CHAPTER I

INTRODUCTION

Malaria is a disease caused by sporozoa of the genus Plasmodium. It remains a major scourage and is still far from being eliminated from the world. It attacks man at all ages and effects the sexes equally. The females of certain species of anopheline mosquitoes are the definitive hosts; man is the intermediate host. Infection is normally transmitted to man by the bite of an infected mosquito. The disease may be induced artificially by injection of either sporozoites or trophozoites.

Malaria is characterized clinically by fever, which is often periodic; varying degrees of anaemia; splenic enlargement; and various syndromes resulting from the physiological and pathological involvement of certain organs including the brain, the liver and the kidneys (Adams and Maegraith, 1953). Sometimes it is characterized by intravascular haemolysis and sudden shock. The pathophysiological responses to the malaria infection which give rise to such clinical states are very complex. They are beleived

to be due to the tissue anoxia caused by (1) anoxemia, (2) deviation in the blood flow from the vasomotor changes, and/or disseminated intravascular coagulation and development of stickness and the sludging of the erythrocytes, (3) alteration in the capillary endothelial cells, (4) histotoxic anoxia, and (5) rigidity of red cell. These factors could be summarized as follows:-

1. Anoxemia. Anaemia is very common in malaria. Since the anaemia is more extensive than the parasitaemia and may occur when the parasitaemia has been negligible, it is usually assumed that both parasitized and non-parasitized cells are destroyed. There are two major factors involved in the removal of erythrocytes from the circulation in malaria infection i.e., erythrophagocytosis (Zuckerman, 1964) and intravascular haemolysis (Devakul et al., 1969). Since the degree of anaemia is quite extensive in some patients, this could cause tissue anoxia.

2. Changes in blood flow.

2.1 Vasomotor changes. In experimental malaria, dynamic vascular changes occur in the liver and kidneys and may be due to hyperactivity of the sympathetic nervous systems.

Skirrow and Maegraith (1964), and Skirrow et al., (1964) demonstrated major constriction in the smaller branches of the portal vein during the late stages of Plasmodium knowlesi infection of rhesus monkeys during the state of shock. Similar changes in the renal circulation have been demonstrated in late P. knowlesi-infected rhesus monkeys (Chongsuphajaisiddhi, 1966). Vasoconstriction and hypotention occurring in the late stage of P. knowlesi infection may be the main aetiology of circulatory shock. Bloch et al., (1966) defines shock as " a state of progessive circulatory failure in which the cardiac output is insufficient to meet tissue requirements for nutrition, oxygenation or waste disposal ". They consider that the major initiating and maintaining mechanism of shock are decreased cardiac output, increased peripheral vascular resistance and decreased effective circulating blood volume. Increase in sympathetic activity is a dominant consequence of reduced cardiac output, the resulting response to this activity is a selective reduction of blood flow to the renal and splanchnic vascular beds and to the skin. They may produce tissue anoxia or clinical sign of shock.

2.2 Disseminated intravascular coagulation. Maegraith (1967) pointed out that another possible mechanism of obstructing blood flow was intravascular coagulation. The mechanism of intravascular coagulation was probably precipitated by the massive haemolysis in malaria (McKay, 1965; and Dennis et al., 1967). Malaria is one of the diseases causing haemolysis which might lead to intravascular clotting as demonstrated by Dennis et al., (1968) and Reid and Sucharit, (1972). The intravascular coagulation may lead to the obstruction of the flow of blood in vessel of various organs which may cause tissue anoxia.

2.3 Sludging. The development of stickness and the sludging of the erythrocytes in the late stages of P. knowlesi infection were described by Knisely et al.,(1945). After the rupture of mature schizonts; a fluffy precipitate (fibrin-like substance) was formed and the sludge-like mass of infected and uninfected red blood cells (RBC) formed could impede the circulation of the blood, giving rise to local tissue anoxia (Knisely et al., 1945).

3. Changes in capillary endothelium. Damage to the vascular endothelium is a common histological finding in case

of severe malaria, and is indicated in the pathological picture by the development of stasis in certain organ, notably the brain and heart. In inflammation, the increase in capillary permeability arises from the action of pharmacological active polypeptides. It has been found that in advanced stages of P. knowlesi malaria the concentration of active polypeptides kinins increase in the circulation where there are presumably capable of exerting their physiological effects such as increasing capillary permeability, producing peripheral vasodilation and stimulating the adrenal medulla. Increase in capillary endothelial permeability to protein which is associated with the loss of fluid, stasis of red cells and diapedesis of red cells through the vessel walls occur, so it reduced the fluid volume of the local circulating blood and lead to general state of tissue anoxia. (Migasena and Maegraith, 1968; Onabanjo and Maegraith, 1970a, 1970b).

4. Histotoxic anoxia. In mammalian malarias the tissue cells are damaged in such a way that they are unable to utilize efficiently the apparently adequate supplies of oxygen. It has been shown that both the respiration and

oxidative phosphorylation of isolated liver-cell mitochondria are profoundly inhibited during overt infection with P. knowlesi and P. berghei (Riley and Deegan, 1960; Riley and Maegraith, 1962; Maegraith et al., 1962). Moreover, sera of infected animals and man contain a factor which causes similar biochemical lesions in normal liver-cell mitochondria (Riley and Maegraith, 1961; Maegraith et al., 1963, 1966). It was further postulated that this factor formed an important link between the parasite and host, possibly acting as an initiating agent leading to the " chain reaction " of pathophysiological process characteristic of acute malaria (Maegraith, 1965).

It was well established that lipids, especially phospholipids, form an essential part of the structure of mitochondrial membranes, the main site of respiration and oxidative phosphorylation in the cell (Green and Fleischer, 1963). On the other hand, it is also well known that certain lipids, notably lysolecithin and certain fatty acids, can interfere with the normal respiratory processes of mammalian cells (Witter et al., 1957; Munoz and Leloir, 1943; Wojtczak and Lehninger, 1961; and Enser, 1964). It was shown that in advanced stages of P. knowlesi malaria, serum lipids in the

host animal were markedly elevated. This hyperlipaemia included a significantly-raised non-esterified fatty acid level (Angus et al., 1971; Maegraith et al., 1965, 1966). Polysaccharides, small polypeptides, inorganic phosphate and lactate were also found to be increased in the serum of P. knowlesi-infected monkey. These serum factors could inhibit the mitochondrial respiration and oxidative phosphorylation as demonstrated by Thurnham et al., 1971a, 1971b) which may cause tissue anoxia.

5. Rigidity of red cell. Much recently accumulated evidence suggested that the internal changes in red cell per se may be responsible for the outset of the pathophysiological changes in malaria. These red cells will loss the deformable properties and will not be able to pass through the capillaries, and may lead to the obstruction of the flow of blood in vessels of various organs which have been demonstrated in autopsies(Dudgeon and Clarke, 1917; Spitz, 1946; and Areekul, 1973).

Erythrocyte deformability may be defined as those geometric and physical characteristic which permit a cell whose greater diameter normal exceed 8 μ to pass through

14 μ or longer segments of normal capillaries which range from 3 to 12 μ in diameter. The remarkable deformability of normal mature erythrocytes appears to depend on at least three factors:-

1. Maintenance of the biconcave shape, which in turn depends on a high ratio of surface area to volume.

2. Normal internal fluidity of the cell, which depends primarily on the properties of normal haemoglobin.

3. Intrinsic membrane deformability which is significantly affected by the relationship between intracellular adenosine triphosphate (ATP), calcium and magnesium, and may be affected by pH and by oxygen tension in local regions of microcirculation (Weed, 1970).

The mean deformability of a population of red cells can be determined by viscosity or filterability measurement. which define the ability of cells to pass through micropore filters. It has been shown that P. coatneyi and P. knowlesi infected red cells have reduced filterability through 5 μ pores of polycarbonate sieves and aggregation in plasma. The viscosity of red cells infected with these 2 species of malaria was found to be increased at both low and high shear

rate (Miller et al., 1971; Miller et al., 1972). Therefore, the red cells infected by P. knowlesi and P. coatneyi become less deformable and could alter the rheologic properties which may explain the mechanism of obstruction of cerebral capillaries. It has been suggested that the deformable red cell in subjects with malaria infection may be due to the lack of ATP (Areekul, 1973). It is well established that ATP is essential for maintenance of cation balance and for the couple sodium-potassium active transport mechanism of the human red cell (Hoffman, 1962). Its major functions are glycolysis at the hexokinase and phospho-fructosekinase steps, provision of energy for cation pumping and ATP is also essential for maintenance of red cell shape and for normal in vivo survival of erythrocyte. If blood is stored for some time, it will have a significant decrease in ATP levels which correlates with its shorter survival in vivo (Akerblom et al., 1967).

All the above findings indicated that damage in severe forms of malaria is probably due to the obstruction of the flow of blood in vessels of various organs. Since no such experiments have been performed in vivo, the present studies

were undertaken to determine whether such phenomena occurred in the brain of rhesus monkeys infected with P. knowlesi. The ATP contents in both the normal and P. knowlesi-infected red cells were also determined in these studies.