Malarial parasites

(plasmodium)

Blood parasites
Four spp. Infect man
***Plasmodium vivax* ,*P. ovale* ,*P. malariae* and *P. falciparum* .**
Vector is female anopheles mosquito also act as definitive host for *plasmodium.*
Man act as intermediate host.
Parasitized red blood cells and hepatic cells (habitats) .
Diagnostic stages :ring, trophozoite, schizont and gametocyte.
Infective stage : sporozoite.
Mode of infection: mosquito bite.

MALARIA

Class: Sporozoa.
Subclass: Haemosporidia.
Family: Plasmodiidae.
Genus: *Plasmodium.*
Species: *Plasmodium vivax.*
Plasmodium malariae.
Plasmodium falciparum.
Plasmodium ovale.
*** Malaria → bad air ..... plasmodioses.**

- **In Algeria 1880 – infected RBCs by the parasite.**
- **In 1894 – mosquito-transmitted disease.**
- **It is one of the greatest killers in the world in addition to cancer & heart diseases.**

Geographical distribution

- **As far north as 64ºN latitude (Russia).**
- **As far south as 32ºS latitude (Argentina).**
- **Dead sea – 400 meters below sea level.**

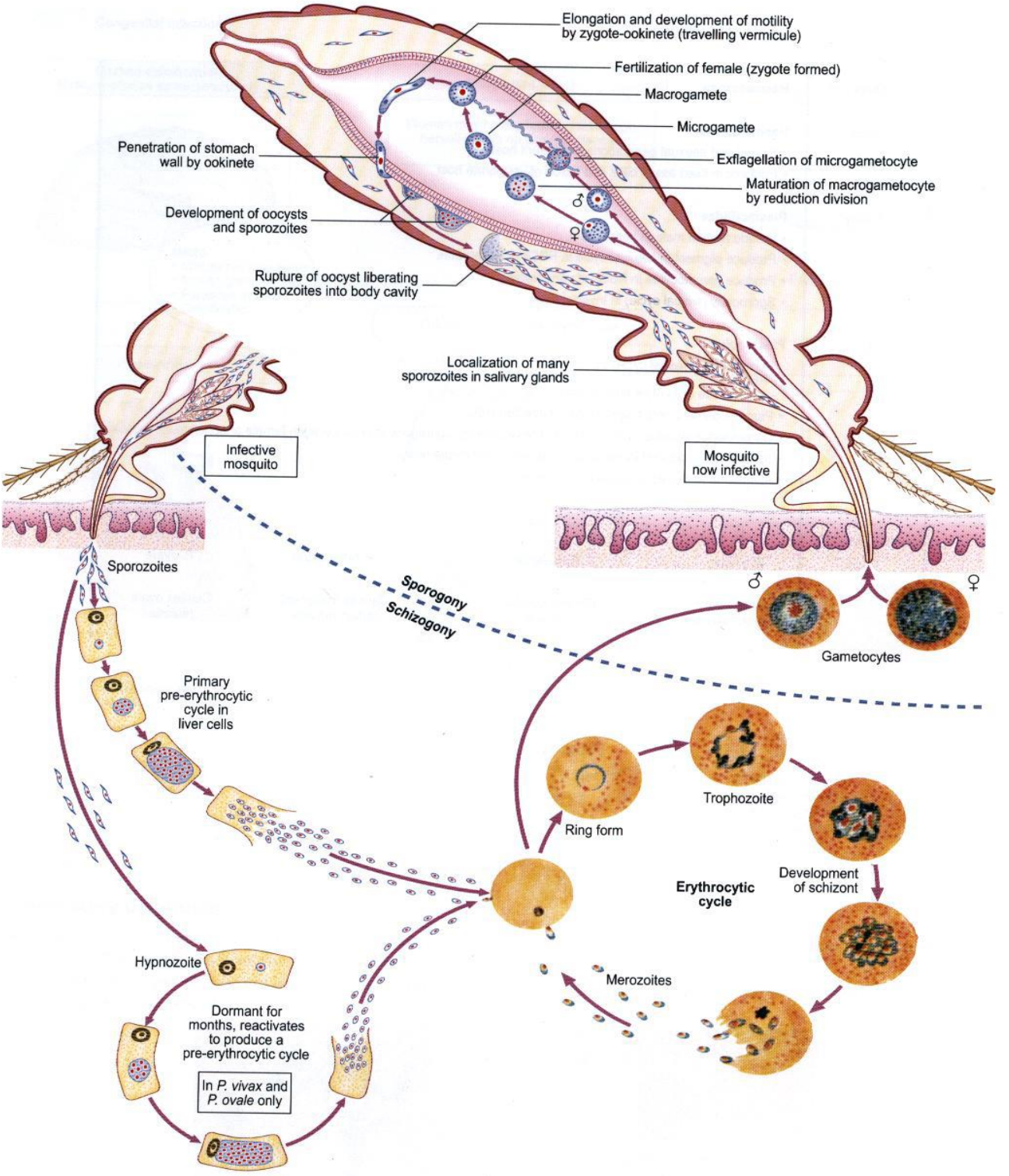
- **At 2600 m. above sea level – Kenya.**
- **At 2800 m. above sea level – Bolivia.**

***P. vivax*= most extensive in distribution.**
***P. falciparum*= tropical & subtropical.**
***P. malariae*= Less common but wide distribution.**
***P. ovale*= East & West Africa.**

Methods of infections & transmission:

1. ♀ ***Anopheles*** **bits.**
2. **Blood transfusion.**
3. **Organ trasplantation.**
4. **Congenital route.**
5. **Hypodermic needle.**

Life cycle

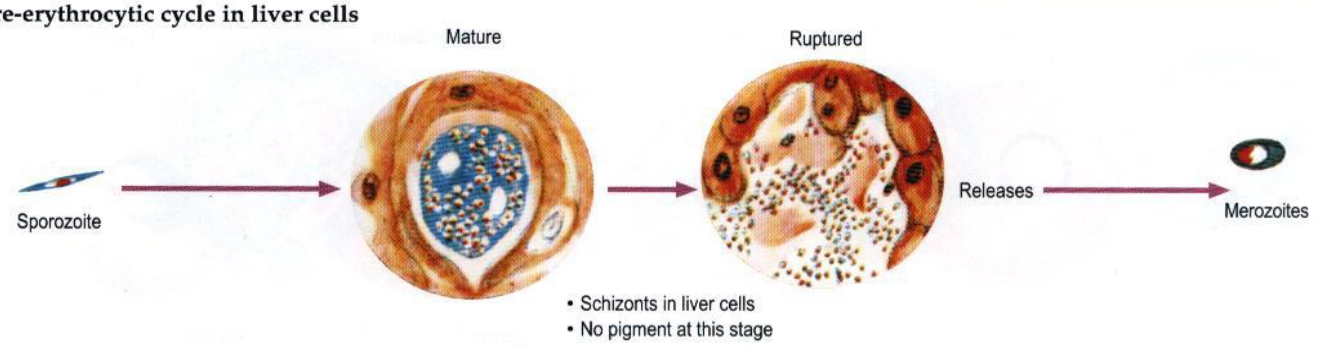

Elongation and development of motility by zygote-ookinete (travelling vermicule)
Fertilization of female (zygote formed)
Macrogamete
Microgamete
Penetration of stomach wall by ookinete
Exflagellation of microgametocyte
Maturation of macrogametocyte by reduction division
Development of oocysts and sporozoites
Rupture of oocyst liberating sporozoites into body cavity
Localization of many sporozoites in salivary glands
Infective mosquito
Mosquito now infective
Sporozoites
Sporogony
Schizogony
Gametocytes
Primary pre-erythrocytic cycle in liver cells
Ring form
Trophozoite
Development of schizont
Erythrocytic cycle
Merozoites
Hypnozoite
Dormant for months, reactivates to produce a pre-erythrocytic cycle
In P. vivax and P. ovale only

Morphology

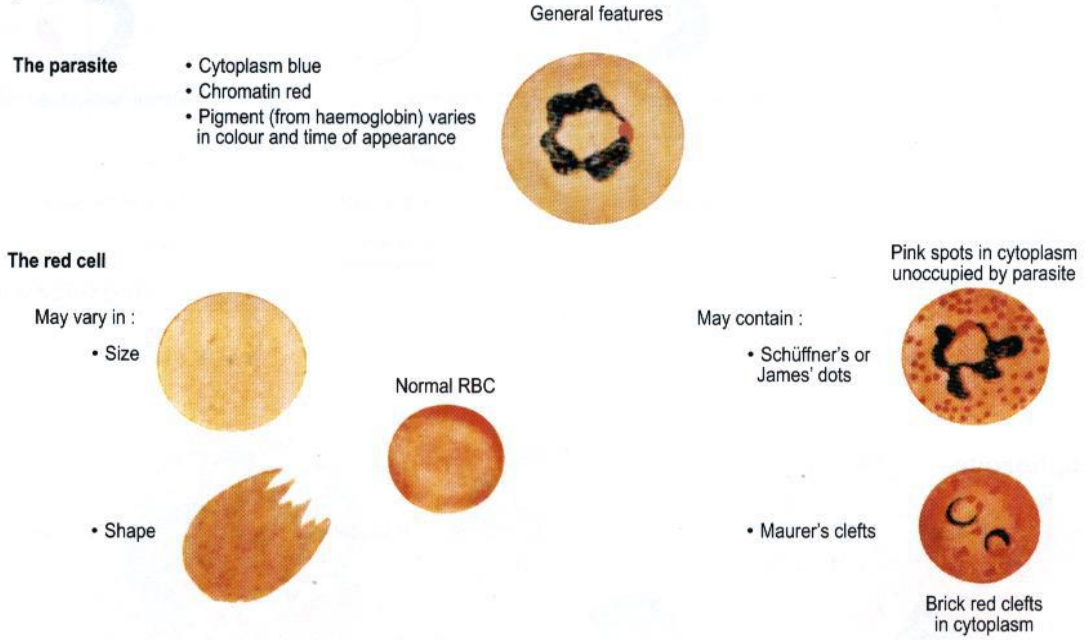
Stained by Leishman or Giemsa

Schizogony (asexual cycle)

Pre-erythrocytic cycle in liver cells



Erythrocytic stage in RBCs

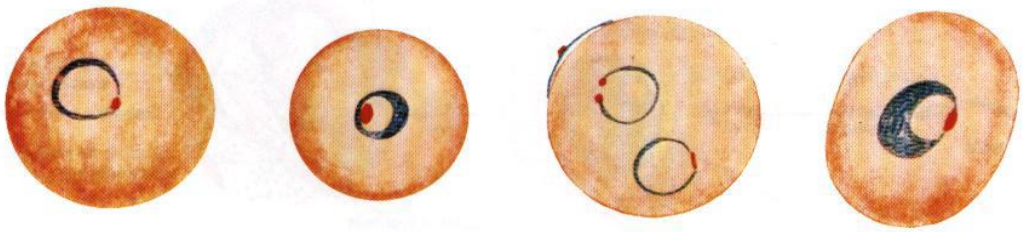


RBC characteristics	*P. vivax*	*P. malariae*	*P. falciparum*	*P. ovale*
Size	Larger than mature RBC	Smaller, older RBC	Mature RBC	Larger than mature RBC
Colour	Pale	Normal	Normal	Pale
Shape	Round	Round	Round May be crenated	Oval May be fimbriated
Cytoplasmic inclusions	Schüffner's dots present	None	Maurer's clefts may be present in late trophozoites	James' dots conspicuous

Morphology (continued)

Stages in thin films

Ring forms (early trophozoites)

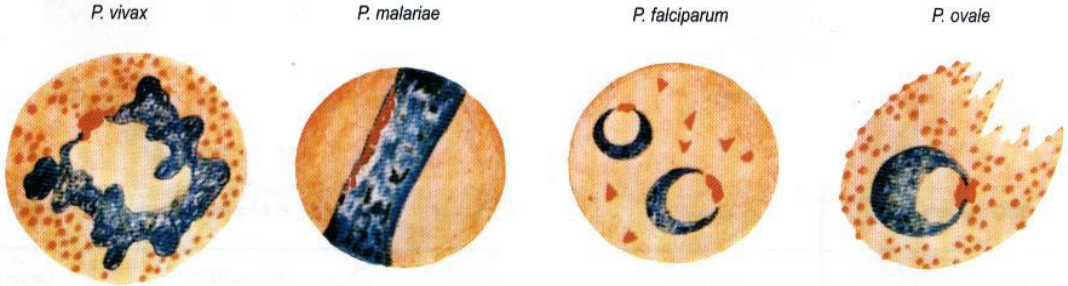


Size	1/3 RBC	Up to 1/3 RBC	1/3 RBC	1/3 RBC
Shape	Delicate ring	Compact ring	Very delicate ring	Dense ring

Chromatin	Fine dot	One mass often inside ring	Fine dots Frequently two	Dense, well-defined mass
Accolé forms*	Sometimes	None	Frequent	None
Pigment	None at this stage	May be present	None at this stage	None at this stage
Multiple parasitized cells	Sometimes	Rare	Frequently with high parasitaemia	Rare

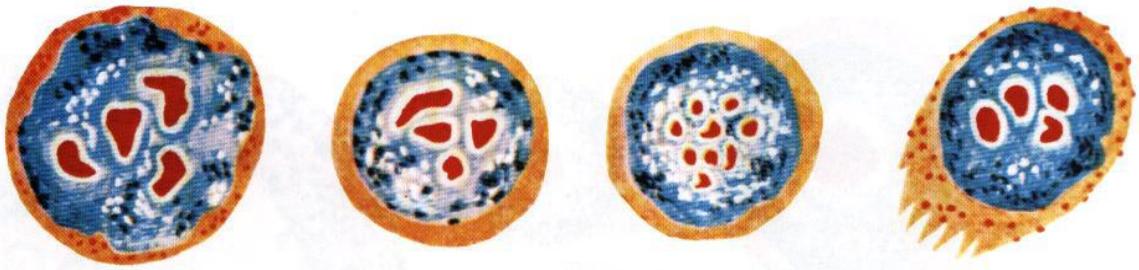
* Forms situated on margin of RBC

Developing trophozoites



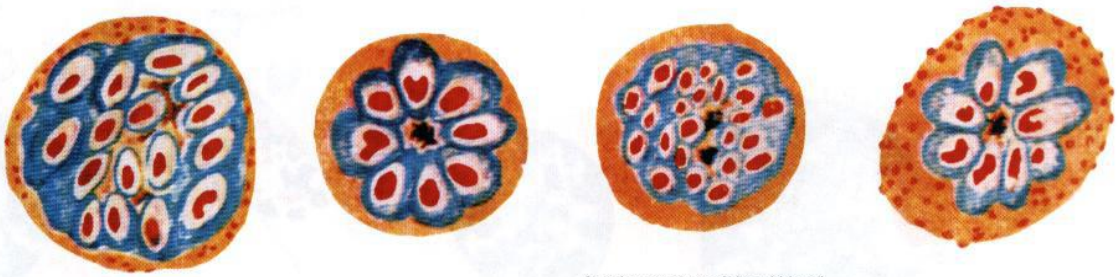
Size	Large	Small, but appears large relative to size of RBC	Small	Small
Shape	Very irregular, amoeboid	Compact, often band forms	Compact, with cytoplasmic vacuolation	Compact
Chromatin	Dots or threads	Prominent, often as a band	Dots or threads	Large irregular clumps
Pigment				
—texture	Fine	Coarse	Coarse	Coarse
—colour	Yellow brown	Dark brown	Black	Dark yellow brown
—quantity	Medium	Abundant	Medium	Medium
—distribution	Scattered fine particles	Scattered clumps and rods	Aggregated in one or two clumps	Scattered coarse particles

Immature schizonts



	P. vivax	*P. malariae*	*P. falciparum*	*P. ovale*
			(rarely seen in peripheral blood)	
Size	Almost fills RBC	Almost fills RBC	Almost fills RBC	Almost fills RBC
Shape	Somewhat amoeboid	Compact	Compact	Compact
Chromatin	Numerous irregular masses	Few irregular masses	Irregular masses	Few irregular masses
Pigment	Scattered	Scattered	Single clump	Scattered

Mature schizonts

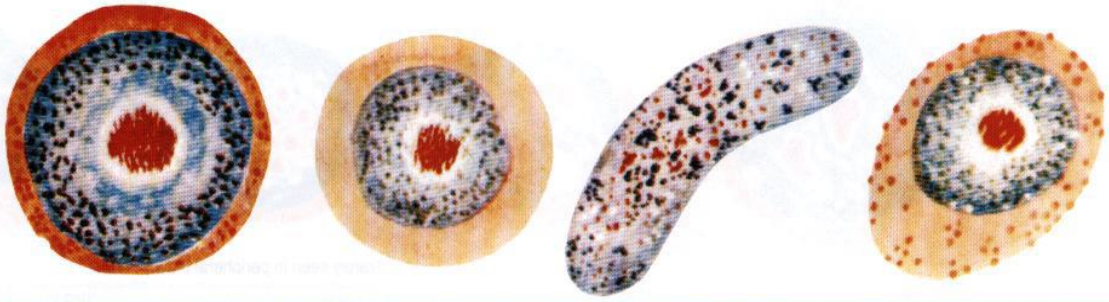


	P. vivax	*P. malariae*	*P. falciparum*	*P. ovale*
			(rarely seen in peripheral blood)	
Size	Fills RBC	Nearly fills RBC	Nearly fills RBC	Fills 3/4 RBC
Shape	Segmented	Segmented daisy head	Segmented	Segmented
Merozoites				
—range	14–24	6–12	8–32	6–12
— mean	16	8	24	8
—size	Medium	Large	Small	Large
Pigment	Aggregated in centre (yellow brown)	Aggregated in centre (dark brown)	Aggregated in centre (black)	Aggregated in centre (dark yellow brown)

Morphology (continued)

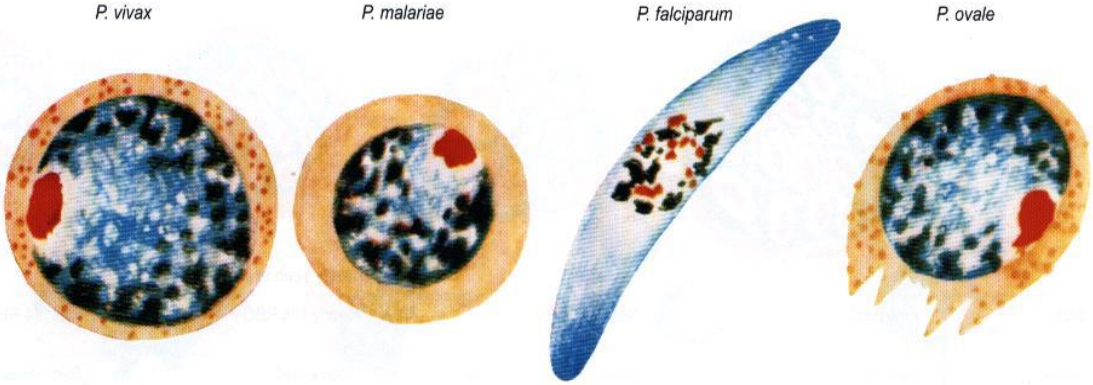
Stages in thin films (continued)

Microgametocytes (male)



	P. vivax	P. malariae	P. falciparum	P. ovale
Time of appearance	3–5 days	7–14 days	7–12 days	12–14 days
Number in bloodstream	Many	Scanty	Many	Scanty
Size	3/4 fills RBC	1/2 to 2/3 fills RBC	Larger than RBC	1/2 to 2/3 fills RBC
Shape	Round or oval compact	Round compact	Kidney-shaped Bluntly round ends	Round compact
Cytoplasm	Pale blue	Pale blue	Reddish blue	Pale blue
Chromatin	Single chromatin mass	*As for P. vivax*	Fine granules scattered throughout	*As for P. vivax*
Pigment	Abundant brown granules throughout	*As for P. vivax*	Dark granules throughout	*As for P. vivax*

Macrogametocytes (female)



	P. vivax	P. malariae	P. falciparum	P. ovale
Time of appearance	3–5 days	7–14 days	7–12 days	12–14 days
Number in bloodstream	Many	Scanty	Many	Scanty
Size	3/4 fills RBC	1/2 to 2/3 fills RBC	Larger than RBC	1/2 to 2/3 fills RBC
Shape	Round or oval compact	Round compact	Crescentic-sharply rounded or pointed ends	Round compact
Cytoplasm	Dark blue	Dark blue	Dark blue	Dark blue
Chromatin	Compact peripheral mass	*As for P. vivax*	Compact masses near centre	*As for P. vivax*
Pigment	Small masses round periphery	*As for P. vivax*	Black, rod-like granules round nucleus	*As for P. vivax*

PATHOGENESIS

P. vivax **= vivax tertian malaria (benign).**
P. malariae **= Quartan malaria.**
P. falciparum **= malignant tertian malaria.**
P. ovale **= ovale tertian malaria.**

CLINICAL COURSE

The periodic febrile response is related to the time of rupture of a sifficient No. of mature schizonts and consequent discharge of merozoites into the blood stream (Synchronised schizogony).

THE SEVERITY OF THE ILLNESS DEPENDS ON:

1. **The degree of parasitaemia.**
2. **The extent of RBCs destruction.**
3. **The defence responses of the host.**

Pathogenesis :-

Pathogenisity of malaria is related to erythrocytic infection (erythrocytic schizogony) . Exo or pre-erythrocytic schizogony has little effect.
Most of the pathogenesis is due to tissue starvation (tissue anoxia) as a result of anemia and in *P.falciparum* also due to localized decreased microcirculation (sludging of blood corpuscular elements in the vessels).
As the number of the parasite increased, number of RBC decreased due to rupture of parasitized and non-parasitized RBC . This will lead to anemia .The type of anemia is normocytic normochromic in acute stage while in chronic and relapsing cases, the type of anemia may resemble pernicious anemia.
Causes of anemia:-
1-Direct RBCs lysis as a result of the life cycle of the parasite .
2-Splenic removal of both infected and uninfected RBCs (both coated with immune complexes) .
3-Auto-immune lysis of coated infected and uninfected RBCs.
4-Increased fragility of RBCs.
5-Decreased RBC production due to bone marrow suppression.

6-Inability of the body to recycle the iron that bound to insoluble malarial pigments (malarial pigments cause depletion of iron) .
Loss of plasma from blood vessels in all types of malaria and agglutination of infected RBCs in *P.falciparum* (infected RBCs bound or adhere to one another and to the lining of blood vessel) are responsible for so-called sludging of corpuscular elements and formation of clot and blockage (thrombosis) in small blood vessels . These will lead to reduction in oxygen conveyance and tissue starvation (tissue anoxia). Tissue anoxia also produce by anemia .
***P.*vivax and *P.*ovale infect only reticulocytes(young RBC) so parasitaemia around 2-5% of available RBCs so they cause low grade anemia.**
***P.*malariae infect older RBCs and cause mild anemia.**
***P.falciparum* infect all types of RBCs so it cause severe anemia , infected cells may exceed 50% of RBCs .**

P.falciparum so called malignant malaria because:-

1-It invade RBCs of all ages (produce high parasitemia).
2-Schizogonic cycle in RBC require not more than 48 hrs..
3-Multiple infection in single RBC.
4-Infected RBCs tend to adhere to one another and to lining of blood vessels which cause blockage and thrombosis of blood capillaries in vital areas (brain, lung, kidneys) leading to oxygen starvation of the tissues.
5-It cause cerebral malaria.
6-Autoimmunity in destruction both the parasitized and non-parasitized RBCs.
7-The toxic products interfere with oxygen utilization by the host cells.
Destruction of RBCs lead to increased blood bilirubin, a breakdown product of hemoglobin which may cause jaundice and the skin become yellowish .
Malarial pigment which produce from metabolism of hemoglobin by the parasite is deposited in reticulo-endothelial system and in severe cases , in liver , spleen, brain become blackish or slaty as a result of pigment deposition .
Malarial pigment consist of hematin and iron porphyrin.

Symptoms and signs of malaria

	Incubation Period	pre-patent period	average No. of merozoite in schizont	time required for one erythrocytic cycle
P.vivax	13-17days	8 days	16	48 hrs.
P.malariae	28-30days	13 days	8	72 hrs.
P.ovale	13-17days	9 days	8	48 hrs.
P.falciparum	12 days	6 days	24	36-48 hrs.

Pre -patent period :- Time from introduction of sporozoite till appearance of parasite in blood (pre-or exoerythrocytic cycle) in liver .

Incubation period :- The time between inoculation (introduction) of sporozoite and the first appearance of clinical signs of which the fever is most common .

Clinical symptoms include:-

Anemia

Splenomegaly

Classic paroxysm with it's cold stage , hot stage (fever), and sweating stage.

The typical paroxysm begins with the cold stage and rigors lasting 1-2 hrs. . During the next few hrs. ,the patient spikes a high fever and feels very hot , the skin is warm and dry . The last several hrs. are characterized by marked sweating and subsequent drop in body temperature to normal or subnormal .

MALARIAL PAROXYSm

It includes 3 stages:

I. COLD STAGE: shivering, intense cold, chatter teeth, rapid pulse, cyanosis of lips & fingers, dry pale skin with goose-flesh appearance. Patient cover himself with clothing & blankets. This stage lasts from 15 min to an hour.

 # Due to: 1. Contraction of the muscle fibers.

2. Vasoconstriction.

II. HOT STAGE: rapid full pulse, headache, nausea, vomiting & high temp. 41ºC. This stage lasts 2-6 hours.

 # Due to: 1. Vasodiltation.

2. The patient would throw away the blankets.

III. THE SWEATING STAGE: temp. falls rapidly, deep sleep, feels weak but otherwise normal. This stage lasts 2-4 hours.

Anemia is normocytic normochromic in acute stage ,in chronic and relapsing cases may resemble pernicious anemia .
***P.falciparum* cause severe anemia because it infect RBC of all ages and the proportion of infected cells may exceed 50% .**
Other possible symptoms (symptoms of acute febrile disease) such as headache , muscular pains , increased pulse respiratory rates .
Also there is diarrhea , vomiting , leukopenia and abdominal pain .
***P.falciparum* cause severe symptoms.**
Following an essentially symptomless remission which varies with the spp. (*P.vivax* and *P.ovale* : 48 hrs. ,*P.malariae* :72 hrs. *P.falciparum* : 36-48 hrs.) , there is a second paroxysm , then followed by several additional ones extending over a period of up to 3 weeks or more before the symptoms are terminated spontaneously . This series of paroxysms called the primary malarial attack .

 # Primary malarial attack: It is a series of malarial paroxysms which decrease in intensity & frequency upto 3 weeks.

 # Schizonts rupture → cells debris, merozoites & their metabolic by-products into the blood stream → stimulate chemo-receptor of the temp. regulating mechanism of the host to conserve heat.

- **In *P.vivax, P.malariae* & *P.ovale*= shaking chills, fever 40-41ºC, headach, muscular pain, malaise, nausea, vomiting, abdominal pain & increased pulse & respiratory rates.**
- **In *P.falciparum*= pernicious manifestation usually occur such as coma, convulsion & cardiac failure.**

Relapse (Delayed malarial attack) :-

Renewal of clinical manifestations and new series of malarial paroxysms following termination of primary attack . There is one to several more attack , months or years after termination of primary attack (either naturally or following treatment) . The parasite completely disappear from the blood after primary attack but there is hypnozoite which is a dormant sporozoite or exo-erythrocytic form in liver which is responsible for these relapse . Hypnozoite present only in *P.*vivax and *P.ovale* .

Relapse may continue over a period of 1 – 3 years before the infection is terminated .

Recrudescence :- Renewal of clinical manifestations and new series of malarial paroxysms after weeks, months or years from termination of primary attack. This occur in *P.malariae* and *P.falciparum* due to persistence of the parasite in blood at levels too low to be detected or to produce symptoms but after weeks, months or years may increase suddenly and initiate new series of paroxysms . There is no hypnozoite .

MALARIA IN HYPERENDEMIC AREAS

The typical malarial manifestation occurs in young children only. Older children & adults who survive previous infection develop tolerance to the disease.

CONGENITAL MALARIA

The mechanism of the transplacental passage of the parasite is obscure. It has not been reported in laboratory animals.

PATHOLOGY

Anemia: Acute = normocytic & normochromic.
Chronic & relapses = Pernicious anemia.
Falciparum malaria = Sludging RBCs.

C.N.S: 1. Congestion of meninges & brain.
2. Occlusion of the capillaries of the cortex.
3. Necrotic lesions in midzonal brain (malarial granuloma).

Spleen: 1. Dark, congested & enlarged.
2. Hyperplasia of red & white pulp.
3. Erythropoiesis & lymphopoiesis.
4. Haemosiderosis.

Liver: 1. Enlarged & dark in colour.
2. Hypertrophy of the kupffer cells with ingested malarial pigments.
3. Degeneration & necrosis in the centro-lobular regions.

Kidney: 1. Falciparum malaria = congestion & Punctate haemorrhages in the Cortex & medulla.
2. Malariae malaria = nephrotic syndrome (hyalinisation of the tuft of the glomeruli & segmental cells. Thickening basal membrane due to Deposition of Ag-Ab complexes. May cause a focal, proliferative, and membranous glomerulonephritis.

Heart: Embolic blockage of the coronary vessels.

Placenta: Falciparum malaria, mature schizonts In the intervillous spaces with histiocytes In the maternal side of the placenta.

COMPLICATIONS OF MALARIA

Quartan malaria → nephrosis.
Falciparum malaria → Cerebral malaria.
Gastrointestinal malaria.
Hyperpyrexia.
Algid malarial.

Black water fever (Hemoglobinuric Fever):

Most oven associated with *P.falciparum* infection.

History of previous malarial attack.

Sudden , intravascular hemolysis results in the passage of dark red or black urine (acidic urine with a high methemoglobin content).

Due to quinine sensitivity and the presence of antibodies acting as hemolysins against RBCs antigens.

There are severe chills with rigor, high fever, jaundice, vomiting, rapidly progressive anemia and dark red or black urine.

NATURAL IMMUNITY

- **Absence of Duffy group determinants among west African & American blacks.**
- **Sickle cell anemia (Hb S).**
- **Haemoglobin C & E.**
- **G 6 PD deficiency.**

ACQUIRED IMMUNITY

 # Premunition immunity.

Resistance to reinfection or superinfection, conferred by a still-exising infection. The parasite remains alive, but its reproduction and other activities are restrained by the host response.

Infants in endemic areas are also relatively immune to malaria infections during the first year of life as result of the presence of a large percentage of HbF, passive immunity from maternal antibodies, and diets deficient in *p*-aminobenzoic acid. Older children and adults who have survived earlier attacks have developed considerable tolerance to the disease. Typical overt manifestations are usually observed in the young. Malaria is a

major cause of death in children (1-5 years old) because of low of antibodies.

Diagnosis:

1-Clinical picture.
2-Thick blood film stains with Giemsa or Wright's stain for diagnosis of the disease (malaria).
3-Stained thin blood film for diagnosis of the disease (malaria) and species of *Plasmodium*.
4-Serological tests.

TREATMENT

I. Treatment of malarial attack:

*** Chloroquine phosphate-orally 1g immediately, then 500mg in 6h, 500mg on the 2^{nd} & 3^{rd} days.**
*** Amodiaquine hydrochloride-orally 780mg immediately, followed by 520mg on the 2^{nd} & 3^{rd} days.**

They have no effect on the exoerythrocytic stages.

II. Suppression:

- **Chloroquine phosphate-orally 500mg weekly during period of exposure.**
- **Amodiaquine hydrochloride-orally 520mg every 2 weeks during the period of exposure.**
- **Pyrimethamine-orally 25mg weekly during period of exposure.**

III. Radical cure & interference with transmission:

- **Primaquine phosphate-orally 26.3mg daily for 14 days. It eliminates falciparum gametocytes.**
- **Quinine can be given in resistant cases.**

IV. Prophylaxis:

- **Primaquine destroys the exoerythrocytic forms.**
- **There is no drug against sporozoites.**

CONTROL

1. Treatment of patients with antimalarial drugs.
2. Elimination of faciparum gametocytes from carrier.
3. Eradication of the vector.

A) <u>Aquatic stages:</u>

1- Elimination of breeding places.
2- Uses of natural enemies.
3- Application of larvicidal compounds.
Paris green.
Non-volatile oils.

B) <u>Mosquitoes adults</u>:

1- Sleeping nets & windows wire.
2- Insecticides: Pyrethrum, hydrocarbons, gammaxane, organophosphorous compound, carbamates.
3- Natural enemies.