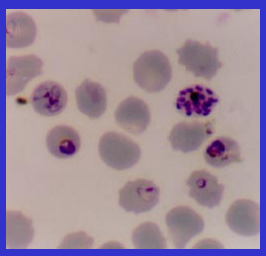
BioMedical Parasitology

Protozoa

Haemosporidia



Prof Peter O'Donoghue

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PROTOZOA

65,000 species

(31,250 extant + 33,750 extinct)

flagellates	amoebae	sporozoa	ciliates
6,900 species	11,550 species	5,600 species	7,200 species
5,100 free-living 1,800 parasitic	11,300 free-living 250 parasitic	all parasitic	4,700 free-living 2,500 parasitic

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Haemo-parasites

protozoa

- flagellates - trypanosomes
- apicomplexa - haemogregarines
  - haemosporidia
  - piroplasms

helminths

- nematodes - filarial worms
- trematodes - blood flukes

All utilize haematophagous insects as vectors

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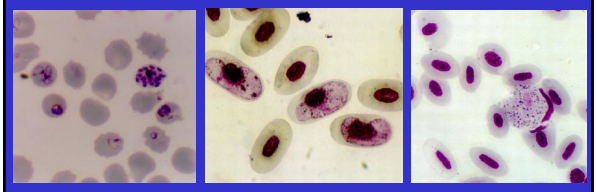
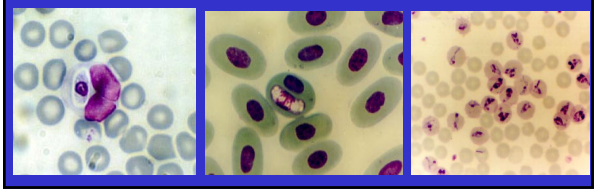
Plasmodium *Haemoproteus* *Leucocytozoon*



Hepatozoon *Haemogregarina* *Babesia*



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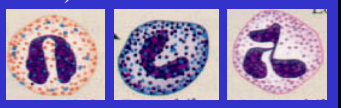
BLOOD CELLS

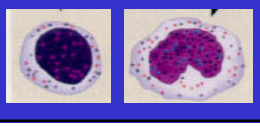
circulating cells divided into:

- erythrocytes (red blood cells)

- leucocytes (white blood cells)
  - granular
    - eosinophils
    - basophils
    - neutrophils



  - agranular
    - lymphocytes
    - monocytes



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Impact of parasites

- range of protozoa parasitize RBC &/or WBC
- multiply and released by destroying host cells
- causing range of haematological abnormalities
- compromise blood function (gas, nutrients, ..)
- may disturb blood delivery (vascular changes)

- burden quantitated as % parasitaemia

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SPOROZOA

Apicomplexa (apical complex) (oocysts)

Microspora (unicellular) (spores)

Myxozoa (multicellular) (spores)

All parasitic

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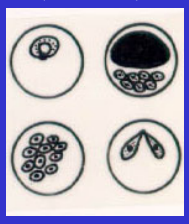
APICOMPLEXA

Coccidea (conoid complete) (small intracellular gamonts)

coccidia

Haematozoea (conoid absent) (motile kinete)



haemospordia/piroplasms

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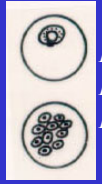
Parasite assemblage

HAEMATOZOA

Haemosporidia

- blood spores
- malaria
- insect vectors



Plasmodium
Haemoproteus
Leucocytozoon

Piroplasms

- pear-shaped bodies
- tick fevers
- tick vectors

Babesia
Theileria

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Parasite problem

MALARIA

- *mal-aria* = bad air (swamp gases)
- disease of mammals (esp. primates)
- can cause extensive pathology (anaemia, ischaemia, anoxia)
- four species infecting humans
  - *P. falciparum* ~40% (infect any RBC)
  - *P. malariae* ~10% (infect mature RBC)
  - *P. ovale* <1% (infect young RBC)
  - *P. vivax* ~50% (infect young RBC)

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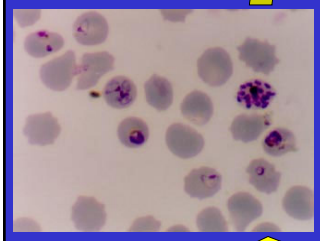
Parasite problem

Plasmodium spp. (malaria)



zoites-schizonts

salivarian transmission

mosquitoes

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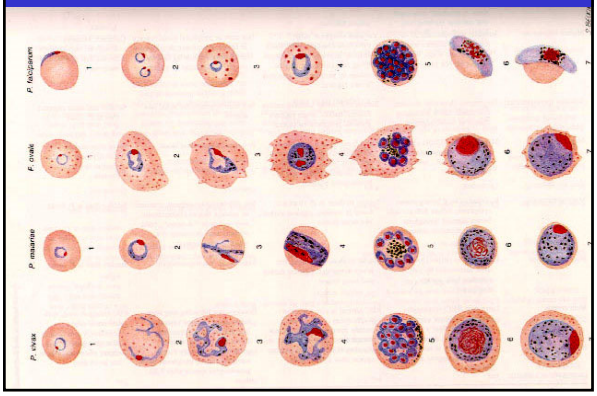
Intra-erythrocytic developmental stages



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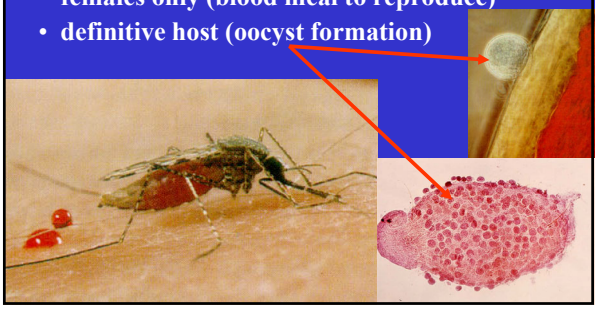
Parasite transmission

Insect vectors

Anopheles mosquitoes (80 of 400 species)

- females only (blood meal to reproduce)
- definitive host (oocyst formation)



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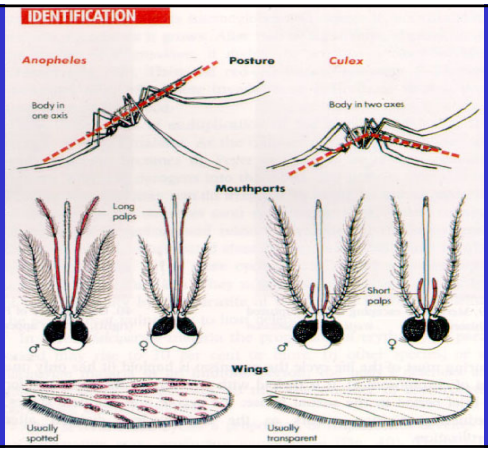
WHO

IDENTIFICATION



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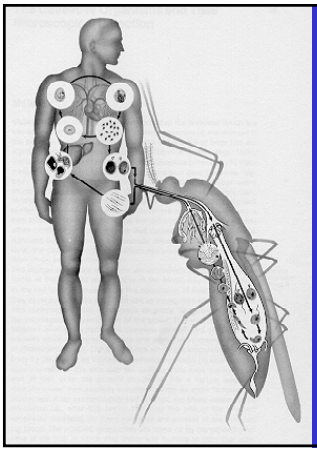

Life cycle

Heteroxenous
(= two-host)

- intermediate host
  = vertebrate
  (asexual development)
- definitive host
  = invertebrate
  (sexual development)

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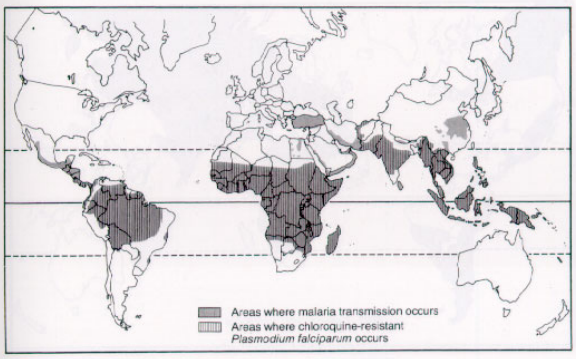
Parasite biodiversity

World distribution



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Parasite transmission

Haematophagous vectors

Parasite	Vertebrate host	Invertebrate vector
P. falciparum	humans	*Anopheles*
P. malariae	humans, monkeys	*Anopheles*
P. ovale	humans	*Anopheles*
P. vivax	humans	*Anopheles*
P. knowlesi	Asian monkeys, humans	*Anopheles*
P. coatneyi	Asian monkeys, humans	*Anopheles*
P. cynomolgi	Asian monkeys, humans	*Anopheles*
P. simium	New World monkeys	*Anopheles*
P. gallinaceum	chickens	*Aedes, Culex*
P. juxtanucleare	chickens	*Culex*
P. relictum	pigeons	*Culex, Aedes, Anopheles*
P. berghei	rodents	*Anopheles*
P. wenyoni	snakes	*Culex*
P. agamae	lizards	*Lutzomyia, Culicoides*

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Parasite biodiversity

Malaria in Australia

<1800 - malaria probably not endemic in Aboriginal population
>1800 - introduced by European settlers, sporadic occurrence
- became entrenched in settlements around mine sites
- records confused, all fevers recorded as 'ague'

1911 - Aust. Inst. Tropical Medicine, Townsville
1919 - WWI, returned soldiers
1922 - mapping of malaria in Australia (endemic above 19°S)
[mostly *P. vivax* transmitted by *Anopheles farauti*]
1930 - Sydney School Public Health & Trop. Med.
1940 - WWII, returning soldiers
1943 - Land HQ Medical Research Unit, Cairns
1946 - QIMR = Queensland Inst. Med. Res., Brisbane
1974 - WEHI = Walter & Elisa Hall Inst., Melbourne
1981 - WHO declares Australia malaria-free
>1990 - miscellaneous cases (travellers, airport, Torres St...)

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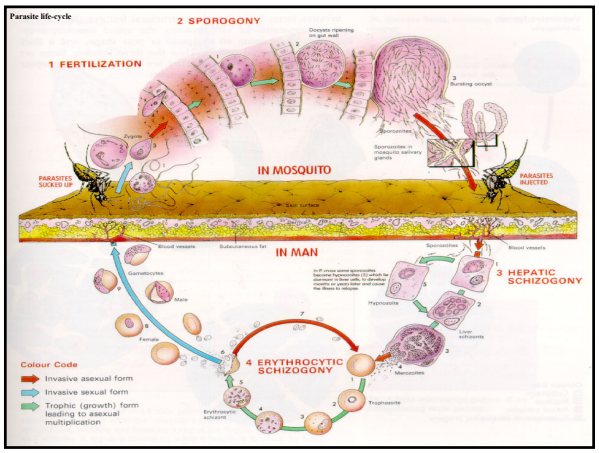

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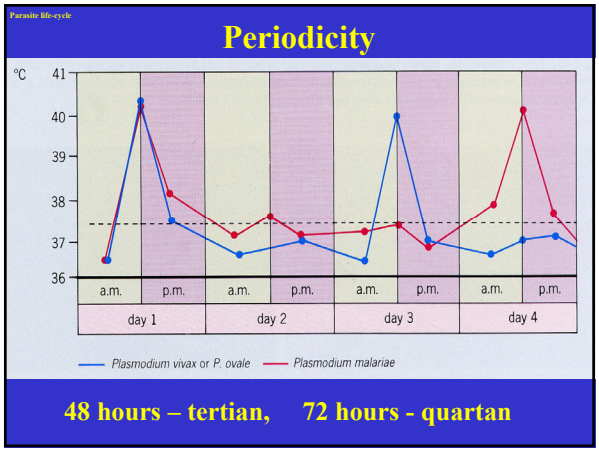

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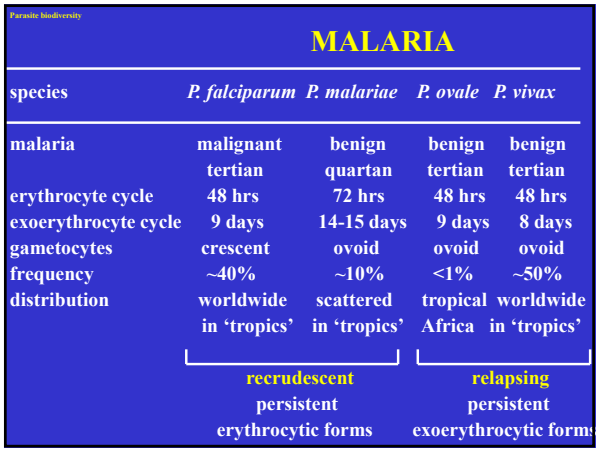

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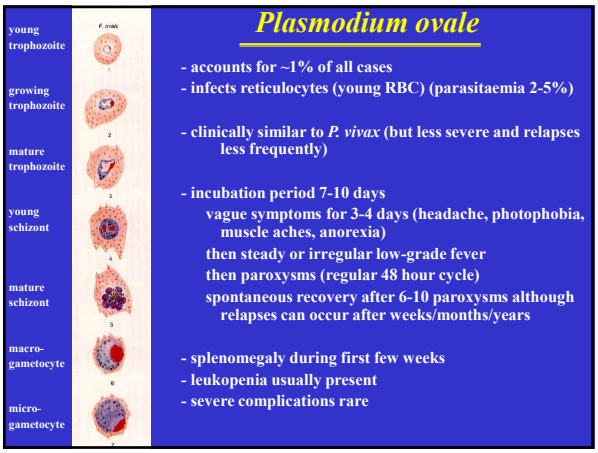

Plasmodium ovale

- accounts for ~1% of all cases
- infects reticulocytes (young RBC) (parasitaemia 2-5%)

- clinically similar to *P. vivax* (but less severe and relapses less frequently)

- incubation period 7-10 days
  - vague symptoms for 3-4 days (headache, photophobia, muscle aches, anorexia)
  - then steady or irregular low-grade fever
  - then paroxysms (regular 48 hour cycle)
  - spontaneous recovery after 6-10 paroxysms although relapses can occur after weeks/months/years

- splenomegaly during first few weeks
- leukopenia usually present
- severe complications rare

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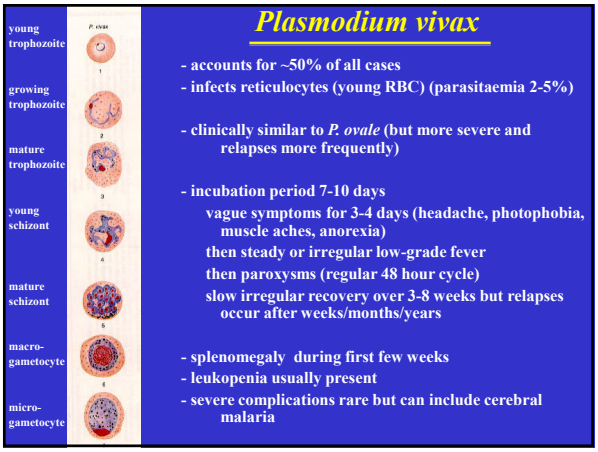

Plasmodium vivax

- accounts for ~50% of all cases
- infects reticulocytes (young RBC) (parasitaemia 2-5%)

- clinically similar to *P. ovale* (but more severe and relapses more frequently)

- incubation period 7-10 days
  - vague symptoms for 3-4 days (headache, photophobia, muscle aches, anorexia)
  - then steady or irregular low-grade fever
  - then paroxysms (regular 48 hour cycle)
  - slow irregular recovery over 3-8 weeks but relapses occur after weeks/months/years

- splenomegaly during first few weeks
- leukopenia usually present
- severe complications rare but can include cerebral malaria

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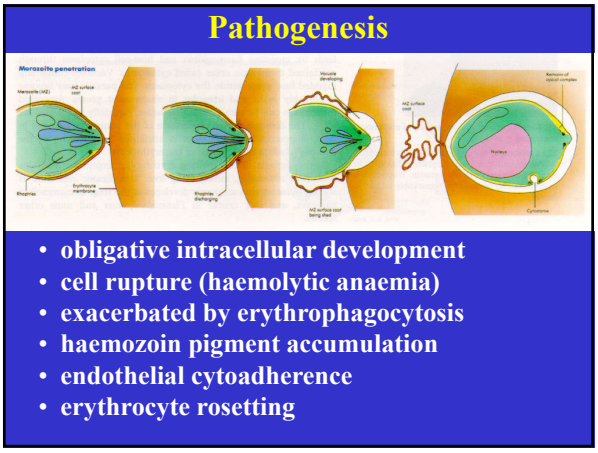

Pathogenesis

- obligative intracellular development
- cell rupture (haemolytic anaemia)
- exacerbated by erythrophagocytosis
- haemozoin pigment accumulation
- endothelial cytoadherence
- erythrocyte rosetting

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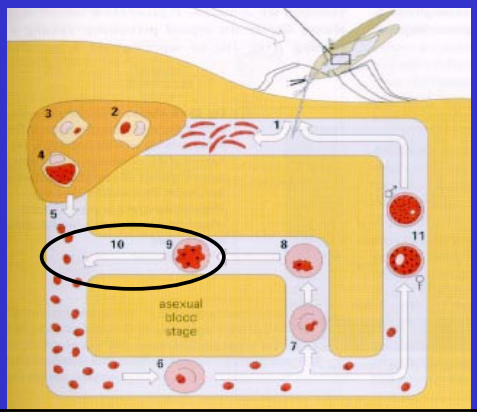
Haemolysis



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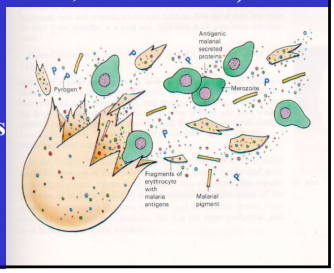
Parasite pathogenicity

Haemolysis

- schizogony culminates in erythrocyte lysis
- cyclical fevers (paroxysms) synchronized with haemolysis (quartan 72 hrs, tertian 48 hrs)
- results in anaemia, splenomegaly, organ hypoperfusion
- altered consciousness (hypoglycaemia)



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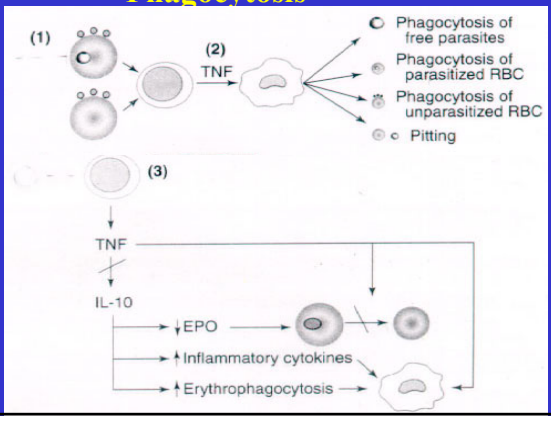

Phagocytosis

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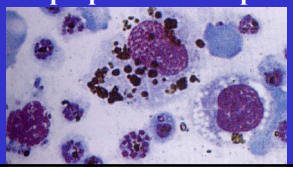
Parasite pathogenicity

Phagocytosis

- activated macrophages (fixed & free)
- phagocytosis of free parasites
- phagocytosis of parasitized RBC
- phagocytosis of unparasitized RBC (autoimmune haemolysis)
  (anaemia disproportionate to parasitaemia)



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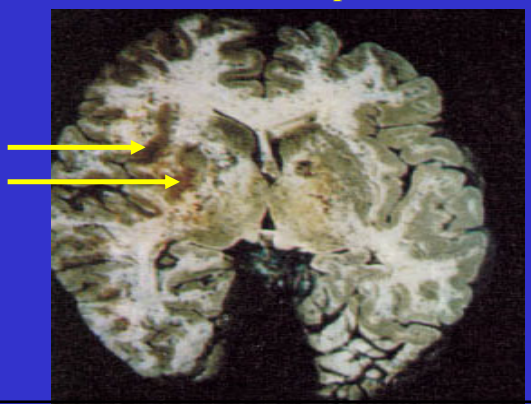
Haemozoin deposits



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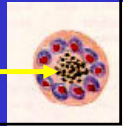
Haemozoin deposits

- haemozoin = malaria pigment (β-haematin)
- inert crystalline substance
- produced in food vacuole of blood-stages
- parasites actively degrade haemoglobin
- proteolysis produces monomeric toxic heme (ferriprotoporphyrin IX)
- parasite unable to cleave porphyrin ring
- heme detoxified by conversion to insoluble haemozoin polymer



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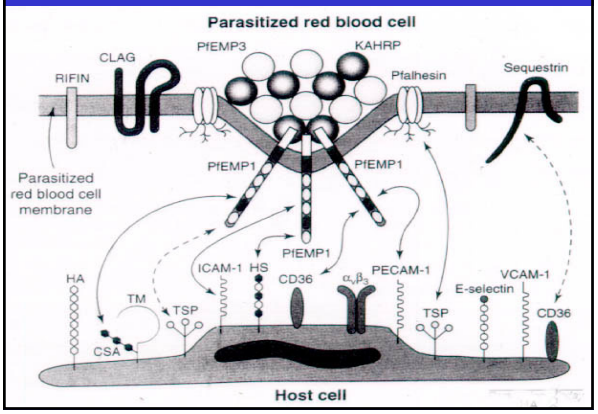
Sequestration - cytoadherence



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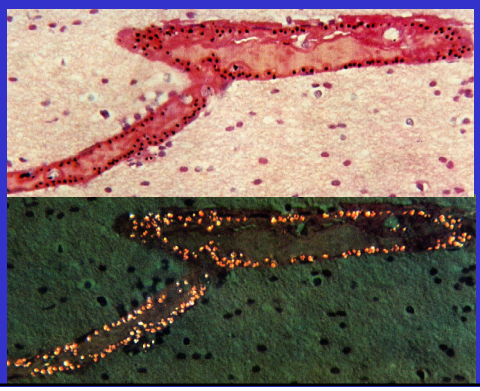
Sequestration - cytoadherence



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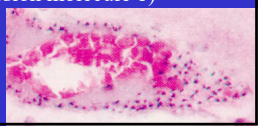
Sequestration

- mediated by stickiness = cytoadherence
  infected RBC with knob-like protrusions due to parasite-encoded protein deposits
- interaction with specific receptors involving:
  - CSA (chondroitin sulphate A
  - PECAM-1 (platelet-endoth. cell adhesion mol. 1)
  - ICAM-1 (intercellular adhesion molecule 1)
  - HS (heparan sulphate)
  - CD36 (sequestrin)
  - TSP (thrombospondin)



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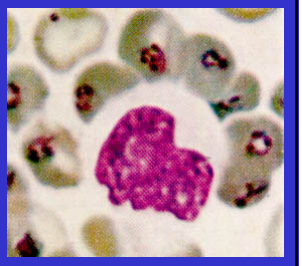
Rosetting



clumping of infected and uninfected cells cell

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Rosetting

- clumping of uninfected and infected RBC forming flower-like rosettes
- interactions involve:
  - PfEMP1 (P. f. erythrocyte membrane protein 1)
  - CR1 (complement receptor 1)
  - blood group A antigen
  - immunoglobulin M
- occasional DIC (disseminated intravascular coagulation) platelet activation, thrombus formation, obstruction, tissue anoxia

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Parasite pathogenicity

Cumulative effect

- haemolytic anaemia
- exacerbated by erythrophagocytosis
- haemozoin pigment accumulation
- endothelial cytoadherence
- disseminated intravascular coagulation (DIC)

- all contributing to tissue anoxia through compromised function and reduced flow
  - cell pathology → anaemia → anoxia
  - vessel pathology → ischaemia → anoxia

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TREATMENT OF MALARIA

1660 - Peruvian Indians use 'fever tree bark' (Cinchona tree)
1820 - Quinine isolated from bark
1914-18 - WWI quinine shortage prompted work on synthetics
1928 - Pamaquine
1932 - Mepacrine
1934 - Chloroquine
1939-45 - WWII shortages
1945 - Proguanil
1951 - Pyrimethamine
1960 - Emergence of chloroquine resistance
1960 - Sulphonamides, Sulphones
1971 - Mefloquine
1974 - series of new compounds from USA
1979 - Artemisinin developed in China

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Parasite treatment

Chemotherapy

	TISSUE STAGE		BLOOD STAGE	
	primary	latent	schizonts	gamonts
Quinine			+++	++
Chloroquine			+++	++
Proguanil	++		++	++
Pyrimethamine	++	+	++	+++
Sulphadoxine/Dapsone	?		+	
Primaquine	++	+++	++	+++
Doxycyline	+	?	++	
Mefloquine			+++	
Halofantrine			+++	
Artemisinin			+++	+
	causal prophylaxis	antirelapse radical cure	suppression clinical cure	prevent spread

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TREATMENT OF MALARIA

NON-RESISTANT MALARIA		target
Attack	chloroquine	blood schizonts
Recrudescence (f/m)	chloroquine	blood schizonts
Recurrence (v/o)	primaquine	tissue zoites
Prophylaxis	pyrimethamine combinations	tissue/blood schizonts
DRUG-RESISTANT MALARIA		
Attack	quinine & combos	blood schizonts
Prophylaxis	mefloquine	febrile reaction

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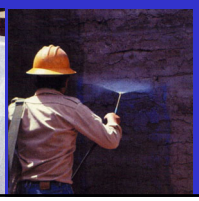
Parasite management

Control

- impose quarantine
- habitat destruction
- spraying programmes
- baiting programmes
- sterilization campaigns

Prevention

- bed nets
- repellants
- UV lamps
- diurnal exposure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Parasite management

VACCINATION

Case for Vaccine?

- immune response complex and poorly understood
- natural infection not highly protective
- immunity species- and strain-specific
- immunity short-lived
- premunition/concomitant immunity already active in high-endemic zones
- enzootic stability destabilised by vaccine
- logistics of provision: frequency, expense
- provider?

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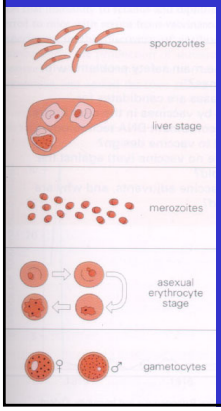
Parasite management

VACCINATION strategies



sporozoite vaccine to induce blocking antibody

sporozoite vaccine to induce cell-mediated immunity to liver stage

merozoite vaccine to induce blocking antibody

schizont vaccine to protect against disease

gamete vaccine to block transmission

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