CHAPTER 5

Clinical Pathology

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A. Introduction

Malaria has always been considered as one of the most important and deadly diseases of man. In 1955 a short-lived hope of malaria eradication was created when a global programme was initiated by the World Health Organization (WHO 1955, 1956). Twenty years later, because of the development of resistance to DDT by the mosquitoes and to chloroquine by *Plasmodium falciparum*, as well as financial problems, the programme was declared a failure (WHO 1975).

In recent years the prevalence of malaria has been noted to be rising sharply in many countries (MCCABE 1966; KIEL 1968; HEINEMAN 1972; O'HOLOHAN 1976), particularly in Southeast Asia, where the incidence is almost three and a half times higher than that in 1972 (WERNSDORFER 1980). The authors have experienced many hundreds of malaria cases in Thailand during the past 25 years and, only recently, we find that disease due to *Plasmodium falciparum* is becoming more severe in terms of clinical complications, with high morbidity and mortality (PUNYAGUPTA et al. 1974). One may try to correlate this change to the development of strains of *P. falciparum* resistant to the standard antimalarial drugs, chloroquine, and quinine. Another explanation is based on the remarkable change in the parasite density seen in the severe cases with multi-organ involvement. In the past it was uncommon to find serious cases with a parasite density of 10% or more. Recent observations of surprisingly heavy parasite density, for example over 90% of erythrocytes infected and frequently with double or triple infections in a single erythrocyte, are both interesting and disturbing.

We must therefore take a new and cautious look into various aspects of malaria, particularly the clinical disease, pathogenesis, and pathology, which may be of benefit to the therapeutic approaches. Moreover, experimental studies of malarial infection in animals have contributed to our understanding of the mechanism of the disease processes in man. The importance of work in animal models has been emphasised by BRUCE-CHWATT (1978).

This chapter is intended to give the reader a short review of the pathogenesis and clinical features, as well as pathological information, and to add some newer aspects of human malaria, particularly falciparum infection, by arranging the data by specific organ systems.

B. Pathogenesis

The life cycle of malaria parasites in the human host consists of three phases, the sporozoite, the tissue phase and the erythrocytic phase. The pathological changes

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in malarial infection occur mostly during the erythrocytic phase. The disease processes may be similar to those caused by other infective agents in which factors from both parasites and host are involved.

I. The Parasites

In all four species of human malaria, the exoerythrocytic and erythrocytic phases are similar in most aspects. However, the clinicopathological manifestations are different. The difference in the degree of merozoite production as well as the capability of the merozoites of each species to invade the erythrocytes probably is one of the main factors which determines the degree of host response. Recently more severe clinical cases of *P. falciparum* infection with multisystem involvement have been encountered. At the same time, some changes in the parasites have been observed, namely the development of resistance to the effective chemotherapeutic agents and the finding of unexpected hyperparasitaemia (DEATON 1970; DENNIS et al. 1967; PUNYAGUPTA et al. 1974; SRICHAIKUL 1973a). The relationship between the parasite density and the mortality has been well documented by FIELD (1949), i.e. the greater the density the higher the mortality.

II. Host-Parasite Interaction

During the complex life cycle in man, the malaria parasites enter the red cells and undergo rapid growth and development. The release of merozoites gives rise to new infection in other red cells. This asexual phase is critical to both host and parasites. In man it is responsible for the clinical manifestations and complications. As for the parasites, only during this stage can they be eradicated. Both specific and non-specific host responses to malaria can occur. The specific changes are mainly related to the red-cell alterations, whereas the non-specific changes involve various systems of the host. All of the systems which are involved in these changes are briefly reviewed in this section.

1. Red Blood Cells

The protective mechanism of erythrocytes depends on several factors. These are the age of the cells, the cellular membrane structure and intracellular biochemical composition including enzymes, as well as the various changes in haemoglobin (PASVOL and WEATHERALL 1980).

It is well known that *P. falciparum* attacks red cells of all ages although the younger population are more susceptible, whereas *P. vivax* and *P. ovale* infect only young red cells and *P. malariae* involves only older cells. Recently many studies have shown that specific receptors on the red-cell membrane may be needed for the invasion of certain malaria species, e.g. Duffy-positive cells would be susceptible to *P. vivax* whereas this selectivity was not observed in *P. falciparum* (MILLER et al. 1975, 1976, 1977). On the other hand, experimental study has indicated that a sialoglycopeptide might act as a receptor for *P. falciparum* (PASVOL and WEATHERALL 1980). It has been shown that *P. falciparum* invasion of the red cells from heterozygotes and homozygotes with sickle cell anaemia is decreased, and the sub-

sequent intraerythrocytic growth retarded. The aggregates of haemoglobin S which occur under low oxygen tensions were proposed as a factor responsible for the retarded growth of the parasites (FRIEDMAN 1978; PASVOL et al. 1978). Furthermore, the decrease in parasite growth or density was also demonstrated in various other red-cell disorders, i.e. in homozygotes with haemoglobin C (FRIEDMAN et al. 1979; THOMPSON 1963), in persistent high haemoglobin F (PASVOL et al. 1976, 1977) and in female heterozygotes for glucose-6-phosphate dehydrogenase (G6PD) deficiency (EATON et al. 1976; BIENZLE et al. 1972). A mechanism for the resistance in G6PD-deficient red cells has been proposed recently (PASVOL and WEATHERALL 1980).

The subsequent pathological changes in the host can be induced by various changes of the red cells. During parasite metabolism, haemozoin or malaria pigment is derived from the utilisation of haemoglobin in the infected erythrocytes (FLETCHER and MAEGRAITH 1972). The role of this substance in cellular injury is still unclear. However, malaria pigment in unbound form is toxic to cell metabolism. Furthermore, massive intravascular haemolysis which occurs in certain individuals with G6PD deficiency or hyperparasitaemia would produce haemoglobinaemia and haemoglobinuria. Massive breakdown of the red cells commonly gives rise to the most two serious complications, namely acute renal failure and disseminated intravascular coagulation (DIC). Excessive haemolysis can also cause hypoxia of many vital organs.

Previous studies demonstrated that there was an increase in stickiness and rigidity, and a decrease in deformability of the erythrocytes infected by *P. falciparum*. These changes possibly cause agglutination of these infected red cells and subsequently lead to the so-called plugging phenomenon of the microcirculation (LUSE and MILLER 1971; MILLER et al. 1971, 1972). The obstruction of the blood flow in the microcirculation by these agglutinated erythrocytes which contain mostly the late schizonts is the consistent pathological finding described in the brains of patients dying from falciparum infection.

2. Reticuloendothelial System and Immune Response

The non-specific host defence mechanism against malarial infection involves reticuloendothelial (RE) cell hyperplasia and various leucocytic responses. Eradication of malaria parasites may be achieved through the phagocytic activity of macrophages in spleen and bone marrow, and also by the specific antibodies produced during the infection. It is well known that in a malarial host without a spleen, the infection spreads very rapidly. In case of such a hyperparasitaemia, severe systemic complications followed by a very high mortality rate are usually observed unless prompt, effective treatment is given.

In the presence of a highly virulent infection the immune responses are very obvious. One interesting pathological finding was unusual proliferation of the lymphoid and reticulum (histiocytic) cells in the walls of the splenic vessels. The proliferation of these cells sometimes protruded from the walls into the lumen of the blood vessels, causing partial obstruction of the blood flow. This phenomenon was first described in bird and duck malaria and was also mentioned in a few falciparum cases (RIGDON 1944a). Autopsy findings by our group in cases of severely complicated *P. falciparum* infection strongly support RIGDON's earlier observation.

Previous immunological studies showed that the antibodies produced consisted of IgG, IgM, IgA, and IgD during malarial infection (COHEN and BUTCHER 1972). In the presence of highly virulent infections which loaded the body with malarial antigen, insoluble immune complexes consisting of both IgG and IgM were formed. These complexes in certain situations became pathogenic. So far, they have been demonstrated in the kidney, causing acute glomerulonephritis in *P. falciparum* and a nephrotic syndrome in *P. malariae* infection in man. These complexes also contribute to the destruction of red cells and platelets (FACER et al. 1979; ROSENBERG et al. 1973; NEVA et al. 1970; WOODRUFF et al. 1979). Complement activation, especially C3, also participates in the pathogenesis of lesions of both kidneys and blood cells.

3. Endogenous Mediators

Activation of the complement system by both classical and alternative pathways has been demonstrated during *P. falciparum* infection (PETCHCLAI et al. 1977; SRICHAIKUL et al. 1975). The causal relationship between the activation of C3 and the severity of clinical complications, namely anaemia, thrombocytopaenia, and DIC, has also been demonstrated. Along with the activation of the complement system various endogenous mediators of acute inflammation are released. The fall of kininogen with a simultaneous rise of kininogenases, as well as an increase in blood histamine, has been demonstrated in experimental animals infected with *P. knowlesi* (MAEGRAITH and ONABANJO 1970; ONABANJO and MAEGRAITH 1971). Recently, the increase in blood histamine has been demonstrated in man infected with *P. falciparum*, and a correlation between the blood histamine level, degree of parasitaemia, severity of complications, reduction of C3 and platelets, and finally DIC has also been found (SRICHAIKUL et al. 1976a). The increase in blood histamine during the acute phase of infection was most likely to be a factor responsible for the development of clinical complications. It can cause vasodilatation and increase in vascular permeability followed by hypovolaemia and circulatory stasis. Experimental studies also indicated the role of histamine in the occurrence of DIC (MCKAY et al. 1971).

4. Microcirculation

An alteration in the microcirculation is probably the most important change in the malarial host. Various mechanisms are responsible for this alteration. In experimental animals infected with *P. knowlesi*, it was shown that there was a generalised vasoconstriction of the vessels to the visceral organs. Simultaneously, an abnormal increase in the permeability of small vessels, particularly in the brain, was observed. Leakage of plasma from the vascular lumen caused hypovolaemia. Both hypovolaemia and vasoconstriction subsequently induced a severe reduction of blood flow to various organs and stasis of the microcirculation would then follow (MAEGRAITH 1974; MAEGRAITH and FLETCHER 1972). In man, a decrease in blood volume as well as a reduction of blood flow was demonstrated in certain cases of falciparum infection with heavy parasitaemia (CHONGSUPHAJAISIDHI et al. 1971). The occlusion of capillaries and venules by the agglutinated infected erythrocytes, as well as the formation of fibrin thrombi, probably occurred at this critical point

when the rate of blood flow was severely retarded. Subsequently, injury of the endothelial cells due to local anoxia would develop and lead to further increase in permeability of the vessels. The most harmful vicious cycle could then occur.

C. Clinicopathological Correlation

The distribution and frequency of human infection by *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* differ in various parts of the world (WHO 1969). The major differences in the clinical diseases, namely the pattern of fever, the incubation period and the severity of clinical symptoms are well known and need not be mentioned in detail here. As *P. falciparum* is the most significant species of all in terms of prevalence, morbidity, and mortality it will be described in more detail as a representative of the other types of infection.

Infection of man with non-human primate malaria such as *P. cynomolgi* has been reported as a laboratory accident or as experimental infections (COATNEY et al. 1971; CROSS et al. 1973; MOST 1972).

The clinicopathological description will be classified into uncomplicated and complicated malaria, and the latter will be further subdivided according to the organ systems affected.

I. Uncomplicated Malaria

Following a variable incubation period according to the species, the patients will experience some constitutional symptoms of malaise, headache, and myalgia prior to the development of high fever with chills. Some may experience aches and pains in the chest, abdomen or joints. At this stage malaria parasites may not be detected in the peripheral blood examination. The classical features of a sudden rise of temperature and shaking chills described as the cold period because of vasoconstriction is most striking, followed by the hot phase when the temperature will rise to as high as 41 °C and remain there for a few hours. These features which are characteristic of endotoxaemia occur at the time that merozoites emerge from infected erythrocytes. During the attack tachypnoea, tachycardia, extreme headache, body ache, nausea, vomiting, profound sweating, and sensorial disturbances are the usual symptoms. Symptoms and signs of orthostatic hypotension are prominent features (BUTLER and WEBER 1973). Between each attack patients may be asymptomatic. In classical textbook cases, which are infrequently seen nowadays, paroxysms of fever with associated symptoms occur at intervals of less than 48 h for *P. falciparum*, 48 h for *P. vivax*, and *P. ovale*, and 72 h for *P. malariae*.

In everyday practice while malaria cases may present with any type of fever, low-grade or high sustained temperature with or without rigors, the most constant associated symptoms are severe headache and vomiting, followed by an afebrile stage during which the patient feels reasonably well.

In the early stage of acute malaria we have found hepatomegaly with or without tenderness to be more frequent than splenomegaly whereas, in the chronic stage, splenomegaly is more prominent. A variable degree of jaundice with slight to moderate anaemia is most commonly noted, particularly in areas where haemolytic diseases such as haemoglobinopathy and G6PD deficiency are prevalent. Minute

petechiae and subconjunctival haemorrhages may be observed. Lymph node enlargement is insignificant.

In chronic malaria the symptoms are less severe. Anaemia with splenomegaly and fever are the main complaints. In *P. vivax* and *P. ovale* the relapses may occur many months or even years later because of the persistence of the hepatic stages (see Chap. 1).

II. Complicated Malaria

Of the four human species, *P. falciparum* is the only species that is notorious for causing complications. The reasons are as follows: firstly, one sporozoite of *P. falciparum* yields as many as 40 000 merozoites to invade the erythrocytes as compared with 1:10 000 in *P. vivax*, 1:15 000 in *P. ovale*, and 1:2 000 in *P. malariae;* secondly, the high capability of *P. falciparum* merozoites to invade all ages of erythrocytes and the high rate of reproduction of asexual erythrocytic forms. Parasitaemia in *P. falciparum* therefore may reach as high as 90% of total erythrocytes, compared with less than 1% in the other species.

Table 1. Maximum level of parasitaemia recorded in 51 falciparum malaria cases and mortality in each group

No. of infected erythrocytes per 100 erythrocytes		No. of cases	No. of deaths	(%)
Below	5	27	2	(7)
	6–10	11	3	(26)
	11–30	5	3	(60)
	31–50	4	2	(50)
	51–70	1	1	(100)
	71–90	2	2	(100)
Over	91	1	1	(100)
Total		51	14	(28)

Table 2. The clinical complications in 51 falciparum malaria cases and associated mortality

Clinical manifestations	No. of cases	No. of deaths	(%)
Cerebral complications	42	14	(33)
Non-oliguric renal failure	18	1	(6)
Oliguric renal failure (< 20 ml/h)	13	13	(100)
Pulmonary complications	20	14	(70)
Cardiac involvement	9	4	(44)
Shock	4	3	(75)
Skin and mucous membrane bleeding only	12	5	(42)
Massive gastrointestinal bleeding	9	9	(100)
Hepatomegaly with abnormal transaminases (> 100 units)	13	2	(15)
Haemoglobinuria	9	6	(67)

Table 3. Multiple organ complications in 51 falciparum malaria patients

Organ involved	No. of cases	No. of deaths	Number of cases with other organs also involved					
			Brain	Kidney	Lung	Heart	Massive gastro-intestinal bleeding	Liver
Brain	42	14 (33)	–	27	20	7	9	9
Kidney	31	14 (45)	27	–	20	9	9	11
Lung	20	14 (70)	20	20	–	9	9	6
Heart	9	4 (44)	8	9	9	–	2	4
Massive gastrointestinal bleeding	9	9 (100)	9	9	9	2	–	1
Liver	13	2 (15)	10	11	6	4	1	–

From 1969 to 1975 the authors studied in detail 51 clinical cases of complicated falciparum malaria at Ramathibodi University Hospital in Bangkok. There were 39 males and 12 females aged 17–45 years. The clinical data from these 51 cases are summarised in Tables 1–3.

As regards pathological data, autopsy specimens of malaria cases already available in the Department of Pathology, Ramathibodi University Hospital, were restudied in detail. A total of 22 cases were reviewed and the pertinent pathological findings in brain, lungs, and kidneys are summarised in Tables 4 and 5. Cases 1–7 were among the same group of patients recorded in Tables 1–3. Cases 11–22 were sent from provincial hospitals and had no accompanying clinical information. Specimens from major organs were submitted for pathological study.

The maximum levels of parasitaemia in each case and the outcome of patients are presented in Table 1. Those who had more than 50% of erythrocytes infected by *P. falciparum* never survived, while those with between 10% and 15% parasite density had a 50% chance of survival. In this series of 51 cases about half had a parasitaemia of over 5% of total erythrocytes, and one-fourth had over 10%. These findings may explain the high mortality of 28% in the whole group.

1. Haematology Complications

Haematological complications, which are the most common of all complications in malaria, have long been an interesting subject of extensive investigations. Changes of the erythroid and leucocytic series along with the RE cell hyperplasia are well-known manifestations. Recently thrombocytopaenia, coagulopathy, and bleeding have been increasingly common problems in complicated falciparum infections (Borochovitz et al. 1970; Neva et al. 1970; Punyagupta et al. 1974). The haematological complications are important because most of them reflect the defence mechanisms of the hosts to malarial infection, as well as the prognosis.

The present review attempts to summarise the haematological complications of human malarial infections. The discussion will be devoted to the complications of various systems including erythroid, leucocytic, and haemostatic changes. Mech-

Table 4. Autopsy findings[a] in 22 cases of *P. falciparum* infection

Case No.	Sex/ age	Histopathology findings									
		Brain			Lung			Kidneys			Others
		PE in vessels	Haemorrhage	Granuloma	Oedema	Membrane formation	Haemorrhage	Haemoglobin casts	Tubular necrosis	Tubular degeneration	Demonstration of fibrin thrombi in
1	M 36	+++	–	–	–	+	–	+	–	+	ND
2	M 24	+	–	–	+	++	–	+	–	+++	Glomeruli
3	M 19	++++	Petechiae	+	+	–	+	+	–	++	Brain, lungs, skin, adrenal
4	M 53	++	Ring	+	+	–	+	+	–	++	Brain, lungs
5	M 35	++	Ring	+	+	+	+	+	++	–	Brain, lungs
6	M 35	–	–	–	+	–	+	+	++	–	ND
7	M 25	++	Massive & old	–	–	–	++	–	–	++	Lungs, skin
8	M 20	+	Ring	–	+	–	+	+	++	+	Brain
9	M 49	–	–	–	+	–	–	+	++	–	ND
10	M 30	–	–	–	+	–	–	+	++	–	ND
11	M 44	–	Petechiae	–	–	+	+	+	+	+	Brain, lungs
12	M 35	++	Ring & old	+	–	+	+	+	++	–	Brain
13	M 20	++	Ring	+	+	–	+	+	+	+	Brain
14	M 35	–	–	–	++	–	+	+	++	+	ND
15	F 30	++	Petechiae	+	++	–	–	+	+	+	Brain
16	M 25	++	Ring	+	++	+	+	+	++	–	Brain
17	M 19	+	Ring	–	++	–	+	+	++	–	Brain
18	M 18	++	Petechiae	–	++	–	–	–	–	++	ND
19	M 28	–	–	–	+	–	–	+	++	–	ND
20	F 24	++	–	–	–	–	+	+	–	++	ND
21	M 30	++	–	–	+	–	–	+	++	+	ND
22	M 22	+	–	–	+	–	–	+	++	+	ND

[a] Clinical data on cases 1–10 are summarized in Table 5

+, ++, +++, ++++: mild, moderate, severe, very severe; –, negative; PE, parasitised erythrocytes; ND, not detectable

Cases 1–7 are in the same series as Tables 1–3

Table 5. Clinical data on ten autopsy cases with complications

Case No.	Parasitaemia		PE in cerebral vessels	Duration of illness	Clinical manifestation	Laboratory evidence of DIC	Pathological evidence of fibrin thrombi	Use of heparin
	max %	at death						
1	2	neg	+++	15	BRPGL	Yes	No	Yes
2	7	pos	+	9	BRP	Yes	Yes	Yes
3	90	pos	++++	6	BRPGC	Yes	Yes	Yes
4	40	neg	++	10	BRPGS	Yes	Yes	Yes
5	40	pos	++	7	BRPG	Yes	Yes	Yes
6	5	neg	−	9	BRPGC	Yes	No	Yes
7	30	neg	++	21	BRPG	Yes	Yes	No
8	40	pos	+	10	BRPG	Yes	Yes	Yes
9	10	neg	−	19	BRPCL	Yes	No	Yes
10	8	pos	−	7	BRP*	NR	No	No

B, brain complication; C, cardiac arrest; G, gastrointestinal bleeding; L, liver failure; NR, no record; P, pulmonary complication; P*, secondary bacterial pneumonia; R, acute renal failure; S, shock

Table 6. Mechanisms of anaemia in malaria

Major mechanisms	Evidence presented	Manifestations
1. Bone marrow suppression	1. Decreased erythroid proliferation	Erythroid hypoplasia, mostly in acute malaria
	2. Suppression of erythropoietin	
	3. Dyserythropoiesis and defective maturation of normoblasts	Ineffective erythropoiesis mostly in chronic malaria
	4. Defect in haem synthesis	Hypochromic anaemia
	5. Iron excess and dysutilisation	
	6. Folate deficiency	Megaloblastic anaemia
2. Haemolysis	1. Parasitised red cells	
	1.1 In RE organs	Extravascular haemolysis
	1.2 In circulation	Intravascular haemolysis
	2. Non-parasitised red cells by:	
	2.1 Membrane changes	Extravascular haemolysis
	2.2 Increased Na influx	
	2.3 Immunological effects	
	2.4 Interaction of drug and G6PD deficiency	Intravascular haemolysis
	2.5 Hyperactivity of reticulo-endothelial system	Extravascular haemolysis and/or hypersplenism

anisms inducing these complications, their clinical significance regarding treatment, and prognosis particularly of *P. falciparum* infection are also briefly reviewed.

a) Anaemia

Anaemia is the most common hematological complication. It occurs in every species of malarial infection, and is always present in complicated malaria. The mech-

anisms of anaemia in malaria are complex and are listed in Table 6. Bone marrow suppression as a causative mechanism of anaemia has two major manifestations, first, erythroid hypoplasia in the majority of acute malaria patients (SRICHAIKUL et al. 1967) and, second, ineffective erythropoiesis found mostly in chronic cases (SRICHAIKUL et al. 1969). The mechanisms inducing the above abnormalities are still unclear at present. However, marked suppression of erythropoietin during malarial infection (T. SRICHAIKUL et al., unpublished data) and a decreased proliferation and/or increased destruction of normoblasts during their development in bone marrow have been found (SRICHAIKUL et al. 1973). In the group having an increased destruction of normoblasts, a defect in haem synthesis was also observed (STRICHAIKUL et al. 1976 b). Recently, a picture of dyserythropoiesis as indicated by an abnormal nuclear structure of normoblasts in the bone marrow has been noted. However, an attempt to demonstrate invasion of malarial parasites into these abnormal normoblasts by electron microscopy was unsuccessful (ABDALLA et al. 1980). Iron overloading with hypochromic anaemia indicating iron dysutilisation was also demonstrated (SRICHAIKUL et al. 1976 b, 1969, 1979). Megaloblastic anaemia caused by folate deficiency has been noted in a few cases (STRICKLAND et al. 1970; SULLIVAN 1969). The megaloblastic erythropoiesis was quite prominent in the majority of our *P. falciparum* patients who presented with severe hyperparasitaemia and multisystem complications. Although these changes were observed transiently, they also contributed to the more severe degree of anaemia which had already occurred from haemolysis resulting from the infection.

Haemolysis, observed in all species of malaria, was most prominent in acute falciparum infection (ABDALLA et al. 1980). Numerous evidence indicated that haemolysis occurred in both parasitised erythrocytes and, probably, a greater number of non-parasitised red cells. Most of the parasitised red cells are destroyed in the spleen by the selective, so-called "pitting" mechanism of the splenic macrophages (BALCERZAK et al. 1972; SCHNITZER et al. 1972; SCHNITZER et al. 1973). The non-parasitised red cells which have membrane defects as a result of injury from previous parasitisation lose their deformability, and finally are captured by macrophages in the spleen (BALCERZAK et al. 1972; SCHNITZER et al. 1972; SCHNITZER et al. 1973). Changes of membrane lipids, ATP, and sodium content in the red cells as a consequence of the membrane defects were demonstrated (AREEKUL 1973; CONRAD 1969, 1971; VARAVITHYA et al. 1972). The attachment of complement containing immune complexes of both IgM and IgG antibodies (FACER et al. 1979; ROSENBERG et al. 1973; WOODRUFF et al. 1979) also causes haemolysis of these cells in the RE organs. All of the above changes produce the picture of extravascular haemolysis which generally occurs in malaria patients. Intravascular haemolysis of mainly parasitised cells was only a minor mechanism except in patients with G6PD deficiency or hyperparasitaemia.

The hyperplasia of the reticuloendothelial system which is always observed during malaria infection causes yet more erythrocytic destruction in the spleen (ABDALLA et al. 1980; SHEAGREN et al. 1970). In chronic malaria the patient's spleen may be very large, producing the clinical syndrome of "hypersplenism" or "big spleen syndrome." These patients usually have a huge spleen accompanied by pancytopaenia and hyperplasia of all the haematopoietic precursors. Erythrophagocytosis is a consistent finding in the spleen and sometimes in the bone marrow.

b) Leucocytic Response

Peripheral leucocytic changes during the malaria infection vary according to the stages of the disease. Usually there is a mild lymphocytosis with low normal, white blood counts in chronic malaria. However, in acute malaria, slight leucocytosis with predominant neutrophilia is observed (DALE and WOLFF 1973; REILEY and O'NEIL 1971). In acute, severely ill falciparum patients, we have observed leucaemoid blood pictures with occasional young forms of neutrophils. Atypical lymphocytes are noted occasionally in both uncomplicated and complicated cases, but more young cells are seen only in severe complicated *P. falciparum*. Recent studies have shown that, during acute malarial infection, there is a defect of T-lymphocytes as indicated by a decrease in total T cells and depressed blastoid transformation with PHA and con A (OSUNKOYA et al. 1972; GILBREATH et al. 1978, 1979; WELLS et al. 1979). Accompanying these findings, lymphocytotoxic antibodies of T-lymphocytes in serum have been demonstrated (GILBREATH et al. 1978, 1979). The abnormalities of the T-lymphocytes during malarial infection indicate a defective cell-mediated immune response (CMIR) in malaria patients. How this defective CMIR could play a significant role in the pathogenesis and the occurrence of high incidence of Burkitt's lymphoma in falciparum endemic areas is still unknown (EDITORIAL 1970; FEORINO and MATHEWS 1974; STEWART 1970; WEDDERBURN 1970; ZIEGLER et al. 1972).

Hyperplasia of lymphocytes and plasma cells has been demonstrated in the bone marrow of the patients infected with *P. vivax* and mild *P. falciparum* (SRICHAIKUL 1967; Srichaikul et al. 1969). Similar findings were found in spleen and lymph nodes together with hyperplasia of the phagocytes (TALIAFERRO and MULLIGAN 1937).

The results of our autopsy studies of falciparum-infected patients who presented with high parasitaemia and multisystem complications were somewhat different from the previous findings. Bone marrow in certain cases revealed a marked decrease of myeloid cell precursors. About 50% of marrow tissue was replaced by lymphoid cells including mature lymphocytes, small and large transformed lymphocytes, with occasional immunoblasts (Fig. 1). Migration of these cells into the sinusoids was noted. Large numbers of mononuclear, phagocytic cells with very active phagocytosis of infected red cells, malaria pigment, and occasional normoblasts were observed throughout the bone marrow (Fig. 2).

The proliferation of lymphoid cells and histiocytes was unusually striking in spleen and lymph nodes. Approximately half of the cells were small lymphocytes, the remaining cells being small and large transformed, cleaved and non-cleaved lymphocytes (Fig. 3). Immunoblasts, transitional plasma cells and plasmocytoid cells were prominent (Fig. 4). These cells appeared also in the red pulp of spleen, paracortical, and medullary areas of the lymph nodes in smaller numbers. There was diffuse and nodular proliferation of lymphoid cells in the subendothelial layer of the trabecular vein of the spleen (Fig. 5). Similar findings were described in the spleens of birds and ducks with malarial infection, and this was believed to be a cause of splenic infarction (RIGDON 1944a). An unusual proliferation of lymphoplasma cells and phagocytic cells in the capsules of lymph nodes and accessory spleen were observed. Moreover, in one of our cases, an active, peculiar penetration of these cells from an accessory spleen into the nearby pancreatic tissue was

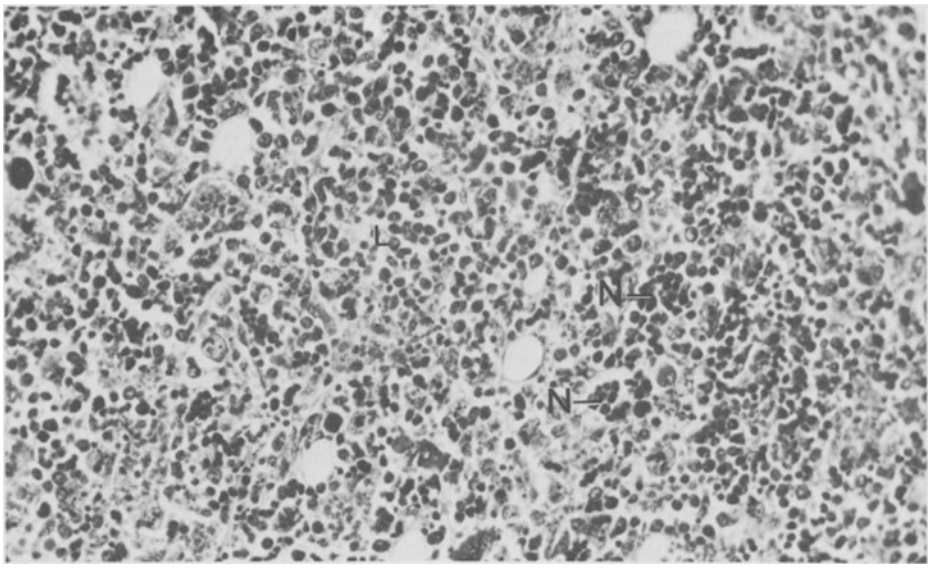

Fig. 1. Bone marrow demonstrating the proliferation of lymphoid and histiocytic cells. *L*, island of lymphoid cells; *N*, clumps of normoblasts. HE, × 368

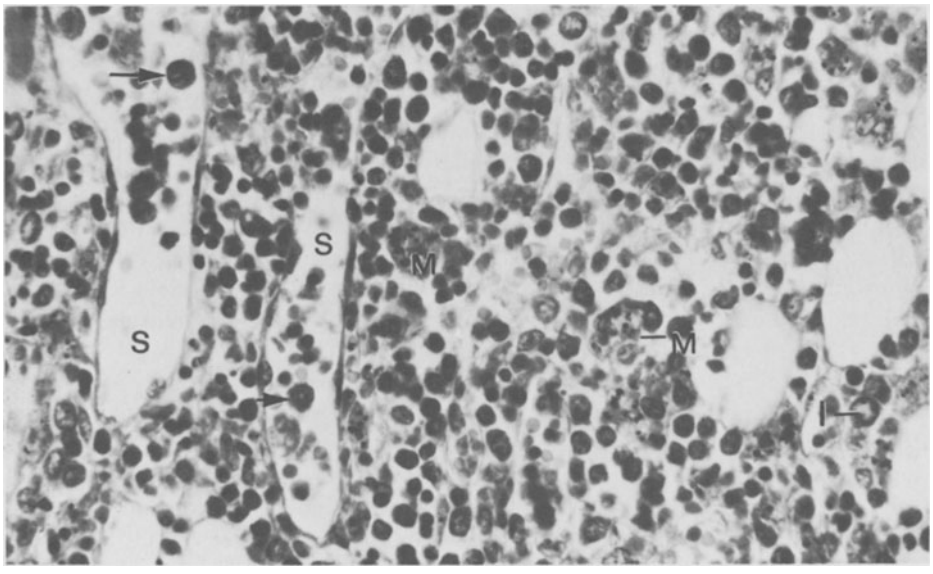

Fig. 2. Bone marrow showing active phagocytosis by macrophages (*M*) and migration of small and large transformed lymphocytes (*arrows*) into the sinusoids (*S*). *I*, immunoblast. HE, × 928

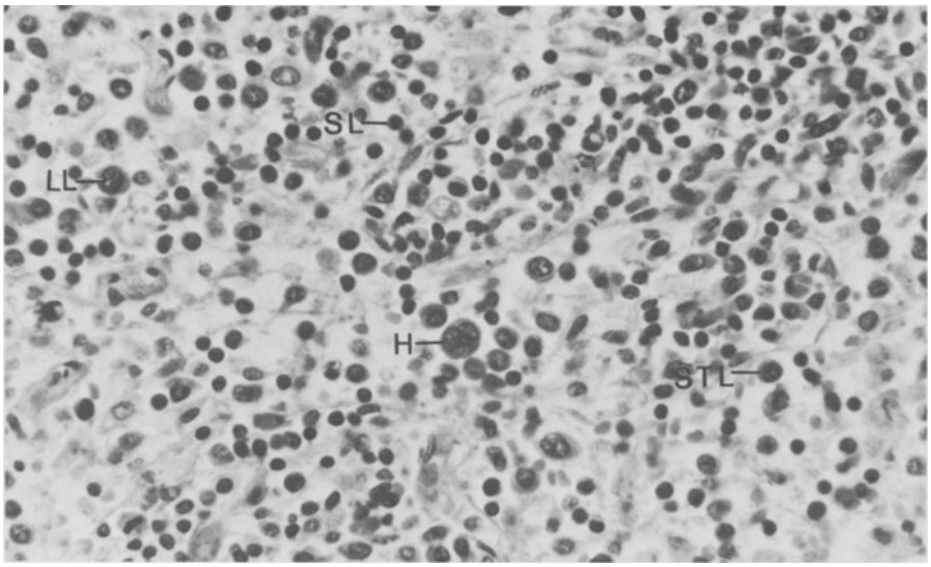

Fig. 3. Proliferation of lymphoid cells and histiocytes in a lymph node. *SL*, small lymphocyte; *STL*, small transformed lymphocyte; *LL*, large lymphocyte; *H*, histiocyte. HE, × 928

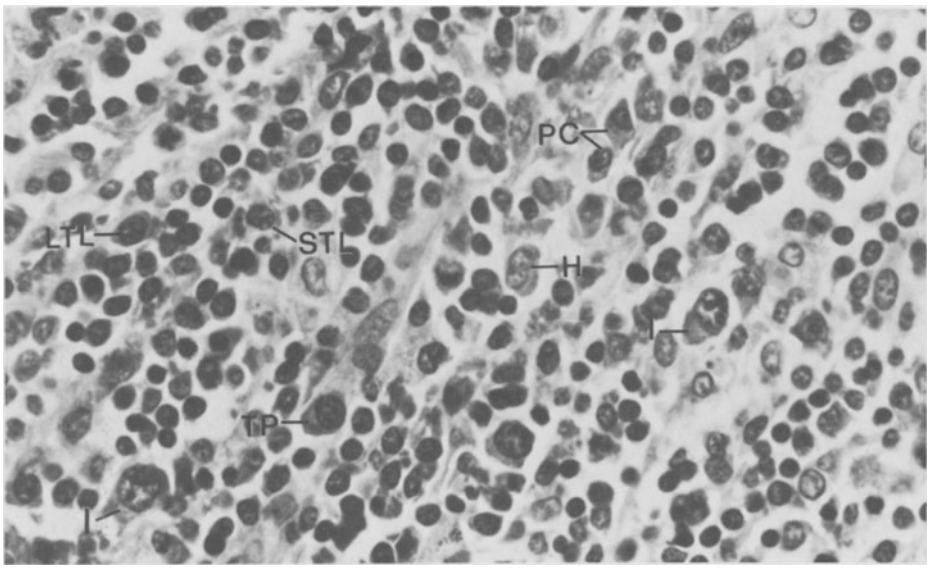

Fig. 4. Spleen is densely infiltrated with cells in the lymphocytic system. *PC*, plasmocytoid cells; *LTL*, large transformed lymphocyte; *STL*, small transformed lymphocyte; *TP*, transitional plasma cell; *I*, immunoblasts; *H*, histocyte. HE, × 1470

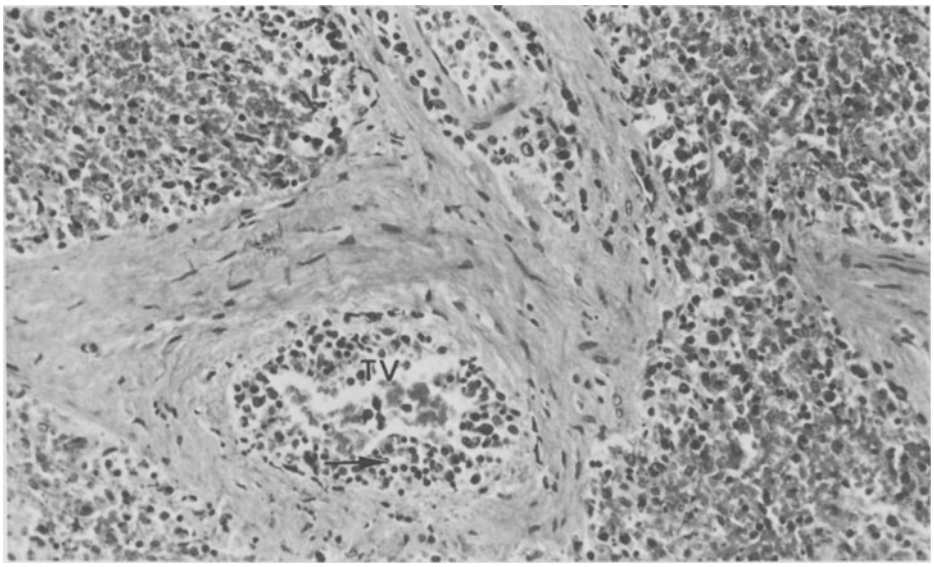

Fig. 5. Spleen in case with severe parasitaemia (90%) DIC and multiorgan involvement demonstrating proliferation of lymphoid cells (*arrow*) in the subendothelium of the trabecular vein (*TV*) with migration of these cells into the vascular lumen. Note the splenic sinusoids are congested with infected erythrocytes. HE, × 464

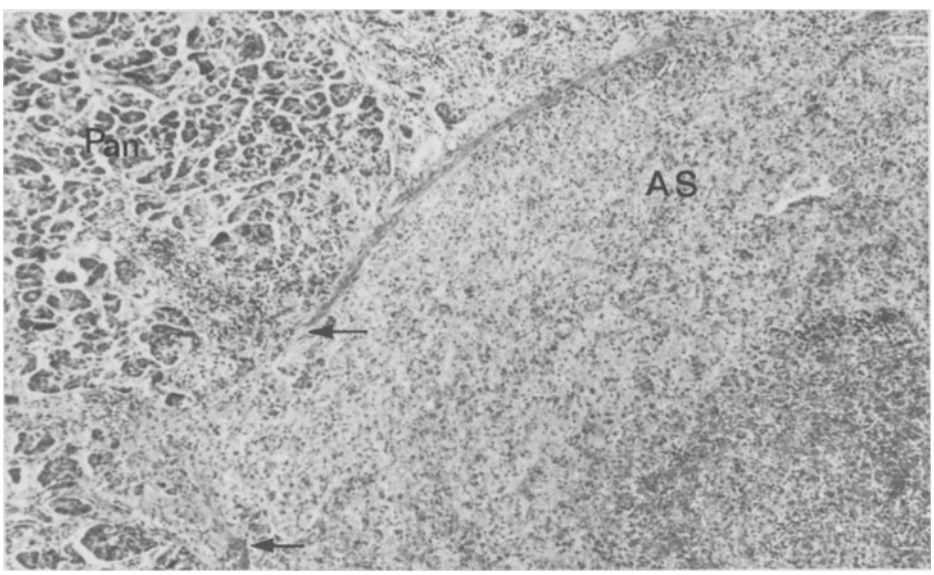

Fig. 6. Accessory spleen (*AS*) embedded in the tail of the pancrease (*Pan*), showing hyperplastic lymphoid cells penetrating through (*between arrows*) the splenic capsule into the pancreatic tissue. HE, × 928

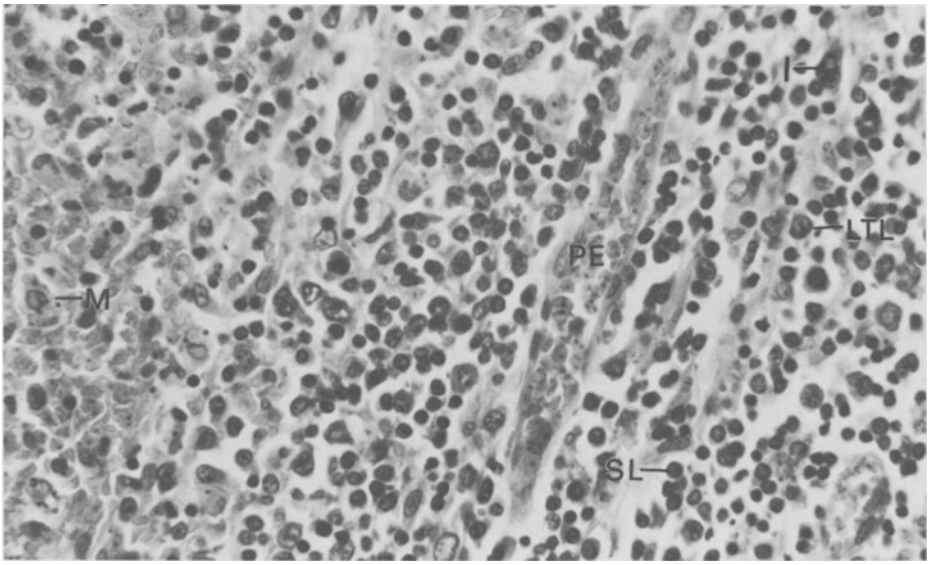

Fig. 7. Spleen showing lymphocytic cell hyperplasia. Splenic sinusoids and vessel are congested with parasitised erythrocytes (*PE*). *I*, immunoblast; *LTL*, large transformed lymphocyte; *SL*, small lymphocyte; *M*, macrophage. HE, × 928

noted (Fig. 6). Active phagocytosis of infected red cells, malaria pigment by macrophages and occlusion of small vessels by infected erythrocytes (Fig. 7) were also found. Evidence of extramedullary haematopoiesis, mostly of normoblastic erythropoiesis, was also present in the spleen.

c) Thrombocytopaenia and Coagulopathy

Thrombocytopaenia in malaria infection was observed by HILL et al. (1964) and was found in both *P. vivax* and *P. falciparum* (FAJARDO and RAO 1971; BEALE et al. 1972; SKUDOWITZ et al. 1973). Two major mechanisms induce thrombocytopaenia in malaria, namely the increased destruction of platelets either by hyperactivity of RE cells and/or by immune destruction (NEVA et al. 1970; SKUDOWITZ et al. 1973), and disseminated intravascular coagulation (D1C) (DENNIS et al. 1967). The latter was more severe and was believed to be more important clinically (BERGIN 1967; BOROCHOVITZ et al. 1970; PUNYAGUPTA et al. 1974).

Coagulopathy has been observed in both falciparum and vivax malaria. However, in mild falciparum and vivax infection a mild coagulopathy, as reflected by either a prolongation of partial thromboplastin time or prothrombin time, without thrombocytopaenia and clinical bleeding was observed (BUTLER and WEBER 1973; JAROONVESAMA et al. 1975). It was believed that hepatic involvement during malaria infection caused this abnormality (BUTLER and WEBER 1973). On the contrary, coagulopathy found in complicated falciparum infection was more severe, as indicated by the significant coagulation abnormalities accompanied by thrombocytopaenia and clinical bleeding. DIC was the most important mechanism for this abnormality.

d) Disseminated Intravascular Coagulation

DEVAKUL et al. (1966) considered that the disappearance of injected ^{125}I-labelled fibrinogen in human falciparum malaria was most likely to be associated with intravascular coagulation. Subsequently the results from various investigations in man and animal models supported the evidence for DIC (BERGIN 1967; DENNIS et al. 1967; DENNIS and CONRAD 1968; BOROCHOVITZ et al. 1970; STONE et al. 1972; JAROONVESAMA 1972; REID and NKRUMAH 1972; GOODALL 1973; PUNYAGUPTA et al. 1972, 1974; JAROONVESAMA et al. 1975; JOHNSON et al. 1977). Massive intravascular haemolysis of the infected erythrocytes with their released thromboplastic substances was postulated to be an accelerated mechanism of intravascular coagulation. Furthermore, the activation of the complement system and massive releasing of blood histamine in severe falciparum-infected cases also initiated the development of DIC and other complications (SRICHAIKUL et al. 1975, 1976). On the other hand many studies have revealed negative evidence against the occurence of DIC (BEALE et al. 1972; BUTLER and WEBER 1973; SKUDOWITZ et al. 1973; VREEKEN and CREMER-GROOTE 1978; HOWARD and COLLINS 1972; REID and SUCHARIT 1972). However, it should be noted that the negative results were obtained from studies in mild or uncomplicated malaria. In our study of 51 severe falciparum malaria cases, DIC was observed in 33 cases (Table 7). The criteria used in the diagnosis of DIC were the concomitant findings of thrombocytopaenia, coagulopathy, increase in fibrin degradation products and the clinical evidence of multisystem involvement. It is also interesting to note that fibrin thrombi were found in 12 out

Table 7. Observed complications during the clinical course of 33 DIC[a] and 18 non-DIC cases among 51 complicated falciparum patients

Manifestations	DIC (33 cases)	Non-DIC (18 cases)
Clinical	No. (%)	No. (%)
Cerebral complications	31 (93)	11 (61)
Non-oliguric renal failure	11 (33)	7 (39)
Oliguric renal failure (< 20 ml/h)	13 (39)	0 (0)
Pulmonary complications	20 (60)	0 (0)
Cardiac involvement	9 (27)	0 (0)
Shock	3 (9)	1 (6)
Skin and mucous membrane bleeding only	10 (30)	2 (11)
Massive gastrointestinal bleeding	9 (27)	0 (0)
Hepatomegaly with abnormal transaminase (> 100 units)	7 (21)	6 (33)
Haemoglobinuria	8 (21)	1 (6)
Mortality	14 (42)	0 (0)
Laboratory	Range/mean (%)[b]	Range/mean (%)[b]
Number of infected erythrocytes/100 erythrocytes	5–100/ 20 (100)	5–20/ 4 (100)
Platelets ($\times 10^3$/mm^3)	20–50/ 38 (100)	50–90/65 (80)
Partial thromboplastin time (s)	50–88/ 78 (100)	35–55/48 (22)
Fibrin degradation products (μg %)	40–160/120 (100)	0–20/15 (45)

[a] Criteria for the diagnosis of DIC: see text. [b] Percent of abnormal results in each group

of 22 autopsy specimens (Tables 4, 5). The evidence of intravascular fibrin deposition lacking at autopsies reported previously (MAEGRAITH 1974) might be due to technical problems. To be able to demonstrate fibrin thrombi in the histopathological material a thorough search is essential, including multiple sections of various organs, and serial sections of the suspected areas which must be stained with special fibrin stain.

e) Bleeding

This complication has been observed only in falciparum infection. In general, petechiae, and purpura of the skin are the early manifestations. Subsequently, epistaxis, gum, and conjunctival haemorrhages are noted. Massive bleeding from the gastrointestinal tract is the terminal event. Nineteen out of the 33 DIC patients had bleeding from haemostatic failure, and nine presented massive, fatal, gastrointestinal bleeding (Table 7). This is in contrast to the non-DIC patients, of whom only two experienced milder bleeding. Furthermore, there was a definite correlation between the severity of bleeding and degree of coagulopathy.

The interrelations of DIC and bleeding could be demonstrated by histopathological study of the skin obtained from our autopsy specimens from falciparum-infected cases who had had bleeding. Grossly, the haemorrhage in the skin ranged from petechiae to ecchymoses and even diffuse hemorrhages. Microscopically, several specimens of skin obtained from small haemorrhagic spots showed arterial fibrin thrombi. The arteries and arterioles of subcutaneous tissue were the most common place to find the thrombosis (Fig. 8). Usually, large amounts of malarial pigment and nuclear debris were included in the thrombi. Thrombus was rarely detectable in the capillaries in the dermal papillae. Necrosis of the thrombosed arterial walls was an additional finding occurring together with haemorrhage and necrosis in the surrounding soft tissue (Fig. 9).

2. Water and Electrolyte Complications

The results of studies of the blood volume in acute malaria are contradictory, probably depending on the stage, the severity of the disease and the groups of individuals concerned (FELDMAN and MURPHY 1945; KEAN and TAYLOR 1946; MALLOY et al. 1967; SITPRIJA et al. 1967; CHONGSUPHAJAISIDHI et al. 1971). However, in mild to moderately severe cases increased plasma volume, water retention, and hyponatraemia are usually recognised (MALLOY et al. 1967), while in more severe cases a reduction in blood volume has been observed (CHONGSUPHAJAISIDHI et al. 1971). In some cases dehydration due to severe vomiting, inability to drink and marked perspiration from high fever are found. In such instances, hypovolaemia and hypotension may be observed and the increase in capillary permeability may lead to the stage of shock.

a) Hyponatraemia

In some severe cases inappropriate secretion of antidiuretic hormone may be the mechanism of production of hyponatraemia (MILLER et al. 1967). In severe hyponatraemic patients, the intravenous infusion of a moderate amount of fluid may lead to serious pulmonary complications. In our series moderate to marked hyponatraemia was a constant finding.

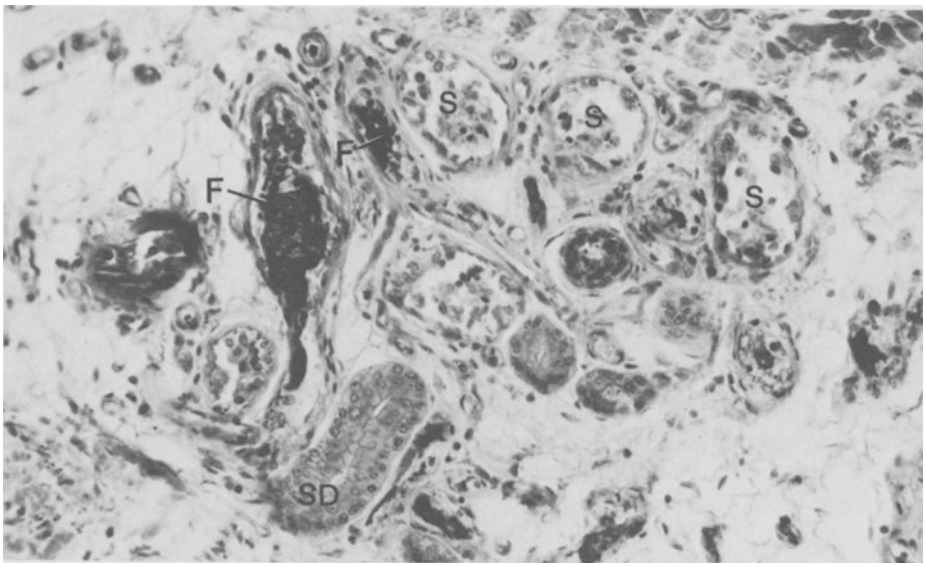

Fig. 8. Skin demonstrating fibrin thrombi (*F*) in arteries of subcutaneous tissue. Note necrosis of sweat gland (*S*). *SD*, sweat duct. PTAH, × 464

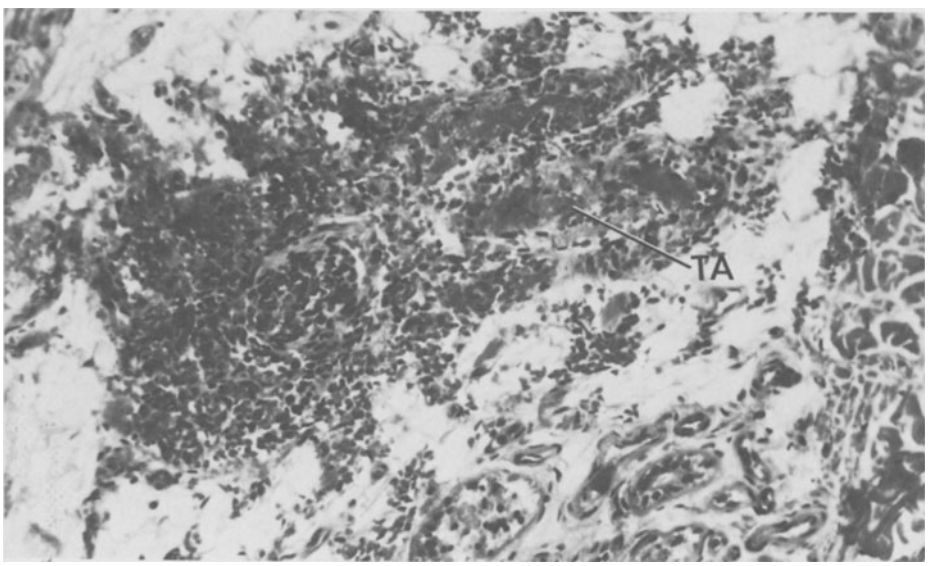

Fig. 9. Skin (same case as Fig. 8) showing necrosis of thrombosed arteries (*TA*) with diffuse haemorrhage. HE, × 464

b) Hypoproteinaemia

Diminished serum protein and albumin and slightly elevated globulin are observed in acute malaria. Only mild proteinuria is found. The increase in serum protein catabolism and probable decrease in albumin synthesis from liver dysfunction may be the responsible factors. Leakage of serum protein, particularly of albumin, due

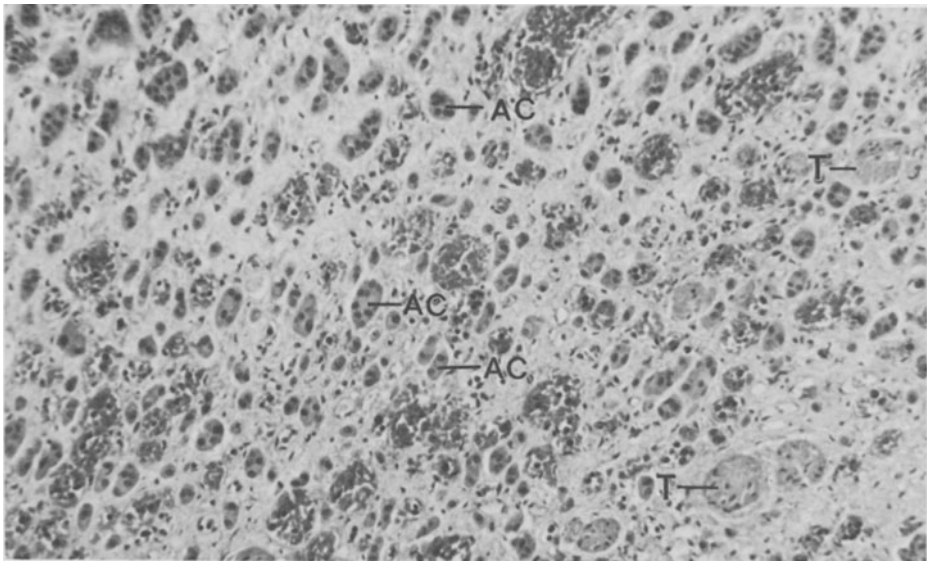

Fig. 10. Adrenal gland showing thrombosis (*T*) of the cortical vessels and severe atrophy of cortical cells (*AC*) with fibrosis. HE, × 232

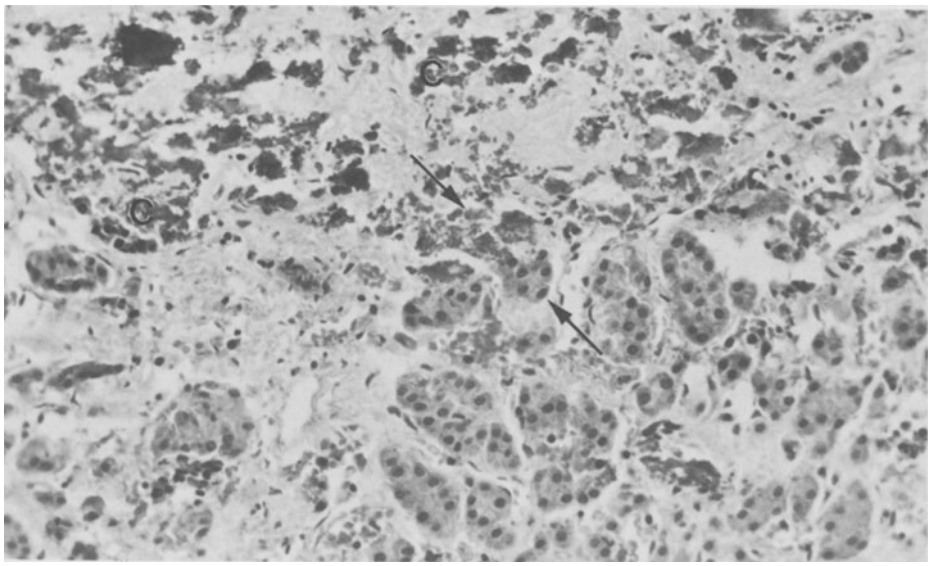

Fig. 11. Adrenal gland (same case as Fig. 10) demonstrating necrosis and calcification of cortical cell cord (*between arrows*). *C*, diffuse calcification in necrotic areas, HE, × 464

to the increase in vascular permeability has been considered. However, MALLOY et al. (1967) found that no marked loss of albumin across capillaries occurred. In our series hypoalbuminaemia and hypoproteinaemia were constant and, in some serious cases, the serum albumin was as low as 1 g/100 ml during the acute stage. This probably leads to further serious complications, particularly pulmonary oede-

ma. Oedema in malaria may be due to a combination of increase in vascular permeability and fluid retention.

The symptom complex of hyponatraemia, diarrhoea, vomiting, and hypotension are characteristic evidence for adrenal cortical insufficiency. Pathological studies of adrenal glands have shown some changes, namely lipid depletion, of the adrenal cortices with some degree of oedema, haemorrhagic necrosis, degeneration, thrombosis, and cellular infiltration. BROOKS et al. (1969), however, found an increase in plasma 17-hydroxy corticosteroids, but a decrease in urinary steroids, probably reflecting decreased hepatic conjugation, and they concluded that the pituitary-adrenal function was normal.

The adrenals were studied microscopically in all our postmortems. In general the sinusoids were engorged with malaria pigment-laden macrophages (MPLM) and small numbers of infected red cells. In about 50% of cases, there were mild to severe degrees of cortical cell degeneration and lipid depletion, particularly of the zona fasciculata. In some cases, cells in this zone showed foamy and cystic degeneration, and necrosis. Each cord of these cells was replaced by mononuclear leucocytes and macrophages. Interestingly enough, one case in our series (case 3, Table 4) showed diffuse sinusoidal occlusion with fibrin-platelet thrombi associated with severe diffuse cortical cell atrophy (Fig. 10), with diffuse necrosis and calcification (Fig. 11). This case died in shock.

3. Liver Complication

Even though hepatomegaly is commonly encountered in acute or chronic malaria, serious liver complications are unusual (DELLER et al. 1967; RAMACHANDRAN and PERERA 1976). Jaundice is frequently observed and haemolysis may be the significant mechanism. In this study liver complications were much less frequent than those of brain, kidney or lungs (Tables 2, 3). Significant hepatic enlargement associated with hypertransaminasaemia of over 100 units was found in only 13 of the 51 cases. Liver function tests may be abnormal, increased liver enzymes indicating some degree of liver-cell injuries. Increased alkaline phosphatase is probably correlated to the Kupffer cell hyperplasia and the reduction in serum protein as already discussed. On microscopic examination of liver biopsy or autopsy specimens, the most specific feature of malaria infection is the presence of malaria pigment in the Kupffer cells. In SRICHAIKUL's (1959) correlative study of liver function, degree of parasitaemia and liver biopsies, malaria pigment was present in Kupffer cells as early as the 6th day after the beginning of clinical symptoms, and would disappear between 3 and 6 months later. Although malarial pigment is an end product of the digestion of haemoglobin by the parasite, the amount of malaria pigment in the liver is not related to the degree of parasitaemia but depends on the duration or chronicity of the disease. In *P. falciparum*-infected *Aotus* monkeys, the pigment was first seen in the perilobular Kupffer cells, while later on the midzonal and centrolobular Kupffer cells were involved (AIKAWA et al. 1980). In experimental *P. lophurae* infections in young ducks, RIGDON (1944 b) demonstrated phagocytic activity of the Kupffer cells beginning as early as the 2nd day of infection. Ultrastructurally, malaria pigment appears in two forms, a rectangular crystalloid formed in mammalian malaria, and a uniform electron-dense mass in avian and reptilian malaria (AIKAWA 1971). Some additional information on liver histopathology

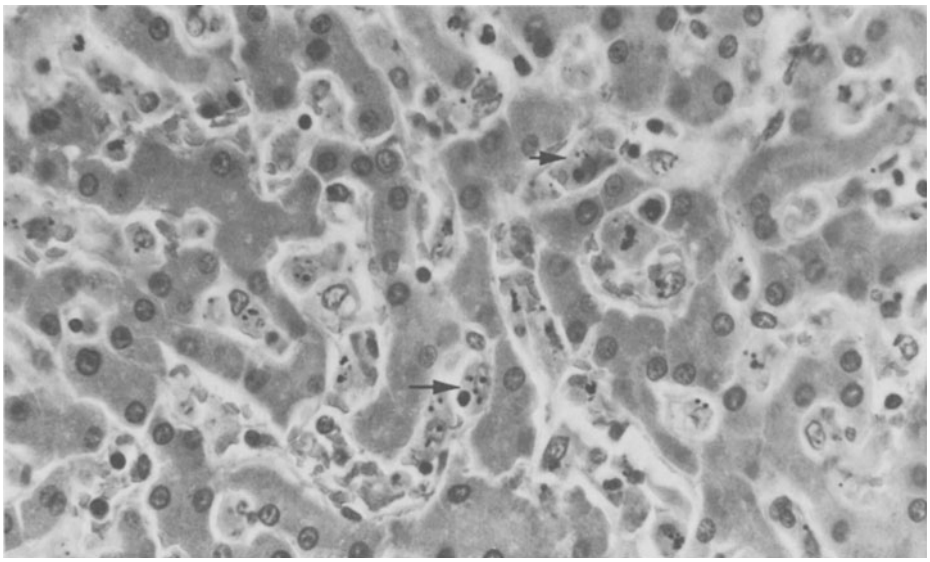

Fig. 12. Malarial pigment in Kupffer cells. Parasitised erythrocytes and mononuclear cells are also phagocytosed by Kupffer cells (*arrow*). HE, × 928

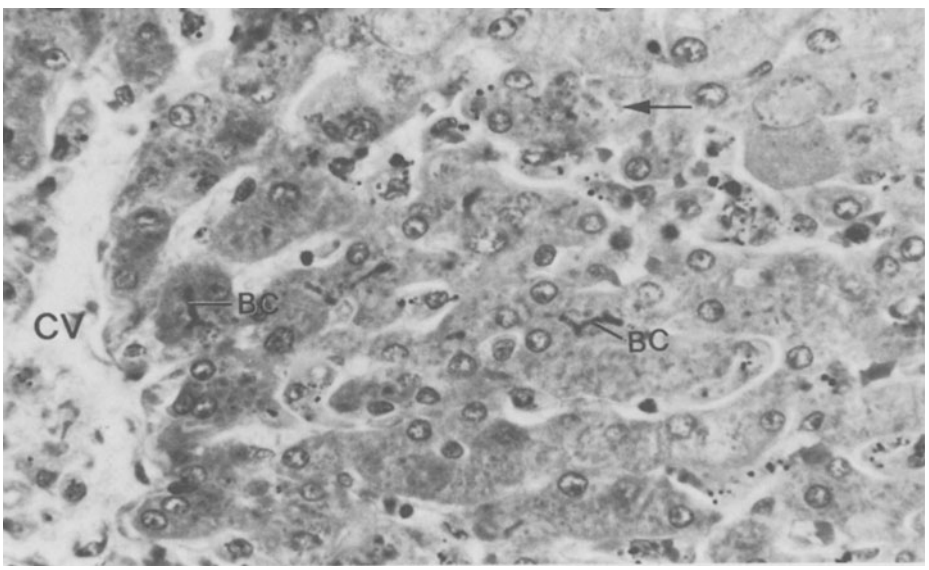

Fig. 13. Bile stasis in bile canaliculi (*BC*). Necrosis of certain liver cells is demonstrated (*arrow*). *CV*, central vein. HE, × 928

emerged from a series of liver biopsy studies. For instance, pre-erythrocytic forms of *P. vivax* were demonstrated in a liver biopsy obtained from a patient receiving treatment by mosquito-induced malaria on the 7th day after the first mosquito feed (SHORTT et al. 1948). In general, microscopic abnormalities of liver parenchy-

ma were demonstrable in almost all biopsies from patients who had hepatitis associated with *P. vivax* (McMAHON et al. 1954) and *P. falciparum* (DELLER et al. 1967) infection. In addition to hyperplasia and hyperactive phagocytosis by Kupffer cells, the liver cells showed mild to severe degeneration with necrosis of individual cells. Mitosis of liver cells was prominent. Acute and chronic inflammatory cell infiltration and non-specific granulomata were found randomly in the hepatic sinusoids and portal areas, and were most prominent in patients with hepatomegaly and jaundice (RAMACHANDRAN and PERERA 1976). On the contrary, WHITE and DOERNER (1954) found no hepatocellular lesions in a series of biopsies on *P. falciparum* or *P. vivax*-infected patients, although all of them had abnormal liver function tests. An electron microscopic study was made of a liver section taken 15 min postmortem from a patient with falciparum malaria associated with multiple complications. It showed plasma membrane disruption and mitochondrial dense bodies in liver cells. Kupffer cells or sinusoidal lining cells were vacuolated and contained parasitised or non-parasitised erythrocytes, and malaria pigment. This pigment appeared as membrane-bound osmiophilic bodies in which rectangular or trapezoidal areas were incorporated (ROSEN et al. 1967). Gross characteristics of autopsy liver in acute falciparum infection are enlargement and diffuse slate-grey discoloration of both capsular and cut surfaces. Microscopic lesions include all of the above-mentioned features as well as dense, mononuclear cell infiltration in the portal areas. Occasional presentation of small, round, hyaline material in the liver cells and Kupffer cells associated with necrosis of the liver cells has been described (SPITZ 1946). Centrolobular necrosis may be caused by portal venous constriction as a result of an adrenergic effect in acute malaria infection (MAEGRAITH 1974). In experimental studies by RAY and SHARMA (1958), the hepatic centrolobular lesions can be prevented in thoracic sympathectomised animals.

In our autopsy studies, histopathological lesions of the liver in *P. falciparum* infection could be divided into two main groups, the first without hepatic-cell alteration, and the second showing definite hepatocellular damage. Both groups had similar general characteristics of Kupffer cell hyperplasia with prominent phagocytic activity. The phagocytosed material included malaria pigment, infected or non-infected red cells, nuclear debris and occasional mononuclear leucocytes. Hepatic sinusoids were engorged with distorted erythrocytes, MPLM, lymphocytes and plasma cells. The liver cells of the first group were well preserved without definite mitotic change (Fig. 12). Local atrophic changes of the liver cells in this group were detectable and attributed to increased pressure in the sinusoids. Individual liver cell necrosis was rarely detectable. This group comprised the majority of patients who had moderate parasitaemia. In the second group, the liver cells were irregularly swollen with multiple nuclei and occasional patchy necrosis. There was centrolobular bile stasis in bile canaliculi (Fig. 13). The cytoplasm of these liver cells was clouded with small, round, hyaline masses, and occasional haemosiderin pigment. The patients in the second group had high parasitaemia and severe jaundice associated with other serious complications.

4. Brain Complication

The incidence of cerebral involvement in *P. falciparum* malaria is between 0.25% and 2.3% (DAROFF et al. 1967). The mortality varies greatly from none to as high

as 50%. In our study cerebral complications were the most commonly encountered in 42 out of 51 complicated cases and the mortality was 33% (Table 3). In *P. vivax* infection cerebral complication is rarely observed (DHAYAGUDE and PURANDARE 1943) and it has never been recognised in *P. malariae* or *P. ovale* infection.

The change in the sensorium is usually progressive from confusion, disorientation, and lethargy to deep coma. Some may present with abrupt personality changes or frank psychosis. Others may experience focal neurological signs of tremor, twitching, chorea, myoclonus or hemiparesis. Those who recover will recover fully without residual neurological signs except in some rare instances.

Cerebral malaria is usually observed in patients with high parasitaemia but it may be found in cases with low parasite blood levels. Jaundice, anaemia, and renal impairment are frequently noted at the time of cerebral involvement. With effective therapy patients may recover rapidly within the first 24 h, but some may take a few days to regain consciousness. Some may not recover at all and die with cerebral as well as other complications.

There are various yet inconclusive explanations for the mechanism of cerebral malaria. Normally the cerebral vessels are permeable only to specific substances such as small carbohydrate molecules. Malaria infection induces some vasoactive substances which may cause the endothelium of the cerebral vessels to dysfunction, allowing a leakage of water and protein into the brain tissue. This leads to an increase in plasma viscosity, stasis of the cerebral circulation, and packing of erythrocytes, particularly those containing late schizogonic stages in the cerebral capillaries (MAEGRAITH 1969; MAEGRAITH and FLETCHER 1972).

It has been observed that, following the administration of quinine and chloroquine, the recovery of cerebral symptoms is very rapid in spite of the fact that parasitaemia may still be noted. MAEGRAITH and his colleagues at Liverpool showed that the protein leakage in the brain can be inhibited by anti-inflammatory drugs including chloroquine and corticosteroids.

In falciparum malaria deep schizogony occurs in various visceral organs (LUSE and MILLER 1971). The changes in the erythrocytic membrane which attaches to the endothelium may enhance the agglutination and trapping of erythrocytes to the small vessels, the so-called stickiness. Thus plugging of the vessels may contribute to the cerebral damage (AIKAWA et al. 1975). Investigation in rodent *P. berghei* malaria disclosed the fact that immune mechanisms may cause agglutination of infected red cells (WRIGHT 1968) and cerebral lesions can be prevented by antithymocyte antiserum (WRIGHT et al. 1971).

Studies in human falciparum infection have shown that involvement of the brain is associated with the presence of fibrin degradation products in the circulation (REID and NKRUMAH 1972; JAROONVESAMA 1972); yet the role of DIC in the pathogenesis of cerebral malaria is still inconclusive. A direct effect of "malarial toxin" on the blood vessel walls has not been proven. A role for malaria pigment in the production of cerebral thrombi was demonstrated in monkeys infected with *P. knowlesi* or by intravenous injection of disodium ferrihaemate (ANDERSON and MORRISON 1942). Of particular interest, BOONPUCKNAVIG et al. (1973) demonstrated by electron microscopy a focal injury of the glomerular capillary wall at the site of attachment of the sequestrated, parasitised erythrocyte in *P. berghei*-infected mice. They suggested that the lesion may represent a direct injury of

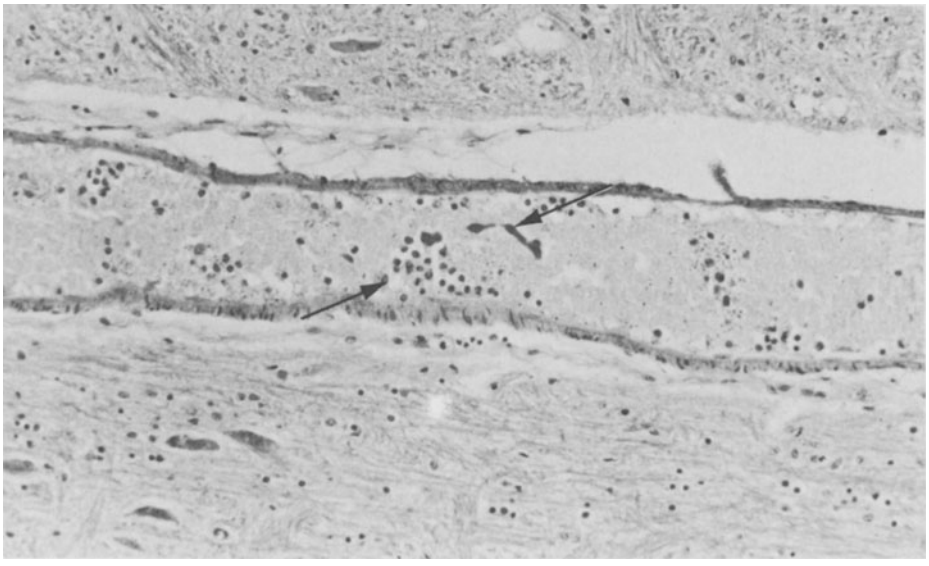

Fig. 14. Groups of infected erythrocytes, macrophages, mononuclear leucocytes, and fibrin thrombi (*between arrows*) circulating in an artery of the brain stem. HE, × 232

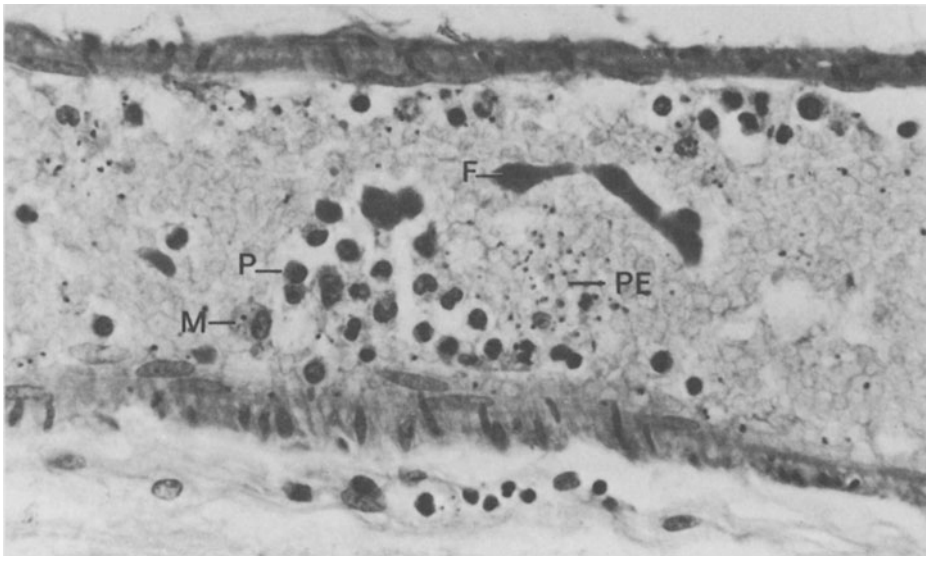

Fig. 15. Higher magnification of Fig. 14 showing details of the cells. *PE*, group of parasitised erythrocytes; *F*, fibrin thrombi; *M*, macrophage containing malaria pigment; *P*, plasma cell. HE, × 928

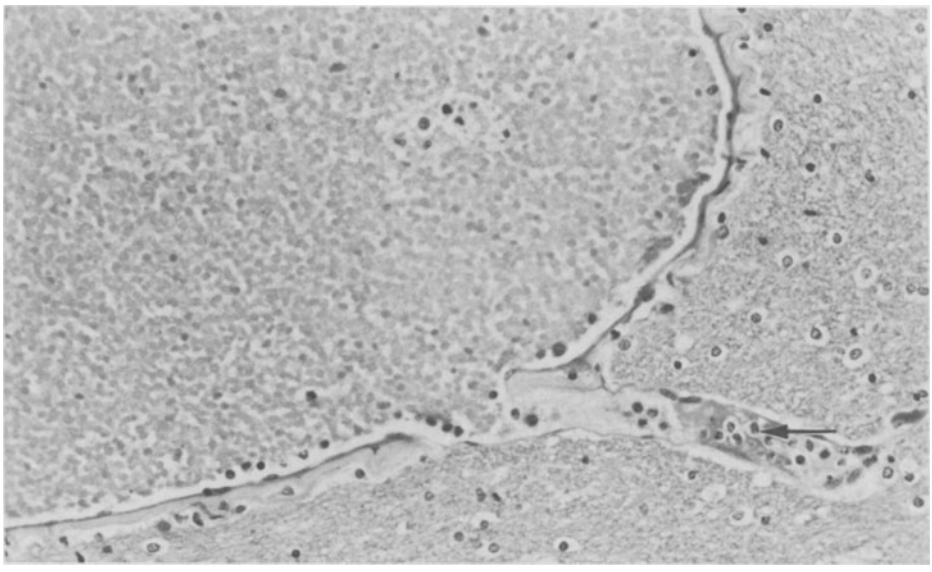

Fig. 16. Brain showing cystic dilatation of an arteriole. The outflow capillary is occluded (*arrow*). HE, ×464

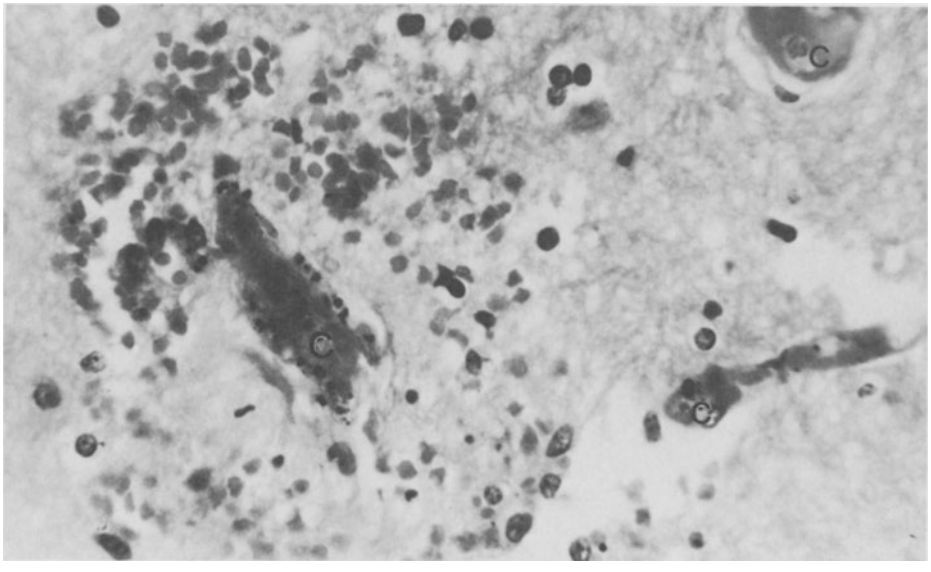

Fig. 17. Early developed ring haemorrhage and demyelinisation of brain tissue around a thrombosed capillary. Note all three capillaries (*C*) are occluded by fibrin thrombi. HE, ×928

glomerular capillary walls by malaria parasites or their metabolites. There have been several reviews of brain pathology in falciparum infection (DHAYAGUDE and PURANDARE 1943; SPITZ 1946; WINSLOW et al. 1975; AIKAWA et al. 1980). Others are primarily concerned with the clinicopathological correlations (THOMAS 1971) and pathogenesis (MAEGRAITH 1948; MAEGRAITH and FLETCHER 1972). Grossly, brain may show only severe oedema and congestion. However, the striking characteristics of brains in cerebral malaria are distinct slate-grey discoloration due to the deposition of malaria pigment and numerous petechiae, usually seen in the meninges and on the cut surface of the cerebrum, cerebellum, and brain stem. In our study, specific microscopic lesions of the brain in the fulminating cases of falciparum infection which were fatal in the comatose stage of cerebral malaria are:

a) Vascular Occlusion

Most of the capillaries are congested with parasitised erythrocytes. The numbers and distribution of these infected erythrocytes are not correlated with the degree of antimortem parasitaemia.

Moreover, parasitised erythrocytes remained to be seen in the cerebral vessels in certain cases which had negative parasitaemia before death (see Table 5). In practice, almost all levels of capillaries in the brain and spinal cord are involved. In our study, cerebral vessels were also occluded by thrombi composed of fibrin, and a small amount of malaria-pigmented granules. This association of agglutinated, infected, red cells and fibrin thrombi was seen in 12 out of 22 patients (see Table 4). In the large calibre vessels, the infected red cells frequently rim the periphery of the lumen, and this has been called a margination effect.

Occasionally, in well-preserved specimens of brain, clumps of parasitised red cells, mononuclear phagocytic cells, lymphocyte, and plasma cells with fibrin masses are seen in the arteries (Figs. 14, 15). Consequently, cystic dilatation of the artery that may well be caused by a blockage of capillary outflow by these groups of cells and fibrin is observed (Fig. 16).

b) Haemorrhage

In our autopsy material there are many patterns of haemorrhage in cerebral malaria. Minute haemorrhages can be seen around thrombosed capillaries in the subcortical cerebral tissue and they are rather profuse in the cerebellum. The extravasated red cells in the dilated perivascular spaces are mostly non-parasitised with few infected cells. Haemorrhages that are discussed frequently in the literature, the ring haemorrhages, in our experience are always developed around thrombosed vessels. There has usually been a distinct zone of demyelinisation between the central thrombosed vessels and the area of hemorrhage in this type of lesion (Fig. 17). Patients who survive for a longer period of time and die with other complications present multiple haemorrhagic spaces in the cerebral and cerebellar tissue. These spaces are filled with ghosts of non-infected erythrocytes plus some infected cells (Fig. 18). Blood vessels of larger calibre than capillaries containing no agglutinated erythrocytes or fibrin thrombi are in the centre. However, adjacent to the vessel walls there are accumulations of fibrin and a few microglial cells.

c) Inflammatory Lesions

A variety of cellular reactions within the brain tissue have been described in cases of falciparum infection. The most common lesion, the so-called malarial or Durck's granuloma, occurs frequently in the white matter of all parts of the brain.

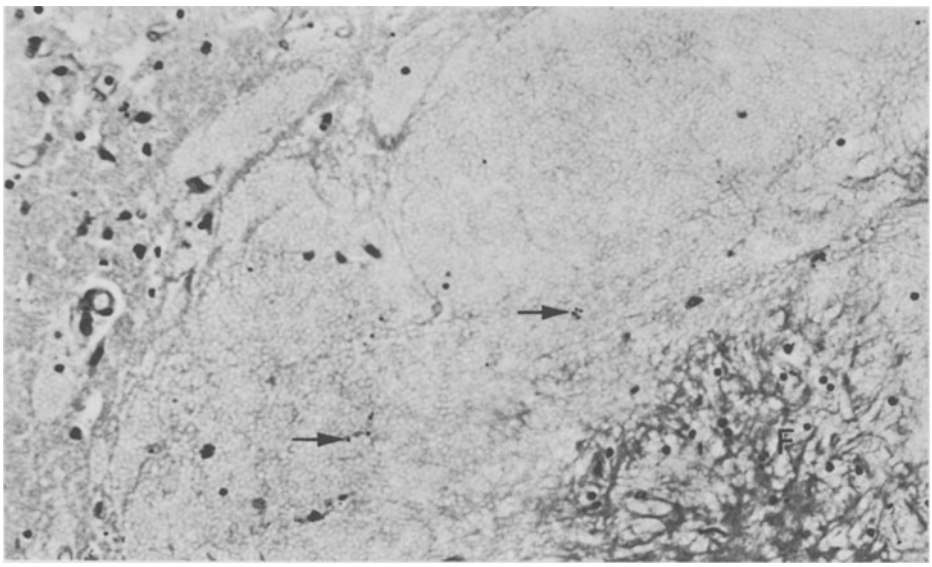

Fig. 18. A part of well-circumscribed space in brain containing ghost red blood cell and fibrin exudate (*F*). Small numbers of infected erythrocytes (*arrows*) are noted. HE, × 464

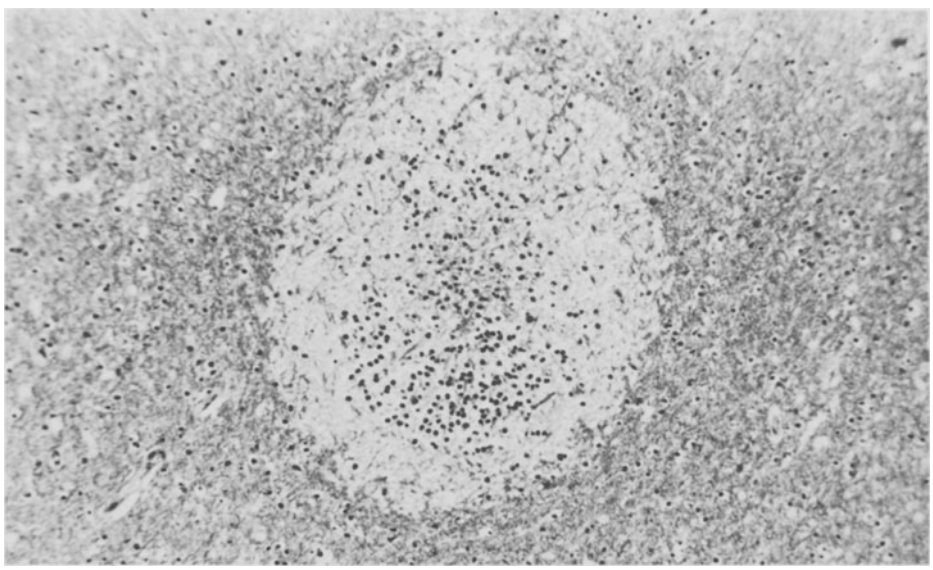

Fig. 19. A well-developed malarial granuloma in brain. HE, × 464

The lesions consist of a centrally located, thrombosed capillary, surrounded by necrotic brain tissue and small numbers of extravasated red cells, with accumulated glial cells. Necrotic neurones with glial reaction may present at the periphery of newly formed lesions. Glial cells and a few mononuclear leucocytes are more condensed in the well-developed lesions, which appear as light-staining, reticulated areas with a dark-staining centre (Fig. 19).

Glial granulomata have been interpreted as part of the repair process (SPITZ 1946). Extravasation of infected red cells, malaria pigment, fibrin, and possibly the free parasites stimulate the normal inflammatory cell, mainly mononuclear phagocyte, reaction in the brain and other organs.

Furthermore, the nerve cells in almost every region of the brain and spinal cord show some degree of degeneration and necrosis, with enlargement of the pericellular spaces (RIGDON and FLETCHER 1945).

5. Kidney

The kidney is an organ commonly involved in malaria, both in acute and chronic infections. Proteinuria of varying degrees is consistently observed. Azotaemia may be found even in uncomplicated cases, probably due to the hypercatabolism.

a) Acute Renal Failure

Renal failure as demonstrated by oliguria, and rarely anuria, as well as increased blood urea nitrogen (BUN) and creatinine, occurs in less than 1% of cases (SHEEHY and REBA 1967). This complication is usually associated with a high level of parasitaemia, haemoglobinuria, and rapidly progressive anaemia (CANFIELD et al. 1968; CANFIELD 1969), liver and cerebral involvement and consumptive coagulopathy. Non-oliguric renal failure may also be observed in acute falciparum malaria. Recently, the pathogenetic mechanism of acute renal failure in malaria has been reviewed (BOONPUCKNAVIG and SITPRIJA 1979). In our clinical study of 51 complicated falciparum cases, 31 developed acute renal failure. Eighteen cases were non-oliguric in type and DIC was clinically detectable in 11 of these. DIC was evident in all 13 oliguric patients. The overall mortality rate of both oliguric and non-oliguric types was 45% and 100% in oliguric renal failure (Tables 2, 3). However, with early haemodialysis the mortality of oliguric patients was reduced to 40% (UBOLWATRA et al., personal communication). In 42 cases of acute renal failure reported by STONE et al. (1972) 67% died of pulmonary insufficiency. The oliguric phase may last from a few days to a few weeks with dialysis treatment. During recovery diuresis occurs, but not to the marked degree observed in classical, acute, tubular necrosis.

Blackwater fever is a well-known complication in acute *P. falciparum* malaria. This condition does not necessarily indicate any renal abnormality. Associated azotaemia and oliguria may be seen in some cases. It occurs as a result of rapid and massive intravascular haemolysis. The haemoglobin and its derivatives are successively excreted in the urine (MAEGRAITH 1944). In falciparum malaria haemolysis usually occurs extravascularly. Intravascular haemolysis may occur spontaneously, or it may relate to some therapeutic agents, particularly quinine. In areas where G6PD deficiency is prevalent this complication is commonly encountered (BENJAPONGSH 1966). Blackwater fever may be seen in cases with minimal parasitaemia. DUKES et al. (1968) have pointed out the important effect of a hypersensitivity state resulting from a partial loss of immunity which may cause a severe intravascular haemolysis upon reinfection. The histological changes of the kidney in patients who had clinical evidence of acute renal insufficiency vary from degeneration to tubular necrosis and, in some instances, tubulorhexis may occur. Renal biopsy obtained from patients with non-oliguric renal failure showed only focal

vacuolisation of the proximal convoluted tubules without other abnormalities (SITPRIJA et al. 1967). On the other hand, STONE et al. (1972) reported that in the microscopic renal lesion of 42 cases, tubular degeneration and regeneration were the essential findings in biopsy specimens. The autopsy material showed patchy tubular necrosis and pigmented casts. In addition, these changes included tubular dilatation that was conspicuous in the distal and collecting tubules. The mitotic activity of regenerating cells was more pronounced in the macula densa than it appeared to be in other parts of the distal tubules (BOONPUCKNAVIG and SITPRIJA 1979). Significant tubular necrosis was also described in renal biopsies from patients with acute renal failure, jaundice, and anaemia (MUKHERJEE et al. 1971). Histological and electron microscopic findings in a renal biopsy in blackwater fever included tubular atrophy accompanied by lymphocytic infiltration, the demonstration of iron pigment within fibroblasts and atrophied tubular epithelium, while hyaline and eosinophilic casts in the tubules were reported (ROSEN et al. 1968). In an autopsy study SPITZ (1946) demonstrated deeply pigmented casts in the distal convoluted and collecting tubules associated with necrosis and regeneration of tubular epithelium in 14% of cases with clinical evidence of renal insufficiency. The amount of haemoglobin casts was reported to be greater in those cases with evidence of blackwater fever (WINSLOW et al. 1975).

Our study of fatal cases of acute renal failure concomitant with other severe complications, revealed various degrees of tubular damage ranging from minimal, non-specific degeneration to marked tubular necrosis involving most of the distal tubules, collecting and certain proximal tubules. Patients who recovered from the acute phase of renal failure and subsequently died with other complications have also shown regeneration of tubular epithelial cells, in approximately 80% the tubules containing eosinophilic, granular, haemoglobin casts, and necrotic epithelial cells (Fig. 20). Additionally special stains for haemoglobin and haemosiderin have revealed dense haemoglobin casts occluding the collecting tubules in the renal medulla (Fig. 21). These findings may explain the local severe dilatation of the tubule in the proximal portion (Fig. 22). Moreover, there were haemoglobin and traces of haemosiderin granules in the epithelial lining of the proximal convoluted tubules. By electron microscopy, these proximal tubules were seen to contain dense bodies in their cytoplasm (Fig. 23). Mononuclear phagocytic cells and chronic inflammatory cells were infiltrated in the interstitial tissue in association with severe tubular necrosis and tubulorhexis. Occasionally, these cells infiltrated round peritubular vessels which were occluded by parasitised red cells.

b) Glomerulonephritis

Recently HOUBA (1979) has divided glomerulonephropathy associated with malarial infection into two main groups: (a) acute, transient, and reversible nephritis and (b) chronic, progressive renal lesions.

The first group developed in human falciparum infection (BERGER et al. 1967; HARTENBOWER et al. 1972; BHAMARAPRAVATI et al. 1973; FUTRAKUL et al. 1974), *P. falciparum* in *Aotus* monkeys (HOUBA 1975; HUTT et al. 1975), *P. cynomolgi* in rhesus monkeys (WARD and CONRAN 1966), and *P. berghei* in rodents (BOONPUCKNAVIG et al. 1972; V. BOONPUCKNAVIG et al. 1973; SUZUKI 1974; GEORGE et al. 1976).

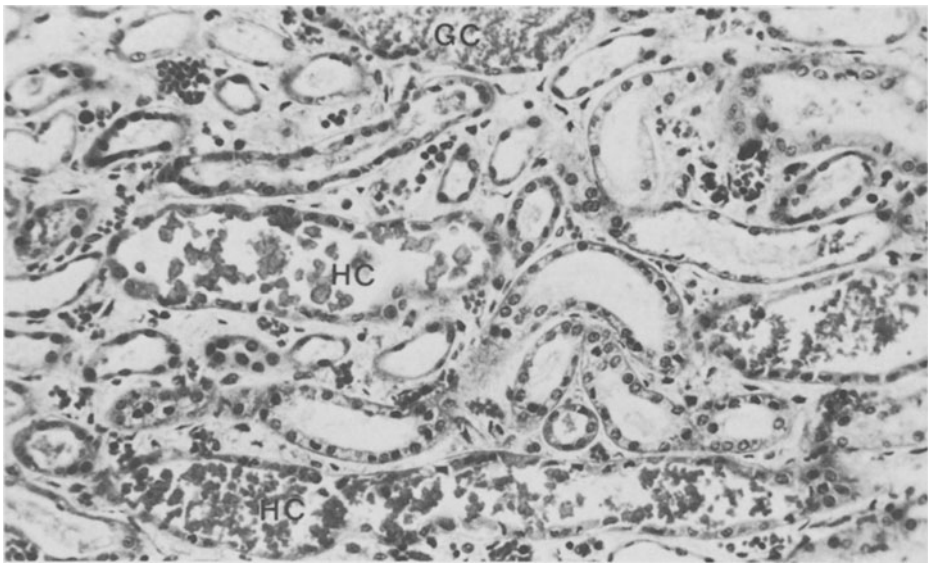

Fig. 20. *P. falciparum* infection with acute renal failure showing haemoglobin casts (*HC*) and granular cast (*GC*) in the convoluted and collecting tubules. HE, × 464

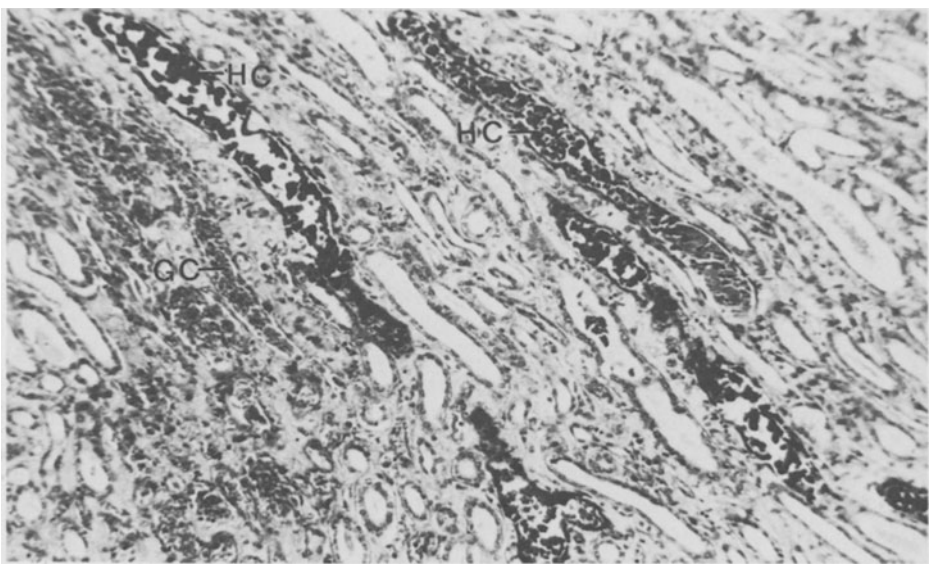

Fig. 21. Renal medulla showing dense collection of haemoglobin casts (*HC*) and granular cast (*GC*) in collecting ducts. Stained for haemoglobin, × 232

In patients with *P. falciparum* infection, urinary abnormality and glomerular pathology could be detected on about the 7th day after patent infection (BHAMARAPRAVATI et al. 1973). Light microscopy of renal biopsy tissue revealed mild hypercellularity of all glomeruli and irregular thickening of certain capillary walls. In our studies on autopsy kidneys, the pathological changes did not always

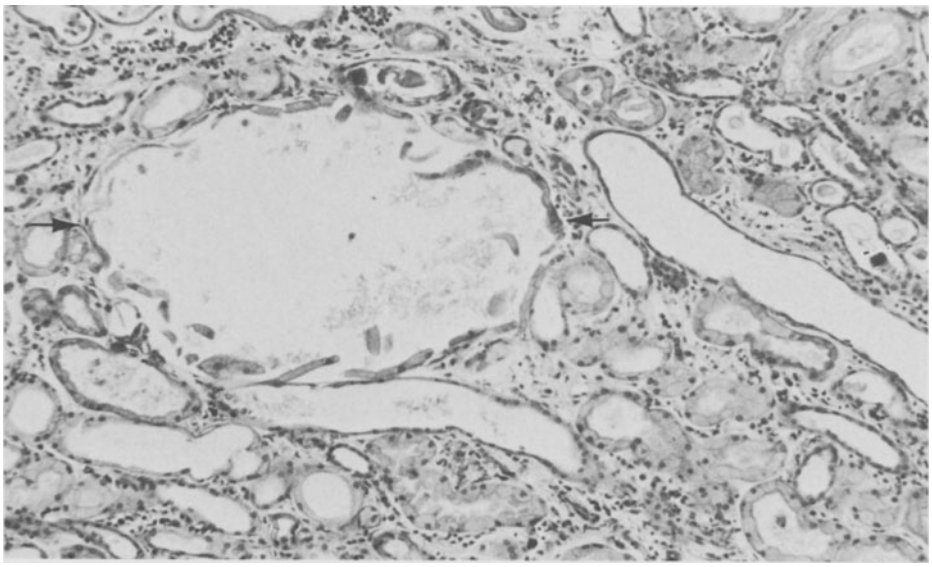

Fig. 22. Same cases as Fig. 21 showing cystic dilatation of a tubule (*between arrows*) in renal cortex. *P. falciparum* infection with acute renal failure. HE, × 232

correlate with the severity of the disease. There was no difference between glomerular alterations in DIC and non-DIC patients.

Glomerular hypercellularity is mainly due to the engorgement of capillary lumens with MPLM and mononuclear leucocytes, together with slight mesangial cell hyperplasia and increased mesangial matrix. A considerable amount of eosinophilic homogeneous or granular material is deposited along the capillary walls and in the mesangial areas (Fig. 24). Special stains show no definite thickening of the basement membrane. It should be added, however, that fibrin deposition in the glomeruli is very rare when compared with findings in the cerebral vessels. This may be explained by the fibrinolytic activity of kidney tissue (MYRHE-JENSEN 1971; SRAER et al. 1973). Fluorescent microscopy of both renal biopsy and autopsy specimens revealed granular deposits of immunoglobulins, complement and, in rare instances, malarial antigen in glomeruli during the 2nd and 3rd weeks of disease. The pattern of deposition is similar in all the cases. The complexes are confined mainly to mesangial areas and extend along certain contiguous loop walls (Fig. 25). IgM and BlC are most commonly deposited, together with IgG and IgA in a few cases. Eluates of immunoglobulin from autopsy kidneys have shown to be antimalarial antibody. Moreover, serum-soluble antigen was detected in cases with high parasitaemia (MCGREGOR et al. 1968; WILSON et al. 1969, 1975a, 1975b). Electron microscopy showed that lesions included electron-dense deposits in the subendothelial and paramesangial areas. Entrapment of deformed or fragmented erythrocytes in the spaces formed by folds of endothelium and subendothelial deposits of granular and amorphous particles were demonstrated (BHAMARAPRAVATI et al. 1973; BOONPUCKNAVIG and SITPRIJA 1979).

The evolution of the glomerular lesions was observed in mice infected with *P. berghei* (BOONPUCKNAVIG et al. 1972; V. BOONPUCKNAVIG et al. 1973). By im-

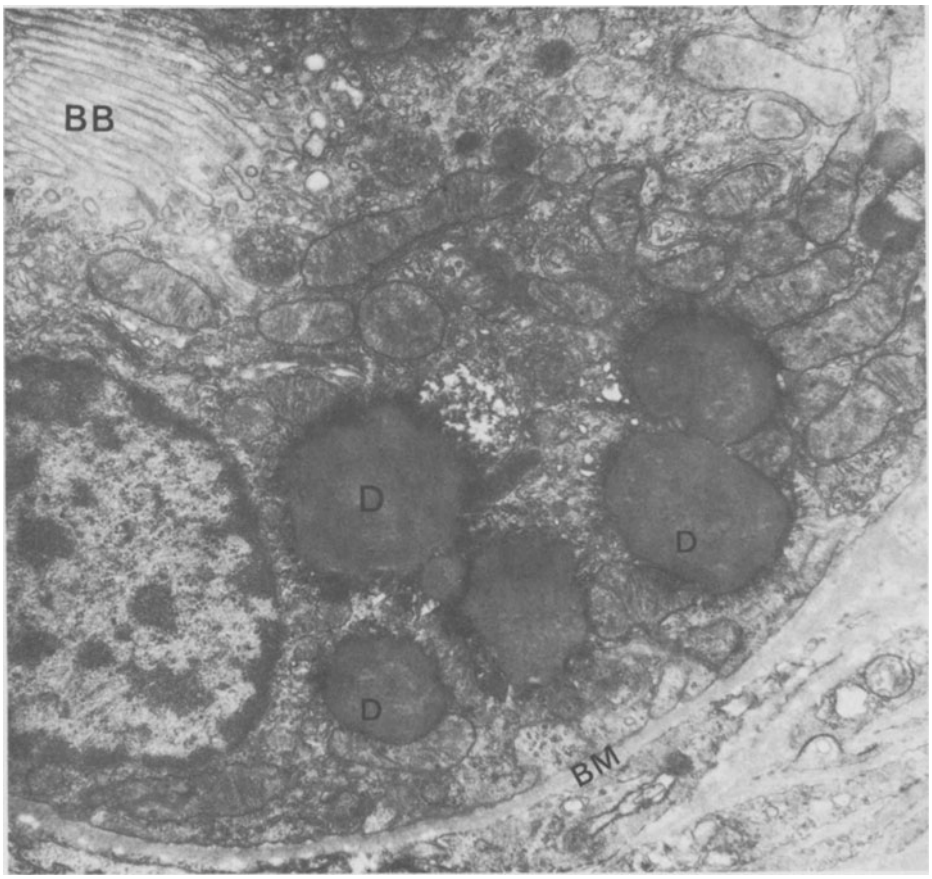

Fig. 23. Electron dense bodies (*D*) in an epithelial cell of proximal tubule in *P. falciparum* infection. *BB*, brush border; *BM*, tubular basement membrane. Electron micrograph, × 15400

munofluorescent microscopy, malarial corpuscular antigen in erythrocytes was detected in vessels on day 3 of the infection (S. BOONPUCKNAVIG et al. 1973). At the same time, either free-floating parasitised erythrocytes or groups of cells including infected erythrocytes, mononuclear phagocytic cells and lymphocytes appeared within the glomerular capillaries (Fig. 26) as was shown also in the cerebral vessels by light microscopy (Figs. 14, 15).

During the 2nd week of infection granular formed antigen, mouse globulin and C3 were diffusely deposited in mesangial areas and distributed along certain glomerular capillary walls. The eluated gammaglobulin from the kidneys proved to be anti-*P. berghei* antibody. Electron-dense deposits were demonstrated in the glomeruli from the 2nd week of infection onwards (V. BOONPUCKNAVIG et al. 1973). On day 10 of the infection serum-soluble malarial antigen and antimalarial antibody were detected (BOONPUCKNAVIG et al. 1976). By light microscopy proliferative lesions of glomeruli were most severe on day 14 of the infection. The sever-

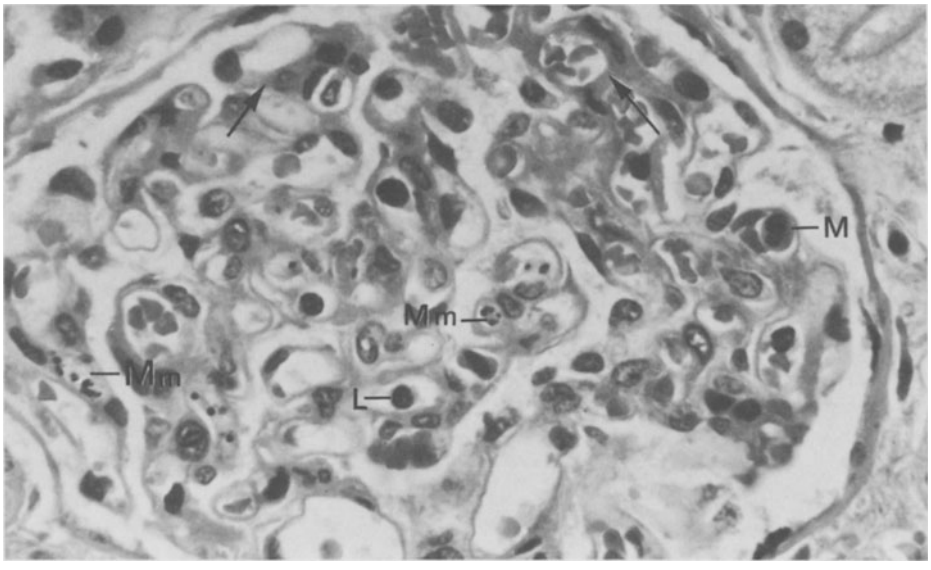

Fig. 24. *P. falciparum* infection, autopsy kidney. A glomerulus showing mild hypercellularity and irregular deposits of homogeneous, eosinophilic material (*arrows*) in mesangial areas. *M*, monocyte; *Mm*, malaria pigment-laden macrophages; *L*, lymphocyte. HE, × 1470

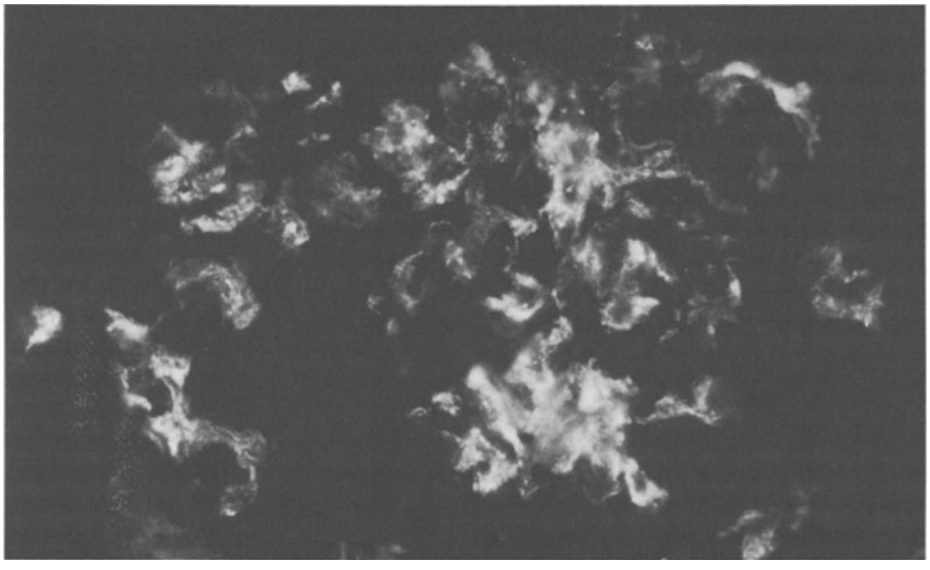

Fig. 25. Same case as Fig. 24 showing granular deposits of IgM in mesangial areas and along certain capillary walls. Fluorescent anti-human IgM, × 1470

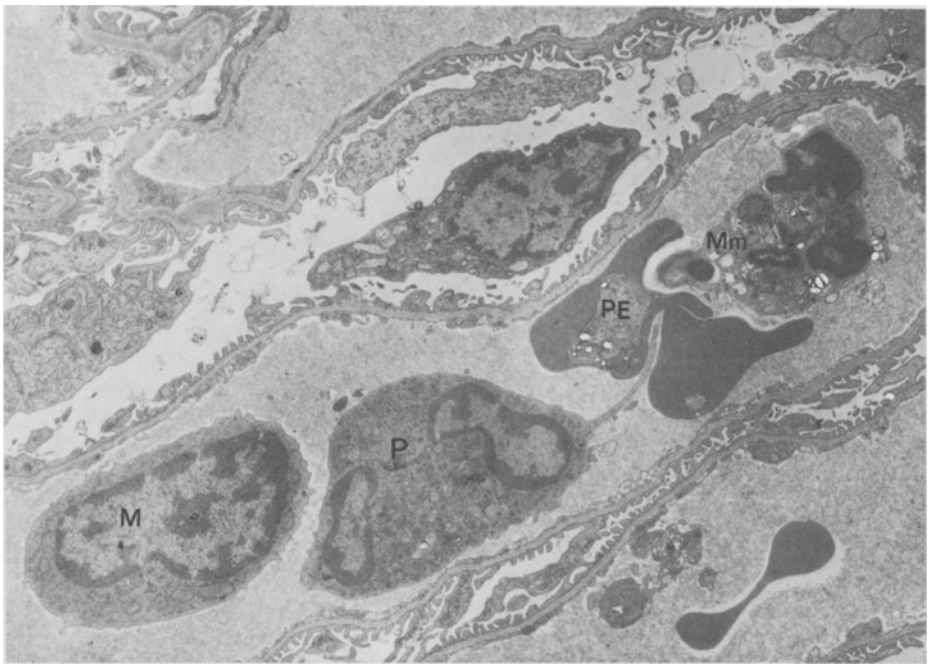

Fig. 26. Kidney in *P. berghei*-infected mouse, day 3 of infection, showing phagocytic activity of macrophage in the circulation. Note a parasitised erythrocyte (*PE*) is about to be phagocytosed by a phagocytic cell (*P*). Glomerular structures appear normal. *Mm*, malaria pigment-laden macrophage; *M*, monocyte. Electron micrograph, × 9165

ity of glomerular pathology, immunopathology, and course of disease could be modified in this experimental model.

The amount of granular antigen and intensity of immune complex deposits on the glomeruli are reduced in mice receiving an injection of colloidal carbon before or during the *P. berghei* infection (S. BOONPUCKNAVIG et al. 1979). Furthermore, malarial immune complexes were not detected in the glomeruli of *P. berghei*-infected mice which were treated with an immunosuppressive drug (cyclophosphamide) on day 5 of the infection (ENDARDJO et al. 1978). Recently V. BOONPUCKNAVIG et al. (1979) reported a different pattern of glomerular lesions in *P. berghei*-infected mice that received a suboptimal dose of the antimalarial drug chloroquine. The hyperimmune animals showed focal, immune complex, glomerular lesions. Recently PARBTANI and CAMERON (1979) reported detailed clinical information on this experimental animal model.

The special feature of this type of malaria glomerulonephropathy is the good response of the disease to treatment by antimalarial drugs.

The second group of glomerulonephropathy is associated with *P. malariae* in children and adults (GILLES and HENDRICKSE 1960, 1963; KIBUKAMUSOKE et al. 1967; KIBUKAMUSOKE 1968; ALLISON et al. 1969) and in the *Aotus* monkey (VOLLER et al. 1971, 1973; HOUBA 1975). KIBUKAMUSOKE and HUTT (1967) reported the histological findings in renal biopsies from 77 nephrotic patients in Uganda. Twenty-nine of the 31 cases, both children and adults, in whom *P. malariae* was

found showed various types of proliferative glomerular lesions, including minimal, focal, lobular, and chronic forms. The most common glomerular alteration in adults was reported to be proliferative glomerulonephritis characterised by proliferation of endothelial cells and occasional lobulation. Severe glomerulosclerosis appeared in a few adolescent patients.

HENDRICKSE et al. (1972) presented the results of light and immunofluorescent microscopic studies on renal biopsies in their collaborative clinicopathological study of 63 Nigerian children. Early in the course of the disease, there was thickening of the glomerular capillary walls. This change appeared to be segmental and affected only a few glomeruli. Special stains showed double contours of plexiform arrangements and fibrillary thickening of the basement membrane. Later on, more capillaries were involved and narrowing of some capillary lumens was prominent. Eventually, the whole glomerulus was hyalinised and sclerosed accompanied by extensive tubular atrophy and interstitial mononuclear cell infiltration. The severity of the histopathological lesions was divided into three grades which could be correlated with the results of treatment. Immunofluorescent examination showed glomerular, granular deposits of immunoglobulins in almost all the renal biopsy specimens (SOOTHILL and HENDRICKSE 1967; HOUBA et al. 1970, 1971; HENDRICKSE et al. 1972). There were certain differences in the sizes and patterns of the deposits (WARD and CONRAN 1969). The most common finding was of coarse, granular deposits distributed along the capillary walls. Very fine granules, uniformly distributed along the capillary walls, were found in a minority of cases. A mixed pattern was also observed. The relationship between the pattern of immunoglobulin deposits and response to treatment has been documented (HENDRICKSE et al. 1972). IgG and IgM may be detected together, or either of them may deposit alone. C3 can be detected in certain specimens but less extensively than immunoglobulin deposits. In about one-third of cases, *P. malariae* granular antigen was detected. Soluble antigen of *P. malariae* could be detected only by sensitive radioisotopic techniques in sera of man and monkeys with this infection (HOUBA et al. 1976).

Electron microscopic studies of biopsy specimens showed localisation of the electron-dense material within the glomerular basement membranes (HOUBA et al. 1970; ALLISON and HOUBA 1976). Irregular thickening of the basement membranes was very pronounced. The presence of small, lacunae scattered throughout the basement membrane appeared to be a constant finding in quartan malarial nephritis as described by HENDRICKSE and ADENIYI (1979).

In conclusion, studies in man and experimental animal models indicate that immune complexes play an important role in the pathogenesis of both groups of glomerulonephropathies associated with malaria. However, glomerular injury in the first group is reversible after antimalarial drug therapy. On the other hand, glomerulonephropathy in the second group is progressive and does not respond to antimalarial drugs. Several factors that promote chronicity of the latter group of glomerular disease have been proposed and these hypotheses are well summarised in WHO (1972) and HOUBA (1979).

6. Gastrointestinal Tract

In acute malaria, while gastrointestinal symptoms of anorexia, nausea, vomiting, abdominal pain, and diarrhoea are frequently observed, the true mechanism has

not been elucidated. OLSSON and JOHNSTON (1969) and KARNEY and TONG (1972) reported abnormal D-xylose and other absorptive tests as well as abnormal biopsies of the small intestine in falciparum malaria. Ischaemic changes of the mucosa may in part be responsible for this abnormality (MAEGRAITH and FLETCHER 1972). Vasoconstriction of the intestinal arterioles has been demonstrated, which may be explained on the basis of hyperexcitation of the sympathetic nervous system (SKIRROW et al. 1964).

Gastrointestinal bleeding has been observed in severe falciparum malaria with evidence of DIC. Some patients may present with melaena. In our study of 33 falciparum cases with evidence of DIC, nine experienced massive gastrointestinal bleeding and all of these died (Table 7). Bleeding was observed on admission in four cases, was noted during the clinical course in five, and three of these five received heparin administration for the treatment of DIC.

Postmortem examination of the gastrointestinal tract has shown multiple foci of mucosal haemorrhage in the stomach, small intestine and, occasionally, in the colon. Histopathological changes in non-haemorrhagic areas include dense accumulations of parasitised erythrocytes, MPLM, lymphocytes, and plasma cells in the oedematous lamina propria. Fibrin thrombi are demonstrable in submucosal arterioles (Fig. 27) in one case (case No. 3, Tables 4, 5). These changes are more pronounced in the jejunum than in the other parts of the gastrointestinal tract.

7. Cardiopulmonary System

Of all the complications in falciparum malaria cardiopulmonary involvement is considered the most serious that usually leads to a fatal outcome.

Cardiac dysfunction has been noted clinically, particulary in the terminal stage of malaria; yet pathological changes of the myocardium have rarely been specified in previous studies. Acute myocardial infarction complicating falciparum infection has only been documented in a few cases reported by MERKEL (1946).

In our autopsy study of falciparum infection, dilatation of the myocardial capillaries was remarkable. These vessels were distended with both infected and non-infected red cells as well as groups of mononuclear phagocytes, lymphocytes, and plasma cells (Fig. 28). Extravasation of infected and uninfected red cells accompanied by cellular inflammatory responses appeared locally in the interstitial tissue.

In spite of the fact that fibrin thrombi could be detected in several organs in severe cases complicated by DIC, none of these had fibrin thrombi in the coronary arteries and their branches. Acute myocardial infarction was not discovered in our study although cardiac arrest had been the immediate cause of death in three cases.

In recent years pulmonary complications have been noted more frequently than previously. They may be divided into two categories, acute pulmonary oedema and acute respiratory insufficiency.

In cases with acute pulmonary oedema the clinical features simulate those of classical pulmonary congestion of cardiac origin, namely evidence of fluid overload caused either by excessive intravenous infusion or oral intake or both, high central venous pressure, congestive hepatomegaly with hepatojugular refluxes, engorgement of the neck veins and congestive rales in both lungs. In most instances

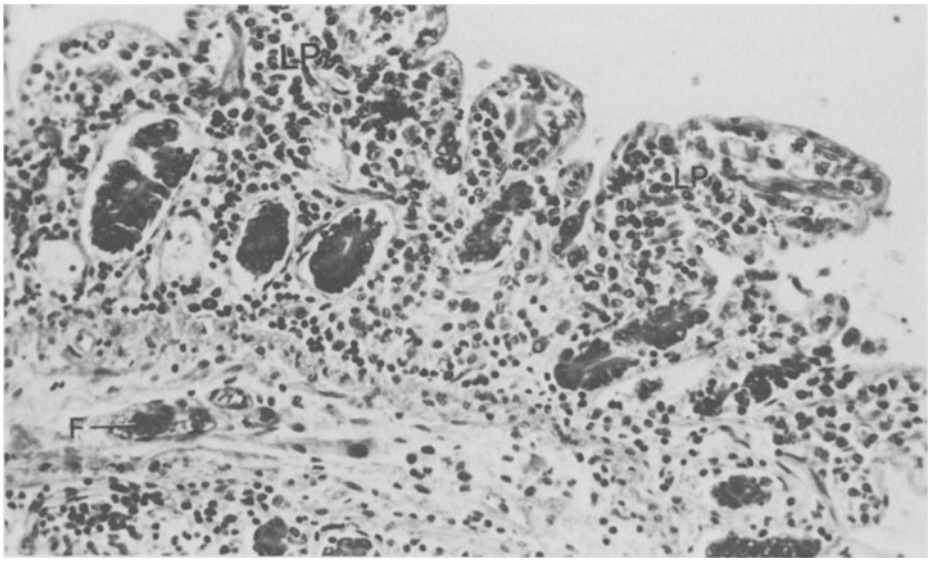

Fig. 27. Jejunum, showing dense infiltration of lymphocytes, plasma cells and malaria pigment-laden macrophages in the lamina propria (*LP*). Fibrin thrombus (*F*) is within the lumen of an arteriole. HE, × 464

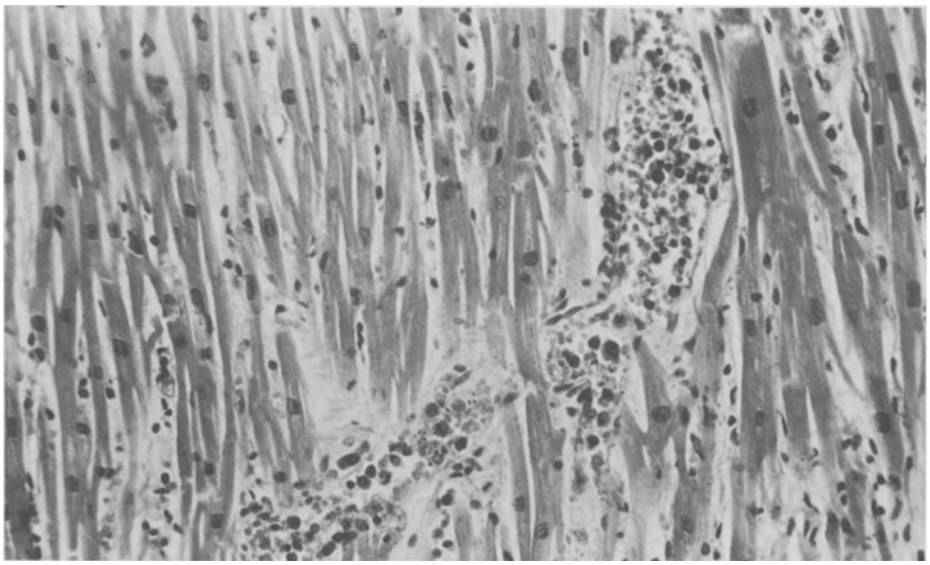

Fig. 28. Left ventricle showing myocardial vessels congested with parasitised erythrocytes and clusters of lymphoid cells and macrophages. HE, × 464

it is found in association with oliguria or anuria with hypoproteinaemia and electrolyte imbalance. Patients usually recover following effective antimalarial therapy and conventional medical treatment for pulmonary congestion. The pathological findings in these cases were similar to those of pulmonary oedema of cardiac origin, except for the evidence of malaria infection.

Another type of pulmonary complication, the so-called malarial lungs or acute pulmonary insufficiency is most serious, least understood and only recently recognised. In fact this is the "adult acute respiratory distress syndrome" (ARDS) reported in various severe bacterial or viral infections. BROOKS et al. (1968), SHEEHY (1975), and DEATON (1970) have reported a total of ten cases of American soldiers in Vietnam, all of whom died in spite of intensive therapy. In Thailand we have reported 12 patients with acute pulmonary insufficiency in falciparum malaria of whom nine died (PUNYAGUPTA et al. 1974).

In our series of 51 complicated falciparum malaria, 20 cases had lung complications, with 70% mortality (Table 2). Cerebral and renal complications were constantly associated with them (Table 3). Pulmonary complications in *P. falciparum* infection were also reported from Africa (MARKS et al. 1977; MARTELL et al. 1979). Other pulmonary changes included reversible interstitial pulmonary oedema (GODARD and HANSEN 1971), and bilateral pleural effusion (AL-IBRAHIM and HOLZMAN 1975). Haemodynamic studies by FEIN et al. (1978) suggested that pulmonary oedema was the result of a change in capillary membrane permeability. TONG et al. (1972) studied the pulmonary function in pulmonary complications of falciparum malaria and found a decrease in arterial oxygen tension, pulmonary shunting and increase in total and resistive work.

This complication of acute pulmonary insufficiency, or ARDS, in malaria is a separate entity from pulmonary oedema, even though in some cases evidence of fluid overload may also be found. The classical features are as follows:

1. It is found in the 1st week or early 2nd week of acute falciparum malaria with heavy parasitaemia.

2. Other complications, particularly of cerebral, renal, and haematological involvement, are recognised prior to the lung complications. In some cases, fluid overload may be the precipitating factor. Central venous pressure is usually low at the time of attack.

3. Patients develop abrupt respiratory distress, namely tightness in the chest, orthopnoea, cyanosis, severe cough, and tachycardia. Laboratory tests show hypoxaemia in spite of intensive oxygen therapy. The disease runs a rapidly progressive course and the patient usually succumbs during the first 24 h or soon afterwards. Extensive respiratory care including a peep ventilator may be life saving if malarial parasites can be eradicated in time, and other complications, particularly those of electrolyte and haematological abnormalities and renal involvement, can be corrected.

Pathologically, in general congestion, oedema, and haemorrhage are among the common gross findings. Microscopically, the pulmonary lesions appear in many forms. Throughout most of both lungs there is distention of alveolar capillaries due to the accumulation of clusters of cells including infected red cells, MPLM, lymphocytes, and plasma cells (Fig. 29). Increased pulmonary reticuloendothelial activity has been demonstrated by the increased lung uptake of technetium 99M-sulphur colloid (ZIESSMAN 1976).

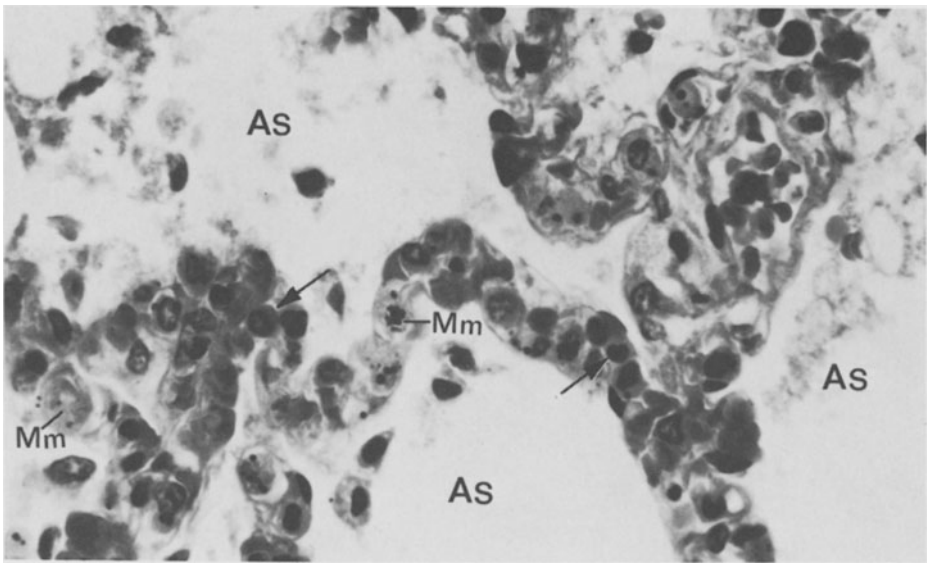

Fig. 29. Pulmonary alveolar capillaries congested with malaria pigment-laden macrophages (*Mm*), lymphocytes and plasma cells (*arrows*). *AS*, alveolar space. HE, × 1470

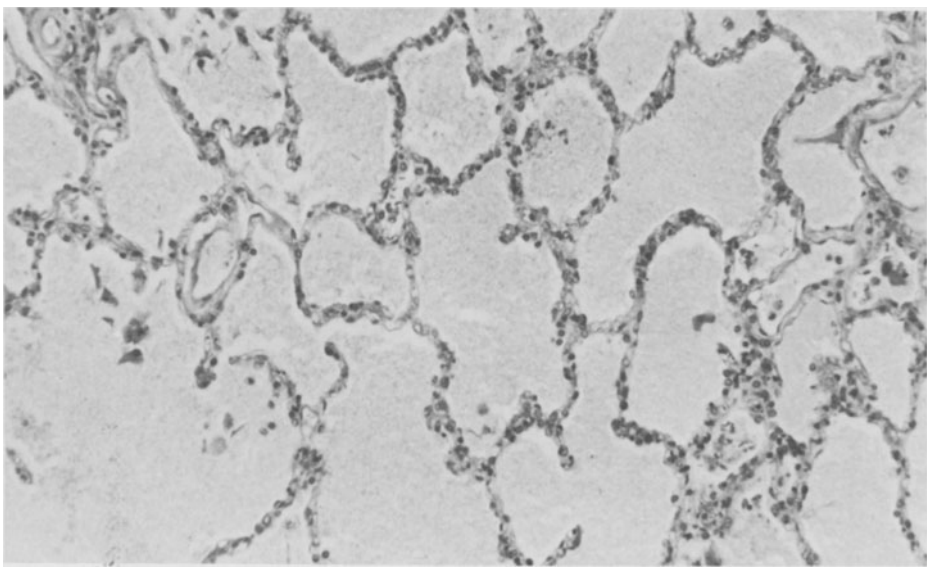

Fig. 30. Showing severe oedema of lung. HE, × 368

In addition, our postmortem examinations of lungs from falciparum-infected patients who had terminal pulmonary complications have shown three distinct histological features. In the majority of cases (see Tables 4, 5) the alveoli and alveolar ducts contain pale, eosinophilic, proteinaceous fluid (Fig. 30) with scattered, small, haemorrhagic foci. Changes are similar in both lungs in all cases except for

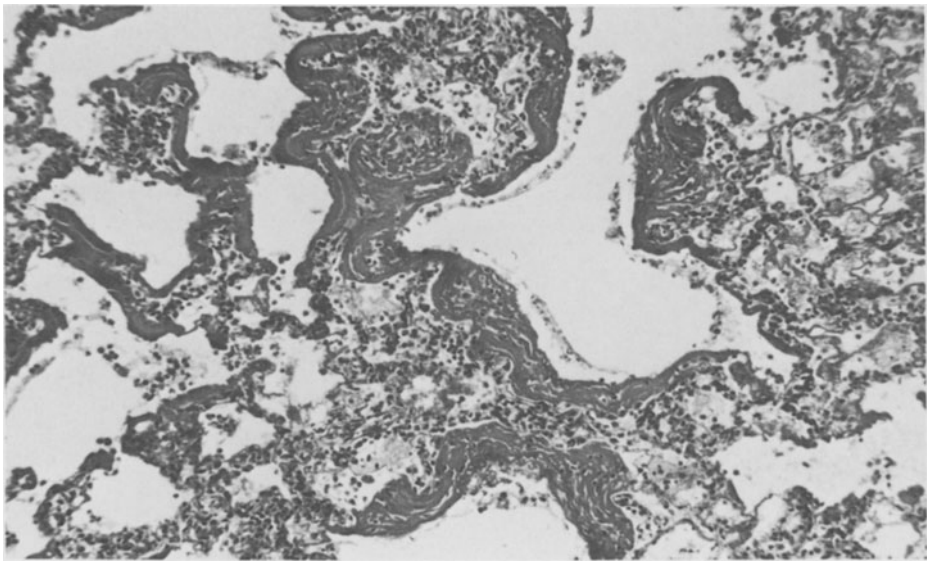

Fig. 31. The inner surface of the pulmonary alveoli is coated with a laminated membrane. HE, ×232

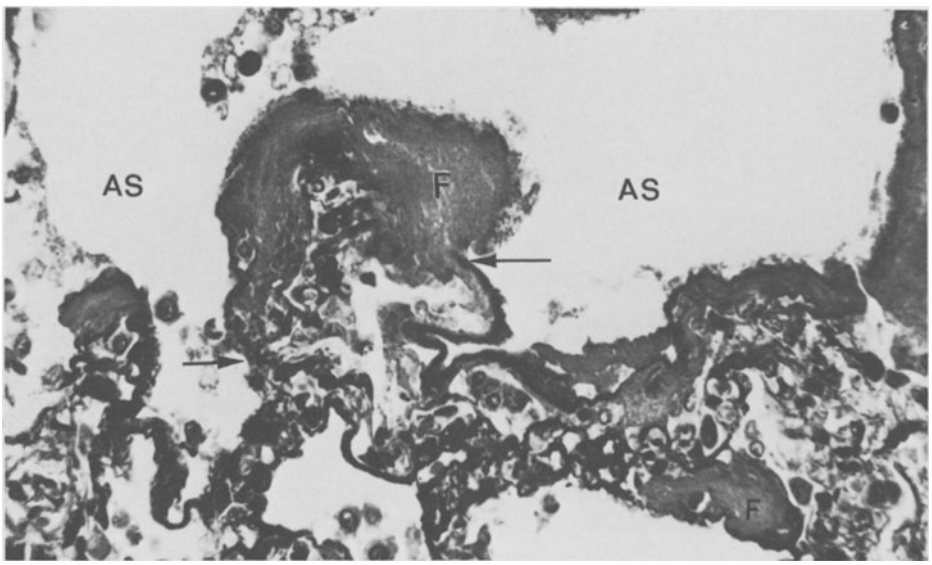

Fig. 32. Fibrin component of the pulmonary alveolar membrane. *Arrows* indicate points of rupture of alveolar basement membrane. *F*, fibrin; *AS*, alveolar space. PTAH, ×928

the degree of severity. Interlobular septae are severely oedematous. Fibrin thrombi can be demonstrated in certain alveolar capillaries. The second group of patients have no or slight pulmonary oedema, but show prominent membrane coating on the inner surface of alveoli, alveolar ducts, and the terminal bronchioles. These

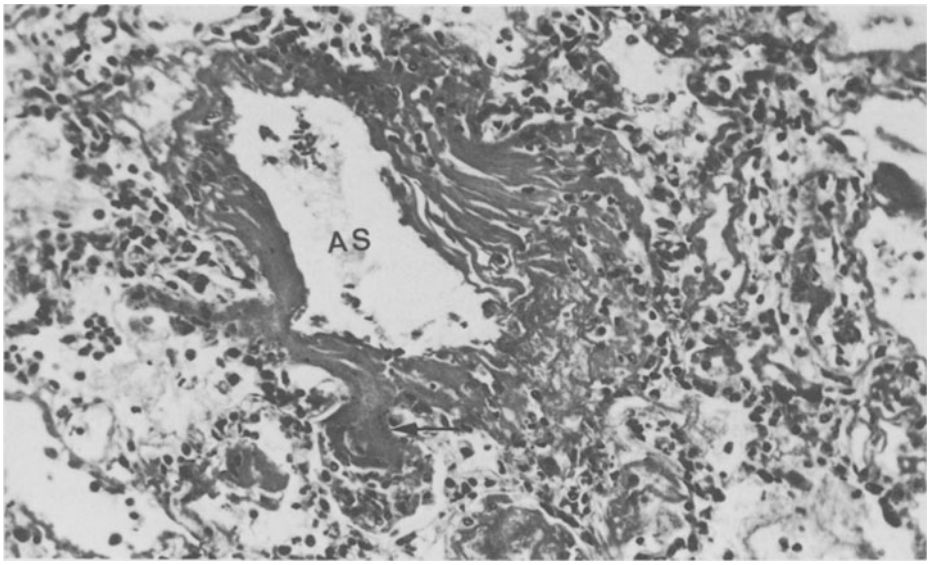

Fig. 33. Severe destruction of pulmonary alveoli by laminated membrane and cellular inflammatory reaction. Note the membrane contains malaria pigment (*arrow*) and cell debris. *AS*, alveolar space. HE, × 464

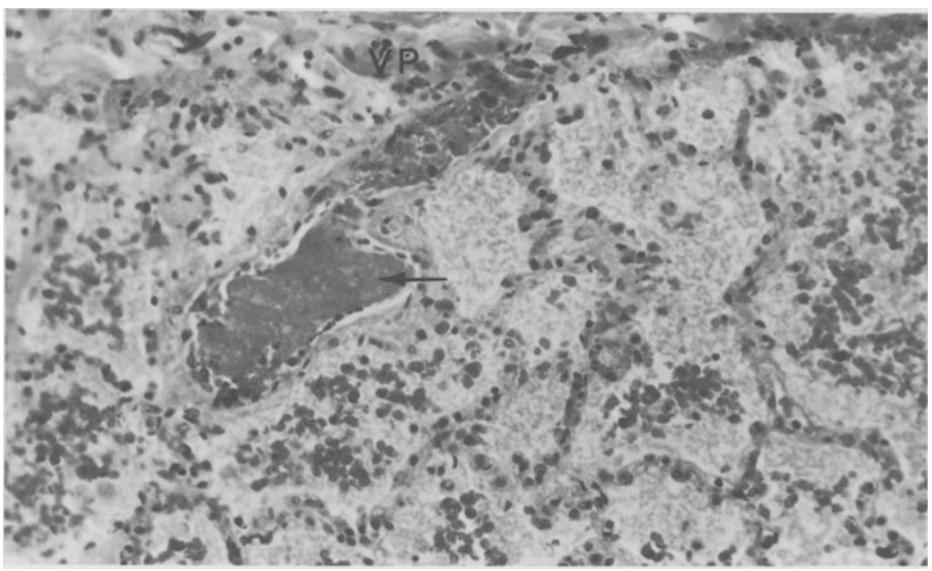

Fig. 34. Oedema and haemorrhage with fibrin platelets thrombus (*arrow*) in a septal vessel of lung. *VP*, visceral pleura. HE, × 464

membranes may be uniformly or irregularly distributed in some pulmonary lobules. Although they have been called "hyaline membrane" by several investigators, according to our observations these membranes have a different histological architecture from the membranes in typical hyaline membrane disease. The out-

standing features of the membrane found in malarial lung include the laminated appearance and the finding of nuclear debris, malaria pigment, and mononuclear leucocytes between each layer of the membranes (Fig. 31). Special stains show that the membranes are composed mainly of fibrin and mucopolysaccharide material, with traces of haemosiderin pigment. Neutral fats and haemoglobin are not present. Occasionally, membranes are prominently located at the junction of the alveolar ducts and alveolar sacs (Fig. 32). Eventually they become thickened, destroy the underlying alveolar walls, and induce cellular inflammatory reactions (Fig. 33). Another group of pulmonary lesions consists of lobular or extensive haemorrhages that are always developed together with pulmonary oedema and the appearance of fibrin thrombi in the vessels of larger calibre than the capillaries. These thrombi may not be seen in areas of haemorrhage (Fig. 34).

Furthermore, SPITZ (1946) has described secondary bacterial infection of the lungs in 42% of patients. Other types of pneumonitis, including atypical pneumonia, were described by APPLEBAUM and SHRAGER (1944). In our series, this type of complication developed in 3 out of 22 cases.

8. Multiple Organ Complication and Concluding Remarks

In complicated falciparum malaria usually more than one of the major organs are involved (Table 3). Cerebral complication is the most frequent and has been detected the earliest. About one-half of all patients with brain involvement also showed renal and pulmonary complications. Renal failure of oliguric or non-oliguric type was the second most common complication, and about two-thirds of them experienced concomitant cerebral manifestations. Lung, liver, and cardiac involvement and gastrointestinal bleeding were also recognised at the same time or later. Almost all cases with pulmonary oedema or pulmonary insufficiency, as well as those with massive gastrointestinal haemorrhages and cardiac involvement, experienced preceding brain and renal complications. Some other complications such as pancreatitis (JOHNSON et al. 1977), nephrotic syndrome (BERGER et al. 1967) and renal failure due to acute glomerulonephritis were not observed in our patients with *P. falciparum* infection.

All falciparum cases with massive gastrointestinal bleeding died in spite of intensive treatment. All of them presented laboratory evidence of DIC. Pulmonary complications produce a very high mortality of 70% followed by cardiac, pulmonary, and renal complications with about 45%. About one-third of patients with cerebral malaria died. Liver involvement offers the best prognosis. However, the cause of death is the result of multiorgan rather than single organ involvement. The overall mortality in these 51 complicated cases of *P. falciparum* malaria was 28%. Table 7 shows clearly the bad prognosis in cases with laboratory evidence of DIC, where the mortality rate was 42%, compared with nil in the non-DIC group.

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