REVIEW OF LITERATURE
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MALARIA

It is an acute infectious disease caused by plasmodia transmitted by mosquito of genus anopheles. This illness is characterized by a cyclic course with periods of acute febrile attacks and paroxysm free intervals as well as by hepatosplenomegaly, anaemia and occasional severe lesions of nervous system, kidneys and other organs (Loban and Polozak, 1985).

CEREBRAL MALARIA

Cerebral malaria is a dreaded complication of malaria especially in paediatric age group, carrying a high fatality rate of about 25%, despite best possible therapeutic measures (Bruce Chwatt, 1978). It is characterized by gradual or sudden development of repeated convulsions, somnolence, stupor and finally coma (Bruce Chwatt, 1978).

HISTORICAL BACKGROUND

According to Loban and Polozak (1985) malaria has been known to humanity since the dawn of civilization. References to epidemic fever, similar to malaria can be found in ancient Chinese and Egyptian manuscripts and also the literary sources of ancient Greece and Rome. According to Sengis (1907) from 600-670 B.C. Hippocrates in his book on epidemics noted the existence of periodic fever divided into febrile, vertigo, sarcasm and melomania which are associated with enlarged spleen.
1638 AD - Hu an del Vega first employed cinchona bark for the treatment of malaria.

1753 AD - Term malaria was coined.

1820 AD - Active principle of cinchona bark (quinine) was isolated.

1831 AD - Bright noted the pigmented appearance of spleen and brain at autopsy.

1880 AD - Laveran discovered the malarial parasite in an unstained preparation of fresh blood.

1881 AD - Laveran described plasmodium malariae (P. malarize).

1883 AD - Marchiafava used meltylance blue for staining of malaria parasite.

1885 AD - Golgi demonstrated erythrocytic schizogony of quartan malarial parasite.

1886 AD - Golgi demonstrated the erythrocytic schizogony of benign tertian malarial parasite.

1890 AD - Grassi and Feletto described plasmodium vivax (P. vivax) and P. malaris.

1891 AD - Romanovsky introduced the staining method of malarial parasite.

1897 AD - Welch identified plasmodium falciparum (P. falciparum). Ronald Ross in sevendrabe found oocysts on the stomach wall of canephale mosquito which had previously fed on a malarial patient.
1898 AD - Ross worked out mosquito cycle of avian malaria while Bignami worked out that of human malaria.

1900 AD - Manson confirmed the mosquito transmission of malaria.

1922 AD - Stephens in Africa discovered plasmodium ovale (P. ovale).

1948-49 AD - Short et al identified tissue forms of P. vivax and P. falciparum.

1960 AD - Emergence of a drug resistant strain of P. falciparum was noted in South America, Africa and South East Asia.

**Anetiology of Malaria**

Malaria occurs following the bite of Anopheles mosquito which transmits causative agents of malaria to human host. Causative agent a protozoa, belongs to class sporozoa order Haemosporidia, family Plasmodidae and genus plasmodium.

Man may host four types of plasmodia namely P. vivax, P. falciparum, P. malaria and P. ovale. He is also susceptible to several types of malarial parasites in monkeys, P. Knowlesi, P. cynomolgi, P. cynomoggi bastianelli, P. inui, P. brasilianum, P. shortea, P. simium which may be contracted not only in experimental conditions but also under natural conditions with the subsequent transmission of infection to another man via mosquitoes (Dumina 1969, Fogg, Cambodia, 1972).
Life cycle of malarial parasite

(After Cruickshank, 1973)

Fig. 1
et al, 1978). For P. vivax, such reports are presented by isocantigens of blood group Daffy (Fy^a/Fy^b) and glyco-
phorines of erythrocytic membrane appear to serve as
receptors for P. falciparum.

Following their penetration into erythrocytes
merozoites enlarge to form trophozoites and undergo
various stages of development—ring trophozoite, juvenile
trophozoite, adult trophozoite, immature and then mature
schizont which consists of 8–24 merozoites depending on
the type of parasite. After the completion of the
developmental cycle the erythrocyte is destroyed and
merozoites become blood borne. Some of them perish, others
attack fresh red blood cells within 10–15 minutes and
invade them. Each cycle of erythrocytic schizogony lasts
48 to 72 hours. In P. vivax, ovale and falciparum it is
48 hours and 72 hours in P. malariae.

(c) Gametocytosis (Leban and Polonsk, 1983):

Some of the merozoites in the red blood cells
generate sexual forms of the parasite (male and female
gametocytes). Mature gametocytes of P. vivax, P. ovale,
and P. malariae appear in the peripheral blood almost
simultaneously with asexual forms and are detected during
first attack of the disease. Gametocytes of P. falciparum
get mature within 10–12 days and appear in the peripheral
blood only 8–10 days after the onset of the disease.
(d) **exo-erythrocytic schizogony (malaria, 1986):**

Until recently it has been considered that in the recurrent forms of human malaria (*P. vivax* and *P. ovale* infections) not only pre-erythrocytic but also exo-erythrocytic schizogony takes place as a result of repeated penetration by merozoites (formed in the course of pre-erythrocytic schizogony) into the hepatic cells of tissue. But this hypothesis has now been challenged and there is more evidence of latent tissue stage (hypnozoites) in the hepatic cells for *P. vivax* and *P. ovale.* As regards *P. malariae,* some recent evidence indicates that their relapses may originate from erythrocytic forms remaining in the body for a considerable period of time.

2. **Mosquito cycle (sporogony) — (Lehane & Polonsky, 1985):**

Mosquitoes of genus *Anopheles* are infected from a malaria patient or a malaria carrier. Along with the blood meal sexual forms of *Plasmodia* get into the stomach of mosquito wherein a macrogamete is formed from the female gametocyte. The male gametocyte extrudes 4 to 8 flagellate microgametes which later break free and enter into the female sexual cycle, fertilizing it. The fertilized ovum, syzyte, is transformed into the oocyst which penetrates through the wall of mosquito stomach reaching external membrane where the oocyst gets round and turns into the oocyst surrounded by a membrane. The oocyst grows, its content and multiplies resulting in
PLASMODIUM VIVAX

TROPHozoITE

SCHizont

FEMALE

MALE

GAMETOCYTES

PLASMODIUM FALCIPARUM

TROPHozoITE

SCHizont

FEMALE

MALE

GAMETOCYTES

(AFTER WHO 1983)
Formation of large amount of sporozoites (upto 10,000) of spindle like form.

After the maturation, the oocyst membrane ruptures, sporozoites are released and together with haemolymph are spread throughout the organism, accumulating in large quantities in salivary glands of mosquito. Such a mosquito is infectious for man remaining in this state for 1-2 months.

CLINICAL FEATURES OF MALARIA (BRUCE CUNATI, L.J., 1978)

After initial infection there follows an incubation period of 12 days (9-16) days for falciparum malaria, 14 (8-17) days for vivax malaria, 28 (18-40) days for quartan malaria and 17 (16-18) days for ovale malaria. This duration may be prolonged with some strains of P. vivax and due to prophylaxis which is inadequate to destroy completely the developing parasite ("H.Ç. 86").

In adults, who have little immunity to the disease, a classical febrile paroxysm of the primary attack is preceded by premonitory signs (headache, anorexia, lassitude, nausea) and is composed of a cold stage with feeling of chill accompanied by a rigor, a hot stage with dry flushed skin, rapid respiration and thirst. This is followed by a sweating stage when the temperature falls by crisis, the patient perspires copiously and feels greatly relieved but very weak.
After a brief period of remittent fever at the beginning of the disease, all types of malaria tend to show a periodicity which is more pronounced in vivax ovale infections (tartian, with attack every second day) and malariae infection (quartan, with attack every third day). It is least obvious in falciparum infection.

In children the classical features of malarial paroxysm, as seen typically in non-immune adults, are not common.

In non-immune infants and children who contract an acute primary attack some variability often occurs. The child at first appears listless, restless or drowsy, refuses food and may complain of headache and nausea. Pallor and cyanosis may be seen. Thirst may be marked, especially after rise of temperature which in breast fed infants displays as repeated attempts to suck, but soon this is abandoned possibly due to nausea. A clear cut cold stage and a definite rigor are uncommon in infants and children, vomiting is often marked, and the vomitus tinged with bile, causing difficulty in feeding, but usually not severe enough to cause dehydration and electrolyte imbalance. Stools are often loose and dark green; mucus may be seen but blood or leucocytes are rare. Infants may appear in abdominal distress. Older children may refer pain to liver or spleen and they may be constipated.
The temperature is very variable, in some is only moderate but in the majority it is high (40°C), often continuous and irregular as the child is flushed and perspires freely. Even when the temperature is moderately high convulsions often occur. They usually last only a few minutes and reflect some cerebral irritation. Hepatosplenomegaly is often found. Splenomegaly develops earlier in vivax malaria, less rapidly in falciparum malaria and very slowly in quartan malaria.

Manifestations are usually masked in immune children. There may be slight restlesspaba, lack of appetite, sweating anemia and occasional rise of temperature. However, unsuspected illness may occasionally flare up into a severe complication.

COMPLICATIONS OF MALARIA

A. Falciparum Malaria

There are a number of complications of falciparum malaria. First and foremost is cerebral malaria (described later). Other complications include:

1. Aloid Malaria (Collapse)

The patient may suddenly collapse possibly when the temperature is subnormal. The blood pressure will be low and the pulse weak, often, there has been much vomiting and possibly diarrhoea. Periphera l circulatory failure due in part to dehydration and in part in some cases to lesions in adrenal glands is thought to be responsible for
this complication, which was formerly referred to as the algid type of infection (W.H.O., 1986).

An expert committee of W.H.O. Malaria Action Programme (1986) is of the view that this disease may result from gram negative septicemia based on the studies of Bygdbjerg and Lønne (1982).

(2) **Severe anaemia**:

It is defined as a haematoocrit less than 20% (Haemoglobin less than 7.1 g/dl) by an expert committee of W.H.O. Malaria Action Programme (1986).

Approximately 30% of patients require blood transfusion (Phillips et al 1986).

(3) **Acute renal failure**:

The shock like mechanism associated with severe malaria, particularly when there are cerebral features, may lead to oliguria or anuria and histologically in such cases acute tubular necrosis will be present (W.H.O., 1986). The clinical pattern is that of reversible dysfunction which in a minority of cases progresses to established acute tubular necrosis (W.H.O. Malaria Action Programme, 1986).

(4) **Gastrointestinal involvement**:

This manifests itself by severe vomiting and diarrhoea, the former may be a prominent symptom in young children, while the latter may be absent, dehydration and electrolyte imbalance may follow (Bruce Chwatt, 1983).
Sweating may further contribute to dehydration (W.H.O., 1986).

(5) Hyperpyrexia:

Hyperpyrexia, defined as rectal body temperature above 39° C (W.H.O. Malaria Action Programme, 1986) which can occur in certain cases of falciparum malaria.

(6) Liver damage:

Abnormalities in liver function tests are common in malaria but they do not necessarily imply impairment of liver function. Jaundice is common, particularly in severe falciparum malaria resulting mainly from haemolysis (W.H.O. Malaria Action Programme, 1986).

Hepatic dysfunction in severe malaria is usually mild and has apparently been exaggerated in previous reports (Mc Meehan et al 1954; Patward et al, 1979). Clinical signs of liver failure are never seen unless there is concomitant viral hepatitis (W.H.O. Malaria Action Programme, 1986).

(7) Pulmonary oedema:

This is a grave and usually fatal manifestation of severe falciparum malaria. The first indication of impending pulmonary oedema is usually an increase in the respiratory rate which precedes the development of other chest signs (W.H.O. Malaria Action Programme, 1986).
(8) **Bleeding and clotting disturbances**:


Thrombocytopenia is quite common but in most cases not accompanied by bleeding.

(9) **Hypoglycaemia**:

Hypoglycaemia can occur in severe falciparum malaria, either without the administration of quinine or with administration of quinine which is the most frequent cause of hypoglycaemia (W.H.O., 1986).

(10) **Black water fever** (W.H.O., 1986):

Classical black water fever consists of a sudden massive haemolytic episode in which the patient who has felt unwell for sometime takes a dose of quinine and within an hour or two has an attack of shivering, feels weak and collapses and the urine, which till then had been normal in colour is almost black when next passed. Marked anaemia, rapidly develops and recurrent rigors and an irregular fever follows. There is almost always a history of having taken small doses of quinine (inadequate dose to suppress the existing P. falciparum infection) (W.H.O., 1986).
Complicating and associated infections like aspiration bronchopneumonia, U.T.I., gram negative septicemia.

B. **Complications of other forms of Malaria (P. vivax, P. ovale and P. malariae):**

1. **Anemia:**
   
   This may develop in any of these malarial infections particularly after repeated attacks or long continued untreated infections (W.H.O., 1986).

2. **Rupture of spleen:**

   Malaria is an important cause of spontaneous spleen rupture, world wide (Covell, 1955). Eighty percent mortality has been reported in patients in whom malaria infection was induced for fever therapy (Covell, 1955) for the treatment of neurophilias. Death occurs from loss of blood (Hamilton and Piskach, 1962).

   Spontaneous rupture is more frequent in vivax malaria than in falciparum malaria (Covell, 1955; Martello et al, 1969).

   The rapid hyperplastic enlargement of the malarial spleen is important to the pathogenesis (W.H.O. Malaria Action Programme, 1986).

3. **Hepatic dysfunction:**

   Hepatomegaly and nonspecific hepatitis with or without jaundice occur in patients with vivax malaria (Ramshandran and Pereira, 1976; Martello et al, 1969).
In addition to jaundice and hepatomegaly, patients may have fever, constitutional symptoms, hepatic tenderness, mild abnormalities in liver function and transient bilirubinemia (W.H.O. Malaria Action Programme, 1986).

4) **Thrombocytopenia:**

Thrombocytopenia occurs in P. vivax infections (Martello et al. 1969; Hill et al. 1964). However, dangerously low levels are rarely seen.

5) **Cerebral Malaria:**

Cerebral Malaria has been described later.

6) **Nephrotic syndrome (W.H.O., 1986):**

A form of the nephrotic syndrome has been encountered particularly in long standing P. malariae infections. It has also been reported in children with protracted P. ovale infection. It results from deposition on the glomerular basement membrane of immune complexes developed against malarial parasite. In these cases gross generalized oedema, with proteinuria and severe hypoproteinaemia occur. Children of either sex and about the age of five years are most likely to be affected. The prognosis is usually favourable.

**Cerebral Malaria**

Manifestations of cerebral malaria include any impairment of consciousness (confusion, delirium, stupor, obtundation, coma), convulsive disorders, focal neurological disturbances or psychoses (W.H.O. Malaria Action Programme, 1986). Since fever alone can cause most of these abnormalities, Warrel et al (1982) have developed a strict definition of cerebral malaria to allow a clear cut distinction from mild or transient cerebral dysfunction not related to underlying pathophysiology of cerebral malaria there must be:

1. Unarousable coma (motor response to maximum stimuli is non-localizing or absent).

2. Exclusion of other encephalopathies. Coma should persist for more than six hours after a generalized convulsion to exclude transient post ictal coma.

Hypoglycemia, meningoencephalitis, eclampsia, intoxications, head injuries, cerebrovascular accidents and metabolic disorders should be excluded as the cause of coma.

3. Confirmation of P. falciparum infection. Asexual forms of P. falciparum must be demonstrated in peripheral blood or bone marrow smear during life, or in brain smear after death.

But Gaulton, 1983 described acute cerebral malaria as one characterized by fever, altered sensomotor ranging from confusional states to coma, abnormal behaviour, convulsions (in about 30%) and less commonly focal neurological deficit.
Clinical features of cerebral malaria:

Anderson (1927) described that agitation and confusion could develop in a patient of cerebral malaria as he recovered consciousness and transient paranoid psychosis or delirium sometimes followed the acute illness.

Arieti (1946) described as chronic sequelae or presentation of malaria, neuroasthenic syndromes, paranoid, schizoid and manic depressive psychoses.

Tareev (1946) noted that malarial coma could occasionally develop in a patient even with normal temperature. Lallof et al (1967) classified the clinical features of cerebral malaria in 19 patients, viz. disturbances of consciousness (90%), acute organic mental syndromes (25%), movement disorders (10%), focal neurological disorders (50%) and acute personality disorders (15%). Some patients had more than one symptom. They also observed that acute personality changes recovered without any residual disability. They further noticed that in patients having focal neurological disorders, residual deficit was mild and rare.

Hendrickse et al (1971) observed that during the first year of life there was a positive and direct relationship between convulsions and malaria. They have observed that convulsions could occur even at moderate parasitemia. Moreover convulsions were more common in
patients with relatively better packed cell volume and those who were well nourished as compared to anemic and malnourished children.

Maraden and Bruce Chwatt (1975) have described permanent sequelae of cerebral malaria like deafness, blindness, hemiplegia, cerebral ataxia and choreiform movements (rare).

In 1976, Illan geeska and Dusylva described an acute cerebral syndrome in P. falciparum malaria.

Bruce Chwatt (1978) was of the view that cerebral malaria could develop gradually or suddenly and manifest itself in repeated convulsions, somnolence, delirium, stupor and finally coma. Usually the child had been ailing for a few days before the first convulsion. There were few if any, symptoms in the nervous system; some children had shown slight neck stiffness. The cerebrospinal fluid was normal in most cases, though occasionally it was under a slightly increased pressure and there was an increase of cells (up to 20 per cu mm) and protein (up to 50 mg/100 ml). Even with the best available treatment, the mortality of cerebral malaria in young children could be as high as 25% and those who survived showed neurological sequelae and mental defects as the author reported.

Vieira (1978) has discussed a variety of neurological syndromes associated with malaria. According to him symptoms of cerebral involvement in malaria could mimic
those of cerebral tumour or very rarely disorders of extrapyramidal system; symmetrical haemorrhagic softening in the corpus callosum and internal capsule had been documented. He had also noted cranial nerves plexias especially oculomotor and facial besides, spinal cord disorders. Neuroasticenic syndromes, paranoid, achimoid and manic depressive psychoses were also been described. Chadda et al (1978) have reported a case of smear positive malaria (P. falciparum) with high fever who presented with cerebellar signs.

Padmini et al (1980) have reported a case of peripheral neuropathy resembling Guillain Barre syndrome who on repeated smear examinations showed P. vivax infection and improved after antimalarial therapy.

Retinal haemorrhages occurred in about 15% cases of cerebral malaria and exudates were rare (Kayembe et al, 1980).

Gopinathan et al (1982) have discussed 6 cases of cerebral malaria presenting with neuropsychiatric manifestations. Various degrees of impairment of orientation to time and place (rarely to person or self identity), memory impairment mostly for recent events, registration and recall and intellectual impairment causing clinical profile of confusion and consequent confabulation and abnormal behaviour was observed. In this series 5 cases were due to P. falciparum while one was caused by P. vivax.
In two cases onset was sudden, in one case it appeared during the therapy while in others these manifestations were observed five days after chloroquine therapy, suggesting resistance to therapy.

Warell et al (1982) and Devis et al (1982) have reported retinal haemorrhages in about 15% cases, whereas exudates were rare.

Gopinathan and Subramaniam (1982) studied 20 cases of cerebral malaria. Clinical features of these cases were classified as follows:

- Pyramidal involvement: 7 (35%)
- Neck stiffness: 7 (35%)
- Urinary incontinence: 5 (25%)
- Apraxia: 3 (15%)
- Convulsions: 3 (15%)
- Hiccups: 3 (15%)
- Papilloedema: 2 (10%)
- Choreaiform movements: 1 (5%)
- Cerebellar signs: 1 (5%)
- Facial paresis (unilateral): 1 (5%)
- Associated renal involvement: 3 (15%)

Sixteen of their cases were caused by P. falciparum, 2 by mixed infection and 2 by P. vivax. Prognosis was poor for patients with multisystem involvement and only 1 out of 3 cases survived. The patients having renal involvement showed heavy parasitemia and evidence of unconjugated hyperbilirubinemia.
Osuntokun (1983) was of the view that symptoms of central nervous dysfunction, especially cerebral alf associated with a febrile illness; headache, muscle pains, vomiting, anorexia and diarrhoea. These are preceded by altered consciousness, convulsions, abnormal behaviour focal signs which are often transient, multiple and evanescent and sometimes signs of meningeal irritation are also present as the author has observed. He further asserts that in cerebral malaria, acute psychiatric disturbances including schizophrenic and manic like syndromes, depression of the exogenous endogenous types, acute malignant anxiety, amok and confusional states, hallucination delirium, amnesia, twilight states could occur although an exact or casual relationship of these to malaria was at best tenuous.

In 1984, Chithara et al reported cerebellar syndrome in children having malaria.

Lohm and Pelzke (1983) have summarized development of malarial coma. When malarial coma developed slowly, three stages could be distinguished, namely, somnolence, precursor state and true coma. Authors further observed that somnolence was related to apathy or excitement, negative attitude, disorientation, confused consciousness and drowsiness, sharp inhibition of all reactions to stimuli, including pain stimuli, intensification and then weakening of the tendon reflexes.
According to authors the precomatose stage was characterized by the following findings: pale face with greyish tinge and dry skin, the oral mucousa, sclera and conjunctiva were subicteric. There was tachycardia and the temperature reached 40-41°C. There was also hepatosplenomegaly, hypochromic anaemia, neutrophil leucocytosis with increased number of monocytes, eosinopenia, a high \( 25k \) proteinuria. Occasionally ataxia, amnesia, convulsions, sometimes of epileptiform nature, progressive inhibition of deep sleep which could be interrupted for a short time only by strong tactile and sound stimuli. Occasionally there could be brief periods of semicounsciousness when the patients gave monosyllabic answers to questions and then rapidly reverted to stupor. The tendon reflexes were increased and pathological reflexes appeared. These authors stated that in true coma, both with slow and rapid development, the patient was unconscious, reacting to no external stimuli. He would be motionless, skin appearing pale or pale yellow sometimes with a greyish tinge. The eyes would be closed or half open and blank, there would be increased muscular tension, trismus, rigidity of occipital muscles, positive Babinski and Brudzinski signs; Babinski and Gordon signs could also be present. The tendon and abdominal reflexes could be absent and the vegetative functions severely disrupted. The pupils could be dilated, the pupillary reflex diminished and
disappearing altogether at the late stage of disease.

According to authors following neurological manifestations could also occur with malarial coma: pareses and paralyses (monoplegia and hemiplegia), not infrequently convulsions (epileptiform), cerebral haemorrhages (seldom), dysarthria, aphasia and amnesia. Psychotic syndromes like delirium, manic states and hallucinations could also arise.

Ahmad et al (1986) in their study of 30 children with cerebral malaria found incidence of hemiparesis, monoparesis, ptosis and facial paresis (3.3% each) besides altered sensorium (100%) and convulsions (76%).

An expert committee of W.H.O. Malaria Action Programme (1986) has reviewed the clinical features of cerebral malaria. According to its report consciousness was impaired, which would be unarousable coma in strict terms. Neck rigidity and photophobia did not occur but mild neck stiffness was not uncommon. There ought to be no signs of raised intracranial pressure. Retinal haemorrhages and rarely exudates could also occur. The pupils would be normal. Disorders of conjugate gaze would be very common and the usual finding ought to be divergent eyes with normal oculosaphalic and oculoventibular reflexes. Convergence spasm would be observed rarely. Consensual reflexes would be preserved unless patient was in grade IV coma. The jaw jerk would be brisk and plant reflexes would be elicited. The gag reflex was usually preserved.
Muscle tone and tendon reflexes were often increased, but a general reduction in tone and reflexes would also be observed. Ankle and sometimes patellar colonus could be elicited and the plantar responses would usually be extensor. Abdominal reflexes were invariably absent. Decerebrate and decorticate postures could occur in severely ill patients. Extensor posturing could be associated with oculogyric crises and cyclical periods of stertorous breathing. Convulsions were common and were usually generalized without focal features. Agitation, confusion, transient paranoid psychosis or delirium could develop as sequelae. Other neurological sequelae included cranial nerve lesions, tremor and persisting coma but were unusual. Extraneural signs were common.

Above mentioned committee (1986) further observed that convulsions were common in children aged six months to five years who had high fever (more than 38.3°C) and it was difficult to differentiate clinically, convulsions caused by malaria from those caused by other febrile illnesses. In one study in Thailand, convulsions associated with falciparum malaria occurred in some 9.6% of children aged less than 5 years, but in only 1.5% of children with falciparum malaria aged 5 to 12 years (Changsuphajaisiddhi, T., personal communication to W.H.O. Malaria Action Programme, 1986). The neurological signs of cerebral malaria in infants and children were those of
symmetrical upper motor neuron and brain stem disturbances
including dysconjugate gaze, decerebrate and decorticate
postures. The committee has further stated that retinal
haemorrhages and exudates could occur. F. examination
was usually normal but in some cases there was a slight
increase in opening pressure and also increase in leucocyte
count (mostly lymphocytes up to 50 cells/microlit.) and
protein content (rately exceeding 150 mg/dl).

**Vivax Malaria as a Cause of Cerebral Malaria**

In 1921, Rosale described lethal haemorrhage in the
cerebellum of 21 year old soldier, during the course of
vivax malaria.

Bystrone (1927), Tareev et al (1943), Nikolaev (1948)
Osiovsky (1949) described cases of cerebral malaria due to
P. vivax in Russian literature as quoted by Lebon and
Polozerk.

Kitchen (1949) believed that serious complications
in the course of vivax malaria could be due to an unfavourable
premorbid background or intercurrent infection.

Mill et al (1963), while reporting case of vivax
cerebral malaria, complicated by aphasia and hemiplegia,
were of the view that P. falciparum parasitemia was
probably missed in the presence of larger and more
uniformally distributed, P. vivax species.

Cerebral malaria caused by P. vivax multinucleatum
had been described by Jiang et al (1963) in Yunnan and Hunan
provinces of China.

Verma and Magotra (1976) reported a few cases of cerebral vivax malaria in children residing in Jammu region.

In 1978, Bruce Chwatt expressed the view that in P. vivax infection cerebral malaria was rare.

Padmini and Paheshwari (1980) described a case of P. vivax malaria presenting as Gullain Barre syndrome.

Chabasse et al (1981) have opined on the rare occasions where cerebral malaria had been attributed to P. vivax, it was difficult to exclude inapparent mixed infection with P. falciparum.

Copinathan et al (1982) reported a case of P. vivax malaria presenting with neuropsychiatric manifestations.

Copinathan and Subramaniam (1982) in their series of 20 patients of cerebral malaria found P. vivax infection in 2 cases and mixed infection (P. vivax with P. falciparum) in 2 other cases.

Ostuntokun (1983) kept only a rare possibility of cerebral malaria being caused by P. vivax.

Sachdeva et al (1985) have described 8 cases of vivax malaria out of which 4 died and one had transitory spastic hemiplegia.

Lohen and Plesok (1985) maintained the view that earlier reported cases of cerebral malaria due to P. vivax in Russian literature were induced by mixed infection,
i.e. malaria and undiagnosed latent neuroviral infection (possibly hepatic), since the later stages of erythrocytic schizogony in case of P. vivax did not have any predilection for capillaries of internal organs and brain unlike that seen in case of P. falciparum.

Kidwai et al (1986) have reported 3 out of 11 cases and Ahmad et al (1986) have reported 4 out of 30 cases of cerebral malaria which were caused by P. vivax.

**Pathogenesis of Cerebral Malaria (A Review of Various Theories)**

Marchiafava and Bignami (1904) observed at autopsy of fatal cases of cerebral malaria, brain capillaries filled with parasitized RBCs even when parasitemia was low.

Gaskell and Miller (1920) noted presence of predominantly late trophozoites and schizonts of P. falciparum in brain capillaries and venules – forms seldom seen in peripheral smears. Sticking together of these parasitized cells leading to impedance and stoppage of cerebral blood flow was suggested by the authors.

In 1921, Druck first described classical granuloma of cerebral malaria which presented as a proliferation of glial elements around ring shaped haemorrhages and perivascular necrosis.

Druck (1921) and Stern (1936) described malarial encephalitis,encephalomyelitis and even lymphocytic meningitis.
In 1941, Kinsley coined the term 'sludging' for the impedance of cerebral flow caused by sticking together of parasitized erythrocytes. Spitz (1946), Fischer and Reichenon (1952) noted occurrence of pulmonary oedema and systemic circulatory failure in some cases of cerebral malaria.

Edington (1954) described characteristic ring haemorrhages and perivascular oedema and pericapillary infarctions in brain tissue.

Tella and Maegrith (1966) described release of vasoactive substances like bradykinin and bradykinogens from ruptured parasitized erythrocytes as an important pathogenic mechanism.

Edington (1967) made the observation that membranes of parasitized erythrocytes became changed and tended to agglutinate and stick together.

Dennis et al (1967) have established that a definite degree of clotting defect occurred due to the insufficient utilisation of fibrinogen in falciparum malaria.

Borochevitz et al (1970) and Herzer and Greepel (1970), Reid and Nkrumah (1972) have noted disseminated intravascular coagulation (DIC) causing bleeding diathesis in cerebral malaria.

According to Schmid (1974) the basis and direct effects of malarial infections on the nervous system comprised of capillary blockage and damage by parasitized
cells which tended to form a peripheral layer closely adherent to the endothelium; micro infarctions with deposition of pigments in the tissues; pericapillary ring haemorrhages with or without evidence of necrotic arterioles.

Punyagupta (1974) and Srikasinchul (1975) reported (DIC) in severe falciparum malaria and reemphasized its role in the pathogenesis of cerebral malaria.

Reid (1975) denied any importance of fibrin in the pathophysiology of malaria and warned against the wide use of heparin like anticoagulants. Mageraith (1976) also did not consider DIC as a significant pathogenetic mechanism in cerebral malaria.

Vietze (1970) found polypeptides in the blood of patients suffering from malaria which are known to inhibit oxidative phosphorylation in mitochondria. This led the authors to consider the possibility of anaemic oedema in the pathogenesis of cerebral malaria.

Salenkeil et al (1980) considered hypoxemia caused by pulmonary oedema as a contributory factor in the pathogenesis of certain cases of cerebral malaria.

Cstuntekum (1983) has reviewed the pathogenesis of cerebral malaria in detail. He rules out the possibility of true encephalitis in malaria. He considers that systemic circulatory failure and pulmonary oedema could occur in severe malaria infections. Could be an additional
mechanism in cerebral malaria which lowered cerebral perfusion as well as caused cerebral hypoxia.

Chanthavanich et al (1983) did not find cerebral oedema as a consistent feature in patients of cerebral malaria.

Usawattanakul (1985) detected endotoxin in patients with cerebral malaria and found that it was not related to clinical syndrome.

Seidel (1985) expressed the view that pathogenesis of cerebral malaria was result of cytotoxic anoxia caused by parasitized erythrocytes in microcirculation.

According to Macpherson et al (1985) the essential pathological feature of severe falciparum malaria was the sequestration of erythrocytes containing mature forms of parasite in deep vascular bed. Sequestration was greatest in the brain.

**THE PERMEABILITY THEORY**

Rigdon (1942) working on Macaca rhesus monkeys infected with P. Knowlesi found increased permeability of blood brain barrier.

Tella and MacGregor (1964) reported release of certain vasoactive substances like bradykinin and histogen from ruptured parasitized RBC's which could increase the capillary permeability.

Migasera and MacGregor (1967) observed that increased permeability was reversed rapidly by hydrocortisone, mepacrine and chloroquine.
Angus (1971) noted release of free fatty acids which could enhance capillary permeability.

Maegraith and Fletcher (1972) described the vasocative substances released from parasitized erythrocytes including kininis, kallikrein, kininogenases, histamine and adenosine peptides. According to his theory the primary pathophysiological abnormality in cerebral malaria was an increase in cerebral capillary permeability with outward leakage of plasma. This was considered to result in cerebral oedema and because of the extravasation of plasma into the cerebral interstitium, local haemoconcentration and reduced microcirculatory blood flow occurred.

A committee of W.H.O. Malaria Action Programme (1986) did not find this theory based on animal studies consistent with observations made in human cerebral malaria. The committee favoured outright rejection of this theory.

**MECHANICAL THEORY**

This theory simply states that the pathophysiology of severe falciparum malaria should be explained by microcirculatory obstruction with consequent local hypoxia and substrate depletion i.e. ischaemia (W.H.O. Malaria Action Programme, 1986).

Miller et al (1973) showed that cells containing P. Knowlesi did not pass through micropore filters as easily as unparasitized cells.
Kilejian et al (1977) noted the formation of knob-like protrusions from the parasitized erythrocytes which by antigen affinity could attach themselves to the capillary endothelium and phagocytes resulting into formation of lumps and aggregates.

According to Udainya et al (1981) infected erythrocytes developed knob-like protrusions by which they attached to endothelium through specific receptor ligand interaction.

Jeandel et al (1982) commenting on the knob-like protrusions from parasitized RBCs and their adherence to capillary endothelium, hypothesized a local vasculopathy as the main factor in the pathogenesis of cerebral malaria.

Leach et al (1984) pointed out these knob-like protrusions from the erythrocyte surface overly accretions of parasite derived antigen.

Cranston et al (1984) demonstrated that P. falciparum infected erythrocytes showed reduced deformability and that this was directly proportional to the maturity of the intracellular parasite.

Macpherson et al (1985) observed that parasitized RBC’s adhered to endothelium via surface knobs.

An expert committee of WHO Malaria Action Programme (1986) did not consider reduced deformability of parasitized RBCs as an important pathogenic mechanism for microvascular-latory obstruction. However, the committee hypothesized selective adhesion of parasitized erythrocytes to endothe-
elium via knob like protrusions to specific receptors presumably more abundant in brain vessels.

IMMUNOLOGICAL THEORY

This theory holds some form of immunologic mechanism responsible for the pathogenesis of cerebral malaria (reviewed later).

COMPLEMENT

The name complement stands for a highly complex multimolecular self assembling biologic system that constitutes one of the major humoral mediators of inflammation and participates in host defence (Nusinow et al, 1985).

HISTORY

The discovery of complement system dates back to 1894 when Pfeiffer demonstrated that the immune system of guinea pigs acquired the capacity to dissolve cholera bacilli (Pfeiffer's phenomenon).

Bordet (1896) identified a heat labile factor in both immune as well as non immune serum besides a heat stable factor present only in immune serum.

Buchner named this heat labile protective activity of blood as 'Aleuria'.

In 1930's there were 4, in 1960's 9 components were known (one of which had 3 subcomponents) C2 fraction was first isolated by Muller Eberhard in 1960.
At present the complement system is recognised to consist of at least 20 separate proteins (14 complement proteins and 6 regulation proteins) that circulate in blood as inactive precursor molecules (Müller Eberhard et al 1976-77).

General properties and nomenclature (Musinow, 1985):

The human complement system consists of more than 20 plasma proteins that are chemically, functionally and immunologically distinct (Müller Eberhard H.J., 1975). The proteins are labelled as components (c) and designated by consecutive numbers in the order of their discovery (C1, C2, C3 etc.). Some of them are labelled by the name Factor which is suffixed by a letter viz. Factor B, Factor D, Factor I (C3b inactivator), Factor H (B1H globulin). Some of the names of regulator proteins are often related to the function of the protein as in the case of C1 inhibitor, C3b inactivator or C4 binding protein. The presence of a bar over a component indicates an active enzyme, as in the case of C1 or B. The presence of a small letter after the number of letters of a complement protein indicates a fragment derived from the cleavage of the parent complement component. For example, the activation of C3 produces two fragments (1) the C3a anaphylatoxin and (2) C3b, the fragment associated with opsonisation.

Table (1) below shows the properties of various complement components (Turner, 1983).
### Table - I
(After Turner, 1983 and Yusinov, 1985)

<table>
<thead>
<tr>
<th>Component</th>
<th>Serum Conc.</th>
<th>Mol. Wt.</th>
<th>Substrate Cleaved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classical pathway</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early components</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 1 q</td>
<td>150</td>
<td>410000</td>
<td></td>
</tr>
<tr>
<td>C 1 r</td>
<td>50</td>
<td>160000</td>
<td>C 1s</td>
</tr>
<tr>
<td>C 1 s</td>
<td>50</td>
<td>83000</td>
<td>C4, C2</td>
</tr>
<tr>
<td>C 4</td>
<td>400</td>
<td>206000</td>
<td></td>
</tr>
<tr>
<td>C 2</td>
<td>15</td>
<td>110000</td>
<td>C3, C5</td>
</tr>
<tr>
<td>C 3</td>
<td>1200</td>
<td>180000</td>
<td></td>
</tr>
<tr>
<td><strong>Alternative pathway</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early components</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>5</td>
<td>24000</td>
<td>B</td>
</tr>
<tr>
<td>B</td>
<td>2000</td>
<td>93000</td>
<td>C3, C5</td>
</tr>
<tr>
<td>C 3</td>
<td>1200</td>
<td>190000</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>25</td>
<td>204000</td>
<td></td>
</tr>
<tr>
<td><strong>Terminal components</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 5</td>
<td>80</td>
<td>200000</td>
<td></td>
</tr>
<tr>
<td>C 6</td>
<td>70</td>
<td>120000</td>
<td></td>
</tr>
<tr>
<td>C 7</td>
<td>65</td>
<td>120000</td>
<td></td>
</tr>
<tr>
<td>C 8</td>
<td>90</td>
<td>154000</td>
<td></td>
</tr>
<tr>
<td>C 9</td>
<td>200</td>
<td>79000</td>
<td></td>
</tr>
<tr>
<td><strong>Central proteins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 1 inhibitor</td>
<td>200</td>
<td>110000</td>
<td></td>
</tr>
<tr>
<td>1 (c3b inactivator)</td>
<td>20</td>
<td>1000000</td>
<td>C3b, C4b, C5b</td>
</tr>
<tr>
<td>H (B1 globulin) 650</td>
<td>150000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum carboxy</td>
<td>35</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Peptidase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Properdin</td>
<td>25</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>C4 binding protein</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>S. protein</td>
<td>-</td>
<td>73000</td>
<td></td>
</tr>
</tbody>
</table>
Sequence of Activation:

According to Yachin et al (1966) complement system is an important mediator of immunological and inflammatory reactions and can be activated by immune complexes or by non-immunologic mechanisms such as proteolytic enzymes of the coagulation system. This view was further strengthened by Osler et al (1973) and Arroyave et al (1977).

Activation of complement system is generally achieved as a result of proteolytic cleavage by the preceding component and usually reveals an enzymatically active site which will in turn act on a latter component (hence cascade). Activated component usually has very short biological half-life and will decay to an inactive form if substrate molecules are not encountered.

In addition, there are several regulator proteins which play a critical role in protecting host tissue against the potentially damaging effects of uncontrolled complement activation. These inherent mechanisms in the system permit both rapid activation and rapid shut. Two pathways of complement activation are recognized, the so-called classical and alternative pathways (Musinow et al., 1985).
**Classical pathway activation**

Recognition of Ag—Ab complexes

Rapid & efficient

Early components

C1qrs, C4, C2

Regulation by
C1 inhibitor
C4 binding
protein I

C3 → C3a & C3b → Amplification loop

**Alternative pathway of activation**

Recognition of Bacteria and other activating surfaces

Early components

D C3 S and P

Regulation by

I, H, P

Slow & inefficient

Mast cell degranulation

Opsonisation

Recruitment of the alternative pathway. Initiation of the membrane attack complex

C5
C6
C7
C8
C9

Membrane attack complex

Lysis

Diagram: Components of the complement system (after W E Paul (1984) and S.P. Nussinov (1985))
The salient features of complement activation are the classical and alternative pathways which interact with each other and yield enzymes (convertases), able to cleave C3 and C5.

In the classical pathway complement activation occurs in the order, Antigen-Antibody-C1, 4,2,3,5,6,7,8 and 9. (Asten et al 1968). In the alternative pathway it occurs in the order, Activator-properdin system (B,D,P,C3) C3, 5,6,7,8,9 (Getz et al, 1971, Gewurz et al, 1972).

Activators of the classical pathway include aggregates of Ig G and Ig M or immune complexes, C-reactive protein, certain lipopolysaccharides (endotoxins), and some viruses (Nusinow et al, 1985). On the other hand, activators of alternative pathway are rabbit erythrocytes, gram negative bacteria, aggregates of IgA and certain B lymphocytes (Nusinow et al, 1985).

The regulatory proteins of the classical pathway include C1 inhibitor, C4 binding protein, C3b inactivator (I) and S-protein. The blood also contains an inactivator of the anaphylatoxins C3a, C4a, and C5a named serum carboxypeptidase B or H. The regulator proteins of alternative pathway are I factor I and H (B-HM globulin) as well as properdin (Nusinow et al, 1985).

Common final pathway of the complement system forms the membrane attack mechanism and leads to lysis of offending organism (Mayne and Fasi, 1987).
Quantitation of complement system:

Immunodiffusion is an important precipitin test used for the quantitative assessment of complements in the serum.

Judin (1946) described a single dimension precipitin test. In this technique antigen is allowed to diffuse through gel containing antibody placed in a convenient sized tube. A band of precipitate forms at the zone of equivalent concentration.

Sleek and Ouchterlony (1948) published their double dimension technique. The authors described that when antigen and antibody were placed in separate wells cut in the gel at a suitable distance from each other and were allowed to diffuse, various types of precipitin lines were formed at the zone of equivalence.

Oakley and Pulthrope (1953) described a double diffusion single dimension system. In this method, a zone of neutral agar was placed between antigen and antiseraum in a tube.

Feinberg (1959) first developed single diffusion double dimension technique of radial immunodiffusion which was later modified by Mannini (1963). Authors observed that antigen diffused radially from the point of application into a gel containing antibody and a circular precipitate was formed at the zone of equivalence. The diameter of precipitin ring was proportional to the concentrations, provided that gel thickness remained constant. Authors
allowed antigen to diffuse until the precipitate ring
stopped enlarging.

Fahey and Mckelvey (1965) further modified radial
immunodiffusion technique. They measured the diameter of
the precipitate ring at the fixed time between 18 and 20
hours.

Biological importance of complement:

The biological activities of complement components
in immunological and inflammatory response are given in
the following table (Turner 1983 and Ruddy 1985).

<table>
<thead>
<tr>
<th>Complement</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 1</td>
<td>Stabilization of Ag-Ab complexes.</td>
</tr>
<tr>
<td>C4b</td>
<td>1. Neutralization of virus infectivity.</td>
</tr>
<tr>
<td></td>
<td>2. Immune adherence to lymphocytes &amp; phagocytes.</td>
</tr>
<tr>
<td>C2b derived</td>
<td>Kinin activity - increases vascular permeability.</td>
</tr>
<tr>
<td>fragment</td>
<td>Anaphylatoxin; evokes histamine release from basophils; potent chemoattractant for monocytes and neutrophils.</td>
</tr>
<tr>
<td>C3a</td>
<td>Major opsonin. Binds to specific receptor on neutrophils, eosinophils and macrophages.</td>
</tr>
<tr>
<td></td>
<td>3. With Bb forms alternative pathway C3 convertase and amplifies alternative pathway.</td>
</tr>
<tr>
<td>C3b</td>
<td>4. Promotes solubilization of immune complexes.</td>
</tr>
<tr>
<td>C3a</td>
<td>Mediates immune adherence through binding to a specific receptor on macrophages.</td>
</tr>
<tr>
<td>C5a</td>
<td>1. Anaphylatoxin, 2. Chemotactic factor.</td>
</tr>
<tr>
<td>C5b67</td>
<td>Chemotactic factor</td>
</tr>
<tr>
<td>C3</td>
<td>Low grade membrane damage.</td>
</tr>
<tr>
<td>C9</td>
<td>Rapid membrane damage.</td>
</tr>
</tbody>
</table>
Role of complement in elimination of immune complexes (IC's):

There are different complement mediated processes which cooperate in immune complex (IC) elimination.

According to Gigli et al (1968) and Ruddy et al (1972), the IC's bearing C3b on surface, were capable of binding to the C3b receptors of polymorphonuclear leukocytes and also to the cells of mononuclear phagocyte system. Thus IC's were finally phagocytosed. Miller et al (1973) reported that C3b in the immune complexes could change the conformation of the complex itself. As a result large complexes were split into smaller ones. These smaller complexes were unable to deposit in the tissues and get ultimately detoxified.

According to Haynes and Fauci (1987) the immunoglobulin isotype composition is a critical factor in determining complement activation and therefore in determining efficiency of clearance of IC's by Fc receptor bearing cells within the immune system. Immune complexes of IgM/IgG activate rapid and efficient classical pathway while IC's of IgA activate slow and inefficient alternative pathway.

**Immune Complexes**

An immune complex is the one produced by interaction of antigen and antibody which may or may not be complement fixing (Nelson, 1977).
Immune complexes - a brief history:

For long, role of immune complexes in host defense was known. It was only in the early part of this century (1911) when Von Pirquet hypothesized their role in certain human diseases. Fifty years later (1951) he and his associates presented an experimental model of serum sickness i.e. an immune complex disease. His observations regarding role of circulating immune complexes (CIC) were later confirmed by Germuth (1953) and Dixon (1958). Since then a number of diseases have been attributed to immune complexes.

Circulating immune complexes (CIC) in health:

Isernbery et al (1981) and Jans et al (1982) have observed circulating immune complexes in normal healthy individuals. According to Endo et al (1985) C.I.C. are not necessarily pathogenic. They represent a physiologic mechanism for the removal of exogenous and endogenous antigens and are usually eliminated without resulting in tissue injury. They further described their detection in normal subjects, a circadian and seasonal variation and variation with food ingestion and exercise.

According to Lawley and Frank (1987) larger complexes are rapidly removed from the circulation in the liver. Complement activation seems to be an important mechanism which cleaves larger complexes into smaller ones which are further detoxified by liver reticuloendothelial system. They have also highlighted role of erythrocytes which acting via
complement receptors attack immune complexes and during their sequestration are stripped off these complexes in the hepatic sinusoids.

**Role of immune complexes in disease:**

Formation of immune complexes can occur under following circumstances (W.H.O., 1977):

1. Antibody reacting with antigen present as a part of a membrane either integral or passively attached. This is the type II allergic mechanism of tissue damage. Antibody that has bound to cell membrane components can be shed secondarily as a complex, from the membrane into fluid phase.

2. Antibody reacting with soluble non-cell bound antigen. This is the type III allergic mechanism of tissue damage. The consequences of this type of reaction vary with the location of complex formation.

W.H.O. Scientific Group (1977) further notes that complexes can be formed:

(a) When both antigen and antibody are blood borne and secondarily localize in blood vessels and perivascular tissues (e.g., in serum sickness).

(b) When antigen locally released in the tissues reacts with blood borne antibody (e.g., in echococcosis) and

(c) When both antigen and antibody are formed locally (e.g., late granulomas around schistosome eggs).
LATTICE THEORY OF MARRACK DEPICTING ANTIGEN ANTIBODY COMPLEXES

ANTIBODY EXCESS

EQUIVALENCE

ANTIGEN EXCESS

(AFTER J.A. LAKIN - 1980)

FIG-3
SIZE OF IMMUNE COMPLEXES (Fig. 3)

According to Lawley and Frank (1987), the size of the circulating immune complexes is an important parameter of toxicity. In general larger (≥ 195) complexes cause more tissue damage than do small complexes. The authors further state that the size is related to the concentration and molar ratio of antigen and antibody, as well as to the avidity of the antibody for the antigen.

In antibody excess, antigen valences are saturated and in general the complexes are small. Under conditions of antigen excess, antibody combining sites are saturated, chances for lattice formation are limited, and again the complexes are small. At equivalence or mild antigen excess, lattice formation is facilitated and large complexes can form. Immune complexes formed at moderate antigen excess are thought to be most pathogenic, perhaps because they are most efficient at activating the various mediator systems like complement cascade.

DEPOSITION OF CIRCULATING IMMUNE COMPLEXES

According to WHO Scientific Group (1977) most of the CIC's are cleared by mononuclear phagocyte system, particularly Kupffer cells. This applies especially to large complexes and those that are complement fixing. Complexes that are smaller, or non complement fixing are cleared to some extent by spleen, or they may become fixed to the renal glomeruli, blood vessel walls or choroid plexus.
Endo et al (1985) consider vascular bed as an important variable when considering possibility of immune complex injury. Immune complexes tend to be deposited in organs with specialized vasculature, like the kidneys, skin, joints, choroid plexus and arterial walls. They further opined that once immune complexes are deposited in tissues, injury may ensue only if the permeability of local vessels is increased by the local release of vasoactive amines. Complement activation by immune complexes may promote the release of vasoactive amines.

Mechanisms of tissue injury by immune complexes:

Endo et al (1985) have summarized various mechanisms of tissue injury as follows:

1. Activation of complement resulting in:
   - Immune adherence
   - Chemotaxis
   - Cytotoxicity
   - Immune complex solubilization
   - Release of leukocytes from bone marrow

2. Platelet aggregation and release of their vasoactive amines.


4. Macrophage phagocytosis

5. Basophil and mast cell degranulation

6. Suppression of B cell by IgG immune complexes


8. Activation of T suppressor cells by IgG immune complexes.

9. Stimulation or inhibition of T helper cells

10. Enhanced or depressed killer cell activity
ELEVATION OF COMPLEMENT AND IMMUNE COMPLEXES IN MALARIA AND CYTREBRAL MALARIA

Catheire (1918) and Vincent (1918) first noted the depression of serum complement in human malaria.

In 1939, Eaton found a soluble antigen in the serum of monkeys heavily parasitized with P. knowlesi. Injected into normal monkeys it gave rise to complement fixing antibodies, but they conferred no protection against plasmodial challenge.

Again in 1948, Dulany et al found that the serum of most patients with induced malaria had diminished complement activity.

Fogel et al (1966) and Cooper and Fogel (1966) made a detailed study of the effects of plasmodium knowlesi infection on complement activity in rhesus monkeys (Macaca mulatta). Nearly all monkeys with heavy parasitemia had depressed total haemolytic complement levels. Initially, a cyclical variation in complement activity was observed, complement levels falling in association with merozoite release. In the terminal stage of the infection a marked fall in serum complement occurred. Complement components C 1, C 2 and C 3 were all depressed.

Cox (1966) detected in the serum of monkeys actually infected with P. knowlesi, an antigen which reacted in gel precipitation tests with sera from animals convalescent from malarial infection.
Berger (1967) reported nephrotic syndrome secondary to falciparum glomerulonephritis and thought of possible immunological basis.

Wright (1968) noted that experimental neonatal thymectomy in golden hamsters infected with P. berghei almost suppressed the development of acute haemorrhages of the brain due to an intravascular antigen-antibody reaction. He also observed low levels of complement in hamsters with cerebral malaria.

Mc Gregor et al (1963) conducted their experiments over sera and plasma of Gambian children. They found soluble malarial antigens in patients either suffering from P. falciparum malaria or recovering from infection. Antibodies were detected in adults, but were rare in children under 6 years of age. They also noted that the antibodies were not detectable once circulating soluble malarial antigens were eliminated. Basing their views on these observations authors opined that soluble antigens were weakly immunogenic. Authors were unable to find any evidence of harmful effects of these antigens, contrary to suspicions of Dixon (1966) that immunopathological sequences may sometimes follow the deposition in host tissue of malarial antigens or Ag/Ab complexes.

Allison et al (1969) found evidence of soluble complexes which got deposited in kidneys along the basement membrane on the epithelial side of Bowman's capsule in
P. malariae infection. But they did not get any evidence of P. falciparum infection in such cases.

Ward et al (1969) studied the nephrotic syndrome due to P. malariae infection in east African children. They found evidence of glomerular deposits of Ig M, IgG, Ig A, complement and fibrin, sometimes with malarial antigen. They were of the view that this deposition was secondary to soluble immune complexes.

Wilson et al (1969) while studying malarial antigens and respective antibodies in Gambian population constantly exposed to P. falciparum infection found four varieties of soluble antigens viz. S (stable to 100°C), R (resistant to 56°C) and La and Lb (labile to 56°C). They detected only transient antibody response to antigens in infected children. La antigens produced antibody response in early childhood and could be detected in virtually all individuals above 6 years of age. Lb antigens stimulated antibody production in a small percentage of adults and adolescents. Authors noted that with heavy parasitaemia S-antigen was found in increased concentrations while La antigen was barely detectable. They suggested two explanations for this discrepancy. First, the antigen (La) might be relatively insoluble, hence not circulating in body fluids. Second, the antigen might be rapidly complexed in-vivo by the specific antibodies which were demonstrable in most individuals.
Wright et al (1971) showed that injection of antithymocyte serum to P. berghei infected golden hamsters and rats suppressed the intravascular antigen–antibody reaction and thus the development of acute haemorrhages in brain. He also noted hypocomplementemia in experimental cerebral malaria.

Houba and Williams (1972) found evidence of circulating immune complexes while conducting their study on soluble malarial antigens of P. falciparum in Nigerian population.

Bhamaraspravati et al (1973) studied ten cases of P. falciparum infection which showed urinary abnormalities. Kidney tissue showed deposition of immunoglobulins (Ig G, Ig M and Ig A) and complement in glomerular basement membrane and mesangial areas in all but one case. Malarial antigen was detected in two cases. Sera of two patients who had evidence of circulating immune complexes showed depressed levels of C3 and C4 suggestive of activation of classical complement pathway. The authors concluded that immune complex nephritis could occur in P. falciparum malaria.

Rosenbury et al (1973) demonstrated in patients with P. falciparum malaria infection that the degree of anaemia correlated well with rising titres of Ig M antierythrocyte antibodies and decreased levels of C3. They proposed an autoimmune mechanisms for anaemia in which complement activation played a role, hence the decreased levels of complement.
Greenwood and Brueton (1974) reported low C3 levels, very low C4 and C1q levels and relatively normal glycine rich B glycoprotein (GBG) in sera of most children with acute falciparum malaria. Their study suggested activation of complement by classical pathway. They further opined that lowering of C3 level was probably due to formation of antigen-antibody complexes with soluble malarial antigen leading to activation of classical pathway. They did not find any correlation between the initial C3 level of children with cerebral malaria and the duration of their impaired consciousness. But they did find a correlation between detection of soluble malarial antigen and significantly lower C3 levels. These authors found a positive correlation between raised fibron degradation products (FDP) levels and low serum C3 levels in children who had neurological signs. According to authors this finding further suggested complement activation by Ag-Ab immune complexes leading to vascular damage in severe falciparum malaria.

In humans with plasmodium vivax infection low levels of serum complement were demonstrated by Nave et al in 1974. They linked complement depletion to schizont rupture and found a direct correlation between low levels of CH50 and C4 with the degree of parasitemia and also to the presence of complement fixing antibody. Also they suggested activation of complement system by malarial antigens leading to depletion of complement components.
Sriksichul et al (1975) found a positive correlation between the reduction of C3 on one hand and clinical complications as well anaemia and thrombocytopenia on the other hand. The patients with falciparum malaria. They further observed more severe reduction of C3 levels in most severe cases of thrombocytopenia in the patients associated with disseminated intravascular coagulation (DIC). The more rapid loss of radiolabelled C1q in parasitic patients was interpreted as a reflection of C1q binding to immune complexes formed in malaria. The authors opined that complement activation leading to disseminated intravascular coagulation and promotion of release of vascular permeability factor could be considered as an important pathogenic mechanism in complicated falciparum malaria.

According to a scientific group of WHO (1975) (quoting Lambert and Houba, 1974), in owl monkeys infected with P. falciparum or with P. brasilianum, an increase of C4, C3 and properdin factor B or (C3PA) was observed during the peak parasitemia. It was followed by a decrease of these three components far below their normal range.

This group also quoted unpublished data of Krattli et al who, in mice infected with P. berghei, found an increase in the level of C3 during the first three days of infection which progressively decreased after fourth day of infection, becoming undetectable in second week of
infection, since the death from cerebral malaria was most frequent in the preschool children this scientific group suggested an allergic response to malaria in such patients as patients of more than one year of age had appreciable level of malarial antibody.

Hoube et al (1976) experimentally demonstrated circulating immune complexes in one monkey infected with P. brasilianum which could be the result of interaction of circulating malarial antigens with antibodies. They noted that circulating immune complexes were deposited in various vascular territories. They showed presence of specific malarial antigen (P. falciparum) in deposited immune complexes in infected owl monkeys.

Petechalai et al (1977) studied complement changes in 31 cases of acute falciparum malaria. They noticed a considerable reduction in C3, C4 and C6 levels in complicated group and a similar but lesser reduction was found in the non complicated group while raised levels of CIq, C3BA, C8, C9 were found in both groups. Increased levels of CIq, C3PA C8 and C9 were explained on the basis of acute phase response which could mask utilization. Activation of classical complement pathway alone was found in seven cases. In another 3 cases activation of both classical and alternative pathways were found.

Tero and Roman (1976) interpreted neuropathological findings in cerebral malaria as resulting from a hyperergic
reaction of the CNS to the antigenic challenge of *P. falciparum* infection. They proposed an immune complex vasculitis as the pathogenic mechanism.

Greenwood et al (1978) studied the role of immunological factors in the pathogenesis of anaemia of acute falciparum malaria in children. Serum levels of immune complexes were normal at the time of presentation and increased only one month later. Low levels of C3 and C4 were detected but only in nonanaemic patients. These workers ruled out the immunological mechanism for anaemia in such cases.

Weis (1978) detected deposits of immune complexes in the lungs of mice infected with *P. berghei*.

Williamson (1978) reported hypocomplementemia in children with *P. falciparum* malaria.

Woodruff et al (1979) showed association of complement containing immune complexes on the red cells surface with their decreased life even after complete eradication of malarial parasites.

Facer et al (1979) suggested a type III immune complex mediated hypersensitivity, involving parasite-antigen-antibody complexes, to explain coombs positivity and sensitization of erythrocytes with complement (C3d and C4b) and immunoglobulin G, leading to anaemia in children suffering from *falciparum* infection.
Perrin et al (1979) observed malarial antigens in serum of patients with acute falciparum malaria which showed a peak before therapy started and rapid decrease after therapy. Specific malarial antibodies became detectable 5-7 days after starting treatment in patients with first infection. Immune complexes were detected in sera of 21 out of 23 patients with peak levels between days 5 and 9. A marked decrease of C3 and C4 was also observed by the authors with normal levels of factor D.

According Houba et al (1979) in acute falciparum malaria circulating immune complexes could localize in glomeruli and initiate kidney lesion which was reversible and responded to therapy.

Boonpuckknaving et al (1979) demonstrated granular deposits of immune complexes in all glomeruli of mice infected with P. berghei and they developed diffuse proliferative glomerulonephritis.

June et al (1979) studied circulating and tissue bound immune complexes in mice infected with P. berghei. The most significant finding was the presence of tissue bound im unoglobulins in the choroid plexus besides glomerular deposits. The appearance of antimalarial antibodies and malarial antigens in the serum was closely associated with a depression of C3 levels and presence of circulating immune complexes (CIC). High levels of CIC were found in primary infection even at relatively low parasite levels. The authors suggested a relevance of tissue bound immunoglobulin in choroid plexus to pathogenesis of cerebral malaria.
In 1980 Contreras et al described development of circulating immune complexes in association with marked depression of C3 levels in various strains of mice infected with P. berghei.

Ehrich et al (1981) while experimentally producing transient glomerular injury resembling human P. falciparum infection in rats infected with P. berghei noticed transient elevation of circulating immune complexes and persistent antiplasmodial antibody in serum. They also showed tissue bound immune complexes in glomerulei on later examinations.

Ade-Carrano et al (1981) showed hypocomplementemia (C3 and C4) in Nigerian children suffering from P. falciparum parasitemia. Hypocomplementemia was greater when forms other than gametocytes were present.

Adam et al (1981) detected circulating immune complexes (CIC) and marked hypocomplementemia in patients with cerebral malaria (CM). CIC were rare and hypocomplementemia was not marked in patients with uncomplicated falciparum malaria. In 7 of the 9 patients of CM shortly after quinine therapy was initiated, there was a marked increase in cryoglobulin and CIC levels, associated in four instances with increase in the severity of the coma. Deranging of coma was explained on the basis of deposition of immune complexes in choroid plexus. Authors further put the possibility of CIC causing pathological
manifestations without being deposited in tissues, i.e., complement activation involving (i) liberation of vasoactive peptides with potential shock inducing activities and (ii) platelet activation and initiation of blood coagulation.

According to Idris Moh. (1982) some of the acute manifestations of cerebral malaria were reminiscent of immune complex mediated disease. He postulated that during acute \textit{P. falciparum} infection, the non immune patient was unduly susceptible to rapid formation of antigen antibody complexes, which being complement fixing tended to deposit in the brain, as well as in other tissues.

Gupta et al (1982) reported low levels of \textit{CH}_4 and \textit{C}3 in serum of patients with malaria which did not bear any correlation with parasite index.

Macrophage receptors for opsonized plasmodia were blocked by immune complexes in vitro (Brown and Krieger, 1982). The authors concluded that immune complexes in the serum of actually infected mice could protect the plasmodia from the activities of macrophages.

Finley et al (1982) noted presence of higher levels of \textit{C1C} and lower levels of serum \textit{C}3 in mice infected with \textit{P. berghei} when its immune mechanism was intact. Cerebral malaria which developed in such mice was more severe as compared to those where immune mechanism was not intact (T. cell dependent mice).
Drawing conclusion from his experimental study, on *P. berghei* infected mice, Hear (1984) suggested that immune complexes modulate the immune response to malaria by inhibiting immune phagocytosis and perhaps by interfering with other effector mechanisms.


Phanuphik et al (1985) noted decreased levels of serum complement components in patients with *P. falciparum* malaria; Clq, C3 and C4 were most significantly reduced. Decrease was more profound in complicated cases with cerebral, renal and hepatic involvement. But they did not find any correlation between hypocomplementemia and the degree of parasitemia or the level of circulating immune complexes.

Kidwai et al (1985) observed hypocomplementemia in patients with malaria. C3 was lesser in falciparum than in vivax malaria but C4 levels were independent of species.

Sachdeva and Man Mohan (1985) found evidence of circulating immune complexes in two children, with vivax malaria who also showed profound decrease of C3 levels. These two children died despite treatment.

Kidwai et al (1986) and Ahmad et al (1986) noted an inverse correlation between pretreatment serum C3 and C4 concentrations and the neurological involvement. They further noted that very low C3 and C4 levels were bad prognostic indicators in cerebral malaria in children.