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Some Remarks on the Life Cycle of the Malaria Parasite in the Human Host.

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The discovery made by *Shortt* and his colleagues fills an important blank on our knowledge about the life cycle of the malaria parasite in the vertebrate host. This discovery gives evidence of the existence of a pre-erythrocytic developmental stage in the incubation period, which is intermediate between the entrance of the sporozoites in the host and the subsequent infection of the red blood cells.

By the work of *Shortt*, *B. Grassi*'s prediction becomes true as follows:

"In the cycle of human malaria parasites, two kinds of generations have been noticed: the first one is a monogonic generation, occurring through sporogony renewing in the human body together with the appearance of febrile access; the other is an amphigonic one, through sporogony in the Anopheles body. A third one must exist in human body in relation with the beginning of the incubation period, that is immediately after the inoculation of sporozoites."

A conception, this one, which remained unnoticed for many years, together with *Golgi*'s happy intuition of the possible existence of the malaria parasite outside their normal habitat into red cells.

But finally, having overcome the *Schaudinn* illusion in regard of the assumed direct entering of sporozoites into red blood corpuscles, *James* formulated his well-known hypothesis on the development of parasites into the reticulo-endothelial cells, and later on, *Raffaele* first recognized the presence and significance of exo-erythrocytic forms in the avian malaria. This discovery was soon followed by the confirmatory work of other observers, who extended the findings of the Italian worker up to the known species of the avian plasmodia.

The history of these researches and of the controversies, which arose about the meaning of the results obtained, is too well known to be mentioned here. We only say that the various findings of several malariologists about the presence of pre- or exo-erythrocytic forms in the human malaria have been matter of debate and not fully substantiated. But the work of *Shortt* in the monkey malaria *(P. cynomolgi)* and in the human malaria *(P. vivax)* now disperses every possible uncertainty on this point, so that the existence of exo-erythrocytic (pre-erythrocytic) stage forms can be regarded as a firm acquisition, valid for the Plasmodium species in its whole.

A question then arose: Is the existence of the exo-erythrocytic parasites confined to the incubation period? Are they definitely exhausted after the invasion of red corpuscles? The answer is given by *Shortt* and his collaborators who found late tissue stages (exo-erythrocytic schizonts) in the parenchyme cells of the liver of a monkey infected about 3½ months before and which had undergone the ordinary endo-erythrocytic infection.

Those who have followed the progress of knowledge on malaria infection know that no other question has been more discussed than the one concerning the origin of relapses. It is also known that the discovery of exo-erythrocytic

forms in the avian malaria has been welcomed as the expected revelation of such a mystery.

Through the evidence given by *Shortt*, i.e. that *P. cynomolgi* exo-erythrocytic forms, of which the resemblance to *P. vivax* is known, persist in fact in the body for months after the entrance of sporozoites in the host, the problem would appear to be very near to its final solution. Namely, nothing would seem to reject the conception that the exo-erythrocytic cycle is fully responsible for the producing of relapses.

At this point, before we express our opinion on this matter, we wish to report a fragment of a paper of *Shortt* and *Garnham* in which the development of the malaria infection with regard to the parasitic cycle is decribed:

"The inoculation of sporozoites by the infected mosquitoes is followed by a pre-erythrocytic development in the parenchyma cells of the liver, with the ultimate production of merozoites. Many of these enter the erythrocytes to produce a parasitaemia and a clinical attack of malaria. Other merozoites enter normal liver cells and repeat the process of exo-erythrocytic schizogony. This latter process repeats itself indefinitely, irrespective of whether the erythrocytic cycle is present or in its abeyance as the result of antimalarial treatment or a naturally acquired active immunity. This active immunity is operative only against the erythrocytic parasites and destroys those merozoites liberated by the exo-erythrocytic schizonts which are destined to enter red cells. Those which enter liver cells to maintain the exo-erythrocytic cycle are protected from this immunity by their intracellular position outside the circulating blood. If, for any reason, the active immunity of the host is impaired, it no longer operates against the merozoites destined to start the erythrocytic cycle and these enter the blood cells and initiate a clinical relapse."

As a whole, the above-mentioned theory, which is strongly supported by the observation of unmistakable exo-erythrocytic persistent forms, is repeating the prevailing conception agreed upon by most students of malaria during the last years, namely, the maintaining of infection, the producing of relapses, the failure of antimalarial drugs administered in the incubation period or in the intra-accessual phases; these are all phenomena strictly connected with the existence of an exo-erythrocytic cycle of the malaria parasite.

In truth, we are not inclined to entirely agree with the postulates of the afore-mentioned theory and we doubt that the exo-erythrocytic development cycle will really be the *deus ex machina* destined to solve all obscure fields, related to the study of malaria infection. We do not feel like to accept that the persistence of the infection is, as most students are brought to believe, necessarily bound to the parallel persistence of exo-erythrocytic forms.

The continuance of the infection beyond the parasitemic febrile phases and relapses have in fact a sufficient and evidential basis in the persistence of endo-erythrocytic parasites, which continue in reproducing themselves, apart from the peripheral blood, in the circulatory bed of some internal organs and, above all, in the spleen.

The value of this statement is supported by clinical experiences as well as by some experimental data.

Investigations performed in this Institute (*D'Alessandro, Oddo* and *Smiraglia*) which confirm and, under some aspects, amplify *Corradetti*'s previous experiments, demonstrate that in *P. gallinaceum* infection the acute septicemic phase is followed in most of the survivors by a period of latency extending for several months. During this period of latency the endo-erythrocytic parasites are not noticeable, or a few of them only, in smears of peripheral blood; on the other hand, the finding of exo-erythrocytic forms which is consistently positive,

especially in cerebral capillaries after a sufficiently prolonged period of parasitaemia, becomes negative, usually towards the end of the second month of the infection.

But, in the following months, when the exo-erythrocytic forms are no longer found, the infection is still active in the internal organs, first of all in the spleen and liver. The finding of some rare endo-erythrocytic parasites and of a recent microgranular pigment, which is likely locally originated in such organs, proves the continuation of the endo-erythrocytic schizogonous cycle which may be accounted for the persistence of the infection, an infection, therefore, mainly focal, but sometimes interrupted by the occasional entering of a few parasites into the circulating blood.

And what about human malaria? The studies now summarized concerning the way of perpetuating the *P. gallinaceum* infection is an experimental confirmation of one fundamental point of the new conception on the human malaria infection, supported by *Maurizio Ascoli*, whose start-point was a happy connection with the theory on the erythrocytes' reservoirs by *Barcroft* and *Binet*.

Evidences given by physiology, pathology and clinical observation have brought into light the existence of a focal phase of the malaria infection, namely the existence of morbigenous persistent *foci sui generis*, which are maintaining the infection and disease even after the decline of the febrile septicemic phase, which is characterized by an intensive development of parasites into the red cells of the circulating blood.

The focal phase has its main place in the spleen, as it is the major and most typical reservoir of red cells. In it, sheltered from the injuries of drugs and antibodies some residual endo-erythrocytic parasites which might be the starting point of new invasions of the peripheral blood are surviving and renewing.

As regards the relationship between the focal phase and the response to drugs, attention must be paid to the findings of *J. W. Jailer*. This author found that the atabrine concentration within the splenic sinusoids which are reservoirs of parasitiferous erythrocytes (*D'Alessandro, Oddo,* and *Smiraglia*) is less pronounced than in the Malpighian corpuscles.

It is now easy to explain why *Ascoli*'s conception has its logical postulate in the adrenalin splenocontractile therapy. The adrenalin treatment through the reduction of splenic *foci*, through the stimulation of the cellulo-humoral defence and other factors, makes the organism able to face and dominate the infection.

We will not be long here in considering the doctrinary and therapeutic aspects of such a conception, which is already known and has been reported by *M. Ascoli, Radvan, Benedetti,* and *Vanzetti* in their monographs on this matter. But we want to go back once more to one of the most characteristic aspects of the focal phase, as a true revealer, in a dramatic way, of the existence of endosplenic parasites that multiply without any or scanty circulating plasmodial forms.

Everyone knows how sudden malaria attacks with fever and parasitaemia may occur in individuals, after the infection has been silent for several months or years: it is usually a matter of occasional relapses as a consequence of emotions, surmenage, surgical operations, cold bath, etc. It is to be pointed out that these attacks may occur only a few hours and sometimes immediately after the provocative event. Such relapses result in an unique, seldom repeated access. A malaria attack during the latency period may be provoked also by the intravenous injection of adrenalin through spleen contractions. In our country the activation of the infection by adrenalin constitutes a current method

for diagnostic purpose (*Schiassi*). In truth, the provocation of an attack or the passage in the circulating blood of parasites after adrenalin injection is not always observed. This is largely depending upon the dosis of adrenalin and the route of administration. (We employ 1/40 mg. adrenalin given intravenously.) The way of detecting parasites in the blood is also of importance. The ultra-enrichment method of *Ascoli* and *Sorce* seems to give satisfactory results.

The above-mentioned malaria attacks are revealing the pre-existence of a parasitary charge in progress of development in the splenic reservoir which is led to reach the open field of the circulating blood under the intervention of adrenalin or one of the afore-mentioned occasional events which all cause spleen contraction (*Binet*). Without these activating factors parasites would have continued living and multiplying, hidden in splenic *foci,* in clinical silence, well balanced with the host's defences.

The permanence of parasites in the circulating blood after provocation may therefore be transient or it may be followed by a clinical attack and a parasitary multiplication, according to the power of the humoral defence which behaves with regard to the focal parasites as a filter of a various and fluctuating efficacy.

What is then the meaning of the sudden passage of parasites in the circulating blood, if not that of the existence of a preformed endo-erythrocytic parasitary charge in the spleen and, less frequently, in the extra-splenic *foci*?

Attention must be also drawn to the idea of latent malaria which, in our opinion, is not properly expressing the status of the malaria patient in the interaccessual phases, when one considers the instability of the host parasite balance and, above all, that the spleen *foci* are morbigenous themselves.

We have here the opportunity to discuss briefly another of the arguments which are usually put forth in order to support the idea that the exo-erythrocytic cycle is a *conditio sine qua non* for the maintaining of the infection, namely the behaviour of the blood induced malaria, which otherwise than the malaria induced by sporozoites, meets recoveries without relapses.

Indeed, we do not see this argument as of capital value: in fowls having been infected with parasitiferous blood, it results in a picture of chronicizing infection, sometimes relapsing and the maintaining of the infection, as *Corradetti* and we have also proved, is not always related to the existence of exo-erythrocytic forms but rather with the endo-erythrocytic schizogonous cycle.

Hawking, Perry, and *Thurston* report that "in monkeys with *P. cynomolgi* latent infection a relapse may often be provoked by the splenectomy, but this is observed just the same, both in blood and sporozoite induced infections". This clearly means that the relapse is not necessarily bound to the persistence of forms connected with *Shortt*'s pre-erythrocytic forms.

Considering all this, it seems to us that the findings of *Shortt* and *Garnham,* regarding the persistence of the pre-erythrocytic cycle beyond the incubation period in the *P. cynomolgi* infection, do not necessarily oblige us to reject another great deal of facts of clinical and experimental order that shows the maintaining of the infection going along with the uninterrupted repeating of the endo-erythrocytic cycle.

Shortt's discovery closes the chapter of the malaria parasites' development in that it closes, by means of the knowledge of the pre-erythrocytic cycle, the gap between the anophelic and the human phase of the parasite's life. After its maturation through the pre-erythrocytic cycle the parasite begins its endo-erythrocytic life which goes on without interruption, even during an apparent latency, until the extinction of the morbigenous process.

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