

PATHOPHYSIOLOGY OF MALARIA

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INTRODUCTION

The pathophysiology of malaria is complex with pathologic changes occurring in almost all systems of the body. The mechanisms involved include: (i) direct cell damage. (ii) nonspecific inflammatory processes; (iii) immunological responses.

This paper is a review of the changes in various systems occurring during acute infection of malaria with an attempt to identify the mechanisms of those changes.

Direct cell damage

The only definite evidence of direct host cell damage by malaria parasite is the intravascular rupture of erythrocytes infected with mature schizonts.

The phagocytosis of malaria infected erythrocytes is not just an increase in the usual nonspecific activity of macrophages but is due to highly specific opsonization process. (Taliaferro and Mulligan, 1937; Coggeshall, 1937; Brown *et al.*, 1970).

Spur shape distortion and multiple knob protrusion were observed on the membrane of erythrocytes infected with *P. falciparum* and it is proposed that these changes are associated with the obstruction of cerebral capillaries and adhesion to venous endothelium. (Luse and Miller, 1971; Miller, 1972). The mechanism involved is not yet clear.

Miller *et al.*, (1972) reported that erythrocytes infected with *P. coatneyi* become less deformable with increased viscosity and were prevented from rouleaux in plasma

suspension. They proposed that red cells infected by *P. falciparum in man also have* decreased deformability accounting for cerebral capillary trapping of parasitized erythrocytes. The concept that rigidity of parasitized erythrocytes might be due to ATP depletion could not be verified in the studies in *P. berghei* and *P. falciparum* malaria (Areekul, 1974; 1975).

Brown (1933) demonstrated a reduction in electrical charge on the surface of both parasitized and non parasitized erythrocytes in bird malaria and Conrad (1969) postulated that hemolysis of infected erythrocytes is caused by loss of negative charge from the surface of erythrocytes because the parasite usurps essential metabolic formation of the infected erythrocytes.

Nonspecific inflammatory processes

Maegraith (1974, 1977) suggested that malaria is produced by a chain reaction of nonspecific inflammatory processes initiated by the parasites. One of the links between the parasites and the host seems to be the soluble cytotoxic factor or factors capable of inhibiting mitochondrial phosphorylation. In the latter stages, pharmacologically active substances including kallikrein, kinin and histamine are set free to exert their effects on small blood vessels. The sympathetic nervous system becomes hyperstimulated affecting the circulation of blood in many organs including liver, kidneys and the intestines. Blood coagulation and complement systems are activated. A physiological chain reaction is thus set up leading to local and general disturbances that are at first reversible

and with time, become irreversible.

Increased vascular permeability occurs in acute primate malaria (Maegraith, 1948, Migasena and Maegraith 1965; Desowitz and Pavanand, 1967) and this is attributed partly to the increase in kallikrein, kinin and histamine in the circulation (Onabanjo and Maegraith, 1970, 1971; Maegraith and Onabanjo, 1970; Srichaikul *et al.*, 1976).

Information regarding blood volume changes in malaria appears to be contradictory. Feldman and Murphy (1944) reported a 50 percent reduction in total blood volume in a case of induced *P. falciparum* malaria. Monkeys with severe infections of *P. coatneyi* developed hypovolaemia and hypotension and this was attributed to increased vascular permeability (Miller *et al.*, 1968). Sitprija (1967, 1971) reported that in falciparum malaria patients with renal failure, the blood volume was found to be within normal limits. On the other hand Malloy *et al.*, (1967) reported an expanded blood volume due to a marked increase in plasma volume in acute *P. falciparum* malaria.

It has recently been found that this discrepancy is due to the difference in stages of blood volume determination. In induced *P. falciparum* malaria, there was initially hypovolaemia, followed by hypervolaemia and normovolaemia (Chongsuphajaisiddhi *et al.*, 1971). Sitprija *et al.*, (1977) also found that the blood volume in selected *P. falciparum* malaria patients who had not previously received intravenous fluid, was decreased on admission, then rose following hydration on the 3rd day and finally returned to normal on the 7th-9th day. The hypovolaemia is attributed to increased sensible loss and sweating from pyrexia, decreased fluid intake and increased vascular permeability.

It has been shown that during acute malaria the autonomic nervous system became hyperactive, leading to vasoconstriction and sometimes vasodilatation in various organs.

By portal angiography, constriction of portal venous tree of *P. knowlesi* infected monkeys has been shown. The constriction could be relieved immediately by the administration of phenoxybenzamine, an alpha adrenergic blocking agent (Skirrow *et al.*, 1964).

By heated-thermocouple technique, it has been found that there was a reduction in liver blood flow in the animals with slight anaemia in "early shock" and "prolonged shock" infections. In very anaemic animals of "lytic infection", the liver blood flow was increased despite the portal vasoconstriction. However by portal angiography the livers in the latter cases were poorly perfused due to the opening of the vascular shunts. (Chongsuphajaisiddhi, 1966).

Acute renal failure is a severe manifestation of *P. falciparum* malaria. Maegraith (1948) proposed that the phenomenon is caused by the development of cortical ischemia and reduction in glomerular blood flow, and consequently in glomerular filtration.

It was later demonstrated by renal angiography that there was also constriction of the renal arteries and arterioles, especially in the cortical area, during the last 48 hours of *P. knowlesi* infection. The vasoconstriction within the kidney could be relieved by phenoxybenzamine (Chongsuphajaisiddhi, 1966).

These findings were later confirmed in *P. falciparum* malaria by renal function studies (Sitprija *et al.*, 1967; 1971), selective renal angiography (Arthachinta *et al.*, 1974) and by radio active Xenon (Sitprija, *et al.*, 1977).

The absorption of ¹⁴C-tagged amino butyric acid and D-xylose was greatly reduced in *P. knowlesi* infection and phenoxybenzamine restored the absorption curve toward normal (Migasena and Maegraith, 1969; 1970a, b).

In *P. falciparum* malaria, it was found that absorption of D-xylose and Vitamin B₁₂ was decreased. There were low serum carotene levels in the acute phase; which returned toward normal during the convalescent period (Karney and Tong, 1972). These changes were attributed to reduced blood flow to the intestinal mucosa due to vasoconstriction.

Increase in blood viscosity was observed in the acute phase of *P. falciparum* malaria (Reid and Nkrumah, 1972; Srichaikul *et al.*, 1975; Sitprija *et al.*, 1977). Maegraith (1948) considered it to be due to fluid loss through functionally damaged capillaries. This was later attributed to the increase in plasma fibrinogen (Sitprija *et al.*, 1977). Increased blood viscosity has also been associated with decreased deformability of parasitized red blood cell in experimental malaria (Miller *et al.*, 1972).

Devakul *et al.*, (1966) found that in severely ill *P. falciparum* malaria patients fibrinogen was removed rapidly from the circulation. They suggested that this finding might indicate widely disseminated intravascular coagulation. Dennis *et al.*, (1967) found a decrease in several coagulation factors and decreased plasminogen activation with an accumulation of fibrin degradation products (FDP) in *P. falciparum* malaria and suggested that heparin might be of some value in treatment. The increase in FDP, the degree of thrombocytopenia and the changes in coagulation factors were related with the severity of the disease (Reid and Nkrumah, 1972; Jaroonvesama, 1972; Sucharit *et al.*, 1975; Jaroonvesama *et al.*, 1975). Heparin has been suggested be included in the treatment of severe *P. falciparum* malaria (Smithkamp and Wolthuis, 1971; Punyagupta *et al.*, 1974). However, thrombocytopenia in uncomplicated *P. falciparum* malaria may be the result of splenic pooling of platelets (Skudowitz *et al.*, 1973).

Intravascular coagulation is considered to be a secondary phenomenon resulting from slow flow in the microcirculation rather than the cause of pathogenic processes in *P. falciparum* malaria (Jaroonvesama *et al.*, 1975; Sitprija *et al.*, 1977).

Serum from *P. knowlesi* and *P. berghei* infected animals has been shown to contain factors capable of inhibiting mitochondrial respiration (Thurnham *et al.*, 1971 a, b, c). The factors could be resolved into several components by ultrafiltration and had been found to be small molecules with molecular weight less than 1000.

Immunological responses

Evidence of complement activation has been shown in *P. falciparum* malaria in children (Greenwood and Brueton, 1974) and adults (Srichaikul *et al.*, 1975). Both classical and alternate pathways of complement activation were involved (Petchlai *et al.*, 1977). It has been suggested that complement activation as a result of the formation of immune complexes may play a part in activation the complicated series of changes leading to certain serious clinical complications (Greenwood and Brueton, 1975; Srichaikul *et al.*, 1976).

It is generally accepted that in malaria both parasitized and non-parasitized erythrocytes are destroyed (Maegraith, 1948). It has been shown that the destruction of erythrocytes in monkeys infected with either *P. coatneyi* or *P. knowlesi* occurred mainly extravascularly, in the reticulo-endothelial system (Areekul *et al.*, 1972a,b).

Zuckerman (1964) suggested that an autoimmune hemolysis or opsonization of non-infected erythrocytes occurs in malaria. However it is difficult to demonstrate the presence of anti-erythrocyte antibodies in the plasma of malaria infected people (Voller, 1974). Rosenberg *et al.*, (1973) pointed out that Coomb's test was rarely positive in

malaria because Coomb's antibody was detecting IgG and not IgM. They have shown that IgM class anti-erythrocyte antibodies occurs in *P. falciparum* malaria and can be detected by immunofluorescence technique.

Recently, Woodruff *et al.*, (1979) showed after complete eradication of malaria parasites that erythrocyte life-span is reduced by 4-5 weeks and that the reduction is associated with the presence of complement containing immune complexes on the erythrocyte surface.

Osmotic fragility of both parasitized and non parasitized erythrocytes is increased, possibly as a result of sensitization of erythrocytes with antibody (Fogel *et al.*, 1966).

Hemolysis of non parasitized erythrocyte in *P. falciparum* malaria was observed to be associated with alteration of erythrocyte solutes, an increase in red blood cell sodium and decrease in potassium (Varavithya and Chongsuphajaisiddhi, 1972). The mechanism of such change is not known yet.

Spleen

During malaria infection, splenomegaly develops rapidly and the spleen volume regress rapidly during latency as immunity develops (Voller, 1974). Stimulation with *Plasmodium* leads to splenomegaly, which is largely associated with lymphoidmacrophage hyperplasia (Brown, 1969). Both parasitized and nonparasitized red blood cells are phagocytosed in the spleen (Maegraith, 1948).

The Tropical Splenomegaly Syndrome (TSS) is a disease associated with chronic malaria. It has been reported from areas of East and West Africa, India and New Guinea (Pitney, 1968). It is characterized by extensive chronic splenomegaly with intense lymphoreticular proliferation in the spleen and liver sinusoids and high serum levels of IgM

malarial antibodies anemia and reduced survival times of circulating erythrocytes (Zuckerman, 1977).

Ziegler *et al.*, (1973) suggested that a congenital predisposition of certain individuals to the overproduction of IgM on repeated exposure to malaria antigen may be involved in TSS.

Kidney

Hendrickse and Gilles (1963) suggested that nephrotic syndrome associated with *P. malariae* infection might be due to glomerular damage caused by deposition of circulating immune complexes. This hypothesis was later supported by a series of other studies (Dixon, 1966; Ward and Conran, 1969; Allison *et al.*, 1969; Houba *et al.*, 1971; Hendrickse, *et al.*, 1972).

Berger *et al.*, (1967), reported 3 cases of nephrotic syndrome secondary to acute glomerulonephritis during *P. falciparum* malaria and Hartenbower *et al.*, (1972) reported renal failure due to acute glomerulonephritis in a case of *P. falciparum* malaria.

Bhamarapravati *et al.*, (1973) studied kidney tissue of ten cases of *P. falciparum* malaria with varying degrees of urinary abnormalities, including the presence of albumin or red blood cells. Immunoglobulins and complement were localized in the basement membrane and in the mesangium. Malarial antigen was also detected. It was concluded that immune complex nephritis may occur in acute *P. falciparum* malaria and the immune complex is cleared from the glomeruli relatively fast and the injury is thus reversible in falciparum malaria.

Futrakul *et al.*, (1974) reported acute glomerulonephritis, manifested by transient hypertension, microscopic hematuria and slight proteinuria complicating *P. falciparum* malaria in a 3½-year-old boy. Renal biopsy

showed entanglement of renal glomeruli with proliferation of the mesangial areas and endothelial proliferation in some glomerular capillary tufts.

Brain

Wright (1968) described cerebral malaria in golden hamsters infected with *P. berghei*. These animals became comatose and died at a time when the parasitaemia was low and before severe anaemia developed. The cerebral lesions seen in these animals resembled the ring haemorrhages found in humans who died of cerebral malaria. Acute deaths could be prevented in hamsters by neonatal thymectomy (Wright, 1968), or the administration of antithymocyte serum (Wright *et al.*, 1971). Using electron microscopy, Rest and Wright (1979) showed that in hamster cerebral malaria, hemorrhages occurred following vessel necrosis, without concurrent thrombosis nor packing of capillaries with parasitized erythrocytes. Small vessels contained numerous monocytes which had phagocytosed erythrocytes. Irregular dense deposits were present in the basement membrane of some animals 14 days after infection. They proposed a hypothesis that the pathogenesis of cerebral lesion in hamsters infected with *P. berghei* and probably of cerebral malaria in man relates to immune complex formation.

Based on the examination of the clinical and pathological features of 19 fatal cases of cerebral malaria in Colombia and from the review of the available epidemiologic and experimental evidence, Toro and Roman (1978) consider cerebral malaria as a form of disseminated vasculomyelinopathy. This term, proposed by Poser in 1969, includes the different clinical and pathologic forms of hyperallergic reaction of the nervous system to various infections and vaccinations and to other exogenous or endogenous antigenic stimuli. The sequence of events following these neuroallergic reactions are damage of

the vascular endothelium with subsequent ischemia, perivascular edema, inflammation, perivascular hemorrhage, and myelinoclasia with reactive gliosis.

Lungs

Acute pulmonary edema in malaria usually occurs in the later stage of severe infection. In certain cases, evidence suggested that the condition was primarily in the lung not secondary to heart failure (Brooks *et al.*, 1968; Deaton, 1970; Punyagupta *et al.*, 1974; Marks *et al.*, 1977; Leelarasamee *et al.*, 1978). In these cases immune complex formation might be one important factor in the pathogenesis of the condition.

SUMMARY

The pathophysiology of malaria infection is presented from animal studies and the various manifestations occurring in human cases.

Maegraith (1974) proposed the concept of a chain reaction of physiological processes that leads to the disease following malarial infection.

It may be seen that the malaria parasites first damage the infected red blood cells directly and then initiate a chain reaction of nonspecific inflammatory processes and later on immunological responses aggravating further the inflammatory reactions. Because of the interdependence in nature of these changes as suggested by Maegraith in 1977 it is usually difficult to clearly identify these three mechanisms.

REFERENCES

- ALLISON, A.C., HENDRICKSE, R.G. EDINGTON, G.M., HOUBA, V., DE PETRIS, S. and ADENIYI, A., (1969). Immune complexes in the nephrotic syndrome of African children. *Lancet*, 1:1232.

- AREEKUL, S., RANAKAKORN, K. and KASEMSUTH, R., (1972 a). Studies on intravascular hemolysis in monkey infected with *Plasmodium coatneyi*. *J. Med. Ass. Thailand*, 55 :87.
- AREEKUL, S., KASEMSUTH, R., BOONYANANTA, C. and CHUNTACHUM, Y., (1972 b). Haemolysis in monkeys infected with *Plasmodium knowlesi* malaria. *Southeast Asian J. Trop. Med. Pub. Hlth.*, 3:182.
- AREEKUL, S., THAIJONGRAK, K., KASEMSUTH, R. and MATRAKUL, D., (1974). Erythrocyte ATP levels in mice infected with *Plasmodium berghei* malaria. *Southeast Asian J. Trop. Med. Pub. Hlth.*, 5:492.
- AREEKUL, S., CHAROENLARP, P., MATRAKUL, D., SOOKPRASERT, A. and UKOSKIT, K. (1975). Studies on ATP levels in erythrocytes of patients with *Plasmodium falciparum* malaria. *J. Med. Ass. Thailand*, 58:397.
- ARTHACHINTA, S., SITPRIJA, V. and KASHEMSANT, U., (1974). Selective renal angiography in renal failure due to infection. *Aust. Radiol.*, 18 :446.
- BERGER, M., BIRCH, L.M. and CONTE, N.F., (1967). The nephrotic syndrome secondary to acute glomerulonephritis during falciparum malaria. *Ann. Intern. Med.*, 67:1163.
- BHAMARAPRAVATI, N., BOONPUCKNAVIG, S., BOONPUCKNAVIG, V. and YAEMBOONRUANG, C. (1973). Glomerular changes in acute *Plasmodium falciparum* infection. An immunopathologic study. *Arch. Path.*, 96:289.
- BROOKS, M.H., SHEEHY, T.W., KIEL, F.W. and BARRY, K.G., (1968). Acute pulmonary edema in falciparum malaria; A clinico-pathological correlation. *New Eng. J. Med.*, 279:732.
- BROWN, H.C., (1933). Preliminary observation on electric charge of the erythrocytes in bird malaria. *Trans. Roy. Soc. Trop. Med. Hyg.*, 26:515.
- BROWN, I.N., (1969). Immunological aspects of malaria infection. *Advances in Immunology II*, p. 267.
- BROWN, K.N., BROWN, I.N., TRIGG, P.I., PHILLIPS, R.S. and HILLS, L.A., (1970). Immunity to malaria II Serological response of monkeys sensitized by drug-suppressed infection or by dead parasitized cell in Freund's complete adjuvant. *Exp. Parasit.*, 28:318.
- CHONGSUPHAJAISIDDHI, T., (1966). Circulatory changes in *Plasmodium knowlesi* malaria. Ph. D. Thesis, Univ. Liverpool.
- CHONGSUPHAJAISIDDHI, T., KASEMSUTH, R., TEJAVANIJA, S. and HARINASUTA, T., (1971). Changes in blood volume in falciparum malaria. *Southeast Asian J. Trop. Med. Pub. Hlth.*, 2 :344.
- COGGESHALL, L.T., (1937). Splenomegaly in experimental monkey malaria. *Amer. J. Trop. Med.*, 17:605.
- CONRAD, M.E., (1969). Pathophysiology of malaria : Hematologic observations in human and animal studies. *Ann. Intern. Med.*, 70:134.
- DEATON, J.G., (1970). Fatal pulmonary edema as a complication of acute falciparum malaria; Report of a case. *Amer. J. Trop. Med. Hyg.*, 19:196.
- DENNIS, L.H., EICHELBERGER, J.W., INMAN, M.M. and CONRAD, M.E., (1967). Depletion of coagulation factors in drug-resistant *Plasmodium falciparum* malaria. *Blood*, 29:713.
- DEVAKUL, K., HARINASUTA, T. and REID, H.A., (1966). 125 I-labelled fibrinogen in cerebral malaria. *Lancet*, 2:886.
- DESOWITZ, R.S. and PAVANAND, R., (1967). A vascular-permeability-increasing factor in the serum of monkeys infected with primate malarial. *Ann. Trop. Med. Parasit.*, 61:128.
- DIXON, F.J., (1966). Comments on immuno-

- pathology. *Milit. Med.* (suppl.), 131: 1233,
- FELDMAN, H.A. and MURPHY, F.D., (1945). The effect of alteration in blood volume on the anemia and hypoproteinemia of human malaria. *J. Clin. Invest.*, 24: 780.
- FOGEL, B.J., SHIELDS, C.E. and VON DOENHOFF, A. E. J. R., (1966). The osmotic fragility of erythrocytes in experimental malaria. *Amer. J. Trop. Med. Hyg.* 15: 269.
- FUTRAKUL, P., BOONPUCKNAVIG, V., BOONPUCKNAVIG, S., MITRAKUL, C. and BHAMARAPRAVATI, N., (1974). Acute glomerulonephritis complicating *Plasmodium falciparum* infection. *Clin. Pediat.*, 13: 281.
- GREENWOOD, B.M. and BRUTON, M.J., (1974). Complement activation in children with acute malaria. *Clin. Exp. Immun.*, 18: 267.
- HARTENBOWER, D.L., KANTOR, G.L. and ROSEN, V.J., (1972). Renal failure due to acute glomerulonephritis during falciparum malaria: Case report. *Milit. Med.*, 137: 74.
- HENDRICKSE, R.G. and GILLES, H.M., (1963). The nephrotic syndrome and other renal diseases in children in Western Nigeria. *E. Afr. Med.*, 40: 186.
- HENDRICKSE, R.G., GLASGOW, E.F., ADENIYI, A., WHITE, R.H.R., EDINGTON, G.M. and HOUBA, V., (1972). Quartan malarial nephrotic syndrome, collaborative clinicopathological study in Nigerian children. *Lancet*, 1: 1143.
- HOUBA, V., ALLISON, A.C., ADENIYI, A. and HOUBA, J.E., (1971). Immunoglobulin classes and complement in biopsies of Nigerian children with the nephrotic syndrome. *Clin. Exp. Immun.*, 8: 761.
- JAROONVESAMA, N., (1972). Intravascular coagulation in falciparum malaria. *Lancet*, 1: 221.
- JAROONVESAMA, N., HARINASUTA, T., MUANGMANEE, L. and ASAWAPOKEE, N., (1975). Coagulation studies in falciparum and vivax malaria. *Southeast Asian. J. Trop. Med. Pub. Hlth.*, 6: 419.
- KARNEY, W.W. and TONG, M.J., (1972). Malabsorption in *Plasmodium falciparum* malaria. *Amer. J. Trop. Med. Hyg.*, 21: 1.
- LEELARASAMEE, A., JAROONVESAMA, N., THAMLIKITKUL, V. and MARANETRA, N., (1978). Falciparum malaria with acute pulmonary insufficiency. Report of a survived case. *J. Med. Ass. Thailand*, 61: 659.
- LUSE, S.A. and MILLER, L.H., (1972). *Plasmodium falciparum* malaria. *Amer. J. Trop. Med. Hyg.*, 20: 655.
- MAEGRAITH, B.G., (1948). Pathological process in malaria and blackwater fever. Oxford, Blackwell.
- MAEGRAITH, B.G. and ONABANJO, A.O., (1977). The effects of histamine in malaria. *Brit. J. Pharmacol.*, 39: 755.
- MAEGRAITH, B., (1974). Other pathological process in malaria. *Bull. W.H.O.*, 50: 187.
- MAEGRAITH, B.G., (1977). Interdependence. *Amer. J. Trop. Med. Hyg.*, 26: 344.
- MALLOY, J.P., BROOKS, M.H. and BARRY, K.G., (1967). Pathophysiology of acute falciparum malaria II: fluid compartmentalization. *Amer. J. Med.*, 43: 745.
- MARKS, S.M. HOLLAND, S. and GELFAND, M., (1977). Malarial lung: Report of a case from Africa successfully treated with intermittent positive pressure ventilation. *Amer. J. Trop. Med. Hyg.*, 26: 179.
- MIGASENA, P. and MAEGRAITH, B.G., (1965). The blood-brain barrier in *Plasmodium knowlesi* infection. *Trans. Roy. Soc. Trop. Med. Hyg.*, 59: 2.
- MIGASENA, P. and MAEGRAITH, B.G., (1969). Intestinal absorption in malaria I. The absorption of an amino acid (AIB₁-14C) across the gut membrane in normal and in *Plasmodium knowlesi* infected

- monkeys. *Ann. Trop. Med. Parasit.*, 63:439.
- MIGASENA, P. and MAEGRAITH, B.G., (1970a). Intestinal absorption in malaria III. The absorption of D-xylose across the gut membrane in normal and in *P. knowlesi* infected monkeys. *Southeast Asian J. Trop. Med. Pub. Hlth.*, 1:336.
- MIGASENA, P. and MAEGRAITH, B.G., (1970b). Intestinal absorption in malaria IV. The effect of phenoxybenzamine and Pitressin on absorption of D-xylose in *Macaca mulatta* infected with *Plasmodium knowlesi*. *Southeast Asian J. Trop. Med. Pub. Hlth.*, 1:344.
- MILLER, L.H., CHONGSUPHAJASIDDHI, T. and KANAKAKORN, K., (1968). Comparative studies on the pathology and host physiology of malarial, V. Hypovolaemia in *Plasmodium coatneyi* malaria. *Ann. Trop. Med. Parasit.*, 62:218.
- MILLER, L.H., (1972). The ultrastructure of red cells infected by *Plasmodium falciparum* in man. *Trans. Roy. Soc. Trop. Med. Hyg.*, 66:459.
- MILLER, L.H., CHIEN, S. and USAMI, S., (1972). Decreased deformability of *Plasmodium coatneyi* infected red cells and its possible relation to cerebral malaria. *Amer. J. Trop. Med. Hyg.*, 21:133.
- ONABANJO, A.O. and MAEGRAITH, B.G., (1970). Inflammatory changes in small blood vessels induced by Kallikrein (Kininogenase) in the blood of *Macaca mulatta* infected with *Plasmodium knowlesi*. *Ann. Trop. Med. Parasit.*, 64:227.
- ONABANJO, A.O. and MAEGRAITH, B.G., (1971). Circulating plasma kinins in malaria. *Trans. Roy. Soc. Trop. Med. Hyg.*, 65:5.
- PETCHLAI B., CHUTANONDH, R., HIRANRAS, S. and BENJAPONGS, W., (1977). Activation of classical and alternate complement pathways in acute falciparum malaria. *J. Med. Ass. Thailand.*, 60:174.
- PITNEY, W.R., (1968). The tropical splenomegaly syndrome. *Trans. Roy. Soc. Trop. Med. Hyg.*, 62:717.
- POSER, C.M., (1969). Disseminated vasculomyelinopathy. *Acta. Neurol. Scand.*, 45 (Suppl 37) : 1.
- PUNYAGUPTA, S., SRICHAIKUL, T., NITIYANANT P. and PETCHLAI, B., (1974). Acute pulmonary insufficiency in falciparum malaria : Summary of 12 cases with evidence of disseminated intravascular coagulation. *Amer. J. Trop. Med. Hyg.*, 23:551.
- REID, H.A. and NKRUMAH, F.K., (1972). Fibrin-degradation products in cerebral malaria. *Lancet*, 1:218.
- REST, J.R. and WRIGHT, D.H., (1979). Electron microscopy of cerebral malaria in golden hamsters (*Mesocricetus auratus*) infected with *Plasmodium berghei*. *J. Path.*, 127:115.
- ROSENBERG, E.G., STRICKLAND, G.T., YANG, S. and WHALEN, G.E., (1973). IgM antibodies to red cells and autoimmune anemia in patients with malaria. *Amer. J. Trop. Med. Hyg.*, 22:146.
- SITPRIJA, V., INDRAPRASIT, S., POCHANUGOOL, C., BENYAJATI, C. and PIYARATN, P. (1967). Renal failure in malaria. *Lancet*, 1:185.
- SITPRIJA, V., (1971). Urinary excretion patterns in renal failure due to malaria. The effects of phenoxybenzamine in two cases. *Aust. New. Zeal J. Med.*, 1:44.
- SITPRIJA, V., VONGTHONGSRI, M., POSHYACHINDA, V. and ARTHACHINTA, S., (1977). Renal failure in malaria: A pathophysiologic study. *Nephron.*, 18:277.
- SKUDOWITZ, R.B., MATZ, J., LURIE, A., LEVIN, J. and METZ, J., (1973). Mecha-

- nisms of thrombocytopenia in malignant tertian malaria. *Brit. Med J.*, 2 : 515.
- SKIRROW, M.B., CHONGSUPHAJASIDDHI, T. and MAEGRAITH, B.G., (1964). The circulation in malaria II : Portal angiography in monkeys (*Macaca mulatta*) infected with *Plasmodium knowlesi* and in shock following manipulation of the gut. *Ann. Trop. Med. Parasit.*, 58 : 502.
- SMITSKAMP, H. and WOLTHUIS, F.H., (1971). New Concepts in the treatment of malignant tertian malaria with cerebral involvement. *Brit. Med. J.*, 1 : 714.
- SRICHAIKUL, T., PUWASATIEN, P., PUWASATIEN, P., KARNJANAJETANEE, J. and BOKISCH, V.A., (1975). Complement changes and DIC in *Plasmodium falciparum* malaria. *Lancet*, 1 : 770.
- SRICHAIKUL, T., ARCHARARIT, N. and SIRIASAWAKUL, T., (1976). Histamine changes in *Plasmodium falciparum* malaria. *Trans. Roy Soc Trop. Med. Hyg.*, 70 : 36.
- SUCHARIT, P., CHONGSUPHAJASIDDHI, T., HARINASUTA, T., TONGPRASROETH, N. and KASEMSUTH, R. (1975). Studies on coagulation and fibrinolysis in cases of falciparum malaria. *Southeast Asian. J. Trop. Med. Pub. Hlth.*, 6:33.
- TALIAFERRO, W.H. and MULLIGAN, H.W., (1937). Histopathology of malaria with special reference to the function and origin of the macrophages in defence. *Indian Med. Res. Mem.*, 29: 1.
- THURNHAM, D.I., FLETCHER, K.A. and MAEGRAITH, B.G., (1971a). The inhibition of mitochondrial respiration and oxidative phosphorylation by serum from malaria infected animals. I. The contribution of bilirubin and non-esterified fatty acids to the inhibitory activity in *Plasmodium knowlesi* and *P. berghei* malaria. *Ann. Trop. Med. Parasit.*, 65:275.
- THURNHAM, D.I., FLETCHER, K.A. and MAEGRAITH, B.G., (1971b). The inhibition of mitochondrial respiration and oxidative phosphorylation by serum from malaria infected animal II. The inhibitory activity of serum ultrafiltrates from *Plasmodium knowlesi* infected monkeys and *P. berghei* infected mice. *Ann. Trop. Med. Parasit.*, 65: 287.
- THURNHAM, D.I., FLETCHER, K.A. and MAEGRAITH, B.G., (1971c). The inhibition of mitochondrial respiration and oxidation phosphorylation by serum from malaria - infected animals. III. Sephadex separation of inhibitory serum ultrafiltrates from *Plasmodium knowlesi* infected monkeys and *P. berghei* infected mice. *Ann. Trop. Med. Parasit.*, 65:297.
- TORO, G. and ROMAN, G., (1978). Cerebral malaria. A disseminated vasculomyelinopathy. *Arch. Neurol.*, 35:271.
- VARAVITHYA, W. and CHONGSUPHAJASIDDHI, T., (1972). Erythrocyte composition in *Plasmodium falciparum* infection in man. *Southeast Asian. J. Trop. Med. Pub. Hlth.*, 3:175.
- VOLLER, A., (1974). Immunopathology of malaria. *Bull. W.H.O.*, 50 : 177.
- WARD, P.A. and CONRAN, P.B., (1969). Immunopathology of renal complication in simian malaria and human quartan malaria. *Milit. Med.*, 134 : 1228.
- WOODRUFF, A.W., ANSDELL, V.E. and PETTIT, L.E., (1979). Cause of anemia in malaria. *Lancet*, 1:1055.
- WRIGHT, D.H., (1968). The effect of neonatal thymectomy on the survival of golden hamsters infected with *Plasmodium berghei*. *Br. J. Exp. Path.*, 49 : 379.
- WRIGHT, D.H., MASEMBE, R.M. and BAZIRA, E.R., (1971). The effect of antithymocyte serum on golden hamsters and rats infected with *Plasmodium berghei*. *Brit. J. Exp. Path.*, 52:465.

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ZIEGLER, J.L., VOLLER, A. and PONNUDURAI, T., (1973). Malaria antibodies in tropical splenomegaly syndrome in Uganda. *Trop. Geogr. Med.*, 25:282.

ZUCKERMAN, A., (1964). Autoimmunization and other types of indirect damage to

host cells as factors in certain protozoan diseases. *Exp. Parasit.*, 15:138.

ZUCKERMAN, A., (1977). A Review: Current status of the immunology of blood and tissue protozoa II. Plasmodium. *Exp. Parasit.*, 42:374.