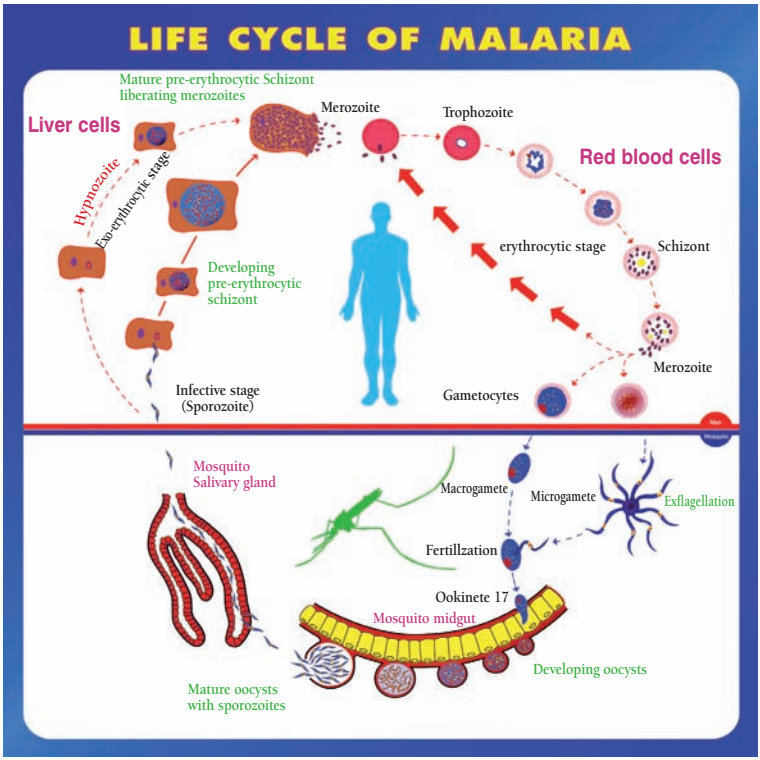


Fig. 2 Life cycle of malaria (Adapted with permission from Assist. Prof. Chotechuang Panasoponkul, Department of Medical Entomology, Faculty of Tropical Medicine, Mahidol University Thailand).

Life cycle

The infective agent is the sporozoite, which is injected into humans by the bite of an infected female anopheline mosquito. Sporozoites disappear from the blood within 1 hour and enter liver cells where they proliferate into merozoites and the exoerythrocytic cycle starts. Development in liver cells requires 1-2 weeks depending upon the species of *Plasmodium* (*P. falciparum* and *P. vivax* 1 week, *P. malariae* and *P. ovale* 2 weeks, no data at present for *P. knowlesi* in humans). In *P. vivax* and *P. ovale*, some sporozoites remain dormant (hypnozoites) for months or occasionally a year or more before proliferation (relapse). After replication in the liver, parasites undergo asexual multiplication in the erythrocytes. The merozoites infect erythrocytes and constitute the erythrocytic forms of the parasite.

Erythrocytic parasite development can follow two pathways. In the first pathway, asexual parasites develop from young ring forms through trophozoites and schizonts, which subsequently rupture, then reinvade erythrocytes. The erythrocytic cycle of schizogony is repeated over and over again, thus continuing the cycle of malaria infection. In the second pathway in *P. falciparum* infection after approximately 1 week, some erythrocytic parasites differentiate into male and female gametocytes, thus entering the sexual pathway. When male and female gametocytes are ingested by female mosquitoes during a blood meal, fertilization occurs, resulting in a zygote, which penetrates the mosquito midgut wall to form an oocyst containing sporozoites. When oocysts mature (10-14 days), they rupture releasing sporozoites, which invade the salivary gland and are ready to be injected back into humans, completing the malaria life cycle (White, 2000). Table 1 shows the characteristics of *P. falciparum, P. vivax, P. ovale* and *P. malariae*. The detailed characteristics of *P. knowlesi* in humans are not available in the literature at present.

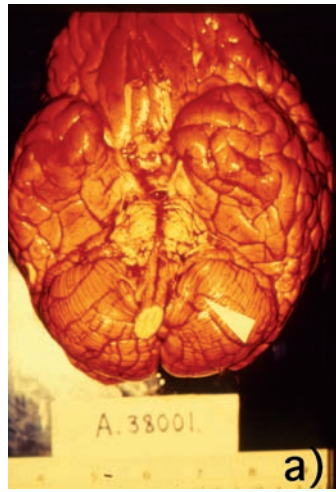
Table 1. Characteristics of 4 species of human malaria (Looareesuwan *et al.*, 1990)

	P. falciparum	*P. vivax*	*P. ovale*	*P. malariae*
Pre-erythrocytic stage (days)	5.5	8	9	14-15
Presence of hypnozoites	-	+	+	-
Pre-patent period (days)	8-25	8-27	9-27	15-30
Incubation period (days)	12 (9-14)	15 (12-17) or up to 6-12 months	17 (16-18) or longer	28 (18-40) or longer
Erythrocytic cycle (hours)	48	48	48	72
Nature of host erythrocyte	All	Reticulocytes and young normocytes, Duffy group positive	Reticulocytes and young normocytes	Normocytes
Enlargement of host erythrocyte	-	+ +	+	-
Parasitemia/mm^3				
Average	40,000	2,000,000	20,000	50,000
Maximum	9,000	30,000	6,000	20,000
Primary attack	Severe in non-immune	Mild to severe	Mild	Mild
Febrile paroxysm (hours)	16-36 or longer	8-12	8-12	8-10
Relapse	-	++	++	-
Period of recurrence	Short	Variable	Variable	Very long
Duration of untreated infection (years)	1-2	2-5	2-5	3-50
Stripping of host erythrocyte	Maurer's clefts	Schüffner's dots	Schüffner's dots	Ziemann's stripping

Pathology

In fatal falciparum malaria, autopsy specimens usually show cerebral edema. Brain herniation and brainstem compression can happen, but this occurs in less than 5% of cases (Fig 2a) (Looareesuwan *et al.,* 1990). Cut surfaces of the brain reveal petechial hemorrhages (Fig 2b). Microscopically, minute petechial hemorrhages are frequent, particularly in the white matter (Fig 3a). The microvasculature of the vital organs is packed with erythrocytes containing mature forms of the parasite. Blood vessels become occluded due to sequestration of parasitized red blood cells (PRBCs). The process of sequestration is possible due to the attachment of PRBCs to the vascular endothelium (Fig 3b). Sequestration is not uniformly distributed; it tends to be greatest in the brain followed by the heart, lungs, and small intestine (Pongponratn *et al.,* 1991).

There is abundant intra- and extra-erythrocytic pigment deposit in vital organs, such as the liver (Fig 4a), spleen, and placenta. In the liver, these hemosiderin pigments are seen to be packed within the sinusoidal areas (Fig 4b). The kidneys of fatal malaria cases often show congestion and areas of petechial hemorrhage (Fig 5a). PRBCs, as well as hemosiderin pigment, are densely found within the glomerular tufts (Fig 5b).



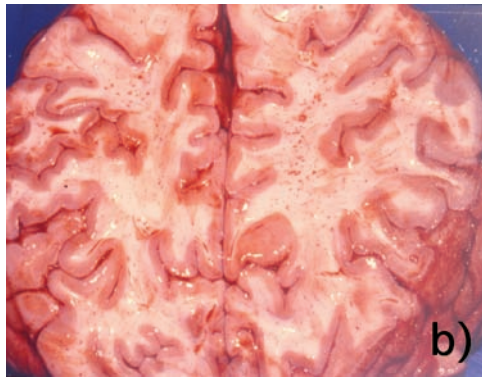


Fig. 2 Brain of cerebral malaria. a) Brain edema with herniation can be seen. b) Cut surface of the cerebrum shows dispersed petechial hemorrhages, particularly in the white matter (Courtesy, Department of Tropical Pathology, Faculty of Tropical Medicine, Mahidol University, Thailand).

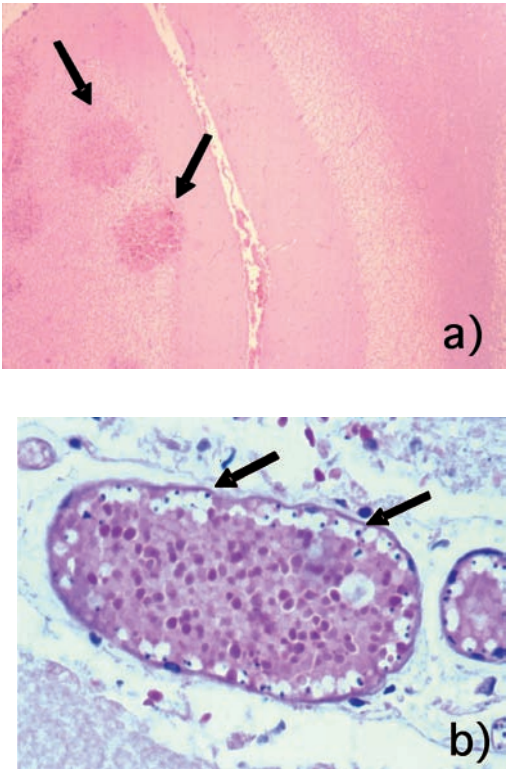


Fig. 3 Microscopic findings of cerebral malaria. a) Petechial hemorrhages are frequently found in the white matter (arrow) (H&E stain X100). b) Parasitized red blood cells seen within the vascular lumen mostly cytoadhere to endothelial cells lining the vascular wall (arrow) (H&E stain X400) (Courtesy, Department of Tropical Pathology, Faculty of Tropical Medicine, Mahidol University, Thailand).

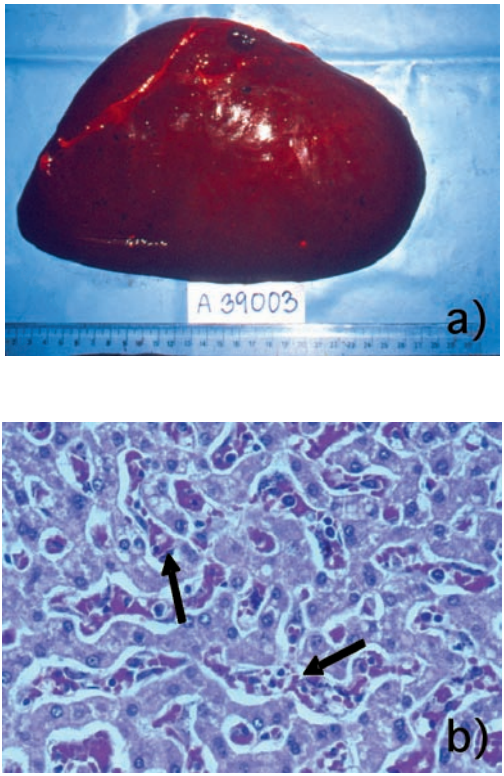


Fig. 4 Liver of severe malaria case. a) Liver is grossly enlarged and appears as deep brown to red. Capsular hemorrhages are seen. b) Microscopic finding of liver showing parasitized red blood cells and hemosiderin pigments packed within the sinusoids (arrow) (H&E stain X400) (Courtesy, Department of Tropical Pathology, Faculty of Tropical Medicine, Mahidol University, Thailand).

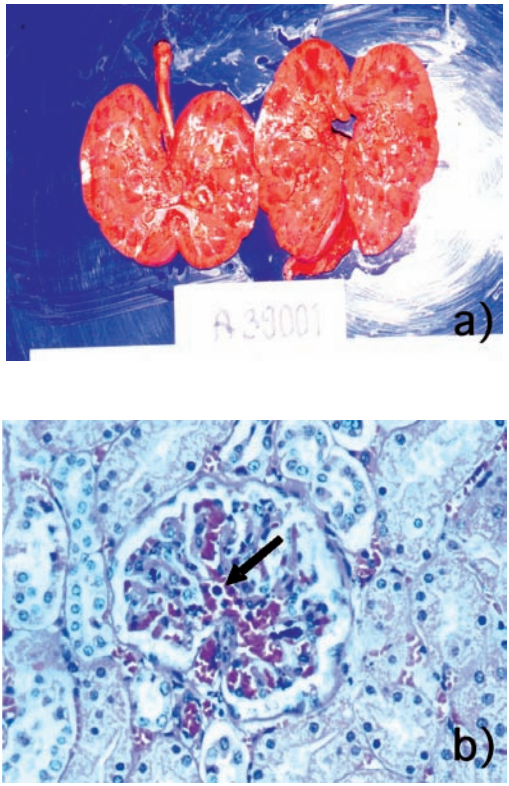


Fig. 5 Kidney of severe malaria case. a) Cut surfaces show hemorrhagic appearance. Petechial hemorrhages are frequently found. b) Microscopic finding of kidney showing congested glomeruli and presence of packed parasitized red blood cells (arrow) (H&E stain X400) (Courtesy, Department of Tropical Pathology, Faculty of Tropical Medicine, Mahidol University, Thailand).

Pathogenesis

Fever in malaria results from the release of tumor necrosis factor (TNF) and other endogenous cytokines in response to parasite antigens. Signs and symptoms of malaria are associated with the rupture of parasitized erythrocytes. In severe malaria, tissue hypoxia is believed to play an important role leading to organ dysfunction. However, the pathophysiological mechanisms are still not clearly understood, especially in cerebral malaria. During the past 30 years, many hypotheses have been put forward to explain this condition. It is thought that sequestration of parasitized erythrocytes, the phenomenon of cytoadherence, rosette formation, and reduced erythrocyte deformability, lead to microvascular obstruction, and along with the effect of cytokines contribute to tissue hypoxia and organ dysfunction (Looareesuwan *et al*., 1997).