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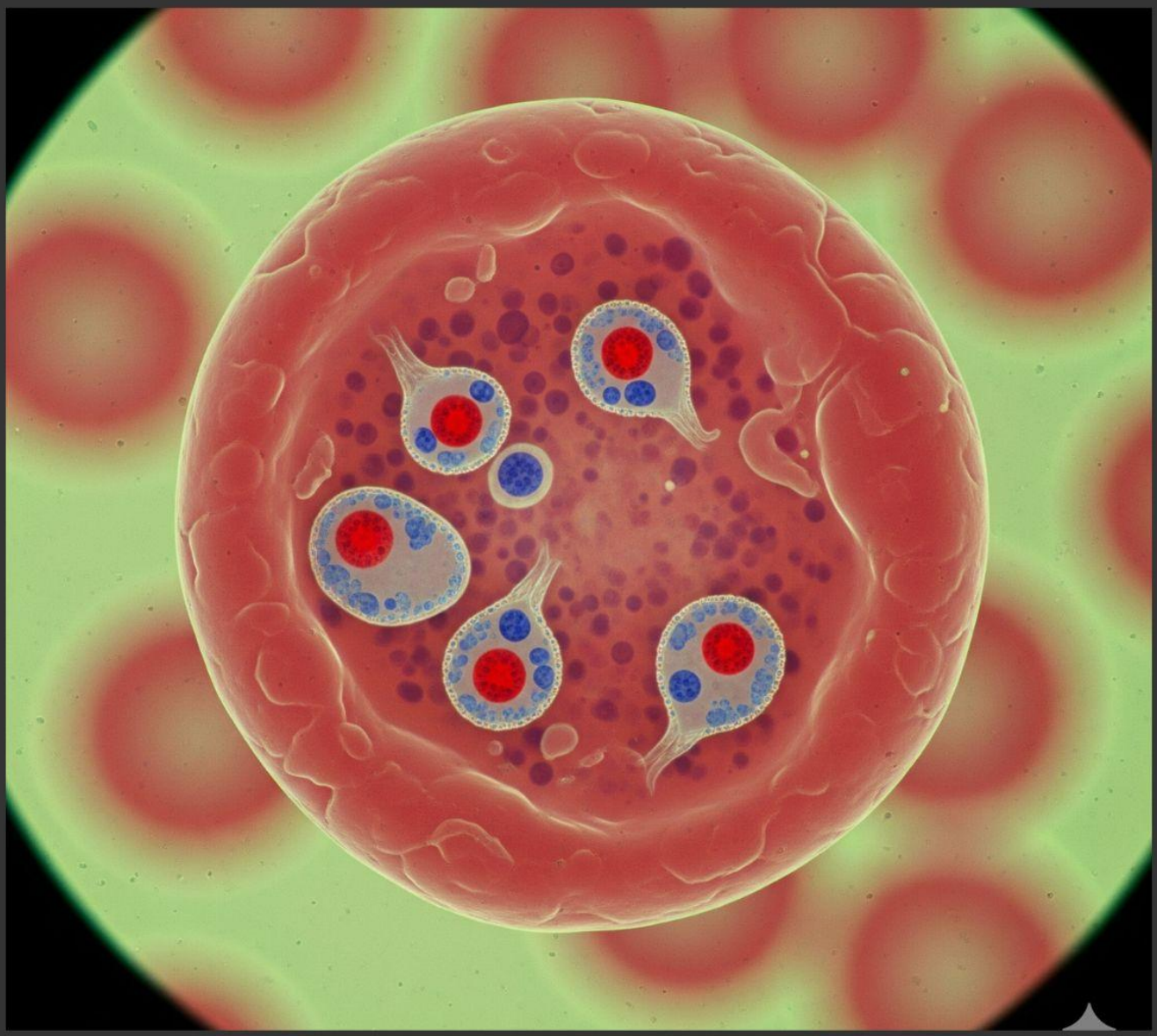
Chapter 3

INVERTEBRATES
CHAPTER SERIES

Plasmodium vivax



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Plasmodium vivax

(The malarial parasite)

CLASSIFICATION

SYSTEMATIC POSITION

Phylum: Protozoa
Subphylum: Sporozoa
Class: Telosporea
Subclass: Coccidia
Order: Eucoccida
Suborder: Haemosporina
Genus: *Plasmodium*
Species: *vivax*

INTRODUCTION

Plasmodium vivax is one of the 60 known species that cause malaria in humans and other animals. Because of their malaria-causing abilities, the species are commonly referred to as malarial parasites. Members of the subphylum Sporozoa lack any organelles of locomotion. These are either intracellular or intercellular parasites of both invertebrates and vertebrates. Many sporozoans are causative organisms of dreadful diseases like malaria, coccidiosis, cattle fevers, deaths in cultivated honeybees and silkworms. *Plasmodium* resides in the liver cells and red blood corpuscles of the man, reproducing in them and finally destroying them. Mosquitoes, especially the *Anopheles* are the transmitting agents or vectors of *Plasmodium*. The geographical distribution of the species of *Plasmodium* is widespread in tropical and temperate countries. Migratory birds are the hosts for the parasite. Thus, it has spread all over the world. Four species of *Plasmodium* are known to cause different types of malaria in man.

(i) P. *vivax*
(ii) P. *ovale*
(iii) P. *malariae*
(iv) P. *falciparum*

Out of the human-infecting parasites, P. *vivax* is the most widely distributed species. It is found mainly in temperate regions of the world. Its fever is characterised by a 48-hour chill cycle. Life cycle of P. *vivax* has been described below in particular as it is the most common type of malarial parasite.

LIFE CYCLE OF PLASMODIUM VIVAX

P. *vivax* is the most widely distributed species and the most common of the human infecting malarial parasites. Life cycle of Plasmodium vivax can be differentiated into two phases: asexual and sexual and completes inside two hosts.

Hosts. Life cycle is completed in two hosts, man and mosquito. Thus, Plasmodium is said to be digenetic. The asexual phase of life cycle is completed in man whereas sexual phase is completed in female mosquito.

(A) ASEXUAL CYCLE IN MAN

This part of the life cycle does not include gamete formation or their fusion, thus referred to as asexual. The asexual life cycle occurs in man. Whenever an infected female mosquito bites a human, this cycle starts in man. The asexual cycle can further be subdivided into two phases. First phase starts in the liver (Liver Schizogony) and the second phase occurs in red blood cells (Erythrocytic Schizogony). Here, schizogony refers to the multiplication of the organism.

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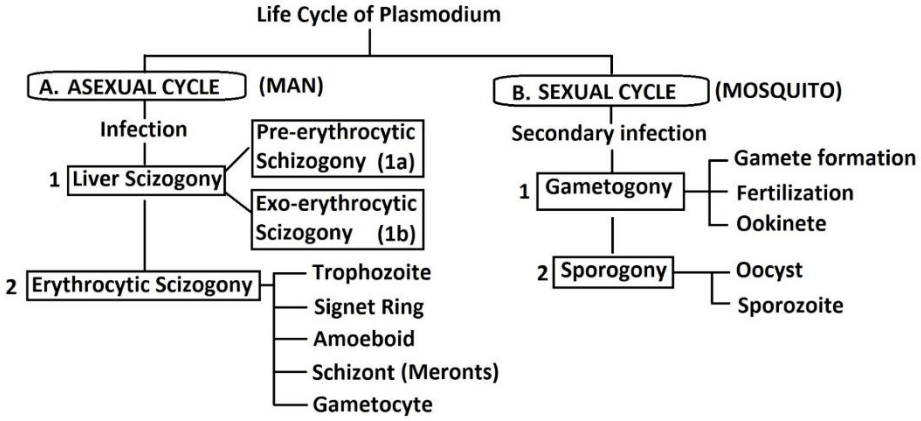

Figure 1. Generalized life cycle of *Plasmodium vivax*

Infection. Humans get malaria from the *Anopheles* mosquito. Thus, infection is the primary source which starts with the bite of a female mosquito carrying the organism in its salivary glands. Whenever a female mosquito bites, it releases a stage called "Sporozoite" in the blood of humans. These sporozoites are present in the salivary glands of the mosquito. Thus, sporozoites are the infective forms of *Plasmodium* which enter first and infect the humans. Hundreds of sporozoites enter with a single bite of an infected mosquito. These are small spindle shaped organisms measuring about 10µm in length. Sporozoites have a nucleus, mitochondria, scattered endoplasmic reticulum, a micropyle and an apical cap followed by connective rings. These sporozoites in the blood have to enter the liver cells. Paired organelles present in the sporozoites secrete lytic juices which help in penetration into liver cells of humans.

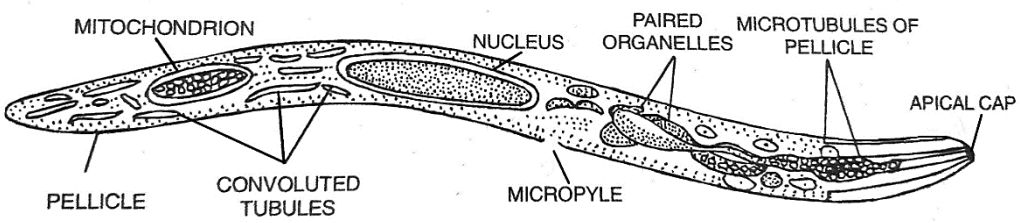

Figure 2. Sporozoite, the infective stage of P. *vivax*

1. Liver schizogony (Multiplying in hepatocytes)

Schizogony refers to multiplication. So, liver schizogony is the multiplication of organism inside liver cells or hepatocytes. After the infection by the mosquito, hundreds of sporozoites circulate in the blood of the infected human for about half an hour and finally reach the liver. With the help of lytic juice from paired organelles, sporozoites lyse or break the plasma membrane of the liver cells and enter into them. Now, the sporozoites have entered the liver cells. Here, they multiply asexually by schizogony. Liver schizogony can be divided into two phases:

(1a) Pre-erythrocytic schizogony

After penetrating a hepatic cell each sporozoite changes into a "cryptozoite". Cryptozoites grow for a number of days and become spherical. This stage is referred to as "Schizont". Schizonts divide by schizogony (multiple fission) and form a large number of uninucleate cells, the "Cryptomerozoites". These can be produced inside the liver cells in several thousand numbers. Cryptomerozoites are liberated into blood when the liver cell bursts. With the liberation of cryptomerozoites, pre-erythrocytic phase ends. Time period from infection upto the release of first cryptomerozoites in blood is referred to as the pre-patent period.

Sporozoites ---> Enter Liver cells ---> Cryptozoites ---> Grow ---> Schizonts ---> Multiply ---> Cryptomerozoites ---> Liver cell burst ---> Cryptomerozoites liberated out

Figure 3. Schematic representation of exo-erythrocytic phase

(1b) Exo-erythrocytic schizogony

Cryptomerozoites that were liberated in the pre-erythrocytic phase enter fresh liver cells and change to "metacryptozoites". These forms grow in size and form "schizonts". Schizonts again undergo schizogony and multiply into enormous numbers and the forms are now called "metacryptomerozoites" (MCMZs). MCMZs are of two types. Smaller are referred to as "Micro-metacryptomerozoites" (Micro-MCMZs) and larger as "Macro-metacrytomerozoites" (Macro-MCMZs). Out of these two forms, macro-MCMZs enter fresh liver cells to multiply further and micro-MCMZs enter the red blood corpuscles and start the next phase in RBCs.

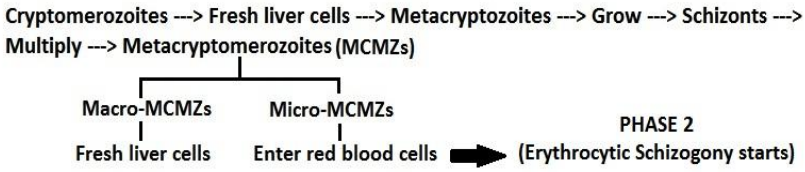

Figure 4. Schematic representation of exo-erythrocytic phase

Time period between the entry of the sporozoites into the human body (infection) and first appearance of parasites in blood is called 'pre-patent period'. It corresponds to the pre-erythrocytic schizogony period. This period is approximately 8 days in P. *vivax*. Time period between the entry of the sporozoites into the human body (infection) and appearance of malarial symptoms is called 'incubation period'. This period is approximately 14 days in P. *vivax*.

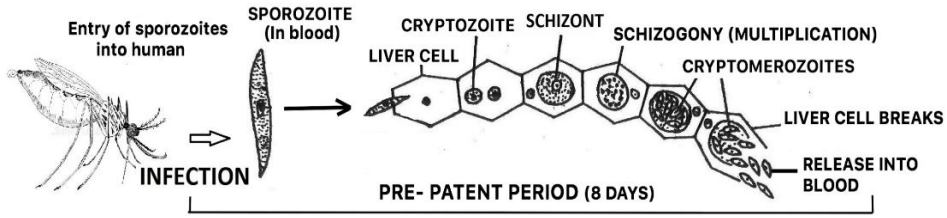

FIGURE 5. Pre-patent period in P. *vivax*

2. Erythrocytic schizogony

Micro-MCMZs entering into the red blood cells start the erythrocytic cycle. This cycle starts with the trophozoite stage formation inside the R.B.Cs. Following are the stages in erythrocytic schizogony:

(a) Trophozoite stage. When micro-MCMZs enter the R.B.Cs, these become round and get modified into trophozoites.

(b) Signet ring stage. Trophozoites grow in size within R.B.Cs and a central vacuole is developed so that the nucleus of the trophozoite is pushed to one side. This stage is referred to as signet ring stage as it resembles a ring. The vacuole resembles the space to put a finger. The peripherally located nucleus looks like a diamond stud in the ring. As this stage is formed inside the R.B.C., it starts ingesting the cytoplasm of R.B.C. and secrete digestive enzymes into it. These enzymes in the cytoplasm of R.B.C. break the haemoglobin into hematin + protein part. Out of these two end products, signet ring trophozoite takes up the protein part as food. The remaining hematin converts into 'hemozoin' - a toxic malarial pigment which induces high fever and shivering in the infected person.

(c) Amoeboid stage. Signet ring trophozoites after ingesting the protein from the R.B.Cs grow and develop into amoeboid trophozoites. These trophozoites acquire the amoeboid shape by extending pseudopodial processes into the cytoplasm of the R.B.Cs. Small red eosinophilic granules known as 'Schuffner's granules' appear in the cytoplasm of the R.B.Cs.

(d) Schizont. After the formation of amoeboid trophozoites, these feed and become rounded forming 'schizonts'. These round schizonts undergo schizogony or multiplication inside R.B.Cs. Nucleus divides to form 12-24 nuclei which then arrange at the periphery gathering cytoplasmic masses surrounding them. Each nucleus with its surrounding cytoplasm forms a merozoite. Thus 12-24 merozoites are formed inside one schizont. With the rupture

of the R.B.Cs, these merozoites are liberated into the blood. The liberated merozoites can re-enter fresh R.B.Cs and the cycle can restart.

Formation of gametocytes. Some merozoites after entering the red blood corpuscles increase in size to become rounded gametocytes. Gametocytes formed are of two types: male and female. Male gametocytes are smaller in size whereas larger gametocytes are bigger in size. These gametocytes formed in the blood remain there.

B. SEXUAL CYCLE IN MAN

Sexual cycle involves the formation of gametes (gametogony), fertilization and sporozoite formation (sporogony). It takes about 15 days to complete. Sexual cycle of P. *vivax* starts with the secondary infection. This secondary infection is from human to the mosquito. It starts whenever a female mosquito (not infected) bites an infected person and sucks his blood having gametocytes. Now, the gametocytes (male and female) enter the mosquito gut.

1. Gametogony (Gametocytes to gametes). This process involves the 'formation of gametes'. It is also known as gametogenesis. Gametocytes are of two types: microgametocytes and megagametocytes. Microgametocytes give rise to microgametes or sperms whereas megagametocytes give rise to macrogametes or ova. This process takes place in the midgut.

(a) Microgamete formation. The male or micro-gametocytes undergo a process called exflagellation to form multiple numbers of male gametes. This process begins in the midgut of the mosquito. Nucleus of each gametocyte divides into 6-8 daughter nuclei (N) which arrange themselves on the periphery. After the nuclear division, the gametocyte gives off several flagella-like structures. Each nucleus slides into one flagella-like outgrowth. After the entry of nuclei into these slender structures, these projections break away as sperms. Thus, one microgametocyte gives rise to 6-8 sperms.

(b) Megagamete formation. Megagametocytes give rise to megagametes in a rather simpler way. Female megagametocytes undergo structural and physiological reorganization to become female gametes. Mature ova develop a 'reception cone'. The formed megagametes (ova) are ready for fertilization by the sperms.

Fertilization. The mature ova develop reception cones which are the outgrowths of the ova meant to receive the sperms. Nucleus of the ovum comes close to the receptive cone. A single microgamete (sperm) is received by the reception cone. It penetrates the ovum and fertilization occurs. After the fusion of male and female nuclei, a diploid zygote is formed.

Ookinete formation. Zygote formed in the midgut soon elongates and becomes motile. This motile and elongated form (approx. 20µm in length) is known as 'ookinete'. This form has a nucleus, pigment granules, dense cytoplasm, mitochondria and ribosomes. Ookinete moves and glides in the medium of the midgut and finally reaches the stomach wall. Motility is provided by microtubules and ectoplasmic myofibrils.

Oocyst formation (Encystment). Ookinete, the elongated zygote (2N), soon penetrates the stomach wall and starts to secrete a cyst wall. The cyst wall is thin and elastic. This wall is secreted by ookinete as well as the midgut of the mosquito. This encysted stage is termed 'Oocyst'. These oocysts remain there in the stomach wall and can be seen from outside of the stomach as boils.

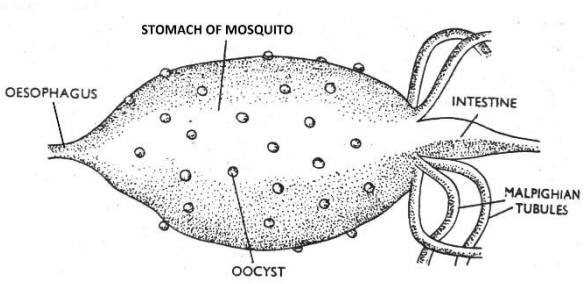

Figure 6. Oocysts in the wall of the stomach in mosquito

2. Sporogony. Oocysts (2N) residing in the stomach wall now undergo multiplication or sporogony. The nucleus of each sporocyst first undergoes meiosis and forms haploid nuclei. These haploid nuclei further undergo mitosis. This

multiplication results in the formation of a huge number of haploid nuclei. Each haploid nucleus gathers some cytoplasm. Later, finger-like processes are given out, each process having a haploid nucleus inside it. All these processes develop into spindle shaped bodies known as 'Sporozoites'. Recent studies have shown that about 5000 sporozoites can be formed by each oocyst. Whenever the oocyst wall breaks, sporozoites are liberated out and these reach the salivary glands of the mosquito. Now the mosquito becomes infective with sporozoites in its salivary glands. When this infected mosquito bites a healthy person, it will inject the sporozoites from the saliva into the blood of the person and the asexual cycle in man starts again.

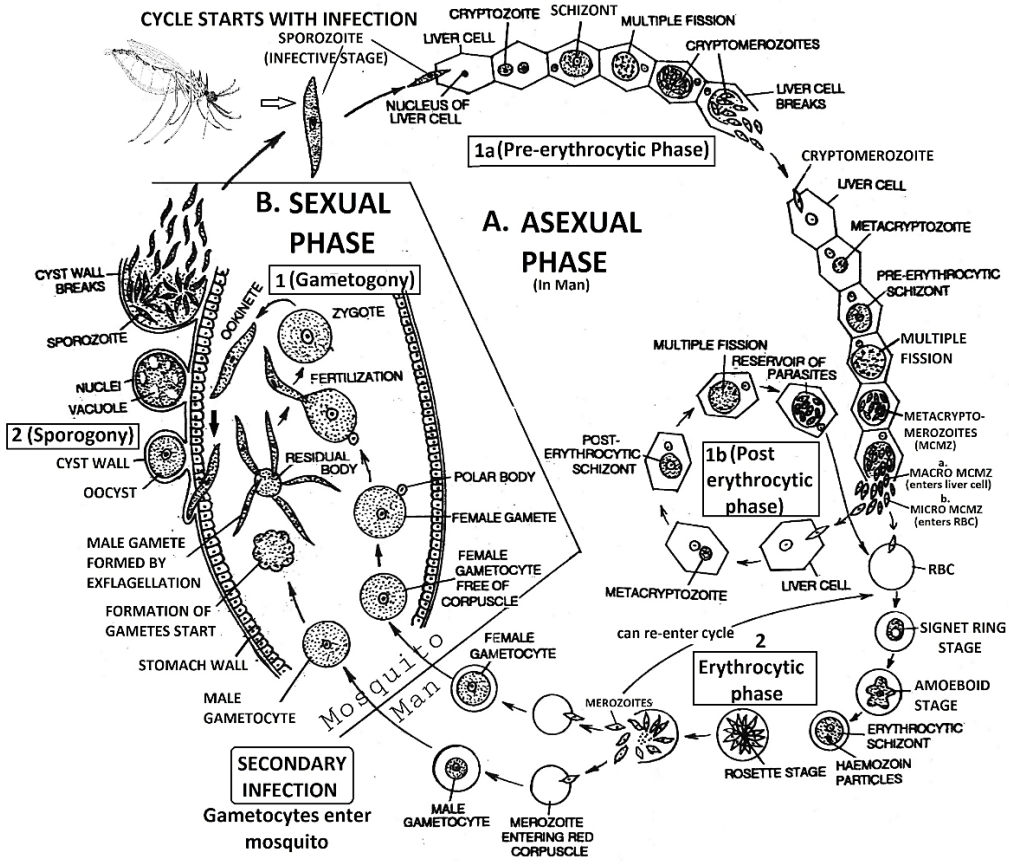

Figure 7. Schematic representation of whole life cycle of P. *vivax*

Symptoms of malaria. Malaria is characterized by a typical 48 hour chill cycle. Each cycle of fever shows three stages.

1. Chill phase. At the onset of malaria fever, the patient suffers from a severe shaking chill. His teeth chatter in spite of warm coverings. This phase can remain for an hour.

2. Hot phase (Fever phase). As the first phase passes, the body temperature rises high and can reach upto 105°F. The patient gets a high fever with a headache. This phase can remain for 1 to 4 hours.

3. Sweating phase. After the passage of hot phase, the body temperature of the patient lowers down and the patient sweats. With sweating, body temperature falls down and becomes normal.

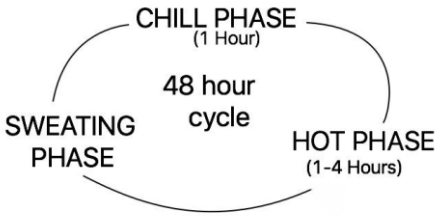

Figure 8. Fever cycle in P. *vivax*

After the sweating phase, the patient becomes comfortable until the next attack. All the three phases repeat with regular intervals of 48 hours in case of vivax malaria. Malaria fever occurs when schizonts in red blood corpuscles burst and merozoites along with malarial pigment (hemozoin) are released in the blood. All the schizonts burst at the same time. Hemozoin is toxic and induces shivering chills and high fever.

Malaria and anaemia. Anaemia is the condition in which the blood doesn't have enough healthy red blood cells. This leads to reduced oxygen flow to the body's organs. The reasons for the origin of anaemia in malarial patients can be:

(1) Destruction of erythrocytes on liberation of merozoites.

(2) In malarial infections, the spleen releases lysolecithin, which destroys erythrocytes.

(3) In malaria, parasites produce hemolysin which is capable of causing lysis of the normal red blood cells, resulting in the release of hemoglobin.

CONTROL OF MALARIA

Control of malaria is the most important aspect in the breeding or rainy season of vector mosquitoes. Control of malaria can be done at different levels. It may include the control on the mosquito populations, prevention of mosquito bites, treatment of malaria by drugs and supportive therapies. All these control measures are discussed below.

1. Control of mosquito population. Adult mosquitoes may be controlled by spraying residual insecticides. Mosquito larvae are controlled by spraying oils and chemicals in breeding sites. Flooding and flushing of breeding places of mosquitoes should be done. Elimination of breeding places such as lagoons and swamps should also be done. Domestic species can be largely controlled by eliminating receptacles that hold water, such as tin-cans, buckets, cisterns, barrels, etc. Bushes and shrubs should be cleared off. Open drains should be closed or made underground.

2. Prevention of mosquito bite. Personal protection should be done by proper use of mosquito nets while sleeping. Wearing protective clothing that minimizes contact with mosquitoes. Mosquito repellents should be used.

3. Antimalarial chemotherapy. Drugs including Chloroquine, amodiaquine, chloroguanide, pyrimethamine, quinacrine hydrochloride, primaquine, proguanil and quinine can be given to the patient. Derivatives of artemisinin such as mefloquine and sulfonamides including sulfadoxine are used to treat chloroquine resistant malaria.

4. Supportive therapy. Antipyretic drugs to lower the temperature and cooling blanket can be used to treat hyperthermia. Fluids and electrolytes are given to maintain cardiac output, renal perfusion and prevent fluid overload. Transfusion of blood to treat severe anaemia can be done.

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