ANALYSIS OF LITERATURE
REVIEW OF LITERATURE

HISTORY: Malaria is one of the oldest recorded diseases in the world. Malaria or ague as it was commonly known, has been described since antiquity. A disease resembling malaria was mentioned in Charak and Susruta Samhita and associated it with the bite of mosquito (1ST Century A.D.) (Gosh, 1970).

Hippocrates is usually credited with the first clear description amongst accidental writers. In epidemics he distinguished different patterns of fever and his aphorisms he describes the regular paroxysms of intermittent fever in the 5th Century B.C. In Europe seasonal periodic fevers were particularly common in marshy areas and were frequently referred to as Paludial (L. palus- Marshy ground).

Malaria was thought by Italian writers in (1753) to be caused by the offensive vapours emanating from the Tiberian Marshes. The word 'Malaria' comes from Italian and means literally 'bad air'. Malaria was known by various name such as marsh fever, Roman fever, changes fever, intermittent fever, Jooria, Paludism, etc.

Present knowledge of malaria disease has been the result of extensive work done by different workers from time to time.
1- Meckel (1847) and Virchow (1849) had been observe the presence of pigment (Black material) in the organs with malarial infection.

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

3- Marchiafava in 1883 used methylene blue for the staining of malaria parasite.

4- Romanowsky (1891) introduced the staining method of malarial parasite.

5- Ross (1897) in Secunderabad found oocysts on the stomach wall of an anopheles mosquito which had fed previously on malarial patient.

6- Ross (1898) in Calcutta worked out on mosquito cycle with the parasite of bird malaria, whereas Bignami et al demonstrated the same with parasite of human malaria.

7- Patrick Manson (1900) proved the theory of mosquito transmission.

8- Shortt and others (1948) worked out the pre-erythrocytic schizogony of malaria parasite in the parenchymal cells of liver first with cynomolgi malaria then with vivax malaria. They also demonstrated the exoerythrocytic schizogony of malarial parasite in cynomolgi malaria.
9- Shortt and other (1949) demonstrated the pre-erythrocytic schizogony of *Plasmodium falciparum.*

10- Garnham et al (1954) discovered the pre-erythrocytic schizogony of *Plasmodium ovale.*

There are four species which cause malaria in human beings (i) *Plasmodium vivax* (ii) *Plasmodium falciparum* (iii) *Plasmodium malariae* (iv) *Plasmodium ovale.*

All four species possess a life cycle which shows alternation of generation accompanied by an alternation of host. Asexual cycle occurs inside the red blood cells of vertebrate and sexual cycle occurs in an invertebrate host.

The gametogony (Formation of gametocytes) start inside the red blood cells of vertebrate host and completed in various species of blood sucking mosquito with production of sporozoite, the form infective to the vertebrate host (Chatterjee, 1974).

**LIFE CYCLE**: Malaria parasite passes its life cycle in two different hosts.

**IN MAN**: The parasite residing inside the liver cell and red blood corpuscle reproduce the asexual method.
IN FEMALE ANOPHELES MOSQUITO: For the initiation of the mosquito cycle sexual form are first developed inside the human host. These are then transferred to their insect host where they develop further and are transformed into sporozoites.

HUMAN CYCLE: Human cycle starts with the introduction of sporozoites by bite of infected anophales mosquito. It comprises the following stages.

(I) PREERYTHROCYTIC SCHIZOGONY: Sporozoites does not enter directly into a red blood corpuscle to start its erythrocytic schizogony but undergoes a developmental phase inside the tissue of man. This phase of development has been referred to as pre-erythrocytic schizogony and consists of only one generation of pre-erythrocytic schizont, the cycle lasting approximately 8 days in P. vivax, 6 days in P. falciparum and 9 days in P. ovale. The pre-erythrocytic schizogony occurs inside the parenchyma cells of the liver. The liberated merozoites are called cryptozoites. The smaller ones (micromerozoites) enter the circulation and larger ones (macromerozoites) re-enter the liver cells.

(II) ERYTHROCYTIC SCHIZOGONY: During this phase the parasite resides inside the red blood corpuscle and passes through the stages of trophozoite, schizont and merozoite.
1 to 6, P. Vivax. 1, 2, 3, trophozoites (1 early ring from, 2 & 3 larger ring forms with Schuffner's dots, 3 ameboid form); 4, 5, 6, schizonts - early to mature (rosette) stage.
7 to 12, P. falciparum 7, 8, 8, trophozoites 10,11, 12, growth of a schizont (inside the capillary of internal organ); 8 showing multiple infections with form "acole"; 9 & 10 showing Maurer's dots in the host cell. Note the normal size of the infected cell.
13 to 20, mature gametocytes of P. vivax (13 male, 14 female), P. falciparum (15 male, 16 female), P. Malariae (17 male, 18 female) and P. Ovale (19 male, 20 female)
These asexual form of parasite can be demonstrated in the thick smears of the peripheral blood 3 to 4 days after the completion of pre-erythrocytic schizogony i.e. in P. vivax infection about 12 days and about 9 days in P. falciparum after exposure. Each cycle of erythrocytic schizogony tests 48 to 72 hours. In P. vivax, P. ovale and P. falciparum it is 48 hours whereas in P. malariae it is 72 hours.

The parasitic multiplication during the erythrocytic phase is responsible for bringing on clinical attack of malaria. The schizogony cycle may be continued for a considerable period, but in course of time the infection tend to die out either due to exhaustion of asexual reproductive capacity or to spontaneous destruction of parasite.

(III) GAMETOGENY: After parasite have undergone erythrocytic schizogony for certain period which varies with the different species some of merozoites instead of developing into trophozoites and schizonts give rise to forms which are capable of sexual function after leaving the human host. These are called gametocytes and develop in the red blood cells of the capillaries of internal organs (Spleen and Bone marrow). Only the mature gametocytes are found in the peripheral blood. The maturation is completed in about 4 days. Gametocytes do not cause any febrile reaction
in the human host and are produce for the propagation and ultimate continuance of the species. The individuals who harbours the gametocytes is known as a carrier.

(IV) **Exoerythrocytic Schizogony**: After the establishment of blood infection the initial tissue (Pre-erythrocytic phase) disappears completely in *P. falciparum* whereas in *P. vivax*, *P. ovale* and probably in *P. malariae* it persist in the form of a local liver cycle. The persistence of this late tissue phase is described as exo-erythrocytic schizogony and are responsible for relapses of vivax, ovale, and quartan malaria. In absence of fresh infection this phase forms the source of asexual parasites.

The following scheme represents the tissue phase of *P. vivax*, *P. malariae*, *P. ovale*.

```
Sporozoite -- Pre-erythrocytic schizogony -- Exo-erythrocytic schizogony
  ↓  Erythrocytic schizogony  ↓  Erythrocytic schizogony
  ↓  Primary malaria  ↓  Relapses
```
The following scheme represents the tissue phase of *P. falciparum*:

```
Sporozoite    --  Pre-erythrocytic
               schizogony  --  No exo-erythrocytic
                      schizogony
                        ↓
  Erythrocytic
    schizogony  No relapses
          ↓
Primary fever and
reconvalescences result from
persistence of blood infection
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**Malaria and Abnormal Haemoglobin:**

**Haemoglobin - S:** Parasitization predisposes to the red blood cells from heterozygotes with sickle haemoglobin (AS) to sickling by decreasing the intracellular pH and deoxygenation of haemoglobin (Friedman, 1978; Pasvol, 1978). Leakage of potassium ions from AS cells upon deoxygenation affects parasite growth (Friedman et al, 1979).

Parasitized sickle cells are preferentially phagocytosed by macrophages (Luzzatto, 1990).

**Haemoglobin - F (Hb-F):** The growth is retarded in the presence of Hb-F both in cord blood cells and in Hb-F containing red blood cells obtained from infants as well as from adults with hereditary persistence of fetal haemoglobin (Pasvol et al, 1977).
HAEMOGLOBIN - C (Hb-C) is beta chain variant. The red blood cells from heterozygotes, who have high level of Hb-C, a reduced invasion rate and impaired growth of parasite found (Friedman et al 1975).

SPHEROCYTOSIS AND OVACYCTOSIS: The effect of hereditary spherocytosis on parasite multiplication has been tested in vitro and found to be unremarkable (Koeweiden et al, 1979).

The ovalocytosis type of red blood cells are particularly resistant to penetration by plasmodium falciparum (Kidson et al, 1981).

PARASITE INVASION OF RED BLOOD CELL: The attachment of the merozoite to the red blood cell is mediated by a specific erythrocyte surface receptor. In plasmodium vivax thus is related to the Duffy blood group antigen Fya or Fyb (Miller et al 1976). The receptors for plasmodium falciparum have not been identified.

ANAEMIA: The suggested mechanism of anaemia in malaria are basically three -

i) Destruction of parasitized red cell

ii) Destruction of non parasitized red blood cells

iii) Defective red blood cell production
Destruction of parasitized red blood cells - Direct damage to the red blood cells by invasion and growth of parasite is the major mechanism for premature red cell destruction in all acute forms of malaria (Seed and Kreier, 1980). Increased rigidity and reduced deformability are the main mechanisms of premature cell destruction. The spleen is highly effective filter for damaged or rigid erythrocytes (Miller et al 1971, 1972; Seed and Kreier, 1980).

HAEMOLYSIS BY IMMUNE RESPONSE: Zuckermon (1966) suggested that at least a part of the component of anaemia of plasmodium falciparum malaria result from immune destruction of both parasitized and non parasitized red blood cells occurs. (Pacer et al, 1980). Immune destruction of this type probably play a small role in producing anaemia of acute plasmodium falciparum (Weatherall and Abdalla, 1982).

DEFFECTIVE RED CELL PRODUCTION: Defective red blood cell production caused either by depression of erythropoiesis (Kuvin et al, 1963; Srichaikul et al 1973; Woodruff et al, 1979) inhibition of reticulocytes release or ineffective erythropoiesis (Hendrickse and King, 1958; Srichaikul et al 1973; Rencricca et al 1974) may also play a part in causing anaemia of different type of malaria.
In study carried out by Abdalla et al (1980) the marrow of children with acute infections and high parasitaemias showed normal or reduced erythroid precursor populations which had no gross morphological abnormalities.

**ANAEMIA OF PLASMODIUM FALCIPARUM MALARIA:**

The morphological studies of bone marrow of patients of *plasmodium falciparum* infection indicate that relative number of erythroid precursors is not increased and erythropoiesis is normoblastic with minimal dyserythropoietic changes. The overall cellularity of bone marrow is increased. However largely because of myeloid hyperplasia (Abdalla et al, 1980).

Anaemia caused by chronic *plasmodium falciparum* infection, the most consistent finding was marked dyserythropoietic changes in bone marrow. Although evidence of mild haemolysis was also present. The anaemia seems to be predominantly dyserythropoietic type (Weatherall and Abdalla, 1982).

The other changes with acute malaria include lymphocytosis in bone marrow and reactive lymphocytes, monocytosis and mild neutrophilia in peripheral blood. Phagocytosis of erythrocytes, parasitized cells and nucleated cells was more commonly seen in the macrophages in acute malaria. The megakaryocytes were found to be increased in
number with acute malaria. A proportion of these cells had rounded nuclei probably indicating accelerated platelets turnover (Abdalla, 1990).

The peripheral blood smear in cases of acute malaria is usually normocytic, normochromic and type of anaemia is haemolytic and urobilinogen is usually detected in urine. There may be many parasitized red blood cells, polychromasia, anisocytosis poikilocytosis, target cells and in severe cases nucleated red blood cells (Bruce-Chwatt, 1980).

**Changes in Leucocytes in Malaria**: In malaria slight leucocytosis may present for short duration, during paroxysms, but as parasitaemia progresses leucopenia may develop (Neval et al, 1970). There may be neutropenia (Dale et al, 1973), lymphopenia may also be there which may be because of shift of lymphocytes from the peripheral blood to reticuloendothelial system as well as that of T cells are reduce in peripheral blood in malaria (Playfair, 1982).

In acute malaria in Gambian children peripheral neutrophilia, monocytosis and eosinopenia are but these changes are usually reversed 3 to 7 days after treatment of malaria. Neutropenia occurs in patients with acute
vivax malaria and this was thought to be redistribution of neutrophils in the marginal pool rather than to deficiency in production (Abdalla, 1990).

**PLATELETS**: Thrombocytopenia has long been known to occur during malarial infection. A mild to moderate degree of thrombocytopenia usually occurs in non complicated cases where as marked fall in platelets count is observed in severe complicated P. falciparum infection (Hill, 1964; Shulman, 1970; Beale, 1972; Shudowitz, 1973).

Two mechanism are involve in the occurrence of the thrombocytopenia, namely immunodestruction by Ig M antibodies (Shulman, 1970; Kelton et al, 1983) and disseminated intravascular coagulation (Dennis et al, 1967; Punya Gupta et al, 1974).

Several studies have indicated that platelets hyperactivity occurs during acute malarial infection. The evidence includes increase release of beta thromboglobulin and platelet factor-4 (Essien and Ebhota, 1983). Enhance thromboxane $\text{A}_2$ production (Essien et al, 1984) and in vitro hypersensitivity of platelet response to ADP stimulation (Inyang et al, 1987).
Immune mechanism due to binding by platelets of circulating immune complexes or by absorption of soluble malarial antigen by platelets and subsequent attachment of antibody to such antigen (Abdalla, 1990).

**IMMUNITY IN MALARIA**

In controlling acute infection non specific host defence mechanisms and the development of more specific cell mediated and humoral responses are both important. Protective antibodies inhibit parasite expansion through co-operation with monocyte-macrophage series by binding to parasitized erythrocytes and then activating these cells Fc receptors (Bouharoun et al, 1990).

There is no evidence for synthesis of specific antibody during pre-erythrocytic development of malarial parasite. There is also no evidence of natural infection to induce immunity against pre-erythrocytic stage of plasmodium (Cohen and Butcher, 1971).

The acquired malarial immunity is directed against the asexual parasite cycle in blood circulating gamethocytic of plasmodium falciparum are apparently unaffected by immune serum (Cohen et al, 1961). The protective antibodies act against mature schizonts or extracellular merozoites (Cohen et al, 1961; Cohen and McGregor, 1963).
THE IMMUNE RESPONSE:

The infusion of hyperimmune serum to patients with acute malaria can reduce or eliminate parasitaemia mainly through opsonization, phagocytic cell activation and cytotoxicity and augmentation of ring form infected erythrocytes clearance (Cohen et al, 1961; McGregor et al 1963; Sabcharoeng et al, 1991). Immune serum also reduced multiplication of parasite by agglutinating merozoites.

IMMUNOLOGICAL PROCESSES:

Acute malaria is characterized by non specific polyclonal B cell activation. There is reduction in circulating T cells with an increase in the Y/S T cell subset (Hom et al, 1990). But other T cell proportions are usually normal (Hom and Webster, 1990).

In non immune individuals, the acute antibody response to infection often comprises mostly Ig M or Ig G₂, isotypes which are unable to arm cytotoxic cells and thus kill asexual malaria parasites (Bouharoun et al, 1992).

IMMUNOGLOBULIN(Ig):

Immunoglobulins are serum proteins (Y globulins) produced by lymphocytes and plasma cells in response to antigenic stimulation. By immunoelectrophoresis immunoglobulins can be divided into five group Ig G, Ig M, Ig A, Ig D and Ig E (Bull WHO, 1964) (Fehey 1965a). Two types of light chain have been detected, which are known as K and .
The immunoglobulins are said to be monoclonal if particular class has the same light chain component. If both light chains are present, the immunoglobulin production said to be polyclonal.

Ig G is always a simple monomer and therefore possesses two antibody combining sites. Ig M is always a pentamer with 10 potential antibody combining site. The five basic units are connected by a joining chain to form a ring.

Ig A exists as two related form, serum Ig A and secretory Ig A. Serum Ig A exists predominantly as a monomer but can form dimer and trimer. The immunoglobulin protein is produce by plasma cell in these organ and secretory piece is produce by glandular portion.

Ig D immunoglobulin with monomeric Ig M are present on the surface of the some lymphocyte cell. This antibody appear to play a role as an antigen receptor in lymphocytes activation and suppresion.

Ig E molecule are normally present in the blood serum in very low proportion of the immunoglobulin. The main role of Ig E appear to be protection of external mucosal surface by mediating the attraction of phagocytic cells and initiation of inflammatory response.

The characteristics of serum immunoglobulins are given in detail in Table 'A'.
### TABLE 'A'

**Characteristics of Immunoglobulins**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ig M</th>
<th>Ig G</th>
<th>Ig A</th>
<th>Ig D</th>
<th>Ig E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other terminology</strong></td>
<td>Complete</td>
<td>Incomplete</td>
<td>Univalent</td>
<td>-</td>
<td>Reactin</td>
</tr>
<tr>
<td></td>
<td>Bivalent</td>
<td>Univalent</td>
<td>Secretory</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Natural</td>
<td>blocking</td>
<td>immune</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serum concentration (mg/dl)</strong></td>
<td>120 ± 45</td>
<td>1275 ± 280</td>
<td>225 ± 55</td>
<td>3</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Half life (day)</strong></td>
<td>9-11</td>
<td>25-35</td>
<td>6-8</td>
<td>2-3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Synthesis mg/kg/day</strong></td>
<td>5-8</td>
<td>25</td>
<td>8-10</td>
<td>0.4</td>
<td>-</td>
</tr>
<tr>
<td><strong>Molecular weight</strong></td>
<td>Approx. 9,000,000</td>
<td>Approx. 1,500,000</td>
<td>Approx. 1,500,000</td>
<td>Approx. 1,800,000</td>
<td>Approx. 2,000,000</td>
</tr>
<tr>
<td><strong>Sedimentation Coefficient</strong></td>
<td>19 S</td>
<td>7 S</td>
<td>7-15 S</td>
<td>6 S</td>
<td>8 S</td>
</tr>
<tr>
<td><strong>Location by Electrophoresis</strong></td>
<td>Between Y and B</td>
<td>Y Slow</td>
<td>Between Y and B</td>
<td>Between Y and B</td>
<td>Between Y and B</td>
</tr>
<tr>
<td><strong>Lability to sulphydryl</strong></td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>-</td>
</tr>
<tr>
<td><strong>Effect to Heat (56°C for 3 Hrs.)</strong></td>
<td>Labile</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td><strong>Optimal medium</strong></td>
<td>Saline</td>
<td>Albumin</td>
<td>Saline</td>
<td>Saline</td>
<td>Saline</td>
</tr>
<tr>
<td><strong>Optimal Temp. for activity</strong></td>
<td>5-25°C</td>
<td>37°C</td>
<td>5-15°C</td>
<td>4°C</td>
<td>-</td>
</tr>
<tr>
<td><strong>Complement fixation</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Croses placents</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Sequence in immunization</strong></td>
<td>First</td>
<td>Last</td>
<td>Inter-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sequence in New born Synthesis</strong></td>
<td>First</td>
<td>Last</td>
<td>Inter-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
ESTIMATION OF SERUM IMMUNOGLOBULINS:

Immunoglobulins in the serum has been estimated by various method such as:

1- Single radial immunodiffusion Technique (Mancini and Carbenara, 1965).
2- Immuno-electrophoresis (Grabar, P and Williams, C.A.; 1953).
3- Single linear immunodiffusion of Oudin (Oudin, J.; 1946).
4- Electroimmunodiffusion (Laurell, 1960).

The most frequently used method for the estimation of immunoglobulins has been single radial immunodiffusion of Mancini and Carbenara (1965).

SINGLE RADIAL IMMUNODIFFUSION:

The method was described by Mancini and Carbenara (1965) and modified by Fahey and McKelvey (1965) who reduce the completion time from days (in Mancini method) to 18-24 hours. The immunoglobulin is deposited into well cut into a thin agarose layer containing the corresponding monospecific antiserum in uniform concentration. Incubated in moist environment at room temperature. The radial diffusion of antigen produces a ring of precipitate, the diameter of which is proportional to the concentration of the antigen.
Development of immunity is manifested by tolerance to infection (Cessation of clinical phenomenon despite parasitaemia) which is the result of active immunity (both cellular and humoral) consequent upon the concomitant presence of the parasites. The phagocytic activity of the cells of the reticulo-endothelial system (particularly those in the spleen and liver) helps in the development of immunity to malaria infection and parasite are destroyed and kept at subclinical level. Hence it has been suggested that immunity in malaria depends upon a persistent latent infection known as infection immunity or premunition. Shortt and Garnham showed that the immunity in malaria may be complete and may occasionally persist for some time, even after disappearance of the parasite or termination of infection. Plasmodial antigens derived from asexual erythrocytic phases of the parasite stimulate the appropriate cells of the body to produce specific antibodies, both protective and the precipitating which present in the Ig G and Ig M fractions of the serum gammaglobulin.

The protective malarial antibodies exist in Ig G (7 S) fraction of immune sera where as precipitating antibodies been shown to exist in both Ig G and Ig M components (McGregor and Wilson, 1971).
The alternation in the serum levels of the immunoglobulins Ig M, Ig G and Ig A after inoculation of the four volunteers with P. cynomolgi and challenged with P. vivax. After exposure to infection with P. cynomolgi no volunteers showed significant increases in Ig M globulin during preantibody period. But all the volunteers showed a significant increase in Ig M globulin after the vivax infection ranging from 153% to 368%. For twelve vivax cases with higher parasitaemias of some what long duration (Tobie et al 1966b) observed a mean increase of 357%.

The quantitative determinations show more fluctuation for Ig G globulin than for the other immunoglobulins but that significant increases in Ig G globulin can be readily correlated with the production of malarial antibody (John, E Tobie, 1966).

Malaria is associated with increase gamma-globulins level and in inhabitants of endemic malarial areas production and turnover rates of gamma-globulin are very high (Cohen and McGregor, 1964). In some tropical areas where malaria is endemic and hyperimmunglobulinaemia common there is high incidence of cold agglutinins (Curtain, Baumgarten et al, 1965) and a significantly greater autoimmune complement fixation capacity against
saline extracts of human liver and kidney than seen in Europeans with lower gammaglobulin levels (Curtain, Kidson et al, 1965).

Rowe et al (1968) have compared plasma immunoglobulin concentrations in West African (Gambian) community and in group of healthy British adults. The mean adult British Ig G, Ig A and Ig M levels were 1.2 gm, 270 mg and 89mg per 100 ml respectively and these findings are in reasonable agreement with those of 1.2 gm, 200 mg and 99 mg per 100 ml respectively, reported in healthy adult Americans (Stiehm and Rudenberg, 1966).

Particularly the Ig M fraction the rise of which is known to tally closely with the formation of malarial antibody (Tobie et al, 1966; Zuckerman, 1969) carefully emphasized that all gammaglobulins is not antibody and both Curtain et al (1964) and Turner et al (1966) pointed out that raised levels of immunoglobulins can be due to intercurrent infections, but this studies were conducted among previously healthy individuals, and no coincident disease was detected. Hence that changes in immunoglobulins values reflected changes in malarial antibody (Beale et al, 1972).
Serum Ig G and Ig M levels are increased in most people in many tropical areas. Black Americans have only slightly higher immunoglobulin levels than white Americans, suggesting that environmental factors are important in producing hypergammaglobulinaemia in Africans. Malaria is probably the most important of these environmental factors. The nature and function of the immunoglobulin produced in such large amounts in malaria is uncertain. Some is specific antibody but absorption with malarial antigen suggest that specific antibody forms only a small fraction of the increased immunoglobulin concentration seen in malarial infection.

Production of a B cell mitogen would be expected to lead to an increase in lymphocyte DNA synthesis. It is therefore of interest that two recent studies have shown a high uptake of (3H) thymidine by lymphocytes from children with acute malaria.

Abnormal production of Ig M is probably the basic abnormality in this condition and might be due to an abnormal and prolonged response to a B cell mitogen produced by malaria parasite (Greenwood, B.M. 1974).

Both cell mediated (CMI) and humoral immunity involved in protection from malaria parasites (Playfair, 1982). Different strains of the same parasite may stimulate
a predominantly cell mediated immunity or humoral response
and are used to investigate both these aspects of immunity
(e.g. Clark, Hunt, Butcher and Cowden, 1987; Jarra, Hills,
March and Brown, 1986).

Inhibition of merozoite invasion by immune
sera demonstrated initially with Plasmodium knowlesi
(Cohen, Butcher and Crandall, 1969) was the first malaria
in vitro assay that apparently correlated with in vivo
protection (Butcher and Cohen, 1972). It is now frequently
used to detect putative protective antigens but the limitsa-
tions of assay are rarely given critical evaluation. In
early studies it was shown to reflect the species specific-
city of immunity (Cohen et al. 1969) a feature of assay that
has not ever been repeated. The inhibition was mediated
mainly by Ig G and to a small extent by Ig M, but dependent
on a bivalent molecule (Cohen and Butcher, 1970). In recent
years a number of workers have suggested that the antimero-
zoite activity results from agglutination of the merozoites
preventing their entry into red cells (e.g. Miller, Aikawa

Acute malaria is characterized by non specific
polyclonal B cell activation. Residents of hyperendemic
or holoendemic malarious areas have hypergammaglobulin-
emia. Most of this antibody is not directed against
malarial antigens. In non immune individuals the acute antibody response to infection often comprises mostly Ig M or Ig G2 isotypes which unable to aim cytotoxic cells and thus kill asexual malaria parasites (Bouharoun and Drulhe, 1992).

Ig G, Ig A and Ig M are significantly increased in malarial infection in primary attack. Most of authors have reported increase in Ig M and Ig G levels in their series. Tobie et al considered that Ig G and Ig M levels appear to rise and reach a peak at about same time. It is suggested that there is a strong correlation between Ig M levels and malaria antibody levels. However Greenwood mentioned that high levels of Ig M in malarial infections are possibly due to the production of B cell mitogen by the parasite (Bobhate et al, 1991).

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