Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1974, **50**, 187-193

Other pathological processes in malaria*

BRIAN MAEGRAITH [1]

Research since the World War II has confirmed that, apart from the production of haemozoin from haemoglobin, most of the pathological processes in the evolution of malaria are nonspecific. A few of these nonspecific host reactions are discussed, including the production of inflammatory stasis in certain areas (including the brain) where the vascular endothelium is normally highly impermeable to heavy molecules. This production of stasis is regarded as the basic phenomenon in local obstruction to blood flow. So-called " plugging " of small vessels with " sticky " infected erythrocytes is discussed in relation to stasis and to deep intravascular schizogony. Nonspecific vasomotor effects including shock and renal and hepatic failure are also discussed. Intravascular coagulation is not regarded as a potentially important host response despite demonstrable consumption coagulopathy. The disease malaria is regarded as an example of a chain reaction of physiological–pathological responses in the host, which in the early stages are reversible.

The pathogenic processes in malaria have been extensively reviewed elsewhere (1–4), and in this paper I will refer to only a few points.

In the work we have done in Liverpool over the past 25 years we have studied malaria as such and as a model to determine the reactions of the host to infection. The simple fact has emerged that the host body can respond in only a limited number of ways, dependent on the structure and function of individual tissues and organs and on their interrelation. Superimposed on this general pattern there may be certain specific effects induced by the infecting agent. Examples are the specific effect of exotoxins, as in diphtheria, and the production of haemozoin from haemoglobin during the schizogony of the parasite in malaria and its distribution in the tissues and uptake by macrophages.

Otherwise, most of the host responses to plasmodial infection are nonspecific, although they may be modified by the multiplication of the parasite in the host erythrocyte—for example, the initial remittent fever of the first few days of overt infection with *P. vivax* followed by the periodic fever that develops as the schizogony of the parasites adjusts to regular intervals and the broods of parasites " get into step ".

Nevertheless, the plasmodium is undeniably the originating agent in malaria, even though the host reactions in the disease are similar to those of other infections. We are not yet sure how the pathological processes are initiated and how much the nonspecific effects are modified or maintained by the presence of the multiplying parasite or by its metabolic processes, which may themselves be modified by the reacting host.

I will mention only a few of the nonspecific reactions and some of the factors that initiate and maintain them.

THE CHAIN REACTION

From our studies of mammalian malaria has evolved the concept of a chain reaction of physiopathological processes that leads to the disease following the infection. In malaria the pathogenic processes must be initiated by the parasite. Unfortunately, the links between the parasite and the host have not yet been clearly determined. One link seems to be the soluble cytotoxic factor or factors capable of inhibiting mitochondrial respiration and phosphorylation described by Maegraith and his colleagues (2, 5) but this is probably only one of several agents acting at various strategic points in the host and influencing its biochemical and physiological balance. The situation may be modified further by external factors, such as the nutritional status of the host and changes in the parasite metabolism induced by its presence in the diseased host.

In the later stages of simian malaria the visceral

* Presented at the Symposium on Malaria Research, Rabat, Morocco, 1–5 April 1974.

[1] Dean, Liverpool School of Tropical Medicine, Liverpool 3, England.

sympathetic nervous system becomes hyperstimulated. This affects the dynamics of the circulation of the blood in many organs including the liver, the kidney, and the adrenal glands, with resultant metabolic deviations and upsets in endocrine balance. Pharmacologically active substances including kinins and kininogenases are set free to exert their effects on the permeability of membranes and their dynamic actions on the smaller blood vessels. Protein and water escape through the damaged endothelium. In areas where the vessels are normally highly impermeable (e.g., the brain), inflammatory stasis results, sometimes with complete obstruction to the blood flow. In this way a physiological chain reaction is set up leading to local and general disturbances that are at first reversible but, with time, become irreversible and lead to characteristic pathological patterns in the tissues and finally to the dissolution of the host. As noted above, an important point is the nonspecificity of many of these reactions.

As it develops, the chain reaction causes certain changes in function and structure of the tissues and organs that, when they become irreversible, determine the pathological patterns seen macroscopically and histologically at autopsy.

INFLAMMATORY REACTIONS IN MALARIA

Vascular membranes

In vessels that are normally relatively impermeable, inflammation may allow the escape across the endothelial membrane of large molecules, especially protein, with accompanying escape of water. The final picture is one of impedance of the circulation or " stasis " in small vessels with tightly packed erythrocytes. In vessels so affected there may also be some diapedesis of erythrocytes and escape of leucocytes into the surrounding tissue. In its early stages, stasis is reversible.

The blood vessels of an organ are specific to it and their function at a given time depends on their dynamic responses and on the permeability of the endothelium, which differs from organ to organ. For example, the vessels in the brain are permeable only to small carbohydrate molecules; those in the liver are permeable to practically everything that circulates in the plasma. Agents that increase the permeability of the endothelial membrane thus have more pronounced effects in the brain than in the liver.

In the brains of patients dead from so-called " cerebral malaria " (falciparum) the usual picture described is one of small blood vessels apparently " plugged " with parasitized erythrocytes in which the parasites were usually in the late stages of schizogony. For many years it was considered that such " plugging " of the vascular lumen arose from the parasitized erythrocytes " sticking " to themselves and to the endothelial lining and interrupting the blood flow.

It has now been demonstrated that in *Plasmodium knowlesi* and *P. berghei* infections the obstruction of cerebral circulation occurs before the " packing " with parasitized erythrocytes takes place and the picture seen at autopsy is primarily *post hoc* rather than *propter hoc*. The processes involved in slowing the circulation are primarily dependent not on the parasitized erythrocytes but on the presence of pharmacologically active substances that lead to inflammatory stasis.

The failure of the circulation in the brain in malaria thus arises from endothelial dysfunction.

The parasitization of the erythrocytes constituting the " plug " in the cerebral vessel is a late development following rather than causing the obstruction. The parasites are nearly always in the same late stage of schizogony. Where haemorrhages have occurred near the vessels apparently " plugged " by erythrocytes containing schizonts, the erythrocytes in the tissues around the damaged vessels are not heavily parasitized and those that are contain parasites in any phase of development.

Recent work in Liverpool on *P. knowlesi* and *P. berghei* infections has shown that excessive movement of both protein and water occurs across the endothelium of the brain vessels and of the blood brain barrier as a whole (3, 6). The net movement of iodine-tagged albumin from the blood to the cerebrospinal fluid (CSF) is greatly increased, indicating a change in the permeability of the membranes. The movement from the CSF to the blood is also increased. The relatively small increase in protein in the CSF noted in malaria by many authors thus arises from the fact that the protein moves freely both out into the CSF and back into the blood.

In *P. knowlesi* infection in *Macaca mulatta* the excessive escape of protein across the brain membranes can be rapidly inhibited by chloroquine, mepacrine, and cortisone, all of which are powerful anti-inflammatory drugs (3, 6, 7).

The speedy clinical recovery from coma following the administration of antimalarial drugs indicates that the clinical response to the drugs is much quicker than could be accounted for by antiparasitic

activity and can be explained only on an anti-inflammatory basis. The action of anti-inflammatory drugs has recently been tested in the field by Tranakchit Harinasuta in cases of chloroquine-resistant falciparum malaria treated by sulfonamides, which have a rapid effect on the parasites but promote a slow clinical response (3). When anti-inflammatory drugs are given contemporaneously with the sulfonamides, the clinical response becomes as rapid as and sometimes more rapid than the response of the parasites. This applies to chloroquine itself, even when the relevant parasites are resistant to it!

Peptides

Tella & Maegraith (8, 9) demonstrated that on the fourth to fifth day of infection with *P. knowlesi* in *M. mulatta* there was a dramatic fall in the kininogen and kallidinogen content of the serum. From this period until death the level remained extremely low. There was a concurrent increase in the blood kinin level and in the output of kinins in the urine (10, 8), which Goodwin & Richards in 1960 (11) had reported in rats infected with *P. berghei*. There was also a considerable increase in circulating kininases. Thus the kininogens are rapidly broken down to kinins and these in turn are converted into inactive peptides. This indicates a quick turnover of active peptides in the blood. Unfortunately, at present it is not possible to say what is happening at the tissue face where the changes in endothelial permeability are occurring.

It is interesting to speculate on whether the kinin produced from the kininogen by the kininogenase remains long enough in the peripheral circulation to exert its pharmacological effects before being destroyed by the kininases. It is possible that kinin may be active in such circumstances even though its half-life may be very short. This introduces a concept of very fast intermediate pharmacological reactions, perhaps series of reactions, which is helpful in trying to translate the more static situation in the serum (the only one we can at present measure) into what is happening at the tissue face.

The kininogenases are also considerably increased in the late stages. They are as pharmacologically active as the kinins (even in the presence of kininogenase inhibitors) in increasing endothelial permeability and, in certain circumstances, causing vasodilation or vasoconstriction. Kallikrein obtained from blood protein fractions in infected animals on injection into normal animals also causes leakage of protein and water from capillaries similar to that demonstrated in *P. knowlesi* and *P. berghei* infections (3, 12).

It would appear therefore that both kinin and kallikrein act as nonspecific inflammatory agents in *P. knowlesi* malaria, causing endothelial membranes that are normally impermeable (e.g., in the brain) to become permeable.

The kinin complex is probably only one of many systems operating. Desowitz & Pavanand (13) described an uncategorized " permeability factor " in the serum of gibbons infected with *P. coatneyi*. This may be related to the peptides under discussion but clearly, from the method of extraction, could not have been kinin. Other substances concerned with membrane permeability include histamine, which is also a powerful vasodilator and which is sometimes liberated by antigen antibody reactions. An increase in histamine concentration occurs in the blood of *M. mulatta* in the late stages of *P. knowlesi* infection. Nothing is known about histaminase activity in the infection. Adenosine, which has strong vasomotor activity, has been demonstrated in blood returning from ischaemic tissue; it is also increased in late *P. knowlesi* infection (3, 14).

Vasomotor effects

The vasomotor reactions that occur in acute malaria also have been shown to resemble those of general inflammation. Medical shock is a common end point in acute *P. falciparum* infection in the non-immune subject (1–3). The shock is nonspecific and similar to the shock that may occur in many other acute infections and physiological states.

I have pointed out (15, 1) that one of the factors involved in producing hepatic lesions in acute falciparum malaria and blackwater fever is local circulatory failure associated with centrilobular cellular damage similar to that occurring in other conditions, especially where shock is involved (16). Both the circulatory changes and the cellular damage can be produced artificially in the perfused liver (17).

The hepatic circulation in *P. knowlesi* infection in *M. mulatta* has recently been examined by X-ray angiography. In the severe stages of this infection, obstruction to intrahepatic flow can be demonstrated, accompanied by intense constriction of the small branches of the portal veins. This constriction can be relieved by 1,1′-oxybisbenzene (" phenoxybenzene ") and other blocking agents. Similar vascular changes develop in shock following manipulation of the gut and can also be controlled by blocking agents (2, 3, 18).

Critical reduction of cortical or total renal blood flow with consequent failure of secretion of urine across the glomeruli and resorption in the tubules was first suggested as a cause of renal failure in blackwater fever patients in West Africa (15, 19). Constriction of these vessels has been demonstrated in the later stages of *P. knowlesi* infection in *M. mulatta* by means of the angiography technique. This can also be overcome by blocking agents. In *P. knowlesi* infection therefore the pattern of acute renal dysfunction follows reduced renal circulation. This is a phenomenon common to many other medical states, and is nonspecific (20); it may respond to haemodialysis or peritoneal dialysis (3).

Vasoconstriction of the intestinal arterioles has recently also been demonstrated in experiments on intestinal absorption of amino acids and xylose in simian and human malaria (3).

The general picture of the visceral circulatory changes and shock fits in well with the concept of hyperexcitation of the sympathetic nervous system suggested by Skirrow et al. (18) in *P. knowlesi* malaria.

Ray & Sharma (21) also indicated the significance of sympathetic stimulation as a factor in the production of hepatic centrilobular lesions in *P. knowlesi* infection in *M. mulatta* by performing thoracic sympathectomy before infecting the monkeys. The centrilobular lesions that constantly appeared in normal monkeys after infection were absent in the sympathectomized animals.

" *Stickiness* " *and deep schizogony*

The pattern of cerebral vessels " plugged " with erythrocytes bearing late-stage parasites that is commonly reported in falciparum malaria is usually a feature of parasite species in which there is deep intravascular schizogony. Studies of the latter phenomenon in *P. coatneyi* and *P. falciparum* in man and *Aotus* monkeys have demonstrated a regional distribution of plugged vessels, which are usually found in organs in which the vascular endothelium is normally relatively impermeable but is not uniformly distributed anatomically (e.g., the heart, the brain, and the adipose tissue).

In *P. coatneyi* infection and in *P. falciparum* infection in man and in *Aotus* monkeys the " plugging " in some organs occurs not only in the terminal stages but also locally in various visceral organs during deep schizogony.

In these infections thickenings and irregularities have been described in or immediately below the membranes of the erythrocytes containing late-stage parasites and it has been argued that these are probably responsible for " stickiness ", which causes the parasitized cells to become temporarily attached to the endothelium of the small vessels. This idea is not altogether in keeping with the fact that in *P. knowlesi* infection, in which final schizogony occurs in the deep tissues, late stages of parasites are commonly seen in the peripheral blood in the final development of the disease and the electron microscope does not reveal any unusual changes in the surface of the erythrocytes containing schizonts, although these cells also appear to be " sticky " and adhere to the endothelium of the blood vessels (22–25).

To this mechanical concept of " plugging " Miller and colleagues (26) have recently added a " rheological " hypothesis. They have suggested that the " plugging " of small vessels arises because the infected cells are nonmalleable and their changes in shape lead to shear resistance to the flow. I find this hypothesis (which is based on *in vitro* experiment in fixed-bore channels) difficult to accept as being of major significance. It would be interesting to test the theory in other plasmodial infections, in particular in *P. vivax* malaria in which there is neither deep intravascular schizogony nor " plugging " of small vessels (i.e. no " stickiness "), although the parasitized cells are considerably enlarged and contain much larger and sturdier parasites than *P. falciparum*.

It is possible that membrane changes in the infected erythrocytes and the inflexibility of shape of the erythrocyte containing the late stages of the parasite may ultimately play some part in diminishing the flow through the small vessels but only after the flow has already slowed.

The movement of solid erythrocytes through a small vessel, often with a resting bore smaller in diameter than the cell itself, must ultimately depend on four factors—the head of the flow, the dynamic state of the vessel (which is capable of constriction and dilatation), the mechanical resistance offered by the passing cell, and the state of the endothelium along which it is passing.

The fixation of attention on the changed erythrocyte as described above ignores the other factors. In Liverpool we have tried to keep this in mind and have examined changes in the total circulation, in the dynamic state of the vessels, in their lining endothelium. We have demonstrated, on balance, that most significant changes in malaria occur in the latter, and

the response, in terms of what happens to the infected cell within the small vessel, varies in different anatomical areas depending on the original degree of impermeability of the local vascular membranes and the damage and increase in permeability induced in them during the infection.

The local changes in blood flow are part of a general picture, shared by many infections other than plasmodial ones and by physiological situations such as shock.

Intravascular coagulation

The situation is still not clear, since it is difficult to determine whether the fibrin that is occasionally present in lesions, as in the brain in *P. falciparum* infections, has been developed as a primary reaction or is secondary to inflammatory stasis.

If intravascular coagulation were a factor of major importance in the pathogenesis of the tissue lesions in malaria, evidence of clotting should be regularly visible. Instant microclotting countered by instant fibrinolysis, which has been suggested as a pathogenic factor in shock (27) is difficult to credit in the circumstances and could hardly be involved in obstruction to circulating blood in the small vessels. It seems that intravascular coagulation is probably not a major pathogenic process in malaria and that the occasional clot observed is secondary and results from a failing circulation and does not cause it. Some authors have demonstrated a few fibrin strands and occasional clotting in cerebral malaria but extensive intravascular clotting, such as would be needed to promote impedance of circulation, has not been demonstrated at autopsy in falciparum malaria or in mammalian malaria in the laboratory (28).

Devakul et al. (29) injected fibrinogen labelled with radioactive iodine intravenously into Thai patients infected with local chloroquine-resistant *P. falciparum*. In two severely ill patients with high parasitaemia, but not in three moderately ill patients with high parasite counts, the fibrinogen was rapidly removed from the circulation. It was suggested that the rapid loss of fibrinogen in the severely ill patients might indicate widely disseminated intravascular coagulation but, unfortunately, in these experiments fibrinogen degradation products were not measured.

Dennis and others (30, 31) claimed that heparin was of some value in the treatment of complicated falciparum malaria and demonstrated coagulation defects in *P. knowlesi* infection in *M. mulatta* and in *P. falciparum* infection in man in South Viet-Nam. The conclusion drawn was that some degree of consumption coagulopathy existed in these infections.

Jaroonvesama (32) recently studied coagulation in *P. berghei* infection in mice and found a small increase in fibrinogen breakdown products and a slight increase in plasminogen, indicating that fibrinolysis was active and intrinsic and probably secondary to whatever coagulation there was. The small increase in fibrinogen degradation products indicated that clotting had occurred in the past, not necessarily that it was current. There was a normal range of fibrinogen values in infected animals, suggesting continuing synthesis despite increased use—that is, a greater turnover. This increased turnover associated with a shortened half-life of tagged fibrinogen has also been noted in *P. coatneyi* and *P. knowlesi* infections by Areekul et al. (33) and Pramualmal & Reid (34). On the whole, the picture observed by Jaroonvesama was one of low grade consumption coagulopathy, which in fact represented a current relative inability of the circulating blood to clot.

Knisely's " sludge " (1, 3) is a late phenomenon. It has been suggested that the erythrocytes in the " sludge " mass are cemented together by strands of fibrin. If this is the case, it might account for some of the increase in fibrinogen degradation products found in the late stages of human, simian, and rodent malaria.

Reid & Sucharit (35) in 1972 further examined the importance of intravascular coagulation in simian malaria by treating infected animals with heparin, the antifibrinolytic drug EACA,[a] and the defibrinating drug ancrod.[b] None of these drugs materially affected the process of the parasitaemia or of the clinical features. The authors consider that these findings virtually exclude an important pathophysiological role for fibrin, as such, in simian malaria.

It is nevertheless possible that regional intravascular coagulation may be important occasionally and that the measurement of fibrinogen degradation products could give a lead to the situation in a given patient in terms of whether the use of a fibrinolytic drug such as streptokinase might be rational.

The significance of intravascular coagulation in malaria is open to further discussion. The pathways of the clotting mechanism may be changed in malaria

[a] Acronym for " epsilon amino-caproic acid "—i.e., 6-aminohexanoic acid.

[b] Arvin, derived from *Agkistrodon rhodostoma* venom (Twyford Ltd).

so that the demonstrated increase in fibrinogen degradation products may represent a breakdown of the protein along some pathway not directly connected with coagulation. The possibility is pharmacologically interesting in view of the close similarity of the peptide: peptidase reactions occurring in the kinin complex and the peptidase reactions involved in coagulation.

RÉSUMÉ

AUTRES PROCESSUS PATHOLOGIQUES DANS LE PALUDISME

Les processus pathologiques, au cours du paludisme, sont pour la plupart non spécifiques et analogues à ceux observés chez l'hôte en réponse à un grand nombre d'autres infections et agressions. Le présent article expose brièvement la succession des réactions physiopathologiques provoquées par l'infection paludéenne.

Les réactions de nature inflammatoire modifient la perméabilité et les propriétés vasomotrices des vaisseaux localement et dans tout l'organisme et ont des répercussions sur la circulation. Des substances du groupe des kinines interviennent pour déclencher et entretenir ces réactions qui peuvent entraîner la perte d'eau et de protéines à travers la paroi endommagée de vaisseaux normalement imperméables et la stase circulatoire. Ce phénomène est à l'origine de l'obstruction des vaisseaux cérébraux par les érythrocytes parasités dans le paludisme à *Plasmodium falciparum*. L'«adhérence» de ces érythrocytes ne semble jouer qu'un rôle mineur dans le processus d'obstruction au cours de la schizogonie profonde. Une autre hypothèse attribue l'obstruction des vaisseaux à l'augmentation de volume et au manque de malléabilité des érythrocytes parasités. Quant à la coagulation intravasculaire, elle ne représente pas, apparemment, un facteur physiopathologique important au cours de l'évolution du paludisme.

Les réactions vasomotrices au niveau du foie et des reins sont examinées en relation avec le dysfonctionnement et la défaillance de ces organes, en particulier dans le paludisme humain à *P. falciparum*.

Il importe de reconnaître le caractère non spécifique de certaines réactions de l'hôte dans l'infection paludéenne, susceptibles de régresser sous l'effet du traitement durant les premiers stades de la maladie, afin de pouvoir évaluer l'efficacité antiinflammatoire des médicaments antipaludiques indépendamment de leur activité purement antiparasitaire.

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DISCUSSION

COHEN: I question the evidence for the existence of so-called antitoxic immunity in malaria.

MCGREGOR: I think it originally referred to the ability of young children in hyperendemic areas to carry relatively dense parasitaemias with few clinical signs or symptoms. Evidence of antitoxic immunity has also been shown in mice, in which, despite considerable blood destruction, toxicity is minimal.

BRAY: Max Miller, working in Liberia, has shown that the threshold parasitaemias for symptoms are approximately 12 000 per mm^3 for children and 2 500 per mm^3 for adults with *P. falciparum* and 1 200 per mm^3 with *P. malariae*.

VAN DER KAAY: If we accept the hypothesis that intracapillary plugging occurs secondarily to increased permeability of the endothelial lining of the small capillaries, then treatment of cerebral malaria should include, in addition to intravenous quinine and corticosteroids, 4-aminoquinolines, which are powerful anti-inflammatory drugs.