffusion in the world has remained more or less the same.

Two points concerning the malaria problem have as yet remained difficult to explain: the impossibility of preventing relapses and the failure of quinine as a prophylactic measure in preventing natural infection. The failure of quinine as a prophylactic agent caused much preoccupation during the first World War, in the course of which malaria claimed many victims among troops in malarial regions, especially among the troops in Macedonia, even though large use was made of quinine. JAMES, remembering the failure of therapeutic and prophylactic measures during the same war, has summarised his impression as follows:

«Every one who had actually taken part in efforts to deal with malaria in different parts of the world during the war came home with the uncomfortable feeling that we knew much less about the disease than we thought we did, and that it might be quite a good plan to sink our pride and to begin again, in all humility and with greater respect and reverence, to fathom some of its mysteries."

The failure of quinine prophylaxis during the same war gave rise to great and certainly exaggerated scepticism on the utility of prophylaxis; so much so that the English scientist and malario-

logist, WENYON, who worked among troops operating in Salonica, arrived at the conclusion that the expense and the work entailed in administering quinine for prophylaxis on a large scale was not in any way justified by the results obtained.

The use of malaria therapy in general paresis of the insane, wide-spread after the war, made it possible to define with experimental exactness what in reality was the prophylactic value of quinine. It was thus possible to establish that quinine was able in very many cases to prevent the morbose symptomatology of the disease; but in the majority of cases did not prevent the infection from establishing itself in the body.

In fact is was on the grounds of the deficiencies observed in the action of quinine as a prophylactic that JAMES was led to formulate the hypothesis that the sporozoites inoculated by the mosquitoes did not penetrate the red blood corpuscles; but like those of other *Haemosporidia* penetrated the reticulo-endothelial cells where they underwent a cycle of development from which would originate the red blood cells parasites. JAMES called attention to the fact that after SCHAUDINN no one had ever been able to observe the phenomenon of the penetration of the sporozoites in the red blood corpuscles and that every attempt made to observe it had failed.

In that year I was working on malaria in birds, and I was surprised to find that, however I increased the number of infected mosquitoes which bit animals used for experiments, the incubation period remained practically within the same limits, and after inoculation, a minimum of four days was still necessary before the first parasites appeared in the blood, whether one mosquito bit or whether four or eight bit. This should not have been, if, as we believed, the sporozoites penetrated directly into the red blood corpuscles to become transformed into intraglobular amoebae; since increasing their number or diminishing them should abbreviate or lengthen, at will, the length of the period which intervenes between the inoculation and the appearance of the parasites in the blood. In fact this may be obtained by inoculation of malarial blood; and both in man and in birds, after inoculation of blood very rich in parasites, the incubation period can be practically annulled. This difference in behaviour between inoculation with sporozoites and inoculation with blood seemed to confirm the doubts expressed by JAMES regarding the destiny of the sporozoites after their entrance into the vertebrate host.

Research on the biology of another *Haemosporidium* of birds, *Haemoproteus* (also called commonly *Halteridium*), very common in all our native birds, and very similar in many respects to the malarial parasites, seemed to furnish useful indications of what

eventually occurred in malaria infection. This parasite has an asexual cycle of evolution in birds, and a sexual cycle in the intestine of certain flies of genus *Lynchia,* in every way similar to the cycle of the malaria parasite in the mosquito. In the birds, the asexual cycle is not entirely similar to that of the malaria plasmodia, because the development and multiplication of the parasites does not occur in the red blood cells, but in the reticulo-endothelial cells. Only a part of the merozoites which derive from multiplication of schizonts penetrate into the red blood cells where they are transformed into gametocytes destined to infect flies. The sporozoites of the *Haemoproteus,* therefore, penetrate into the reticulo-endothelial cells where they develop and multiply schizogonically. In studying the biology of this parasite I was always very much surprised to find that even though the blood was frequently very rich in gametocytes it was extremely difficult, after sacrificing the animals, to find reproductive forms in the internal organs. Of five hundred birds examined I was only able to find those forms twice, nor could it be admitted that the infection in the internal organs had disappeared; for, almost always, young gametocytes could be detected in the blood stream, which demonstrated a continual production of sexual forms by the schizonts present in the internal organs.

BRUMPT (1937), in France, had in his part demonstrated the impossibility of finding phases of schizogony of the various species of *Haemoproteus* which are so commonly found in birds, even when the blood stream was full of gametocytes; but that they were present was demonstrated by the fact that, after destroying all the gametocytes present in the blood with plasmochin, after a short time they reappeared, indicating the presence of schizonts in the internal organs. The example of *Haemoproteus* demonstrated how difficult it can be to find parasites in phases of evolution in the internal organs and this fact has always encouraged me in the not easy task of research on the supposed cycle of development of the malaria parasite; a research that "a priori" did not seem destined for success seeming improbable that such a cycle had not previously been observed by any one of numerous scientists who had conducted tests on the internal organs of malaria patients. It was not the first time that the biology of *Haemoproteus* proved of use in the study and the comprehension of the malaria parasite. The significance and the function of the gametocytes in the blood stream of malaria patients was understood only after MACCALLUM (1897) was able to demonstrate, in *Haemoproteus,* the significance of the phenomenon of the exflagellation and the production of those filaments, products of the crescents, thought at first by

LAVERAN (1881) to be forms derived from multiplication of the parasites in the blood. It was possible therefore that an eventual cycle of the malaria parasites in the internal organs might have passed unobserved by the scientists in the same manner that the asexual cycle of *Haemoproteus* and *Leucocytozoon* remained unknown whereas their presence in the blood stream as gametoytes had been observed some time before the evolutional cycle in the internal organs was described.

Let it be noted that to observe the asexual cycle of *Haemoproteus* it is necessary to examine a recently infected bird, otherwise research becomes extremely difficult. It was just this peculiarity which served me as a guide in the research I endeavoured to undertake. Naturally it was not worth attempting research without first repeating the experiments with which SCHAUDINN demonstrated the mechanism of the entrance of the sporozoites into the red blood corpuscles. I repeated those experiments placing sporozoites extracted from the salivary glands of mosquitoes in contact with red blood corpuscles, using both human and avian malaria parasites, and, as had already happened to other workers, I never succeeded in observing the phenomenon notwithstanding the various types of technique used. It seemed, therefore, hardly probable that SCHAUDINN could possibly have observed it.

At the time I was conducting these experiments I was also conducting others aimed at establishing the infecting power of the blood of birds, inoculated with sporozoites, toward healthy birds, and I was able to establish the fact that after the bite of infected mosquitoes the blood of birds inoculated did not infect other birds if four days had not passed from the date of the infecting bite. The same phenomenon was observed later on by other American and German scientists. KIKUTH and MUDROW (1938) observed the same phenomenon even after intravenous inoculations of sporozoites. Similar experiments with human subjects had been attempted in America by BOYD (1934), who, inoculating 10 c.c. of blood from subjects infected by mosquitoes *(Plasmodium vivax),* did not succeed in infecting healthy subjects if 8 days had not passed from inoculation. Later (1937) these experiments with human subjects were repeated by DE SANCTIS MONALDI and myself using the method of a 250 c.c. transfusion of blood from an inoculated individual (by mosquitoes biting) to a healthy subject, and we were able to establish that the time required by the blood to become infectious was, in human subjects, nearly the same as that required by malaria of birds, that is about 4 days. Naturally such a period of time is to be considered a minimum, since in both birds and men it can be even 5 or 6 days. CIUCA (1937)

and his co-workers in Romania, with regard to *P. falciparum* infection, did not succeed in transmitting the infection with 20 c.c. of blood until six days after the infective puncture; although there is no doubt that the blood may contain parasites on the fourth day, as was established by DE SANCTIS MONALDI (1935). It can be therefore concluded that a minimum of four days is common to all parasites of human and bird malaria. This phenomenon, called the negative phase of blood, is not present in those cases of inoculation with infected blood, and the blood of patients so infected becomes infectious immediately after inoculation if this is done intravenously, after a few hours if the inoculation is subcutaneous. These facts are in themselves convincing enough to admit that a longer period of time than heretofore believed, on the basis of SCHAUDINN's experiments, is necessary between the entrance of the sporozoites into the body and the invasion by them of red blood corpuscles, during which time no parasites are to be found in the bloodstream. Evidently, they must be in the tissues where the first phase of their evolution is carried on, which phase makes them capable of penetrating the red blood corpuscles, where the ordinary schizogonic cycle begins and gives rise to the disease.

A proof of the possibility that the malaria plasmodium can have a phase of its cycle *outside* the red blood corpuscles seems to be furnished by the peculiar biology of the *P. elongatum* of birds, described by HUFF in America and found by me in Italian sparrows and put to careful study. This parasite not only develops and reproduces in all the cells of the erythrocyte series, but has also the possibility of reproducing in the reticulo-endothelial cells, so that the liver, spleen, lungs and bone-marrow show many parasites developing inside such cells. In 1934 I called attention to this fact and I deduced the possibility that the plasmodia develop in the cells of the reticulo-endothelial system. I concluded that JAMES' hypothesis was not unfounded. The biology of *P. elongatum,* however, appeared so different from that of malaria parasites in general, and above all, from that of human parasites, that it was not possible to formulate a general law. *P. elongatum* might have been, like *Haemoproteus,* a parasite only partly similar in his biology, to the malaria parasites, but not completely similar to them. This opinion was shared by HUFF and BLOOM.

But further research on a bird parasite whose biology is exactly the same as that of the human malaria parasites, *P. relictum,* enabled me to show that also this species developed and reproduced in the reticulo-endothelial cells. This fact could be observed only during the first days of the infection, if this had been car-

ried out by inoculation of sporozoites; but never after inoculation of infected blood. The parasites that developed in the r. e. cells were very scarce and therefore difficult to find in the smears of the various organs. They were to be found above all in the liver and spleen, rarely in the bone marrow of the inoculated canaries. When the infection had spread to the red blood cells, i.e., eight or nine days after inoculation, no such forms could be found any longer either in the birds which had been sacrificed or in those that, being left alone, died from the infection. It seemed evident that the forms observed in the internal organs originated from the sporozoites and that they rapidly diminished in number after the ordinary development in the red blood cells begun, so much that none could be found. It seemed probable that a similar process should take place in human malaria parasites as well.

After the publication of my findings, other workers made similar observations on *P. relictum* and on other parasites of avian malaria: KIKUTH and MUDROW on *P. cathemerium,* JAMES on *P. gallinaceum* and MANWELL and GOLDSTEIN on *P. circumflexum.* The phenomenon of reproduction of the parasite in the r. e. cells in infections by *P. cathemerium* or by *P. gallinaceum* is striking, because development continues after infection has spread to the erythrocytes. In animals dead of infection, the r. e. cells of their organs are often full of parasites.

One of the principal characteristics of the parasites developing in the r. e. cells is the absence of pigment: hence their name of non-pigmented forms. They are also called exoerythrocytic forms, or, briefly, "E" forms. Differing from the erythrocytic forms, the E-forms are quite similar in the different species of parasites. Usually they are larger than the corresponding erythrocytic forms and they give rise to a greater number of merozoites upon segmentation. The site of development can vary from species to species. All develop in the liver and spleen, but findings may be higher in one of these organs. In the bone marrow they are scarce even when they are abundant in other organs. Some species of avian plasmodia develop prolifically in the endothelium of the cerebral capillaries giving rise to very characteristic findings, for the E-forms retain their relationship with the host cells, while in the case of liver, spleen or bone marrow smears the E-forms appear generally free, the cytoplasm of the host cells being disrupted. *P. gallinaceum* and *P. cathemerium* are the two species usually found in the endothelium of brain capillaries, while *P. elongatum* and *P. relictum* are not. As we said, the E-forms give rise to a very conspicuous number of merozoites: 60, 70 and even 100; sometimes, however, segmentation only gives rise to 24 or 30 mero-

zoites, a number, therefore, more in keeping with the erythrocytic schizonts. The explanation is probably to be found in multiple infections of the same cells, so that the dimensions reached by the single schizonts are smaller and so is the number of merozoites.

The experimental demonstration that E-forms represent the initial form of development into which is transformed the sporozoite, was given by KIKUTH and MUDROW.

The development of the E-forms may or may not continue, according to the different species, after the beginning of the ordinary erythrocytic evolution has begun; and the findings of E-forms in the organs are abundant or scarce according to the greater or lesser tendency which each species possesses to develop in the r. e. cells.

Penetrating into the r. e. cells, the sporozoites are transformed into trophozoites and then into non-pigmented schizonts, from which merozoites originate. A part of these are "haemotropic" and penetrate into the red blood corpuscles to begin the ordinary cycle; another part are "histotropic" and the merozoites return into the r. e. cells to repeat the non-pigmented cycle and reproduce new E-forms. If histotropic merozoites are very numerous, E-forms will be abundant and their finding easy; but if they are scarce, for the segmentation of the E-forms has given chiefly rise to haemotropic merozoites, it will be very difficult to find non-pigmented parasites in the organs. This is the case in human malaria and in *P. relictum* infections of birds.

In man, non-pigmented parasites have been found by me in all three species of human infections, but their discovery has been extremely difficult. I only succeeded in finding a few specimens after having observed great number of fields of many smears of bone marrow obtained by sternal puncture. Other workers confirmed my findings, having succeeded to observe such forms in human malaria (TARSITANO and LUCREZI, BIANCHI, BRUG, CASINI, JERACE, PARAENSE and DA SILVA). Personally I can state that the forms were found by me for the most part in the bone marrow of paralytics inoculated with sporozoites, between the fifth and sixth day of incubation. Only in the case of *P. malariae* infection I have succeeded in observing non-pigmented forms in a patient who had been ill for a long time; he was an infant, four years old, and it may be that in children the search is less difficult. It is not unlikely that the first generations of non-pigmented parasites (i.e. those deriving directly from the sporozoites) give origin to a more conspicuous number of histotropic merozoites than the following generations. That is what certainly takes place in birds infections with *P. relictum* or with *Haemoproteus*. It is probably for this

reason that E-forms are found with less difficulty at the beginning of the infection. In man, in all probability, after the first generations, the E-forms resolve into merozoites which are for the greater part haemotropic; hence the enormous difficulty of finding E-forms. In a certain number of cases, the exoerythrocytic cycle is probably completed rapidly after infection has passed into the bloodstream. There are various reasons to believe that this happens specially in *P. falciparum* infections. Therefore I was never able to find E-forms in the organs of those dead from pernicious malaria, nor would such forms have escaped the attention of the innumerable research workers who have concentrated their attention on such pathological specimens.

One of the most interesting facts noted after the discovery of the non-pigmented forms is their resistance to anti-malarial remedies. Quinine, atebrine, and other similar acridin preparations have no action on them. Moreover, according to some authorities, while quinine destroys the parasites in the blood it favours the development of the non-pigmented forms. Plasmochin appears to exert some action on these forms, but, at least in birds, at high and therefore toxic doses. There seems to be no doubt, therefore, that the ineffectiveness of antimalarial drugs as means of true prophylaxis or of preventing relapses is due to the presence of non-pigmented forms in the patient's organism. Even if E-forms had not been found in human malaria, it would be necessary to assume their existence, if for no other reason, than by analogy with what happens in bird malaria. In so far as the development of the parasites in the blood and the associated pathological changes are concerned, bird malaria is similar to human malaria: moreover, the sexual cycle in the mosquito is exactly similar. It would then be absurd not to admit the analogy between the two infections. And if analogy was not to be used in science, much of physiology and embryology would have to be discarded! Can we doubt, for instance, that human spermatozoa penetrate into the ovum only because nobody has actually observed this phenomenon?

In human malaria there are a great many problems that can only be explained by the existence of these non-pigmented forms; and it is very fortunate that their existence could be demonstrated.

We have spoken of the inefficacy of various remedies in preventing infection or relapses. This inefficacy, however, does not exist when human infection is carried out by means of infected blood instead of sporozoites. General paresis patients who are inoculated with blood containing *P. vivax* parasites do not contract the infection if they are prophylactically treated with quinine or other remedies; and those who, after their fever paroxysms, have

been treated with quinine, have no relapses. This behaviour of the infection is quite different from that of the natural infection; the difference being due to the fact that in inoculations with blood the exoerythrocytic factor is missing, while it is present in infections produced by sporozoites. Even the latter infections do not always have recurrences; usually these occur in 50-60% of the cases. Therefore in about half the cases the exoerythrocytic stage extinguishes itself rapidly and the disease remains confined to the blood and is easily eliminated by the proper remedies.

From what we have said, it can be inferred that the non-pigmented parasites have a tendency to evolve into haemotropic forms and that, in any case, histotropic forms are few in number and difficult to find. In *P. falciparum* infections it is likely that the exoerythrocytic cycle extinguishes itself quickly, whereas in *P. malariae* infections the cycle would seem to last longer, because non-pigmented forms have been found in the bone marrow one year after the beginning of the infection. These findings, incidentally, would explain why the quartan infection is the infection that has the greatest duration of all. Naturally only further research can cast complete light on the behaviour of the exoerythrocytic stage of the human malaria parasites, but I hardly think that this will be done by simply looking for the E-forms in the bone marrow.

What is important is the fact that the presence of these forms in man has been confirmed; thus every doubt regarding the similarity between bird malaria and human malaria has been eliminated. Further progress is likely to be made when we shall know how to transmit monkey malaria through mosquitoes, that is when we shall know the vectors of malaria in monkeys. At any rate it would seem that a more complete knowledge of the biology of the malaria parasites in the vertebrate host will bring a valid contribution to the solution of the problems of chemical prophylaxis and of the not less important prevention of relapses.

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Résumé.

L'auteur expose brièvement les résultats de ses recherches tendant à découvrir l'existence de formes intermédiaires de l'hématozoaire du paludisme entre les sporozoïtes et les trophozoïtes que l'on trouve dans les globules rouges. En 1934, à la suite de ses observations sur le cycle du *Plasmodium elongatum,* il avait suggéré que les hématozoaires pourraient avoir un stade de reproduction dans les cellules du système réticulo-endothélial. Il découvrit ensuite de telles formes (non pigmentées ou exoérythrocytiques) dans les organes d'oiseaux infectés par le *P. relictum.* Plusieurs auteurs confirmèrent ses constatations et décrivirent des formes semblables dans d'autres types de paludisme aviaire. Il a été démontré que ces formes représentent le stade initial du développement du sporozoïte ; ce sont des schizontes non pigmentés qui, au moment de la schizogonie, se divisent en un grand nombre de mérozoïtes dont quelques-uns sont destinés à pénétrer dans des cellules réticulo-endothéliales, alors que, tôt ou tard, d'autres schizontes se forment et sont destinés à entrer dans les globules rouges du sang (histotropes, les premiers, hémotropes, les seconds).

L'auteur a également pu démontrer l'existence de formes exoérythrocytiques dans les trois espèces les plus importantes de paludisme humain, et ces résultats ont été confirmés par plusieurs chercheurs.

Les formes non pigmentées sont caractérisées par leur résistance aux médicaments anti-paludéens. Cela nous explique entre autre :

1° l'échec de la quinine dans la prévention de l'infection paludéenne (quand, par exemple, l'infection à *P. vivax* est transmise par l'inoculation de sporozoïtes, alors que la quinine empêche l'infection si celle-ci est transmise par le sang infecté) ;

2° l'insuccès de la thérapie dans la prévention des rechutes (qui, dans les infections à *P. vivax* ou à *P. malariae,* semble devoir être dû à la persistance de formes exoérythrocytiques).

Zusammenfassung.

Der Autor beschreibt kurz die Resultate seiner Forschungen über das Vorhandensein von Zwischenformen des Malariaplasmodiums zwischen Sporozoiten und Trophozoiten, die in den roten

Blutkörperchen gefunden werden. Auf Grund von Beobachtungen über den Cyclus von *Plasmodium elongatum* sprach er im Jahre 1934 die Vermutung aus, die Plasmodien könnten in den Reticulo-Endothelialzellen ein Teilungsstadium durchmachen. Er entdeckte in der Folge solche nicht-pigmentierte oder exoerythrocytäre Formen in den Organen von Vögeln, welche mit *Plasmodium relictum* infiziert waren. Mehrere Autoren bestätigten seine Feststellungen und beschrieben ähnliche Formen bei andern Arten von Vogelmalaria. Es wurde gezeigt, daß diese Formen ein Anfangsstadium in der Entwicklung der Sporozoiten darstellten. Es sind nicht-pigmentierte (histotrope) Schizonten, die sich im Moment der Schizogonie in eine große Zahl von Merozoiten teilen, von welchen einzelne dazu bestimmt sind, in die Reticulo-Endothelialzellen einzudringen, währenddem sich nach kürzerer oder längerer Zeit andere (haemotrope) Schizonten bilden, die die roten Blutkörperchen befallen.

Der Autor konnte ferner das Vorhandensein von exoerythrocytären Formen bei den drei wichtigsten Arten der menschlichen Malaria zeigen, und seine Resultate wurden durch mehrere Autoren bestätigt.

Die nicht-pigmentierten Formen sind gekennzeichnet durch ihre Resistenz gegenüber Malariamedikamenten. Daraus erklärt sich:

1. das Versagen von Chinin in der Malariaprophylaxe (z. B. wenn eine Infektion mit *Plasmodium vivax* durch Uebertragung von Sporozoiten zustande kommt, währenddem Chinin eine Ansteckung durch infiziertes Blut verhindert);
2. das Ausbleiben eines Erfolges in der Prophylaxe gegenüber Rückfällen (welche bei Infektionen mit *Plasmodium vivax* oder *Plasmodium malariae* scheinbar auf das Ueberleben von exoerythrocytären Formen zurückzuführen ist).