Adjunctive measures for Cerebral Malaria Treatment

Anti-pyretics	Such as *paracetamol* to reduce fever. However, it is not clear if a reduction in core temperature benefits cerebral consequences.
Anti-convulsants	Such as *phenobarbital sodium* for seizures. It is crucial to control or prevent seizures, as they can cause neuronal damage and are associated with a fatal outcome.
Reduce intracranial pressure	Using agents such as *osmotic diuretics*.
Hypoglycemia correction	Using *hypertonic glucose*. However, theoretically, correcting hypoclycemia in the presence of tissue hypoxia can worsen tissue acidosis.
Exchange transfusion	Generally only been justified when peripheral parasitemia exceeds 10% of circulating erythrocytes. The role of these blood transfusions remains highly controversial, as they are both expensive and potentially dangerous in many malaria-endemic areas.
Anti-Inflammatories	Such as *corticosteroids*. However, there have been few controlled studies demonstrating benefit.
Desferrioxamine	An iron-chelating adjuvant agent with antimalarial properties. Reduces formation of reactive oxygen species by reducing amount of free iron.
Microcirculatory Flow	Such as *pentoxifylline*. Reduces red cell deformability and blood viscosity, decreases systemic vascular resistance, and impairs platelet aggregation, thus improving microcirculatory flow.

Psychiatric Manifestation of Malaria

(a) Altered behaviour, mood changes, hallucinosis or even acute psychosis, with or without fever

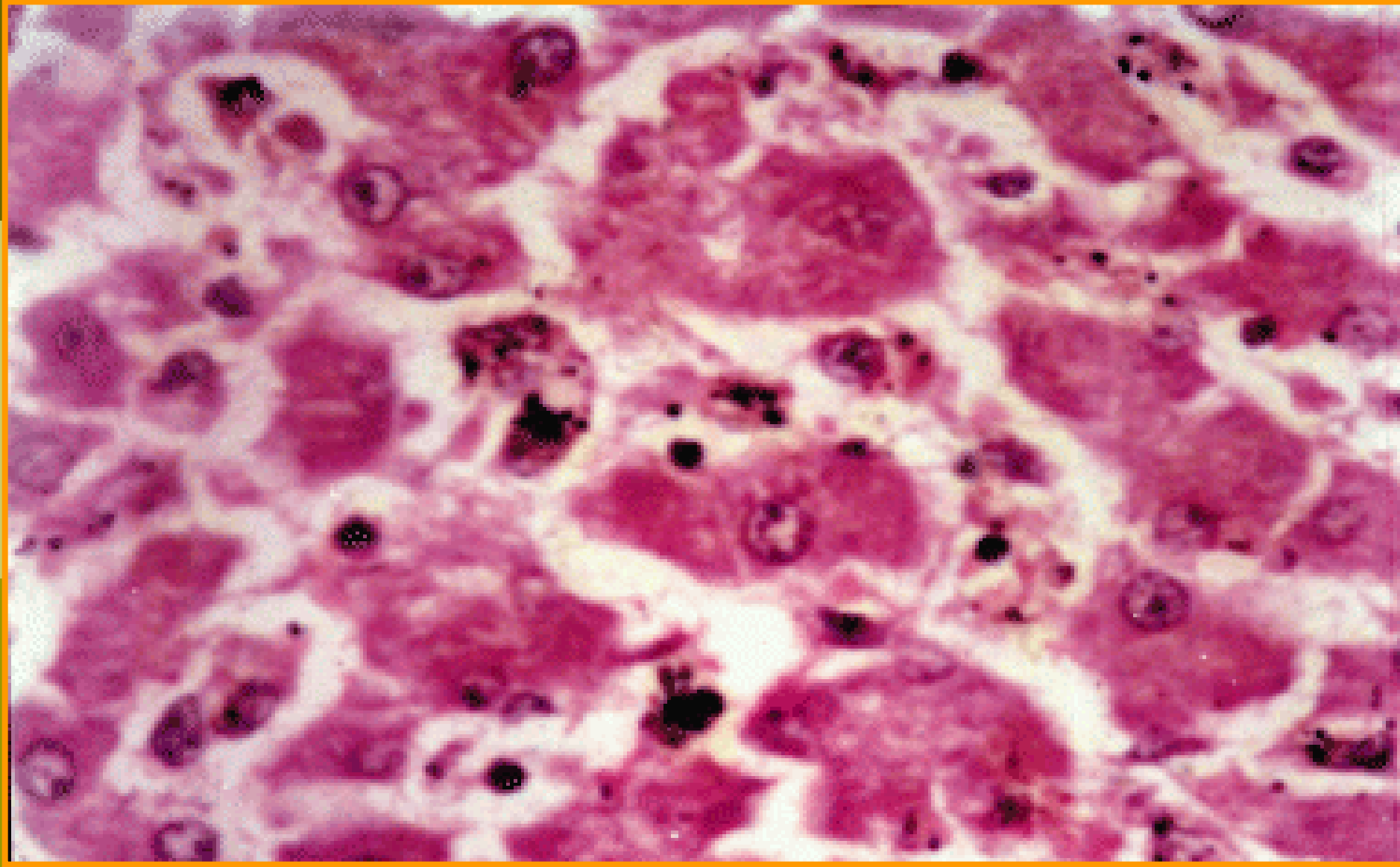
(b) Improve completely with anti malarial therapy

Mangalore, Nagesh Pai, Satish Rao and B.S. Kakkilaya

Feature	(n=118)	Feature	(n=118)
Delirium	22	Organic hallucinosis	12
Organic catatonic disorder	4	Organic delusional disorder	9
Organic mania	7	Organic Depressive disorder	13
Organic anxiety	26	Organic dissociative disorder	2
Mild cognitive disorder	4	Multiple vague complaints > 7days	8
Headache >7 days	11		

Antimalarial drugs like chloroquine, quinine, mefloquine and halofantrine can cause restlessness, hallucinations, confusion, delirium or even frank psychosis.

Falciparum Hepatopathy



Kupffer cell hyperplasia and malarial pigment deposit

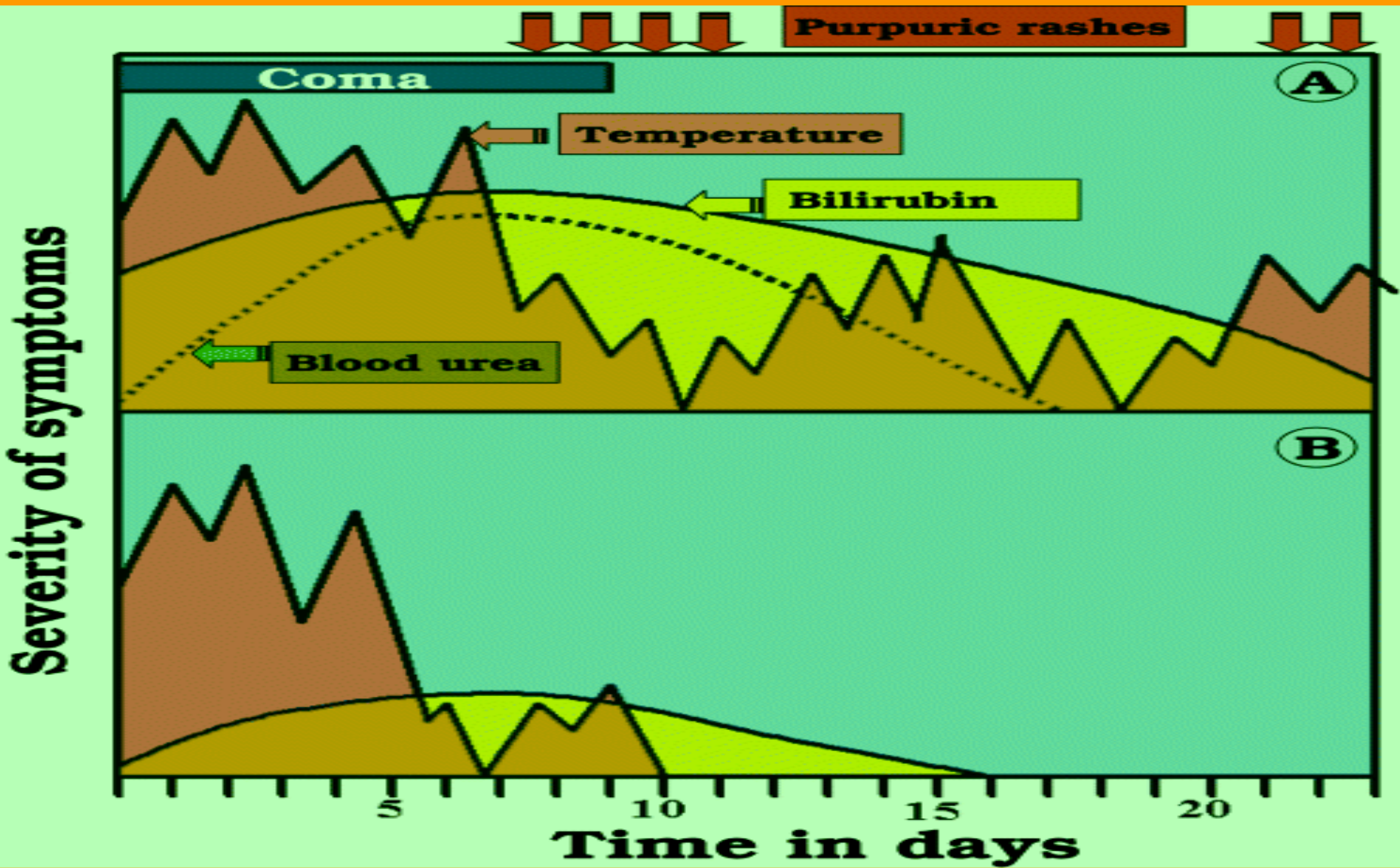
Causes of jaundice in malaria

[Jaundice in malaria. **Anand AC. Puri P.** ***Journal of Gastroenterology & Hepatology. 20(9):1322-32, 2005 Sep.***]

Direct cause:	Malarial hepatitis
	Intravascular hemolysis of parasitized RBC
	Septicemic hepatitis
Indirect cause:	Microangiopathic hemolysis associated with DIC
	G6PD-related hemolysis
	Anti-malarial-drug induced
Unrelated cause:	Coexisting acute viral hepatitis
	Underlying chronic hepatitis
DIC, disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; RBC, red blood cell.	

Two Form of Malarial Hepatitis

Type B is a relatively benign condition while type A is associated with multi-organ failure.



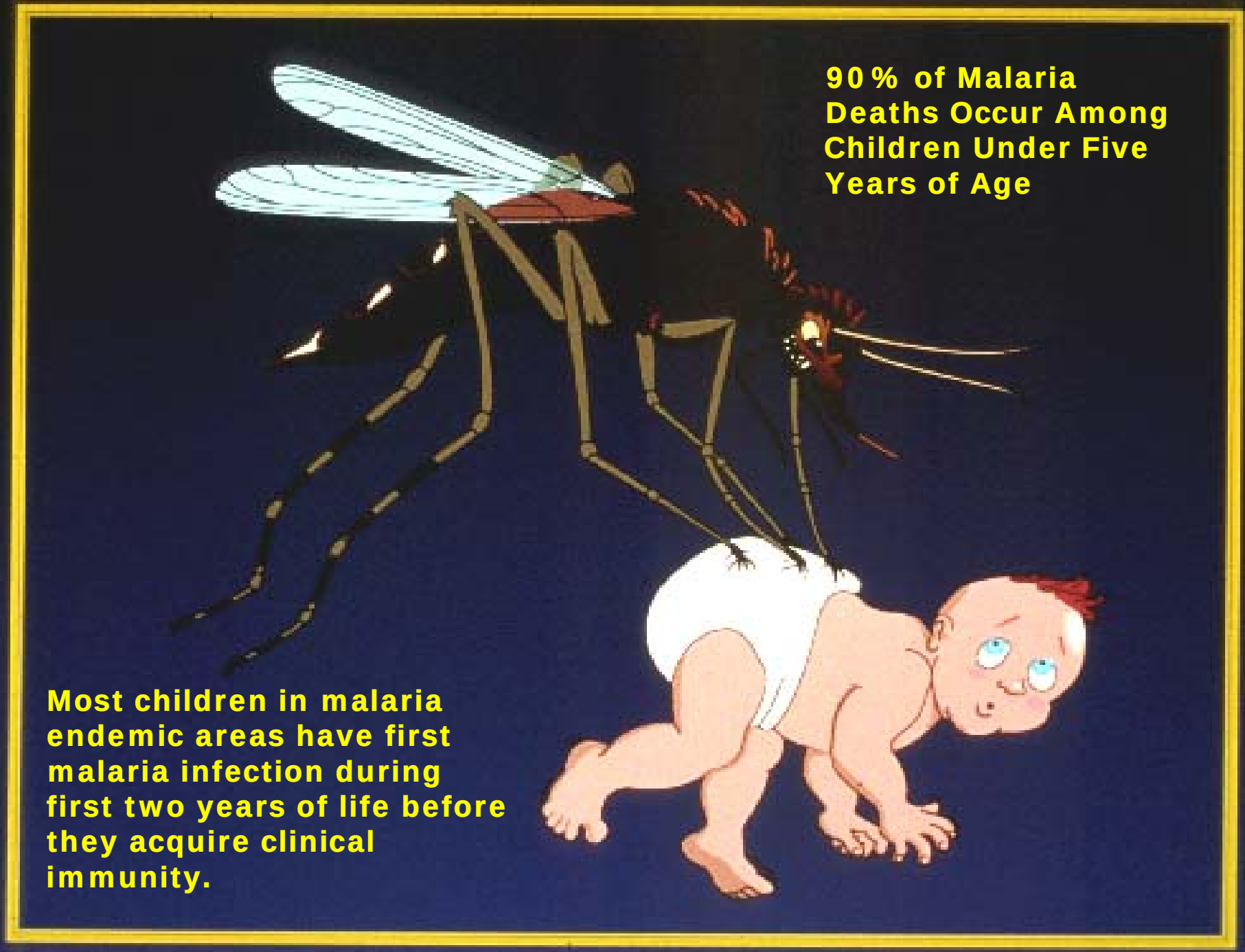
The diagnosis of malarial hepatitis can be made if a patient fulfills all the following criteria:

1. Demonstration of *Plasmodium* infection (*falciparum / vivax*)
2. At least threefold rise in transaminases (especially ALT), demonstrated in two samples, taken 24h apart, with or without conjugated hyperbilirubinemia
3. Absence of clinical / serological evidence of viral hepatitis
4. Response to antimalarial drugs or evidence of disseminated malarial infection on autopsy

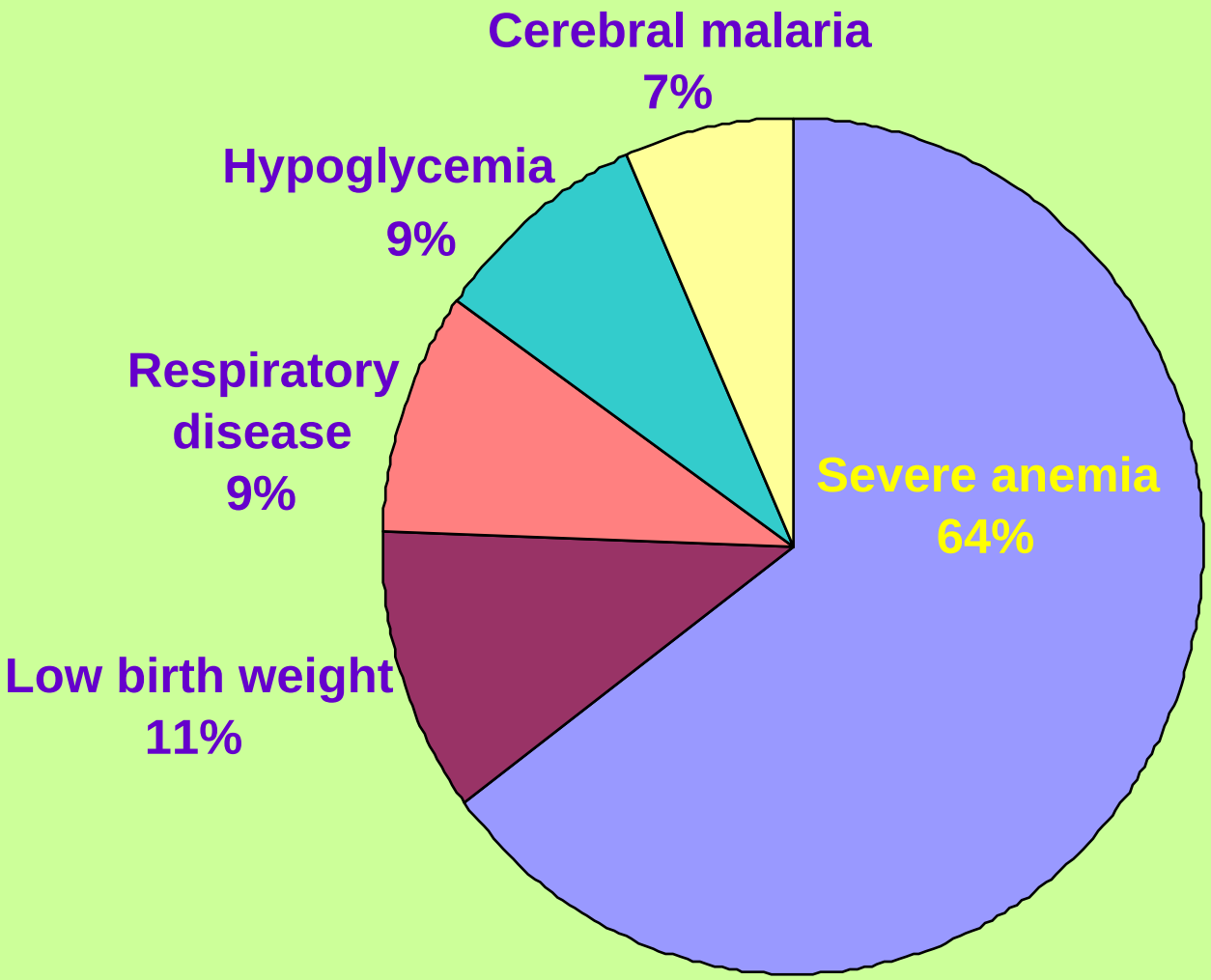
Adapted from Anand AC, Puri P. J. *Gastroentero. Hepatology* 2005; 20:1322-32.

Parameter	MHsFHF	Viral FHF
Hepatomegaly	Common	Uncommon
Splenomegaly	Common	Rare
Hemoglobin	Low	Normal
WBC counts	Normal	Elevated
Platelets	Thrombocytopenia	Normal
Prothrombin Time	Normal	Markedly elevated
AST/ALT	Mild elevation (X 2-3 times)	Marked elevation (X 10 times)
Serum urea nitrogen	Elevated	Normal or low
Serum creatinine	Elevated	Normal

(Adapted from Devarbhavi *et al, Mayo Clin Proc* 2005)

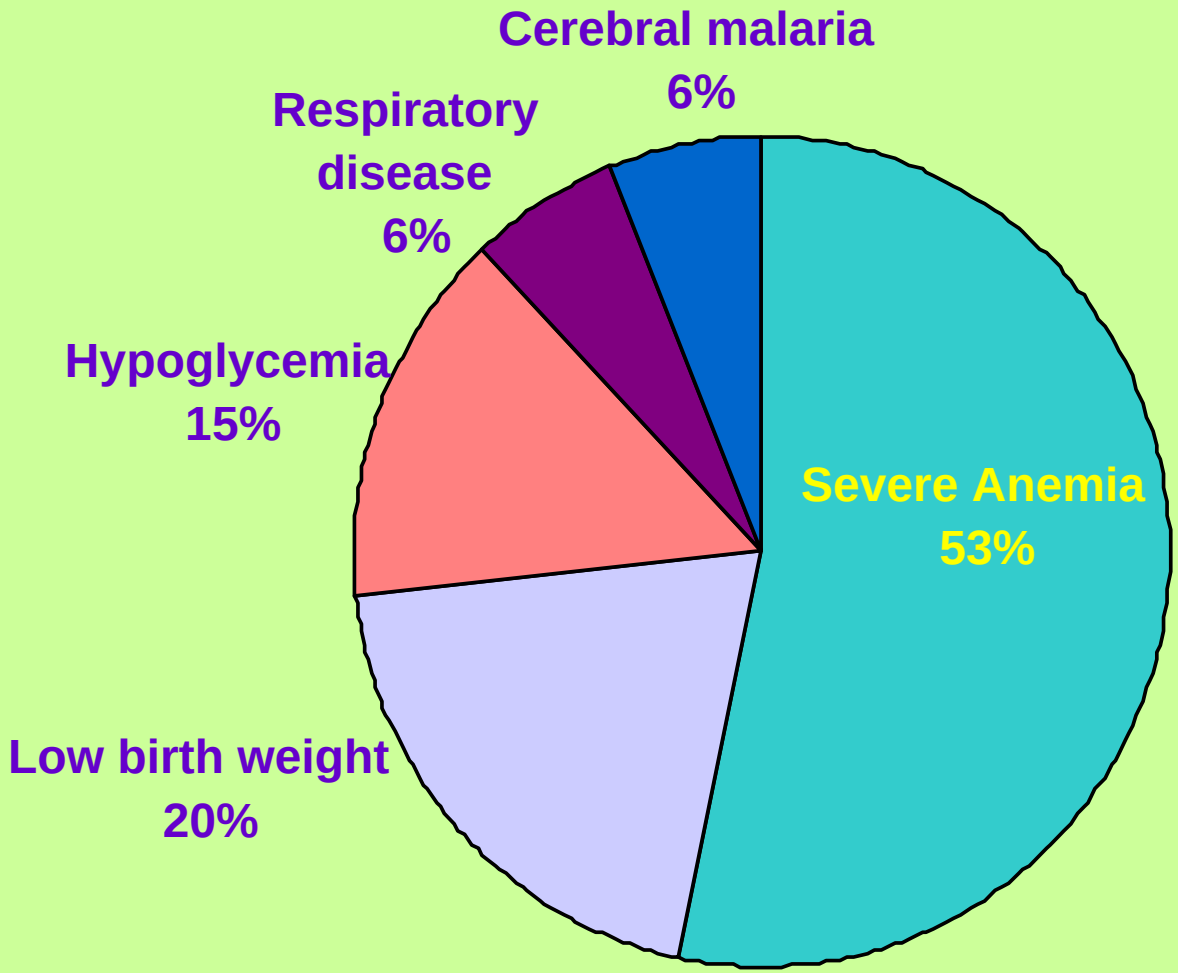

90% of Malaria Deaths Occur Among Children Under Five Years of Age
Most children in malaria endemic areas have first malaria infection during first two years of life before they acquire clinical immunity.

Contribution (%) of Specific Gaps to African Childhood Malaria Morbidity (up to 8.76 million children affected) *



*maximum estimate; all children <5 years of age except cerebral malaria (<10 years)

Contribution (%) of Specific Gaps to African Childhood Malaria (up to 1.82 million children die)

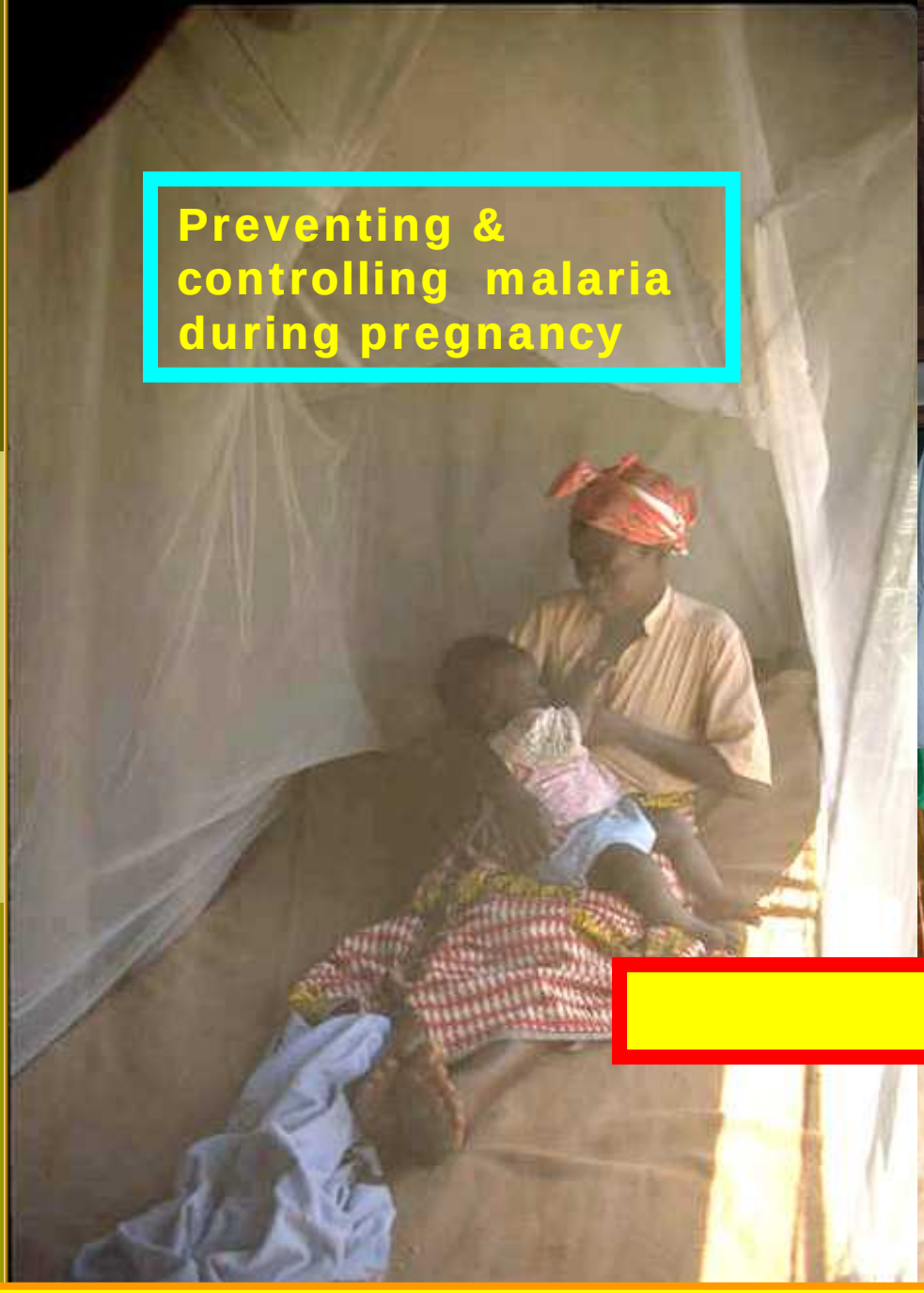


Symptoms and signs	Adults	Children
Cough	Uncommon	Common in early stage
Convulsion	Indicates cerebral malaria or hypoglycemia	Indicates cerebral malaria, hypoglycemia but may be non specific consequence of fever.
Duration of symptoms	Several days	Usually 1-2 days only
Jaundice	Common	Uncommon
Anaemia	Not so common	Common
Pulmonary oedema	Common	Rare
Acute renal failure	Common	Rare
Hypoglycemia	Common in pregnant women, or with quinine therapy, sometimes may be present without quinine therapy	Common before treatment
Seizure	Less common	Frequent
Development of unconsciousness	Insidious	Rapid
Coma recovery time	Slow, usually 2 – 4 days	Rapid (usually 1-2 days)
CSF pressure	Usually normal	Variable, raised
Neurological sequelae	Uncommon	Occurs in about 10% cases

Presentation of severe malaria in the children

Worldwide, the annual death toll of malaria exceeds 1 million, and children under the age of five are its major victims.

Number One Priority For Control of Malaria in Children



Preventing & controlling malaria during pregnancy

Providing prompt access to curative treatment

Promoting the use of insecticide-Rx mosquito nets

Three Effective Malaria Interventions can reduce all-cause child mortality by 20%-25%

Malaria & Global Health

- 2,000,000 deaths per year (leading cause among children < 5 yo)
- 90% of world cases in sub-Saharan Africa
- 1 in 5 childhood deaths in Africa
- 1/3 of deaths preventable with bed nets.

3 SIMPLE WAYS TO PREVENT MALARIA DURING PREGNANCY

- Obtain and use Insecticide Treated Nets (ITN). They will protect you against Malaria.
- Get 2 doses of Sulfadoxine Pyrimethamine (SP).
- If you think you are sick with Malaria, go to the clinic immediately.

This message is supported by

Investing in our future
The Global Fund
To Fight AIDS, Tuberculosis and Malaria

Federal Ministry of Health

RBM Roll Back Malaria

Ministère de la Santé du Burkina Faso

PREVENTION DU PALUDISME
chez la femme enceinte

Pour prévenir le paludisme chez la femme enceinte, on doit lui donner trois comprimés de Sulfadoxine-Pyriméthamine (SP) au

2ème trimestre et au début du 3ème trimestre.

Les deux prises doivent être espacées d'au moins un mois.

COMMENT DONNER LA SP

1. S'assurer que la femme est à son deuxième trimestre et que les mouvements actifs du foetus sont perceptibles
2. Demander si la femme a utilisé de la SP au cours des dernières semaines : si oui, ne pas lui en donner
3. Demander si elle est allergique à la SP ou à d'autres sulfamides (éruptions cutanées graves) : si oui, ne pas lui en donner
4. Si non aux questions 2 et 3, elle peut prendre la SP, donc lui expliquer le but de sa prise.
5. Lui offrir un gobelet d'eau potable et trois comprimés de SP et l'inviter à les avaler
6. Observer la femme avaler les trois (03) comprimés de SP
7. Noter sur la fiche de consultations prénatales et le carnet de santé de la femme que la dose a été prise
8. Donner un rendez vous à la femme

Pour une protection sûre,
L'utilisation de la moustiquaire imprégnée doit être recommandée et encouragée

CONTRE - INDICATIONS

- Donner pendant le premier trimestre
- Femmes allergiques à la SP ou autres sulfamides
- Femmes prenant du co-trimoxazole ou d'autres médicaments contenant des sulfamides
- Donner la SP après le huitième mois

DSF

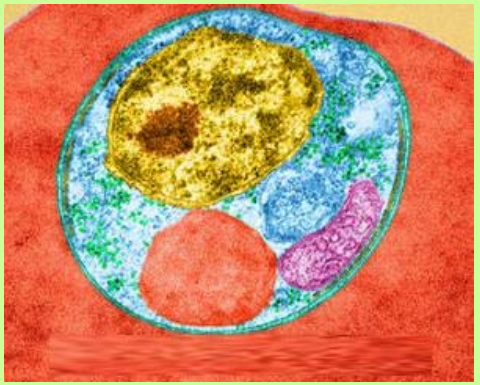
PNLP

USAID DU PEUPLE AMERICAIN

JHPIEGO

access

Malaria during pregnancy high/moderate transmission area



P. falciparum malaria

Asymptomatic Infection

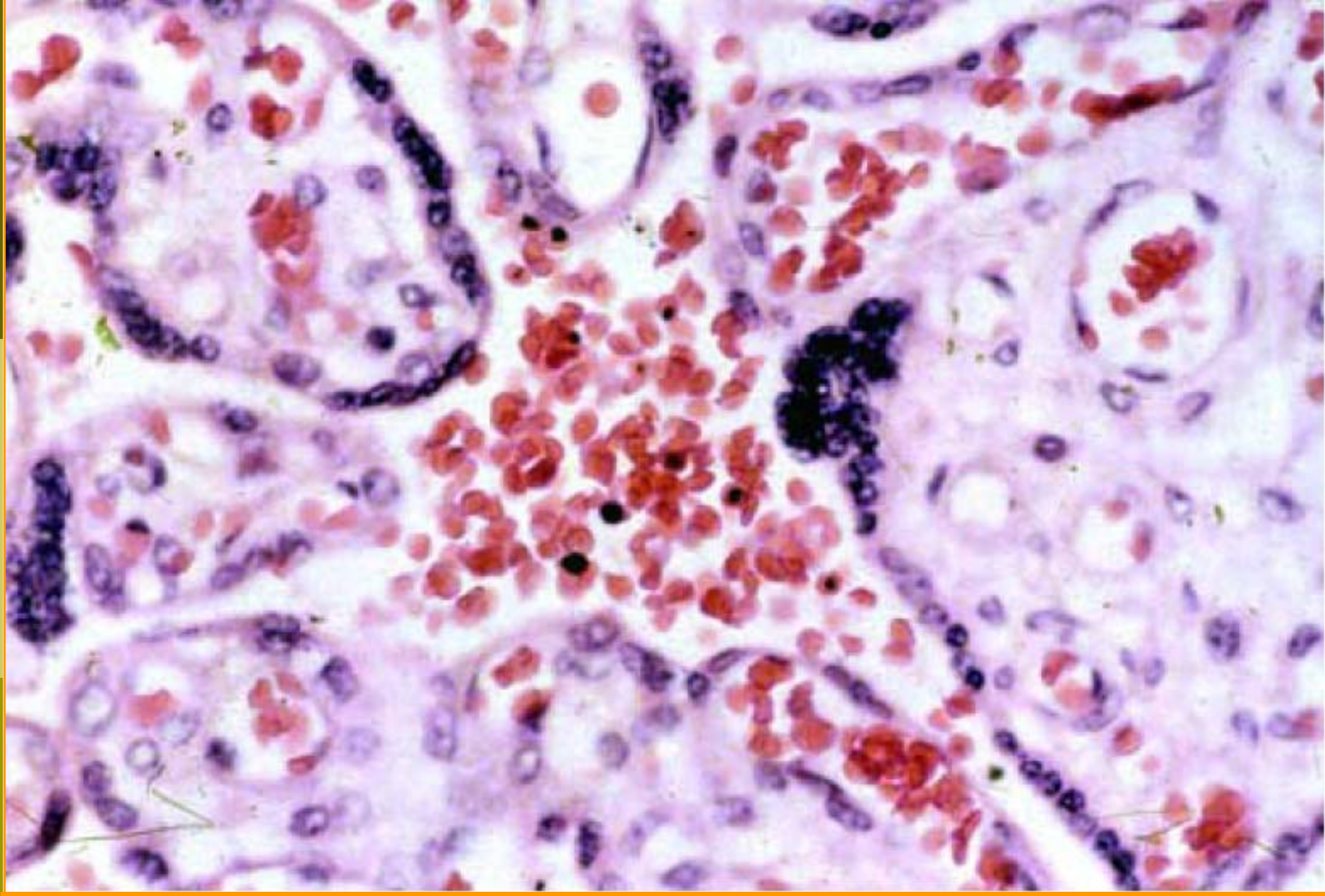
Placental Sequestration

Maternal Anemia

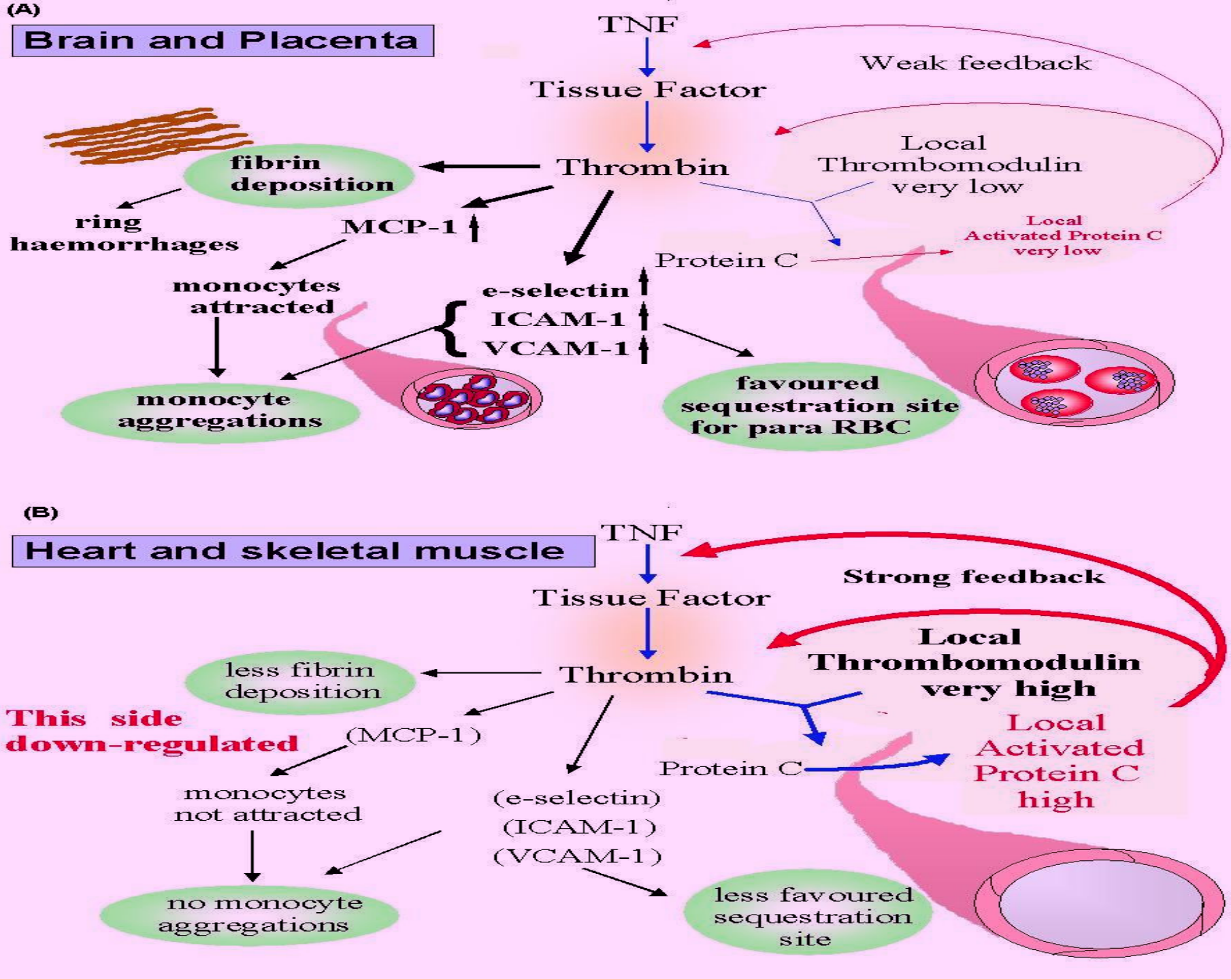
↓ Nutrient Transport

Low Birth Weight

↑ Risk of Infant Mortality



P. Falciparum infestation with monocytosis containing haemozoin pigement in vessels of placenta.


(A)
Brain and Placenta
TNF
Tissue Factor
Weak feedback
Thrombin
fibrin deposition
ring haemorrhages
MCP-1
Local Thrombomodulin very low
Protein C
Local Activated Protein C very low
monocytes attracted
e-selectin
ICAM-1
VCAM-1
monocyte aggregations
favoured sequestration site for para RBC
(B)
Heart and skeletal muscle
TNF
Strong feedback
Tissue Factor
Local Thrombomodulin very high
less fibrin deposition
Thrombin
This side down-regulated
(MCP-1)
Protein C
Local Activated Protein C high
monocytes not attracted
(e-selectin)
(ICAM-1)
(VCAM-1)
no monocyte aggregations
less favoured sequestration site

WHO recommendation for control of MIP in high/moderate malaria transmission area

W.H.O. Target Area

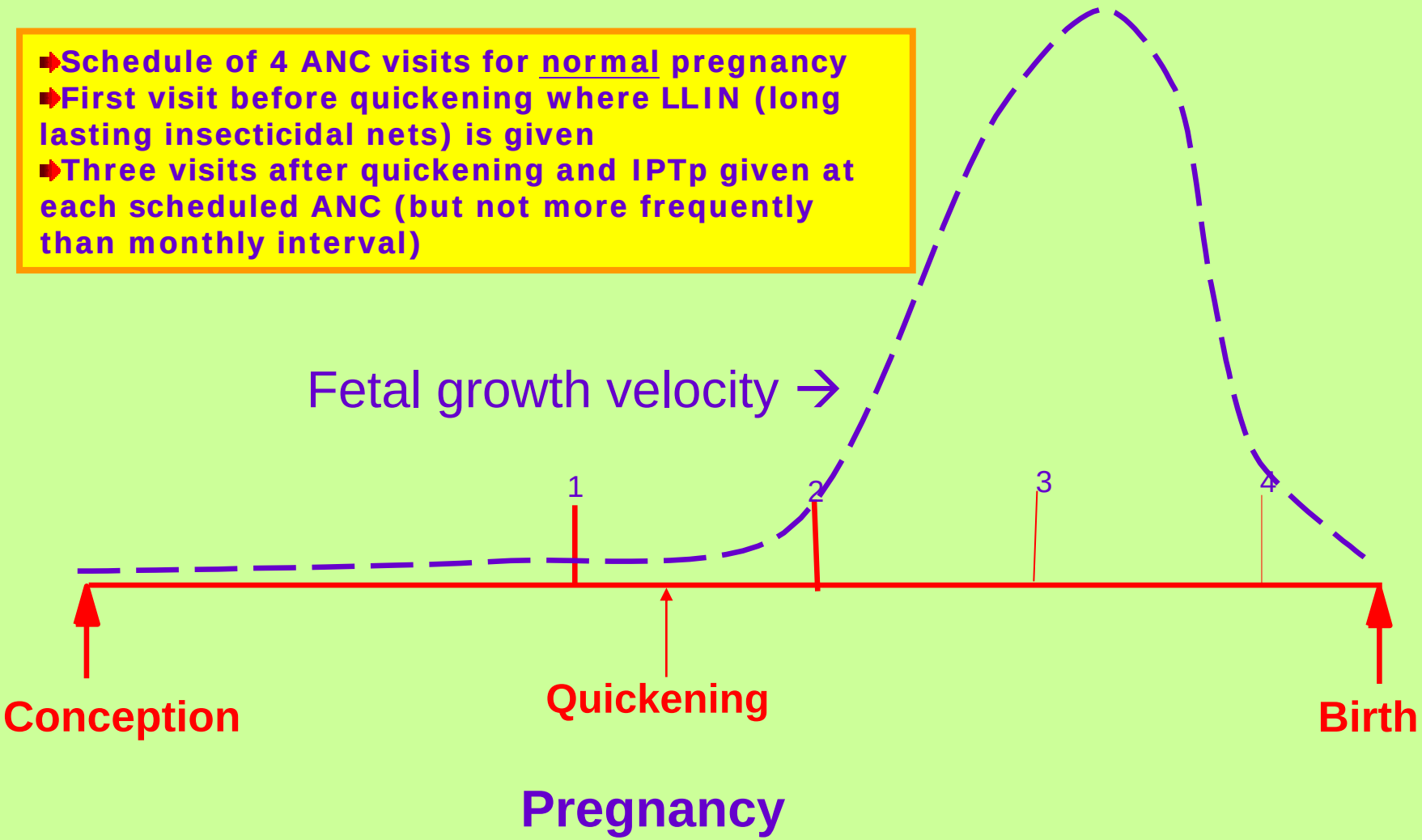
- **Insecticide-Rx Nets**
- **Effective Case Management**
- **Intermittent Preventive Treatment (IPT)**
- **Anemia prevention**
  - ***Folate & Iron Supplement***

- 2 doses of IPT with SP is associated with:
  - Reduction in 3rd trimester maternal anemia
  - Reduction in placental malaria parasitemia
  - Reduction in low birth weight
- At least 2 doses required for optimal benefit
- Regimen is safe and well tolerated
- Not recommended in HIV+ women receiving daily CTX

SP (1500 mg sulfadoxine, 75 mg pyrimethamine)

Intermittent preventive treatment (IPTp)

- Schedule of 4 ANC visits for normal pregnancy
- First visit before quickening where LLIN (long lasting insecticidal nets) is given
- Three visits after quickening and IPTp given at each scheduled ANC (but not more frequently than monthly interval)



Pregnant women attract at least twice as many mosquitoes as non-pregnant patients.

Preterm delivery, IUGR, abortion, stillbirth, eclampsia postpartum hemorrhage, puerperal fever, and maternal/fetal death are some complications associated with malaria particularly with P. falciparum.

Risk factors for adverse outcomes of women infected with malaria during pregnancy include HIV + status, low parity, non-immune, suboptimal treatment, and pregnancy during high transmission season.

Hypoglycemia and lactic acidosis due to malaria is seven times more frequent in pregnancy than in a non-pregnant woman.

Cerebral malaria is a common presentation in pregnant patients. Particularly concerning is the increased case-fatality rate of cerebral malaria in pregnant patients of up to 50%. Case-fatality rates is approximately 20%, and 3% of patient develop permanent neurologic sequelae.

Clinical Features Of Severe Malaria In Pregnant Women

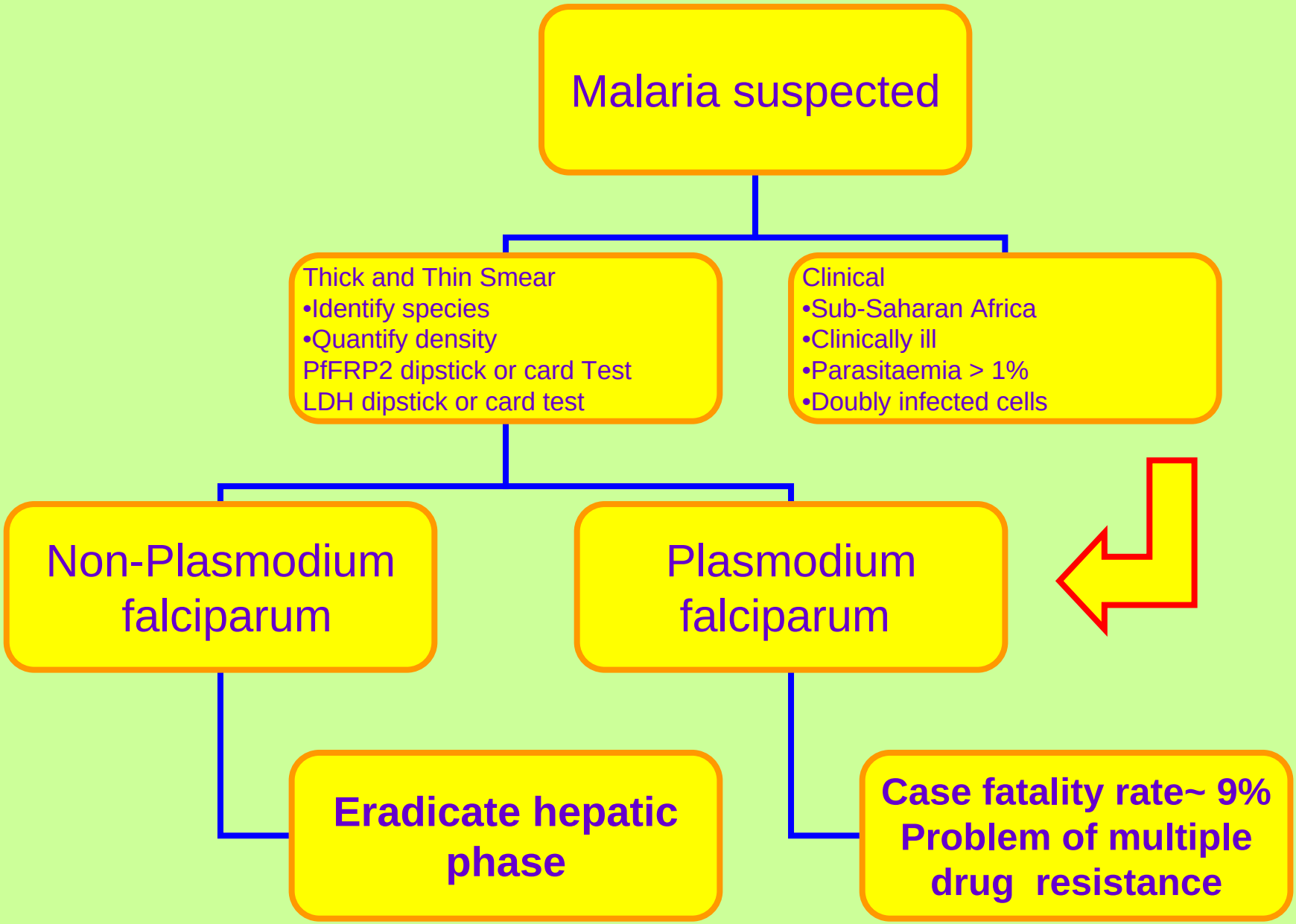
- Pregnant women are more prone to develop multiple complications of malaria. There are several factors that make pregnant women more vulnerable to malaria and its complications including mortality.
- Malaria parasites are preferentially sequestrated in the placenta,
  - Acquired immunity against malaria is known to decline during pregnancy.
  - During the second half of pregnancy, there is a transient immuno-suppression due to high levels of adrenal steroids, chorionic gonadotrophin, alpha-fetoprotein and depression of the role of lymphocytes. Therefore the incidence of malaria relapses, recrudescence & severe malaria is more common during pregnancy.
  - Frequency of heavy parasitemia is more during pregnancy than in the non-pregnant state. Primigravidae are at higher risk of morbidity & mortality from malaria.
    - Severe malaria poses a special problem as placental parasitemia is often associated with pregnancy rather than peripheral parasitemia. They usually have a multitude complications viz. severe anemia, hypoglycemia, acute renal failure, acute pulmonary oedema, ARDS.
    - Risk of mortality is nearly three times higher than nonpregnant women.
    - Associated infections: e.g. Urinary tract infections and respiratory tract infections, septicaemia are more common in the gravid state.

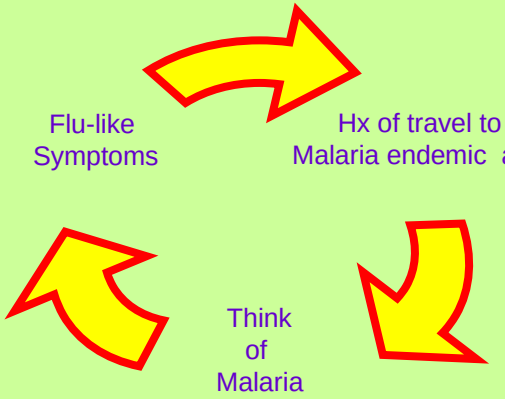
Malaria Complicating Pregnancy

- **Anaemia :** Moderate or severe anaemia is associated with increased morbidity & mortality in pregnant women due to an increased risk of perinatal mortality, maternal morbidity, PPH and pulmonary oedema.
- **Cerebral malaria-** Although incidence of cerebral malaria is same as that of non-pregnant women, however once they develop cerebral malaria, the mortality is three times higher in pregnant women.
- **Hypoglycemia** - This may be present in pregnant women at the time of admission or may develop after quinine infusion. Commonly it is asymptomatic. Abnormal behaviour, sweating & sudden loss of consciousness are the usual manifestations. It may be associated with lactic acidosis, a dreaded accompaniment with mortality upto 70%. Women in second or third trimester of pregnancy may develop hypoglycemia even with low parasitemia.
- **Pulmonary oedema :** This is a serious complication. It may be present on admission, may develop unexpectedly several days later or may develop immediately after childbirth.
- **Premature labour**: In non immunised females, foetal distress and premature labour is common and may occur at the height of fever. Foetal prognosis with premature labour is invariably poor. In endemic areas, pregnant women tolerate heavy parasitemia better than the pregnant women from non endemic areas.
- **Septicaemia:** Pregnancy increases susceptibility to pneumococcal infections and may lead to pneumonia or meningitis. Septicaemia following bladder catheterisation is common in pregnant women with heavy parasitemia.

Safety Of Antimalarials During Pregnancy

- Quinine does not cause abortion in therapeutic dose. The uterine contraction is related to the height of the fever and heavy parasitemia. Hence intravenous and oral quinine can be safely used in all trimesters of pregnancy.
- Artimisinin derivatives are not recommended at present, since extensive trials have not yet been conducted in pregnant women.
- Chloroquin is safe in all trimesters of pregnancy.
- Mefloquin is safe during pregnancy
- Sulfa containing drugs are contraindicated.
- Tetracycline and primaquin are contraindicated in pregnancy.


Malaria suspected
Thick and Thin Smear
•Identify species
•Quantify density
PfFRP2 dipstick or card Test
LDH dipstick or card test
Clinical
•Sub-Saharan Africa
•Clinically ill
•Parasitaemia > 1%
•Doubly infected cells
Non-Plasmodium falciparum
Plasmodium falciparum
Eradicate hepatic phase
Case fatality rate~ 9%
Problem of multiple drug resistance



Malaria Diagnosis

High index of suspicion is required

Fever + Travel Hx To endemic Area

- Clinical Symptoms & signs

Thick & Thin Smears

If negative, repeat every 12-24 hrs for 48-72hrs

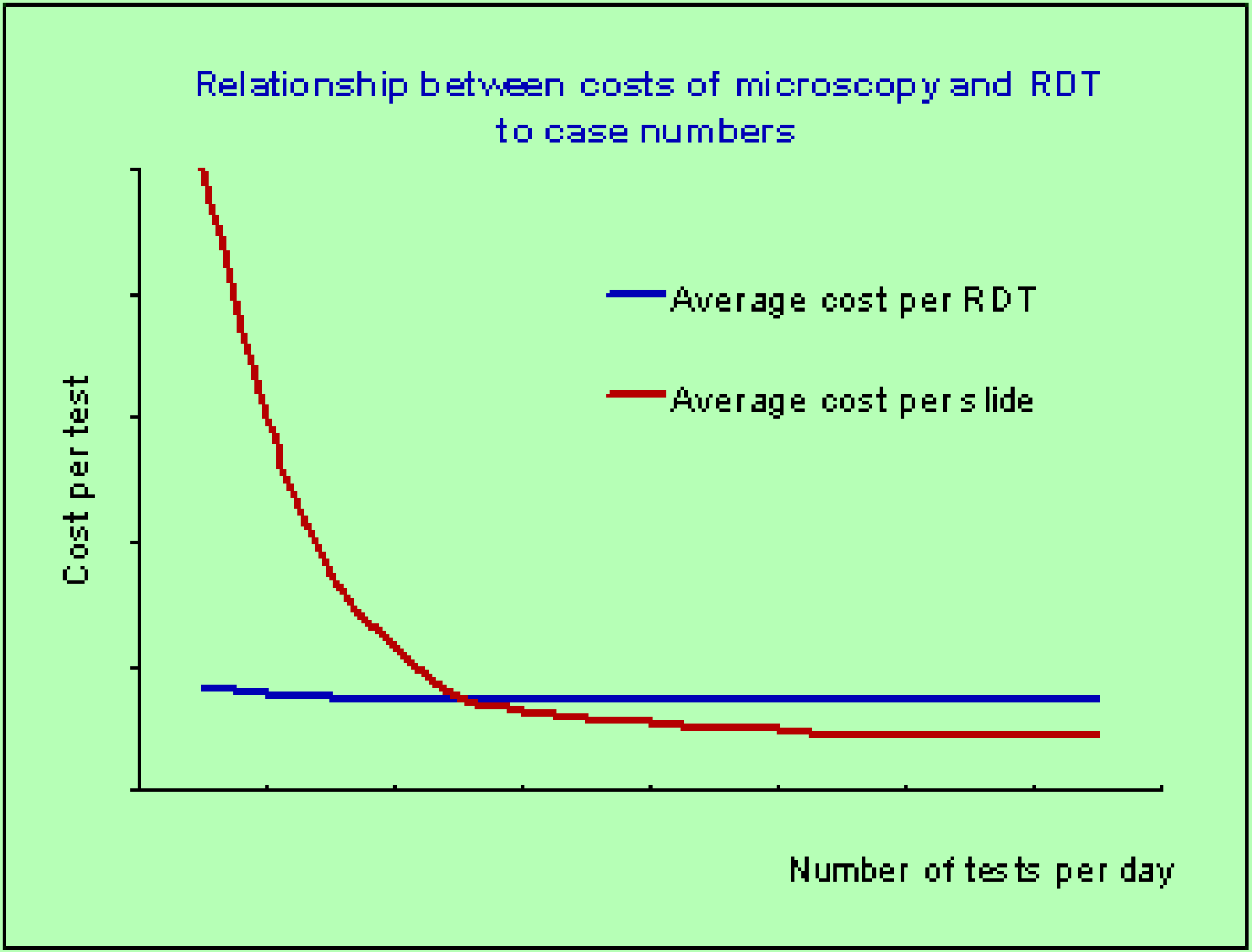
(5 parasites/µl)

(0.0000001%)

- Identify Species
- Determine Parasitaemia

Non-Microscopic Rapid Diagnostic Tests (2-15 minutes)

- **Dipstick Tests**
  - @Plasmodium Ags
  - @Plasmodium LDH
- **PCR**
  - @Plasmodium genome


Relationship between costs of microscopy and RDT to case numbers
Cost per test
Average cost per RDT
Average cost per slide
Number of tests per day

Before reporting a negative result, at least 200 oil immersion visual fields at a magnification of 100x should be examined on both thick and thin smears, which has a sensitivity of 90%.

One negative blood smear makes the diagnosis of ***severe*** malaria very unlikely; however, smears should be repeated every 12 hours for 48 hours if malaria is still suspected.

Plasmodium Falciparum

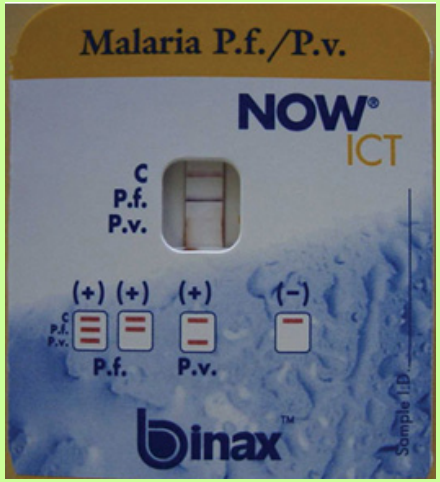
In falciparum malaria, parasitized erythrocytes may be sequestered in tissue capillaries resulting in a **falsely low parasite count** in the peripheral blood ('visible' parasitemia). In such instances, the developmental stages of the parasite seen on blood smear may help to assess disease severity better than parasite count alone. The presence of **more mature parasite forms (>20% of parasites as late trophozoites and schizonts) and of more than 5% of neutrophils containing malarial pigment indicates more advanced disease and a worse prognosis.**

Non-Microscopic Tests for Malaria

Inability to detect P. ovale and P. malariae.

Rapid dipstick Immunoassay (~100 parasites/ μl)

- *Histidine-rich protein-2 P. falciparum*
- *Plasmodium LDH* **Useful in predicting treatment failure**
  - ***OptiMAL-IT can Distinguish falciparum (0.01%) from vivax (0.1%)***
  - *Paracheck-Pf (0.002%)*



Polymerase Chain Reaction (~10 parasites/ μl)

- *Plasmodium genome*
  - *QT-NASBA*

Binax NOW is the only brand of malaria RDT approved for use in the united States. (CDC)

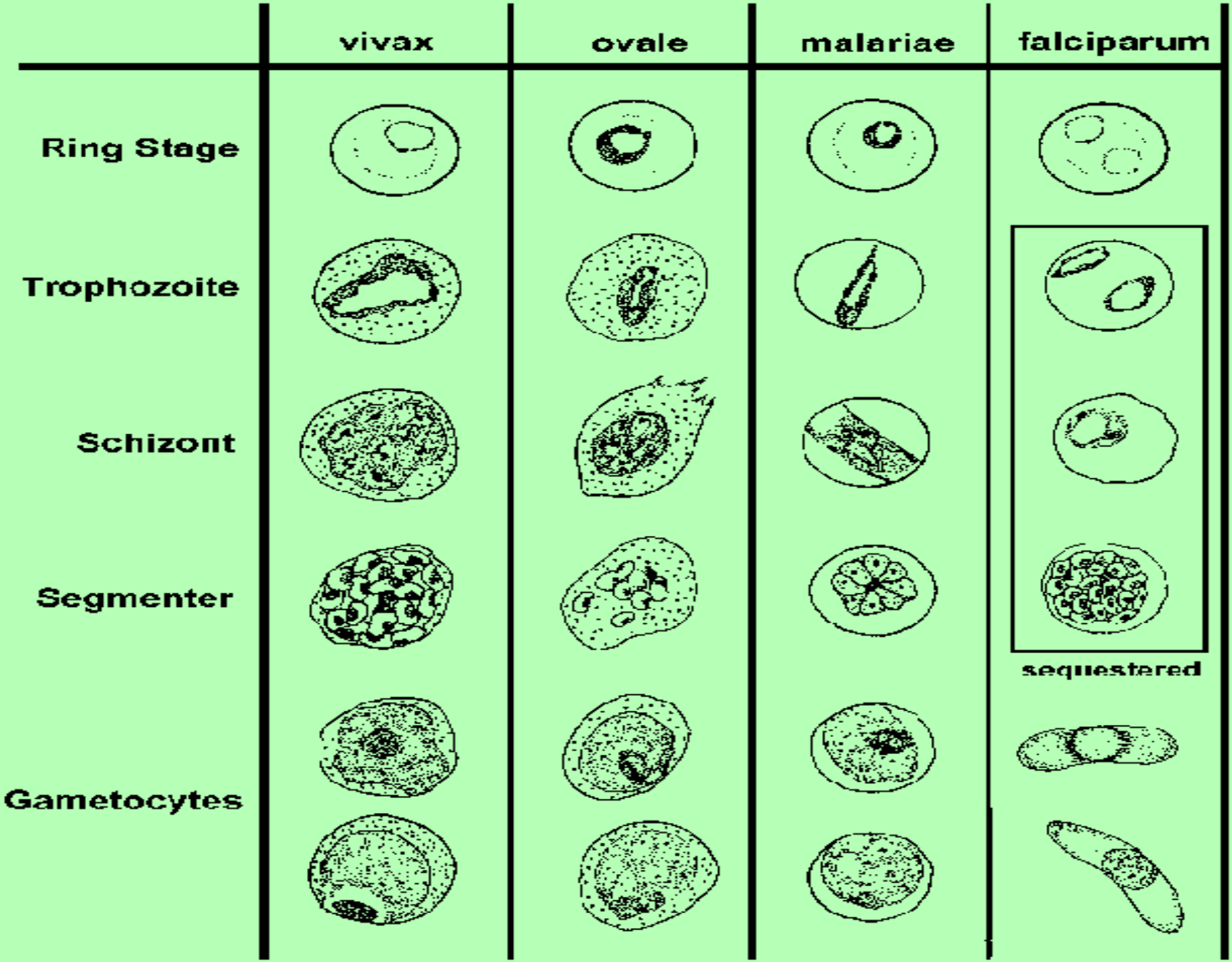
P. falciparum LDH has L-malate dehydrogenase activity.

Thick Smear

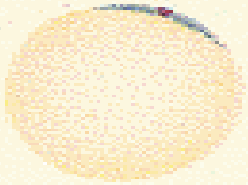
Thin Smear

Light Microscopy Characteristic of Plasmodium Species

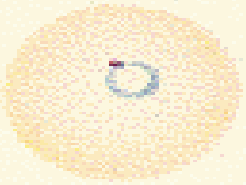
Plasmodium	Falciparum	Vivax	Ovale (Africa)	Malariae
Parasites per RBC	**Multiple parasites** may be present in the same RBC	Commonly one parasite per RBC.		
Ring form	Rings fine and delicate	Mature ring form are usually larger and coarser	Ring enlarged and coarser **Comet form** common	Ring form may have squarish appearance **Band form**
Size of RBC	Normal size	**Enlarged**	**Enlarged.** Ends can be **fimbriated**	Normal size
Typical form of trophozoite	Ring shaped trophozoite	**Amoeboid**	Compact trophozoite	Compact trophozoite
Other characteristics	**Banana shaped gametocytes**, **black pigment in RBCs, rare schizonts**	**Schüffner's granules**: often see gametocytes and schizonts		Often seen gametocytes and **diasy head schizonts** (up to 10 merozoite)


vivax
ovale
malariae
falciparum
Ring Stage
Trophozoite
Schizont
Segmenter
Gametocytes
sequestered

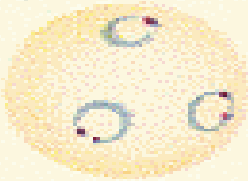
P. falciparum



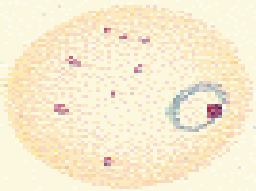
marginal form



ring form

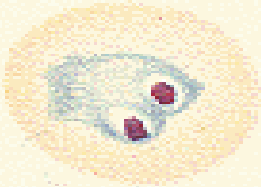


double dotted rings

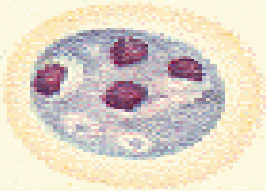


ring form

young trophozoite

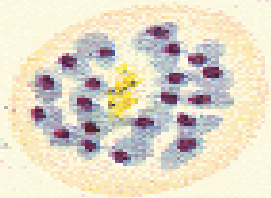


trophozoite

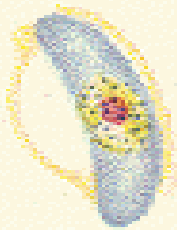


early schizont

schizont



mature schizont

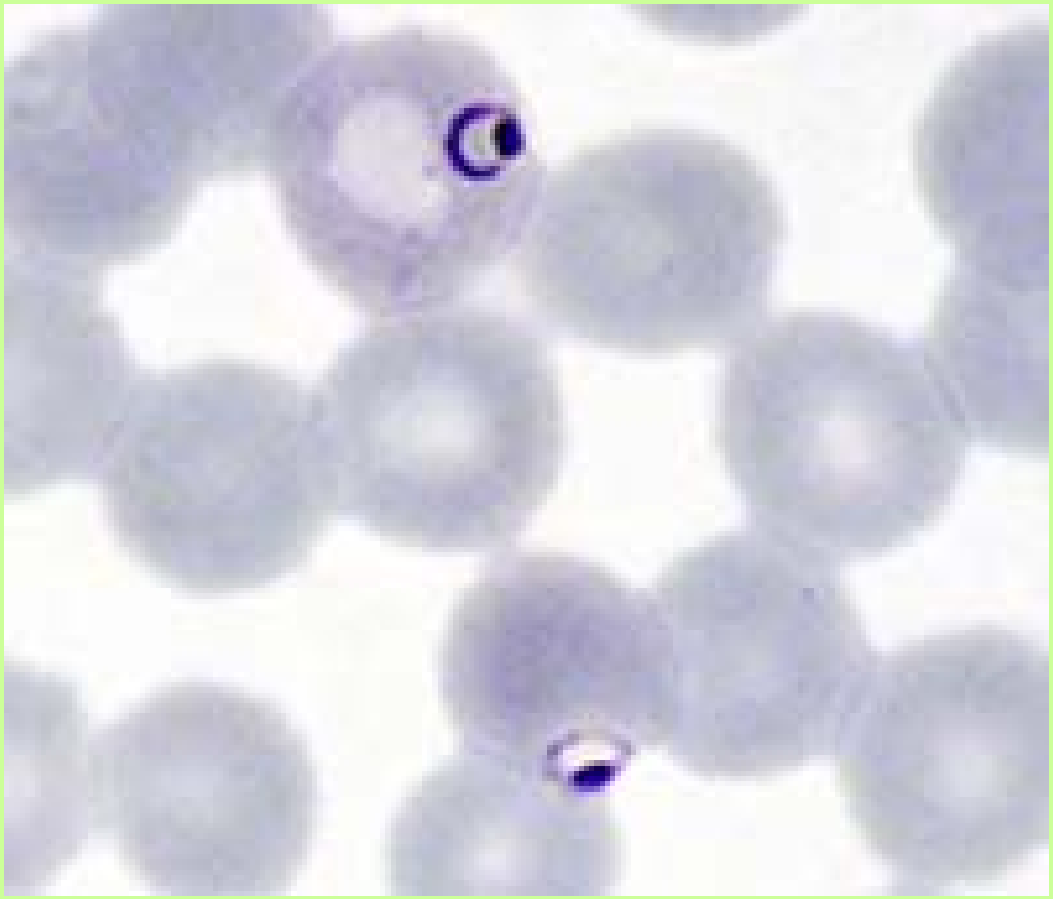


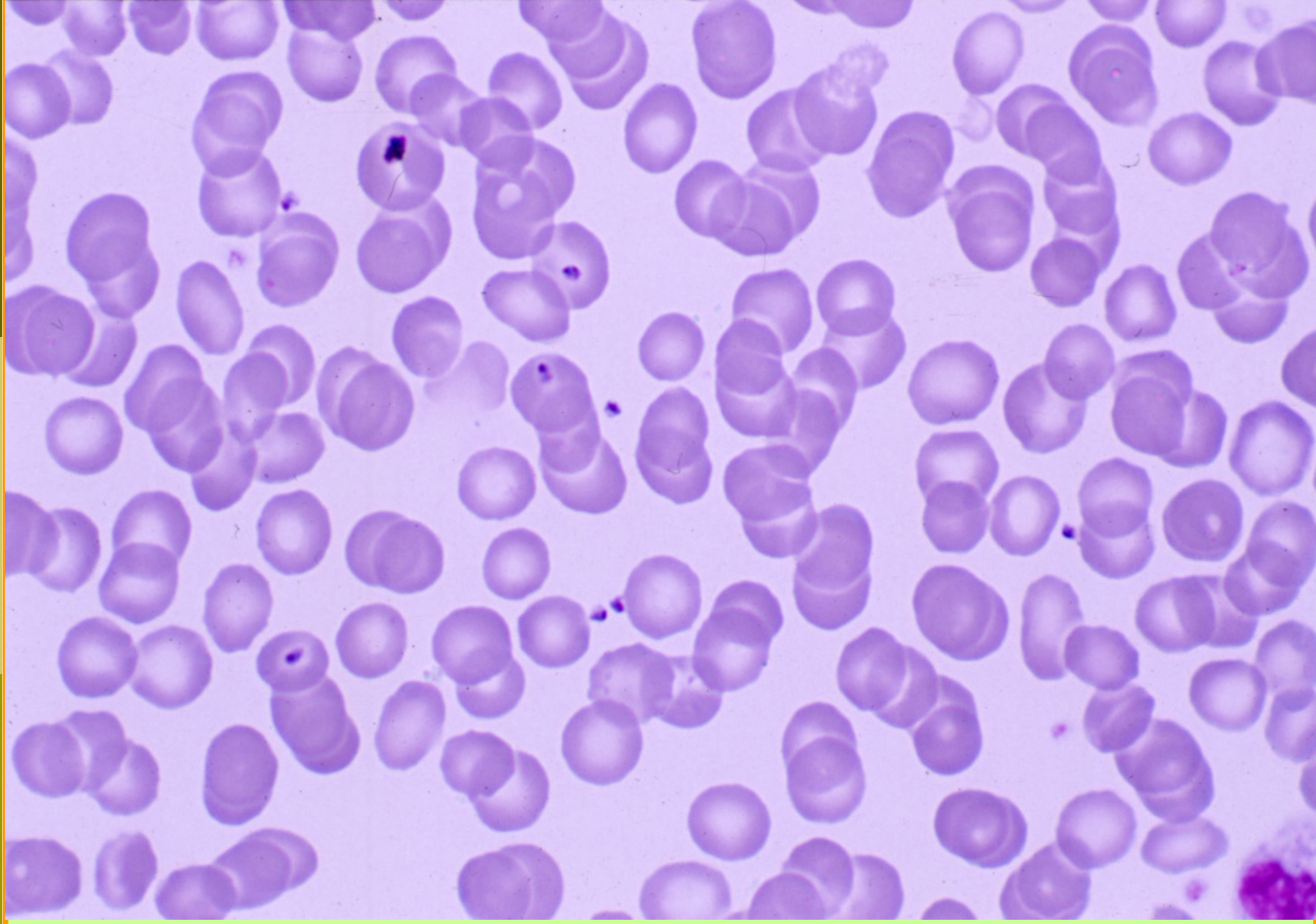
female gametocyte

male gametocyte

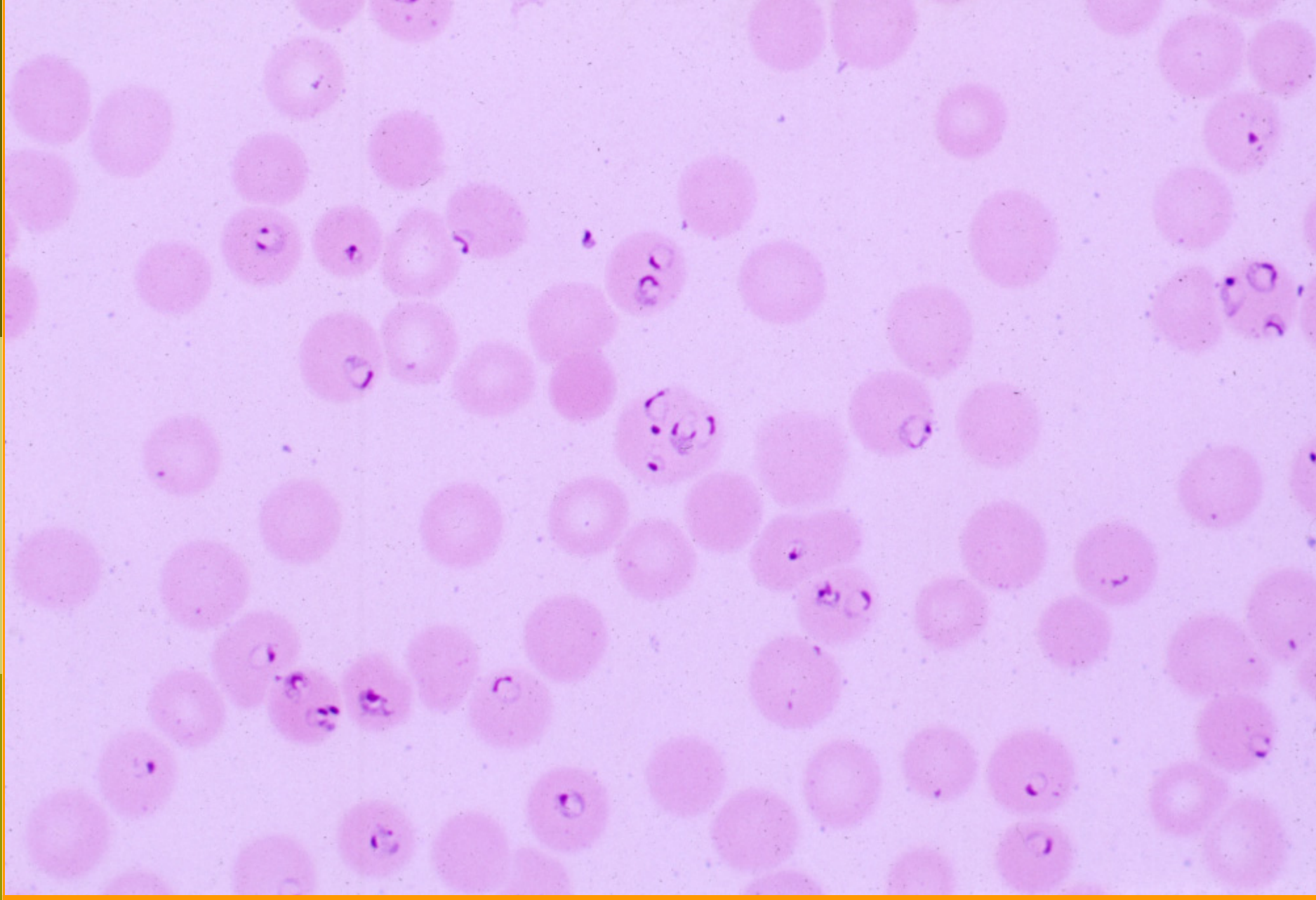
Bananna / Crescent shape

Plasmodium falciparum

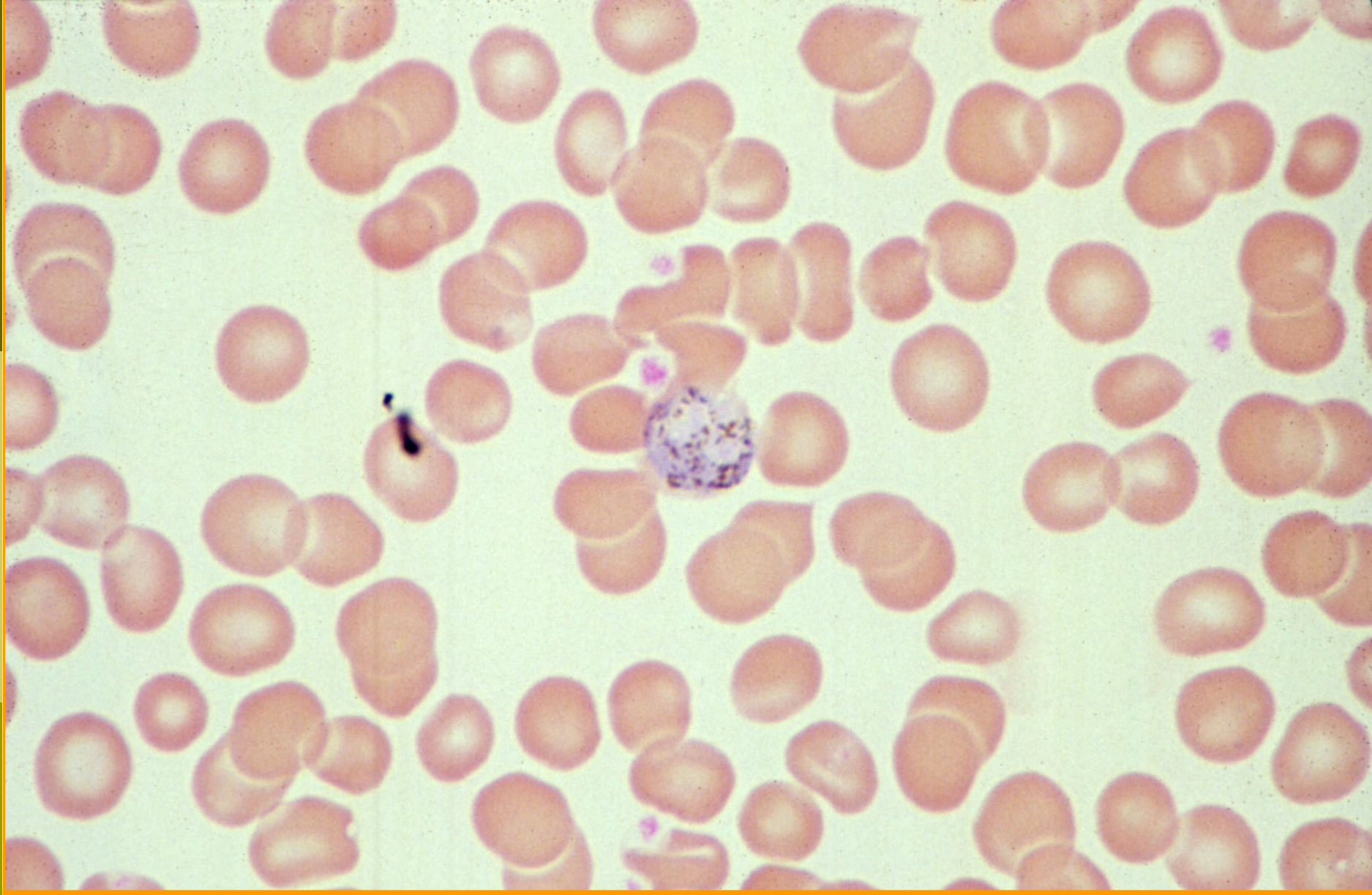




Malarial merozoites inside and outside RBC.

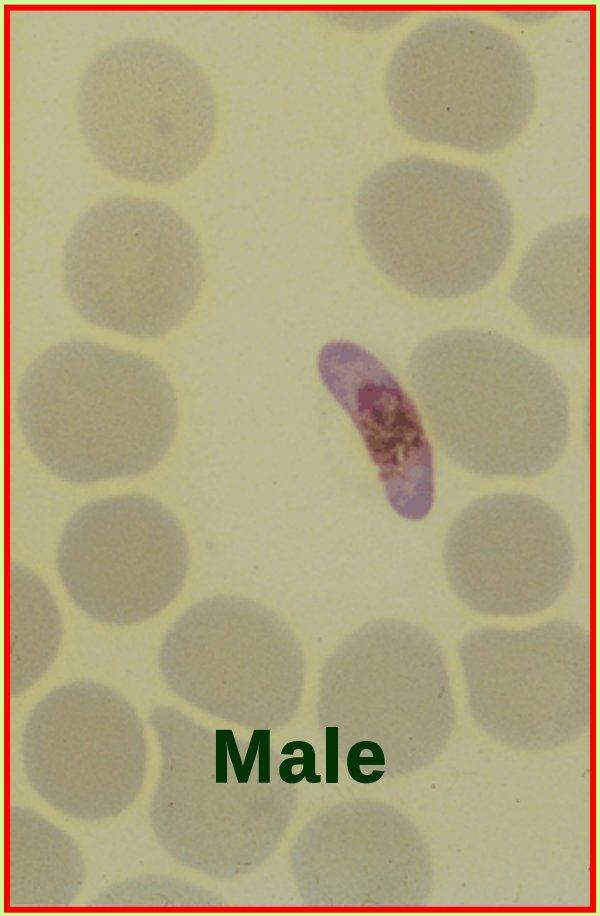


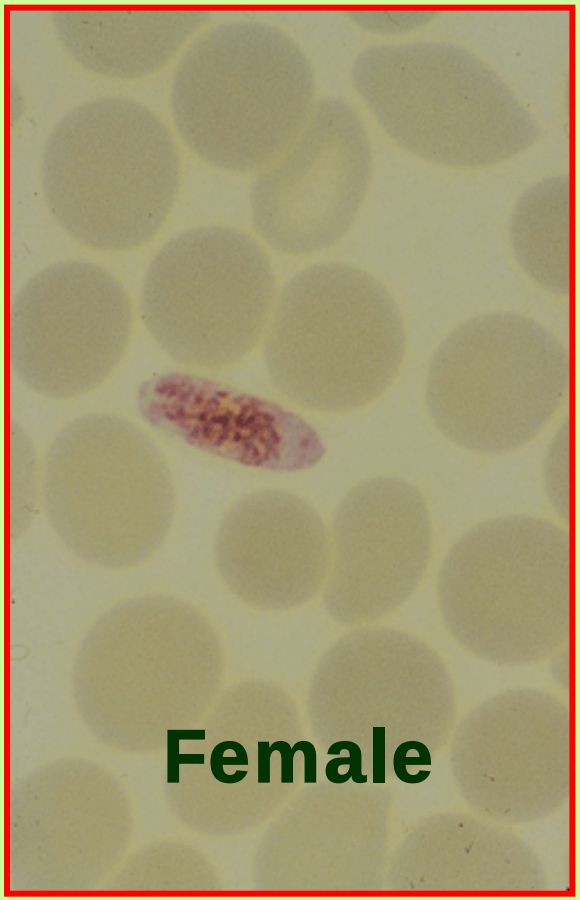
RBCs infected with trophozoites do not produce sequestrins and are able to pass through the spleen.



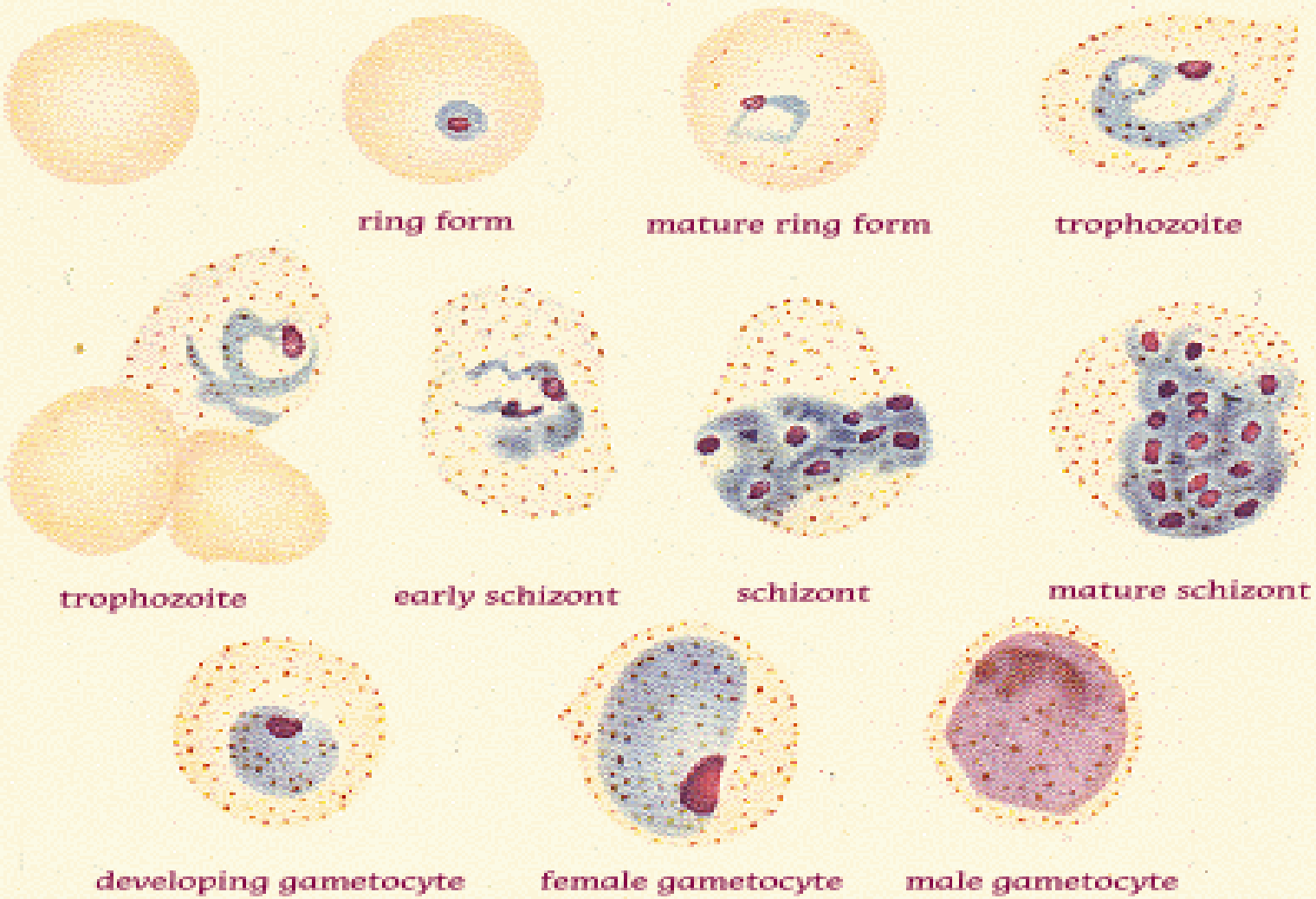
A mature schizont would secrete sequestrins protein on RBC surface enhancing its bounding to endothelial cells and subsequent sequestration in the spleen.

Falciparum gametocytes



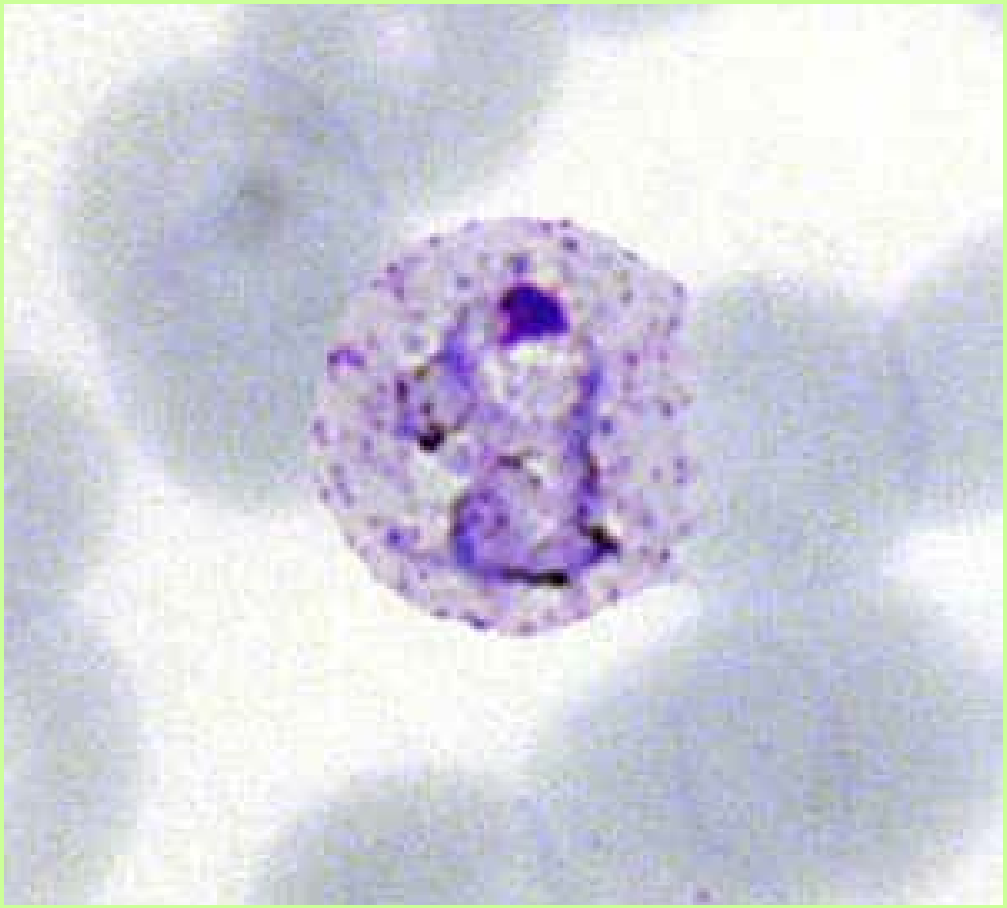


P. vivax



Infected RBCs larger than non-infected RBCs, Schüffner's dots

P. vivax

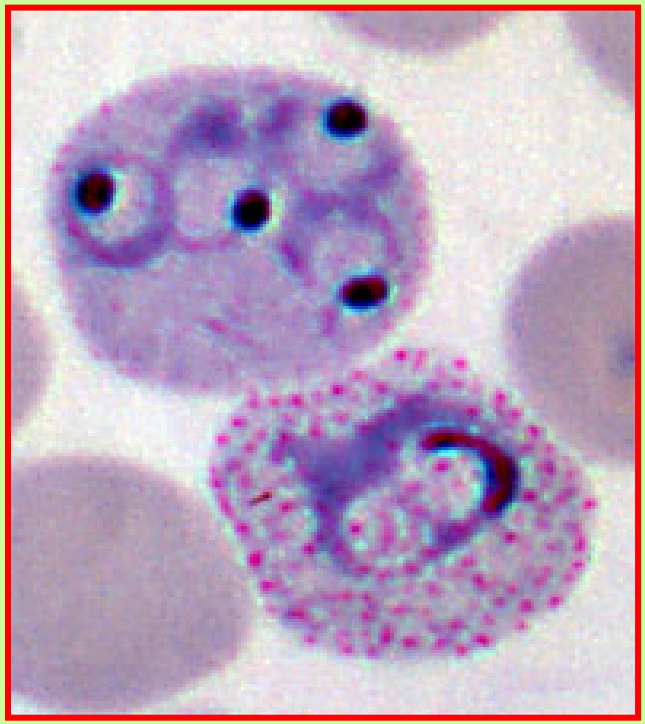


Differentiation of falciparum

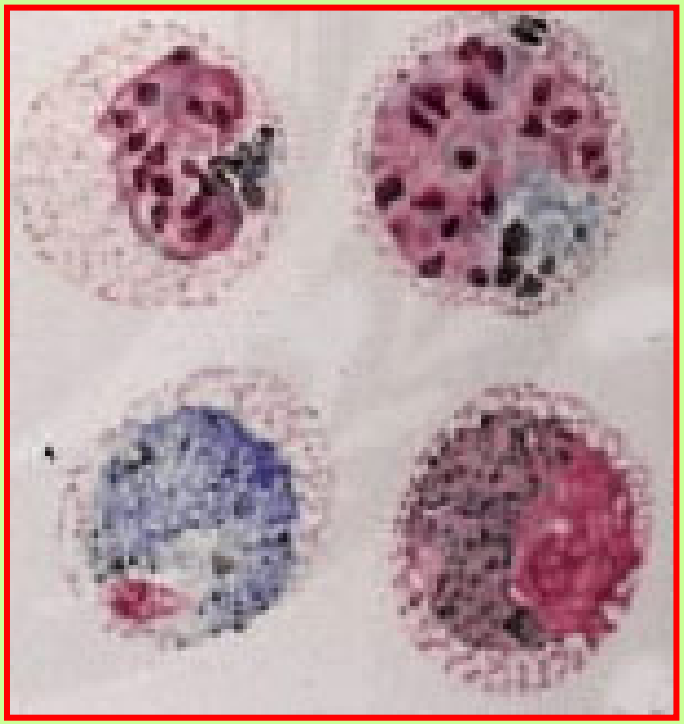
P.falciparum trophozite

P.vivax trophozite

Differentiation of falciparum

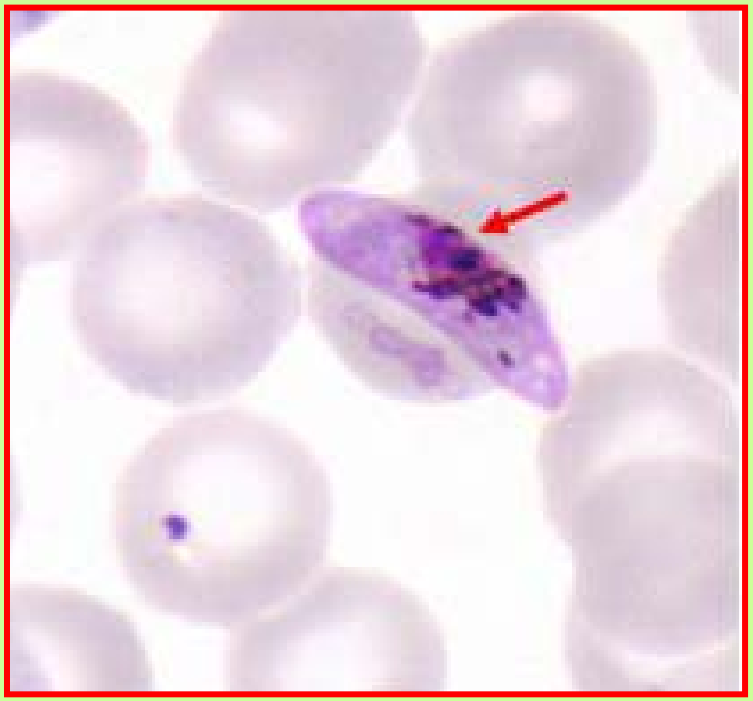


P.falciparum shizont



P.vivax shizont

Differentiation of falciparum

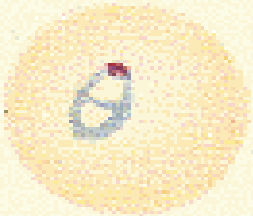


P.falciparum gametocyte

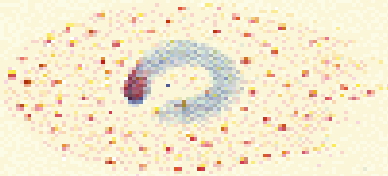
P.vivax gametocyte

P. ovale

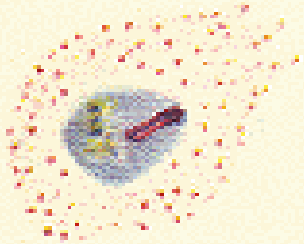
young ring



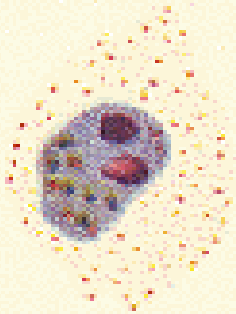
older ring



comet form

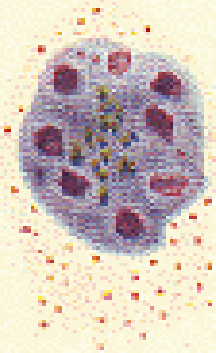


trophozoite

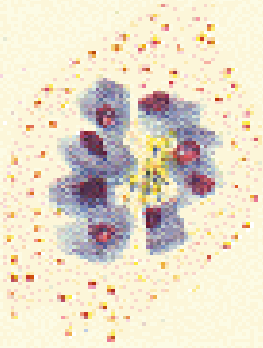


trophozoite

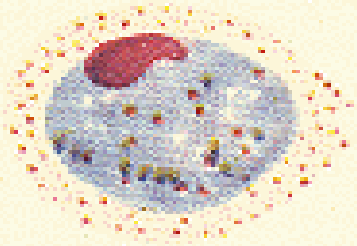
young schizont



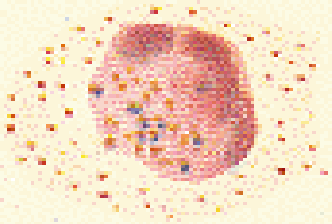
schizont



mature schizont

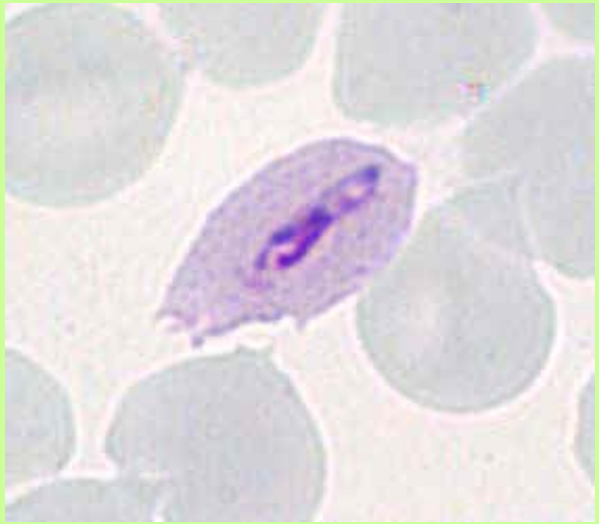


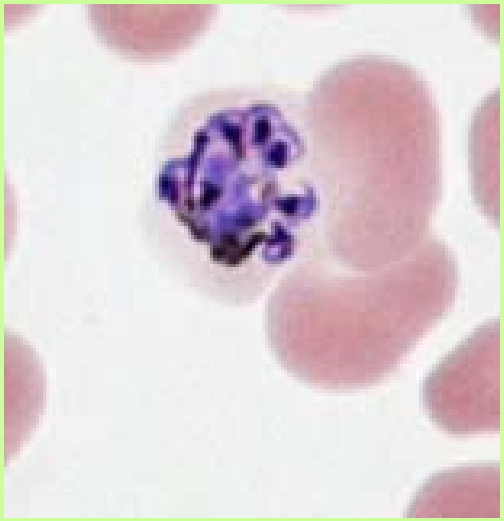
female gametocyte



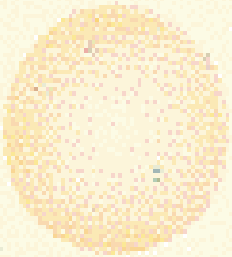
male gametocyte

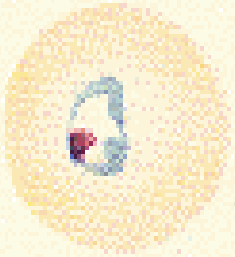
P. ovale





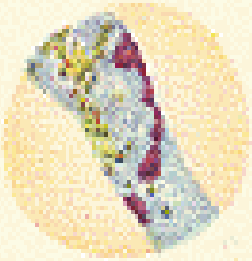
P. malariae



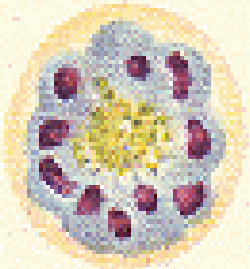


ring form

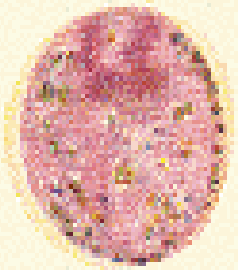
early band form



band form



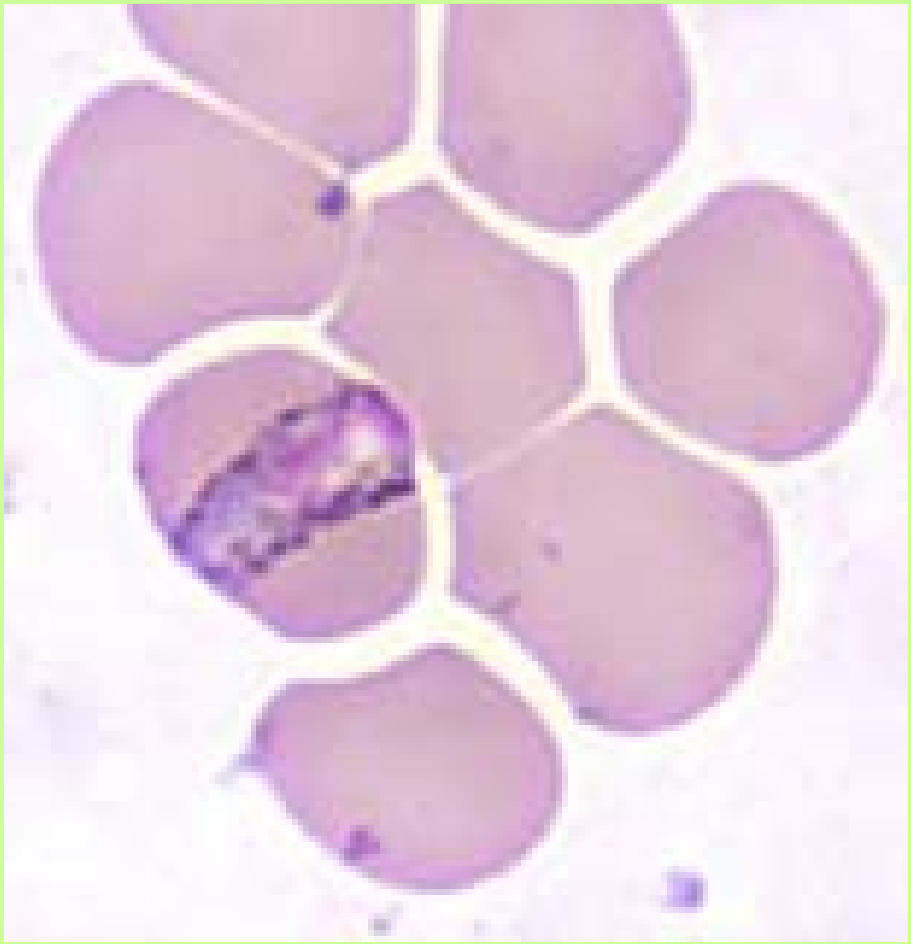
Daisy head appearance



early schizont | mature schizont | female gametocyte | male gametocyte

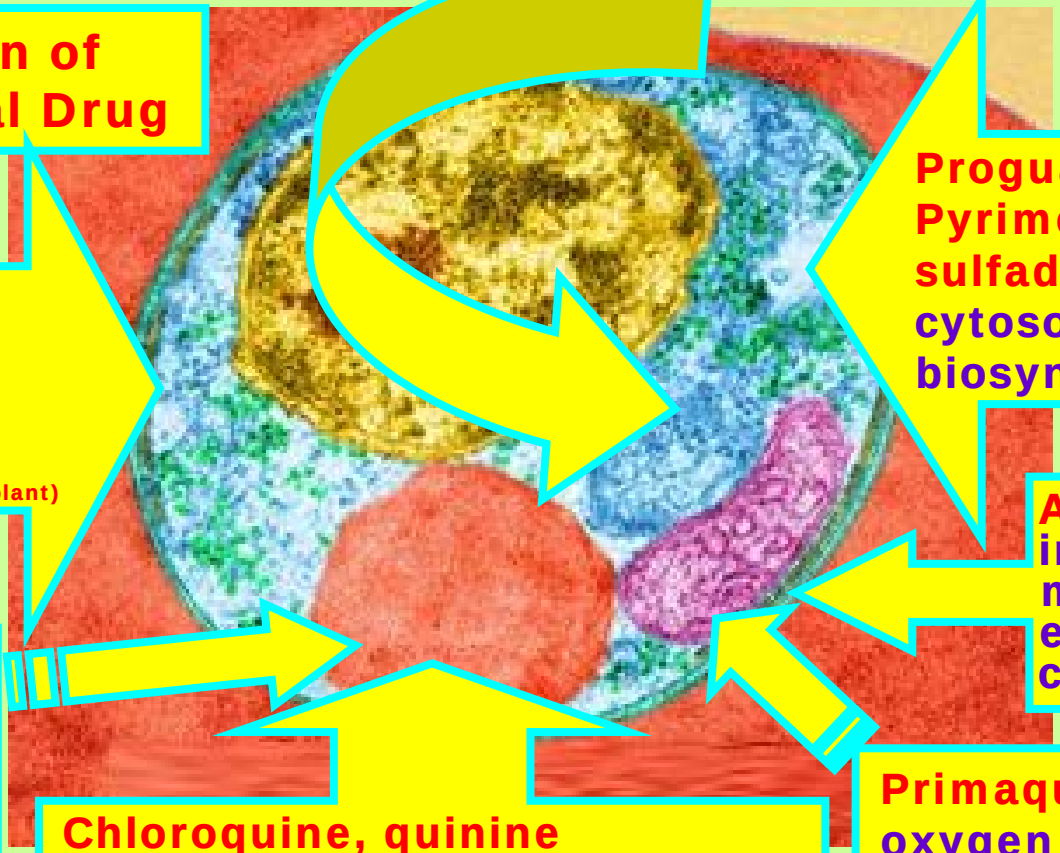
Infected RBCs same size as non-infected RBCs, No Schüffner's dots

P. malariae



Triclosan and **thiolactomycin** inhibit apicoplast fatty acid synthesis, while **fosmidomycin** targets the apicoplast-based DOXP pathway. **Ciprofloxacin** prevents the replication of the apicoplast genome and **rifampicin** acts upon apicoplast RNA transcription. **Clindamycin** seems to act upon apicoplast protein translation, while **Doxycycline** appears to inhibit both apicoplast and mitochondrial protein translation.

Site of Action of Anti-malarial Drug



Glyphosate inhibits a cytosolic shikimate pathway
(aromatic acid synthesis in plant)

Proguanil, dapsone Pyrimethamine–sulfadoxine targets the cytosolic folate biosynthetic pathway.

Atovaquone inhibits the mitochondrial electron transport chain

Artemisinins causes toxic alkylation of heme in food vacuole

Chloroquine, quinine amodiaquine and mefloquine interferes with the process of haem detoxification in the food-vacuole

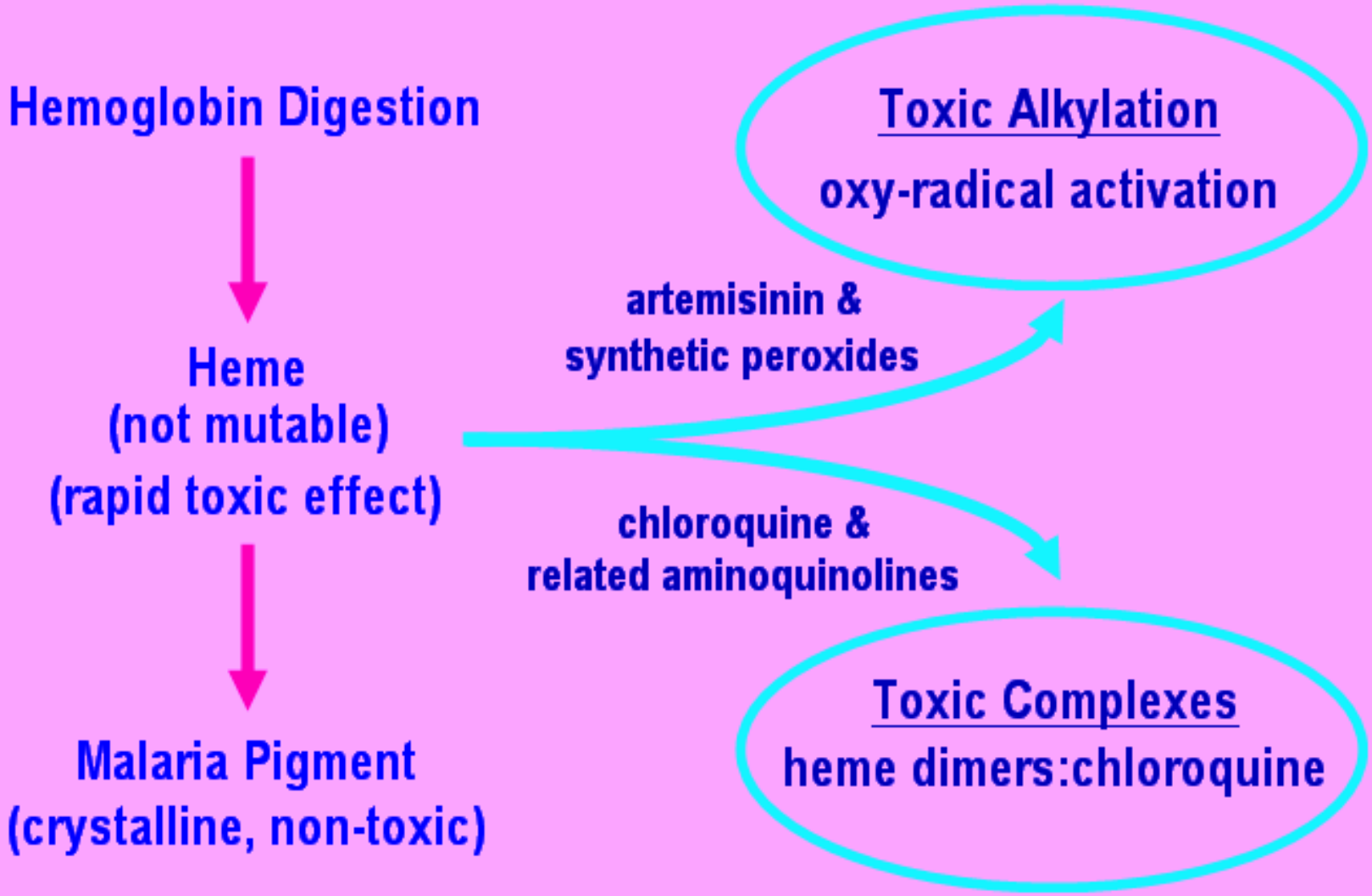
Primaquine create oxygen free radicals that interfere with the plasmodial electron transport chain during respiration.

Targets for antimalarial chemotherapy

Target location	Pathway/mechanism	Target molecule	Examples of therapies	
			Existing therapies	New compounds
Cytosol	Folate metabolism	Dihydrofolate reductase	Pyrimethamine, proguanil	Chlorproguanil
		Dihydropteroate synthase	Sulphadoxine, dapsone	
	Glycolysis	Thymidylate synthase		5-fluoroorotate
		Lactate dehydrogenase		Gossypol derivatives
		Peptide deformylase		Actinonin
	Protein synthesis	Heat-shock protein 90		Geldanamycin
	Glutathione metabolism	Glutathione reductase		Enzyme inhibitors
	Signal transduction	Protein kinases		Oxindole derivatives
	Unknown	Ca^{2+}-ATPase	Artemisinins	
Parasite membrane	Phospholipid synthesis	Choline transporter		G25
	Membrane transport	Unique channels	Quinolines	Dinucleoside dimers
		Hexose transporter		Hexose derivatives
Food vacuole	Haem polymerization	Haemozoin	Chloroquine	New quinolines
	Haemoglobin hydrolysis	Plasmepsins		Protease inhibitors
		Falcipains		Protease inhibitors
	Free-radical generation	Unknown	Artemisinins	New peroxides
Mitochondrion	Electron transport	Cytochrome *c* oxidoreductase	Atovaquone	
Apicoplast	Protein synthesis	Apicoplast ribosome	Tetracyclines, clindamycin	
	DNA synthesis	DNA gyrase	Quinolones	
	Transcription	RNA polymerase	Rifampin	
	Type II fatty acid bio-synthesis	FabH		Thiolactomycin
		FabI/PfENR		Triclosan
	Isoprenoid synthesis	DOXP reductoisomerase		Fosmidomycin
	Protein farnesylation	Farnesyl transferase		Peptidomimetics
Extracellular	Erythrocyte invasion	Subtilisin serine proteases		Protease inhibitors

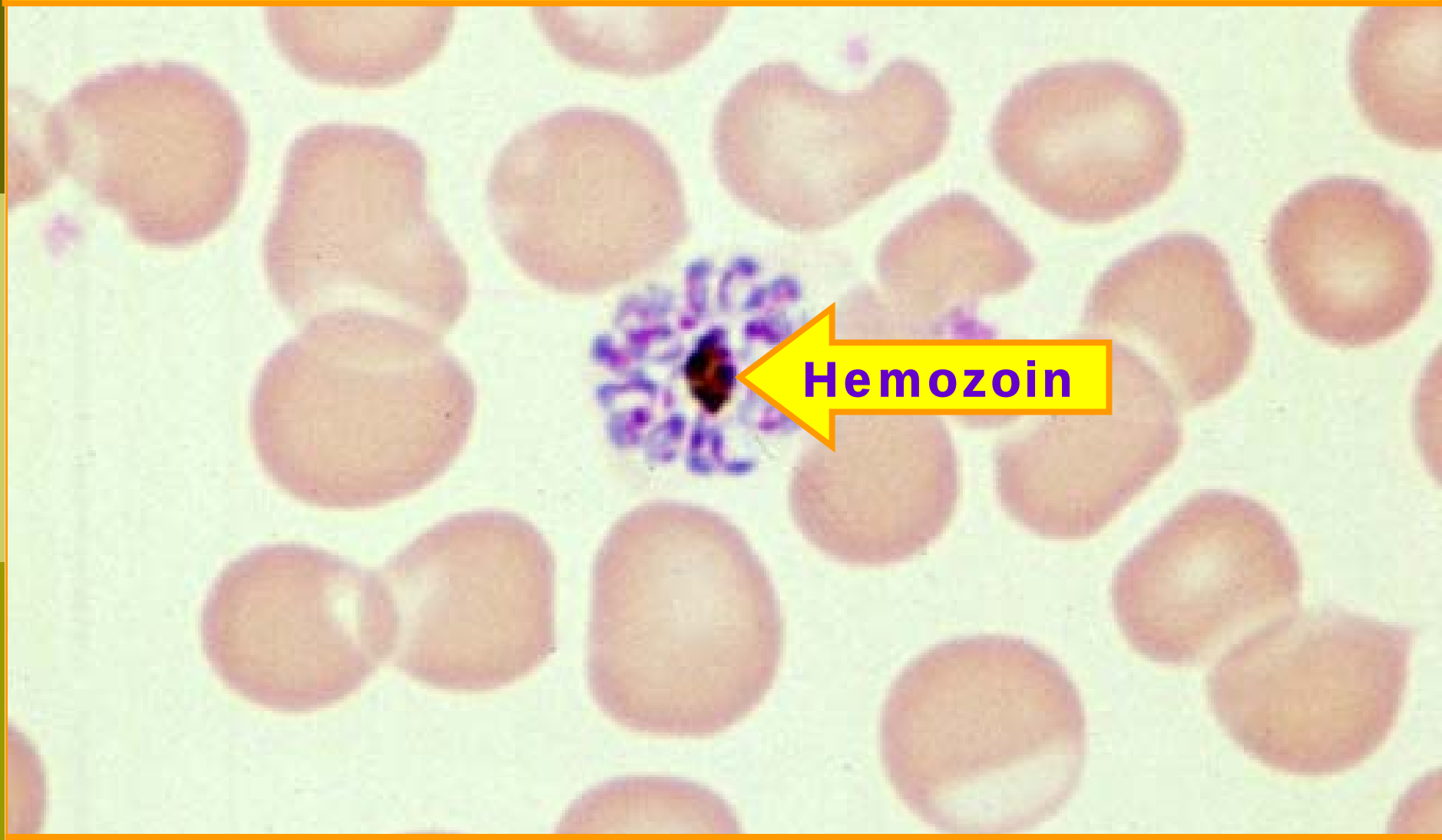
DOXP, 1-deoxy-D-xylulose 5-phosphate; PfENR, *Plasmodium falciparum* enoyl-ACP reductase.

Heme Remains an Effective Target for Drugs

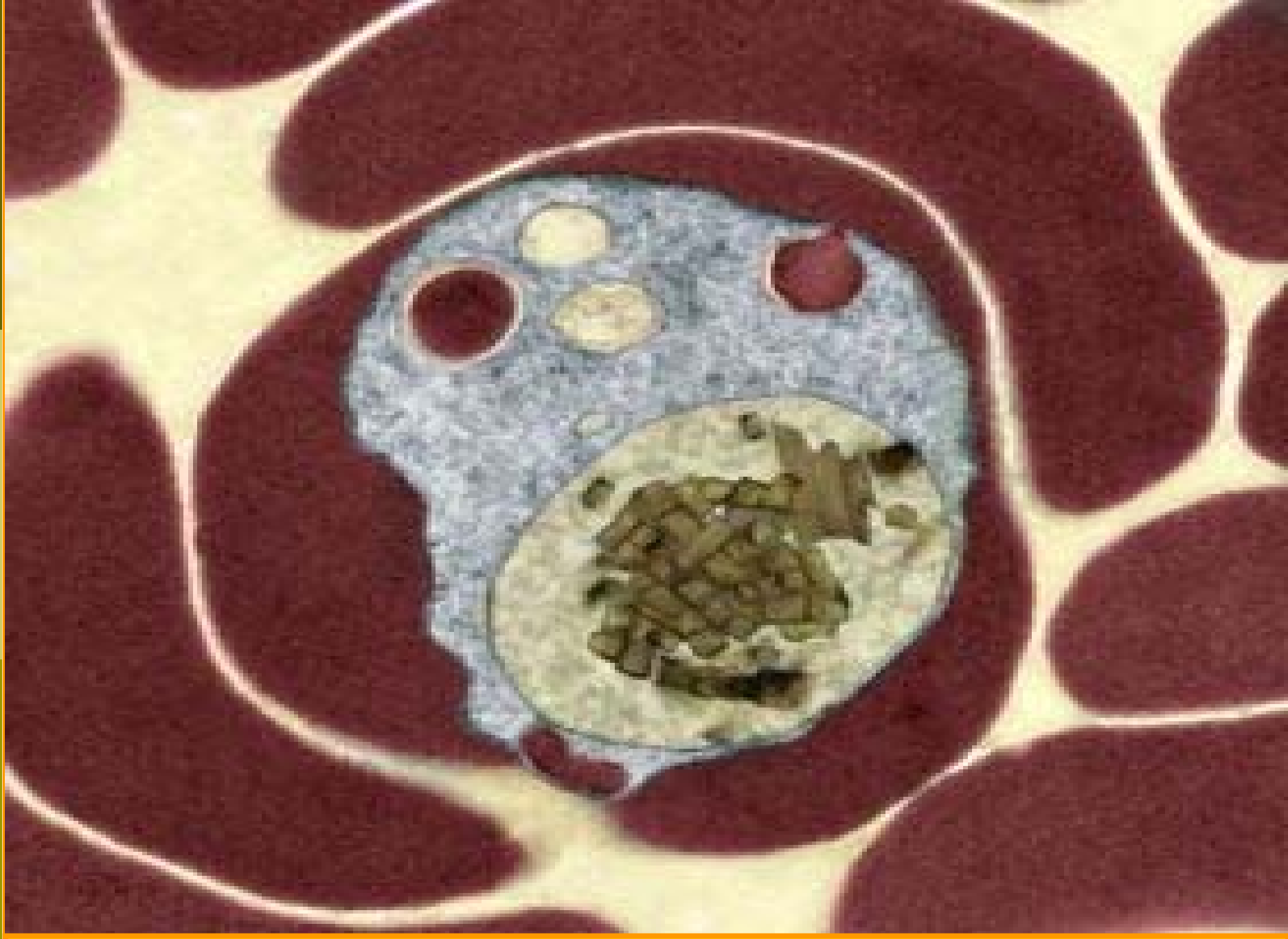


Jefford (2001) *Curr.Med.Chem.* 8:1803-26;
Chou *et al.* (1980) *Biochemistry* 19:1543-9

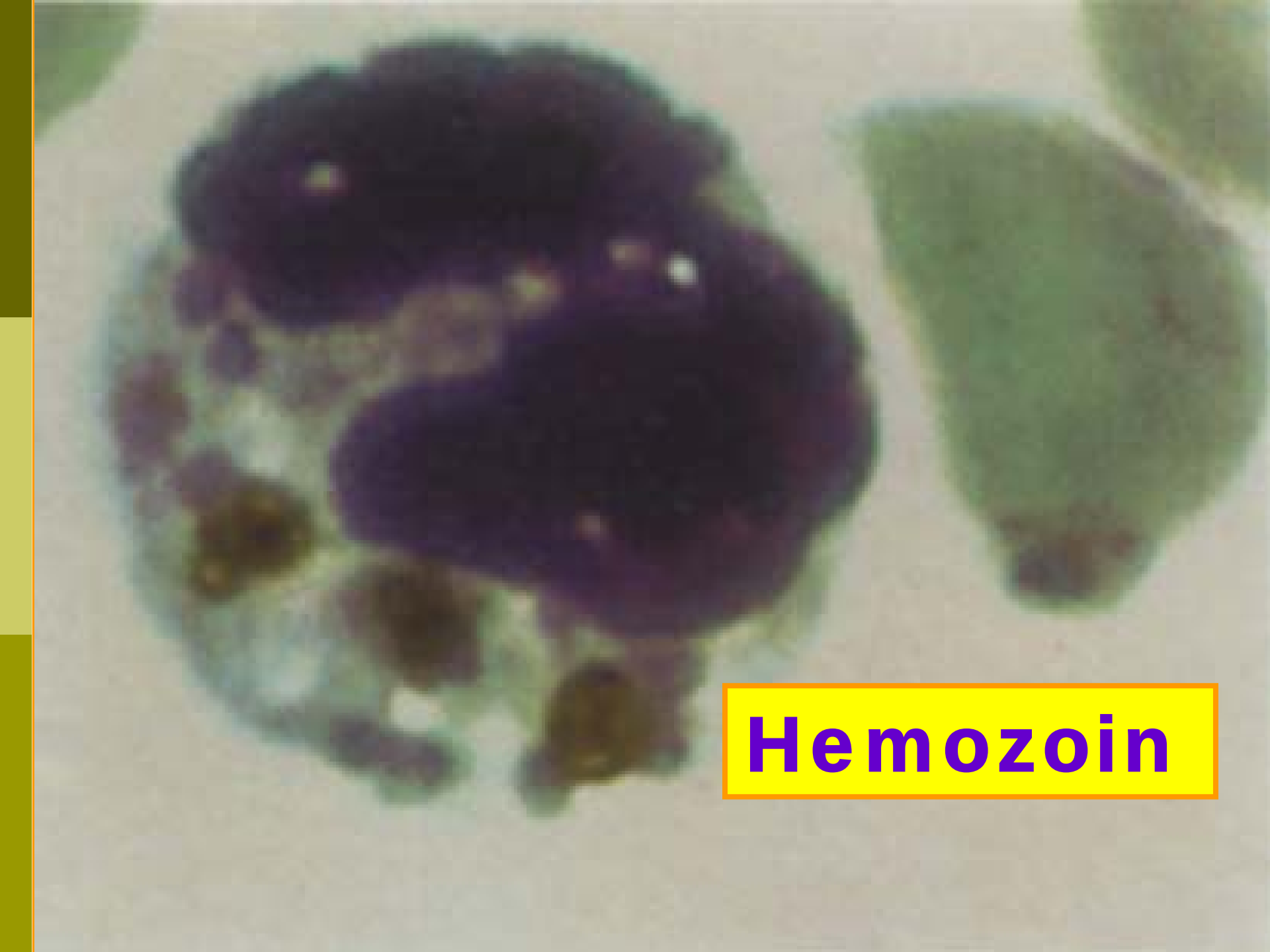
Hemozoin, or malaria pigment, is a paracrystalline precipitate formed when heme polymerase reacts with eme stored within the erythrocyte. Chloroquine inhibit heme polymerase is inhibited, leading to the heme-induced destruction of non–chloroquine-resistant merozoites.



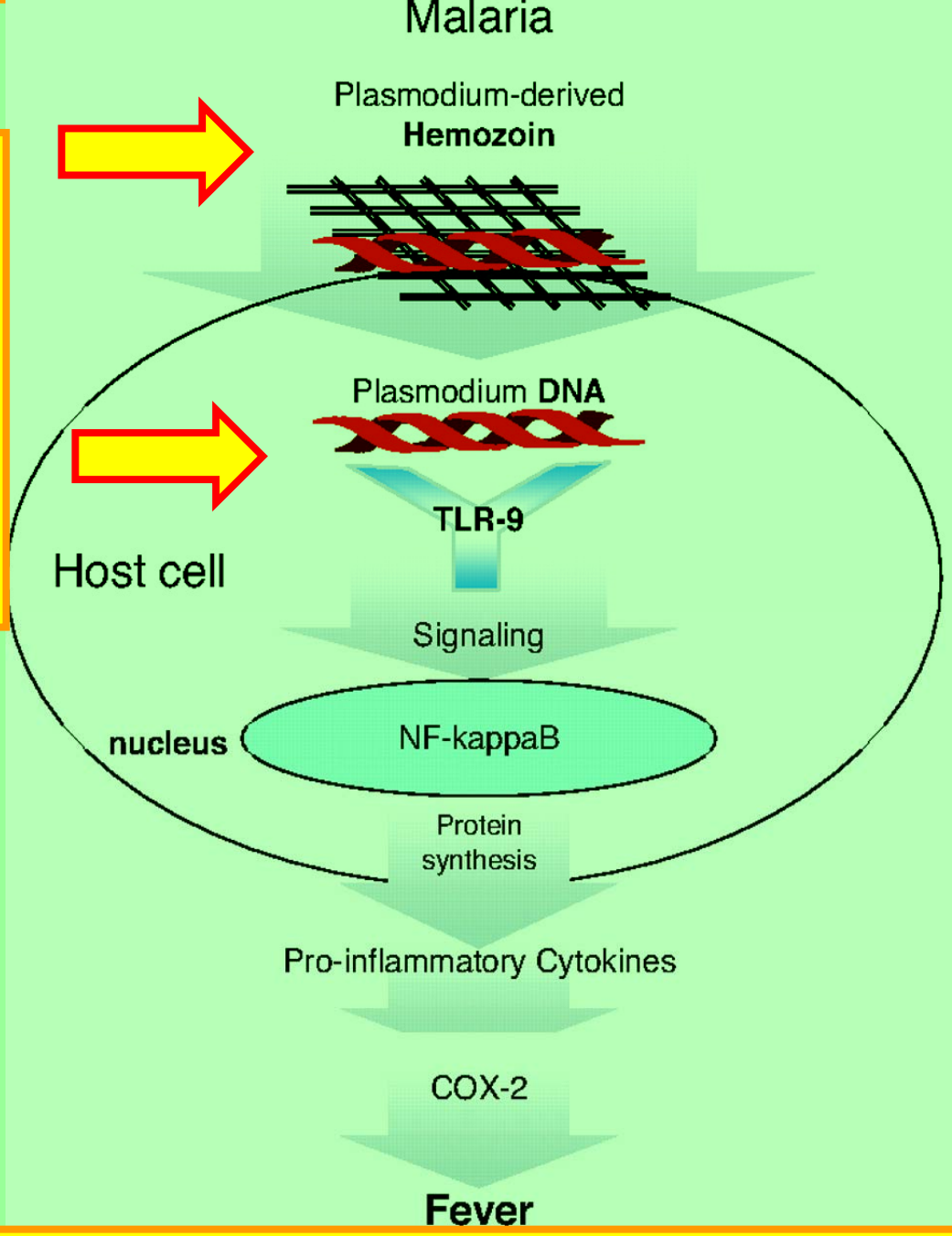
An erythrocyte filled with merozoites



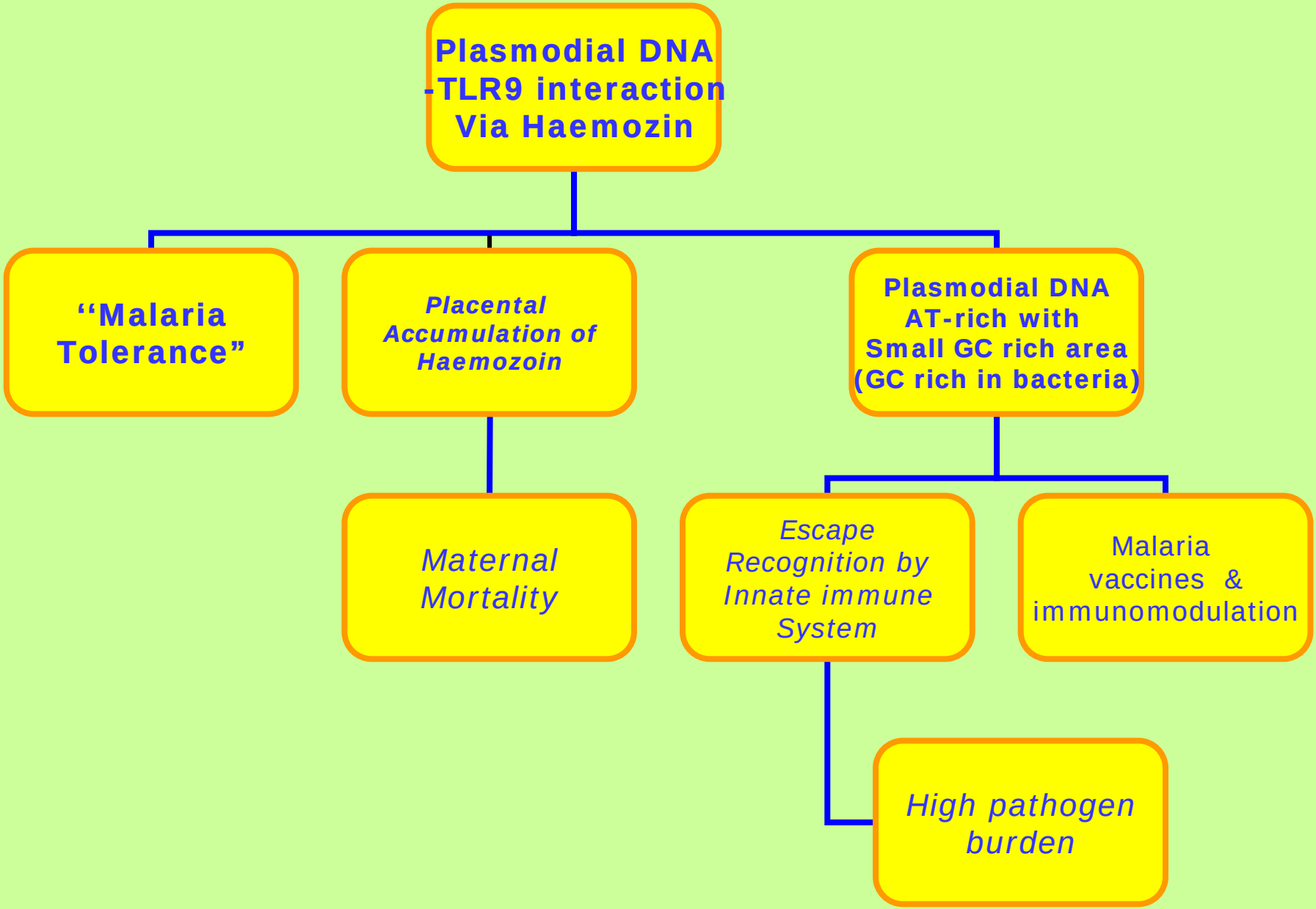
Hemozoin crystals in the food vacuole of the malaria parasite


Hemozoin

Chloroquin interferes with both hemozoin formation and nuclease activity and intracellular TLR9 processing by blocking endosomal acidification.

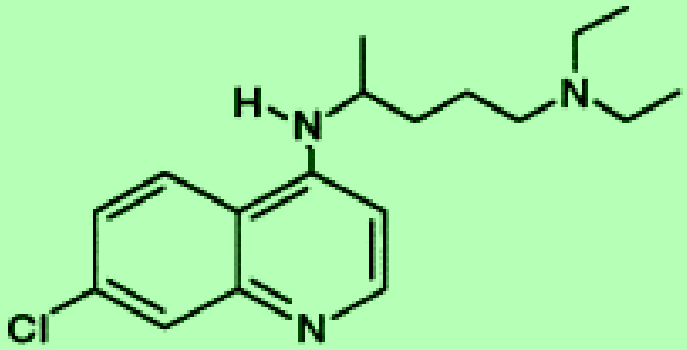


Malarial fever: Hemozoin is involved but Toll-free

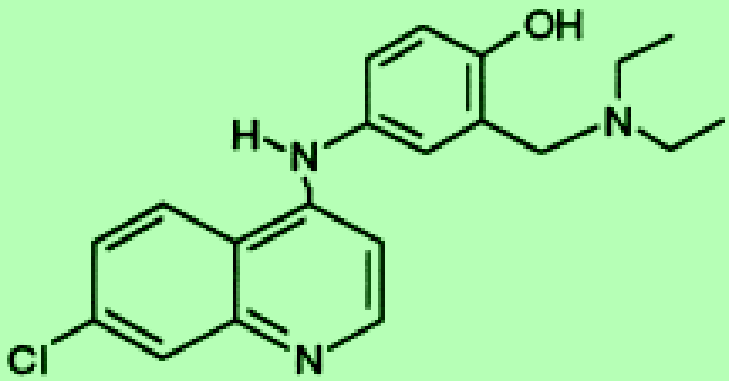


Role of CpG oligonucleotide–TLR9 interaction

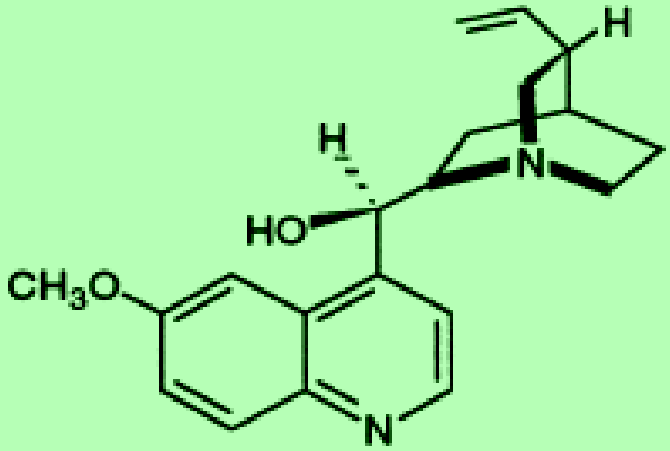
4-aminoquinolines



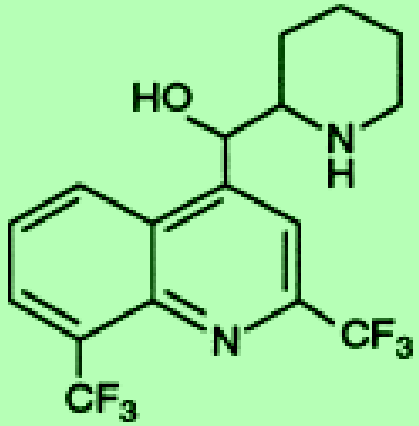
Chloroquine



Amodiaquine



Quinine

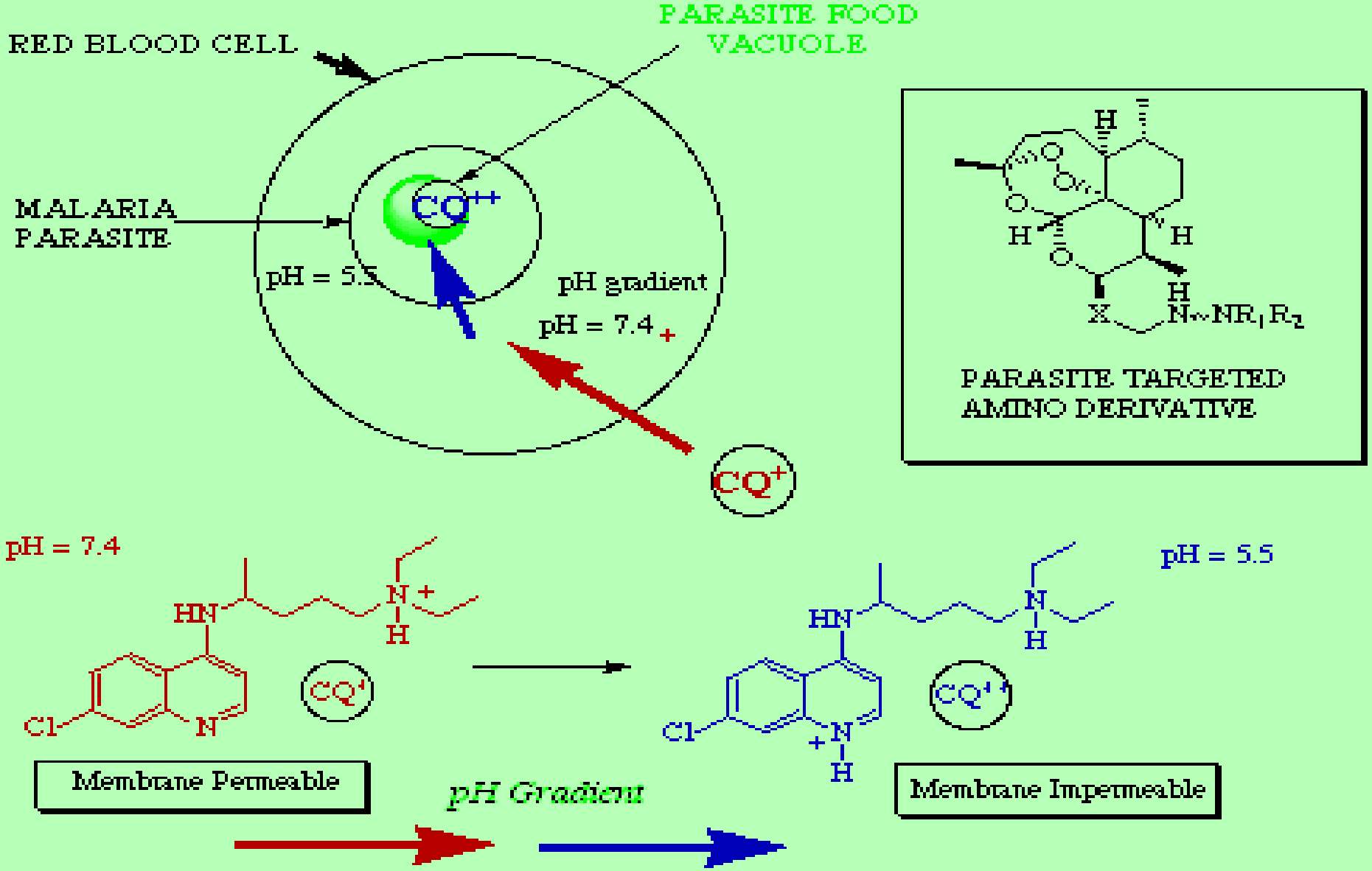


Mefloquine

Side Effects:
Gastrointestinal
Neuropsychiatric
Pneumonitis

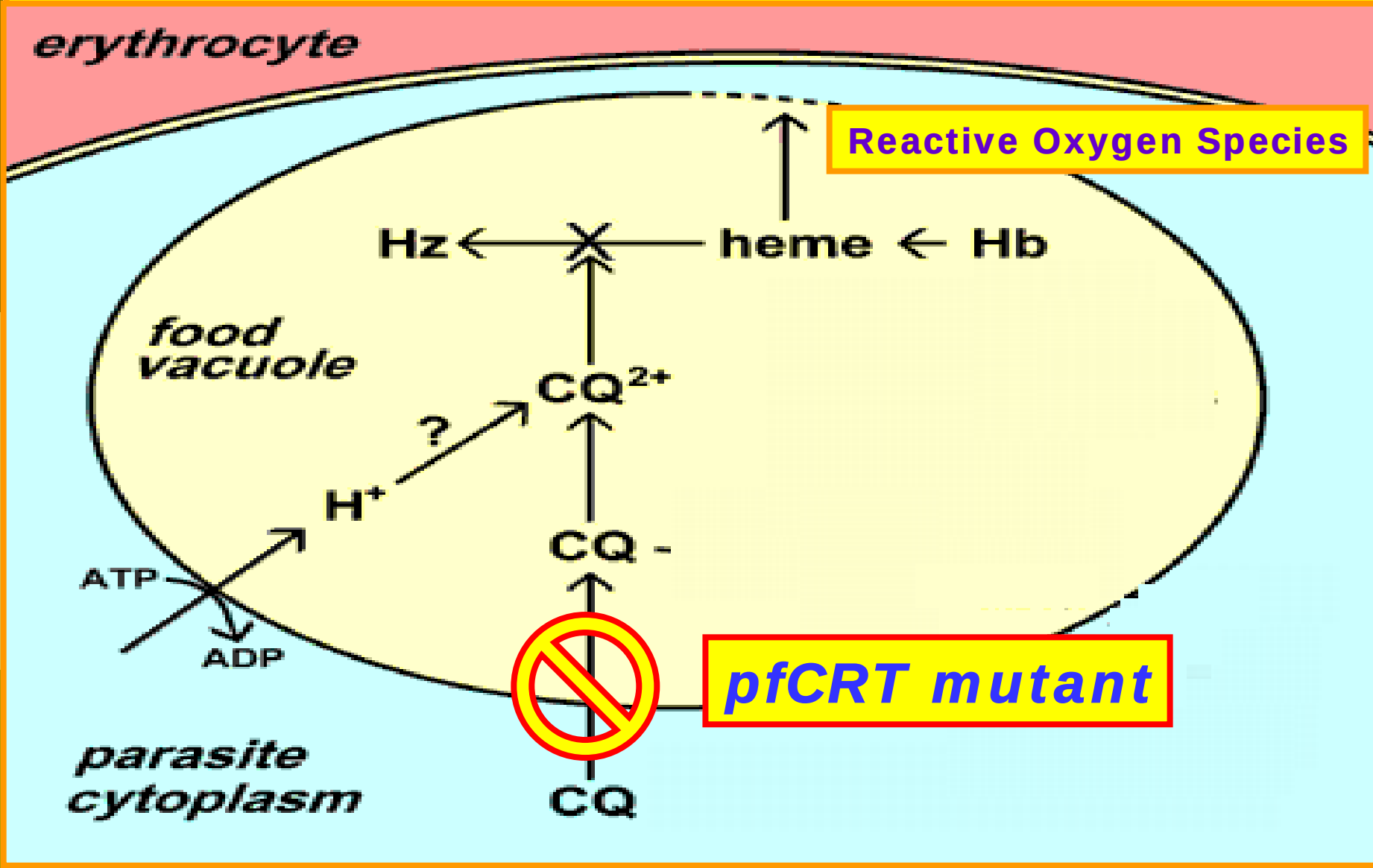
Quinoline-alcohols

Cinchona calisaya (Quinine Tree)



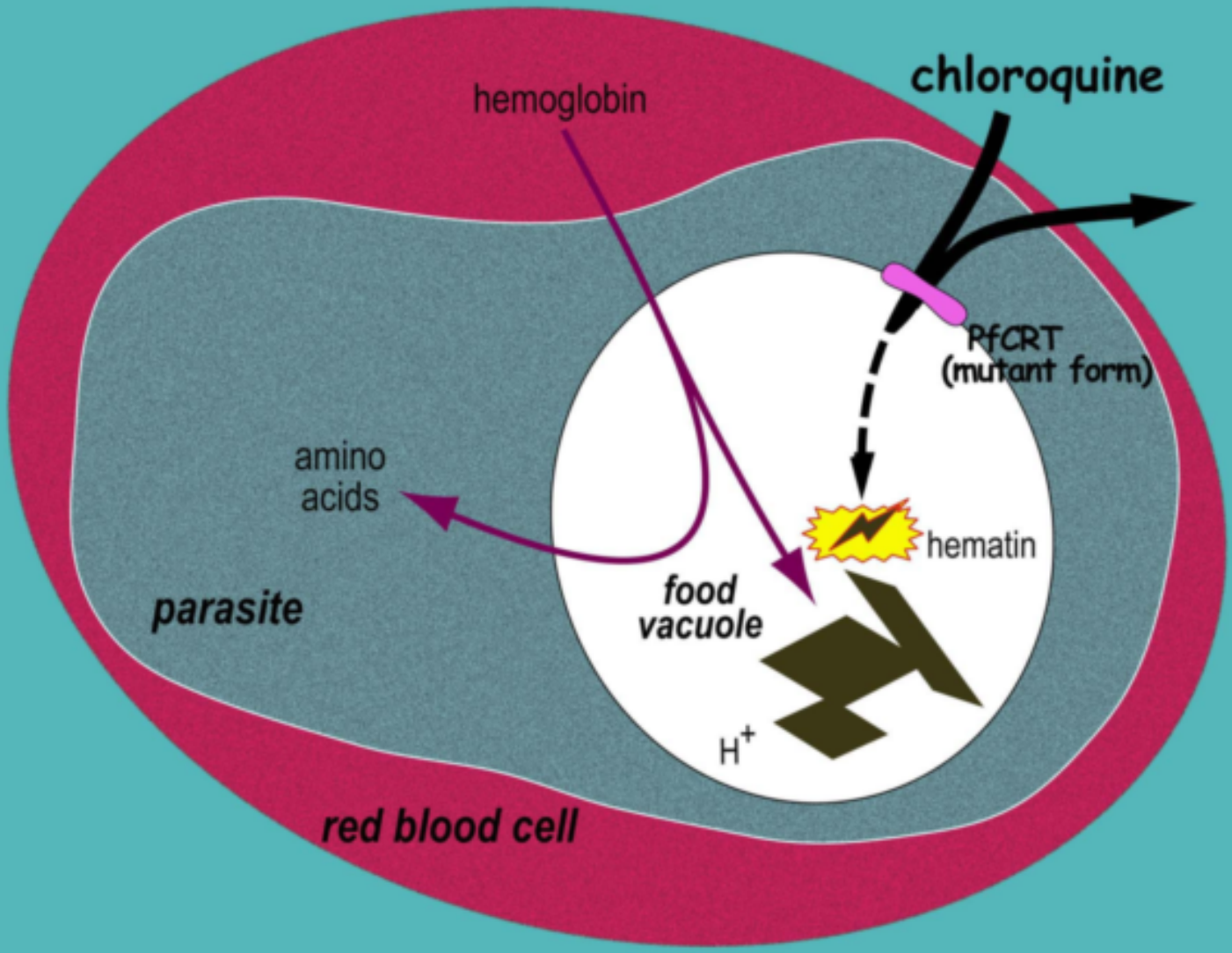
The Mechanism of Accumulation of Chloroquine in the Parasite Food Vacuole. Chloroquine travels down a pH gradient and inside the parasite becomes diprotonated. This form of the drug (shown in blue) is impermeable to biological membranes. On the right of the figure is a generic structure of a parasite targeted artemisinin derivative

Chloroquine concentrates up to several 1000-fold in the food vacuole of the parasite



The major action of chloroquine(CQ) is to inhibit the formation of hemozoin (Hz) from the heme released by the digestion of hemoglobin (Hb). The free heme then lyses membranes and leads to parasite death. Chloroquine resistance is due to a decreased accumulation of chloroquine in the food vacuole by pfCRT mutant.

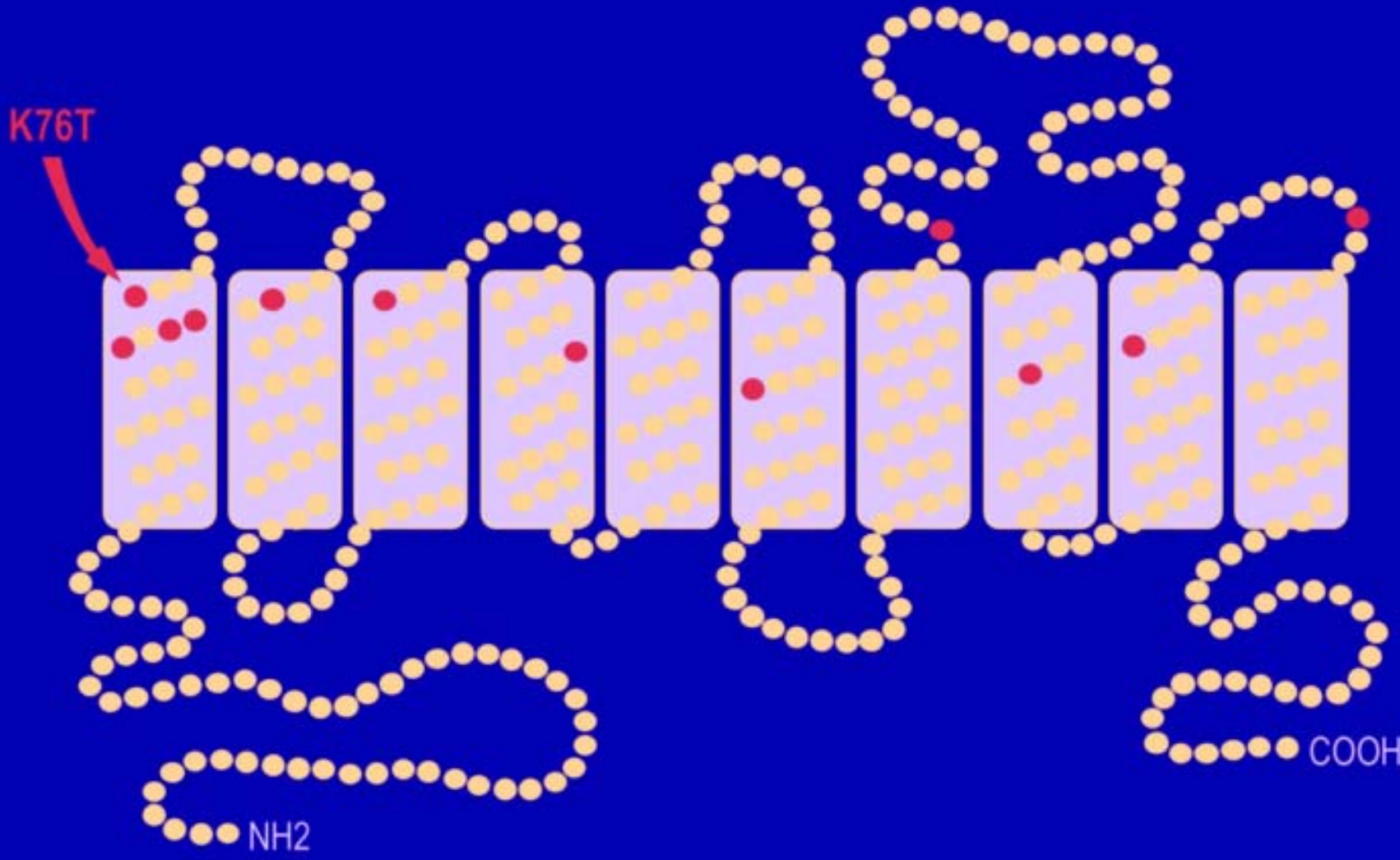
Chloroquine Action & Resistance in the Parasite



Malaria: Big killer and big advancesThomas Wellems (NIAID) and John Robbins (NICHD)

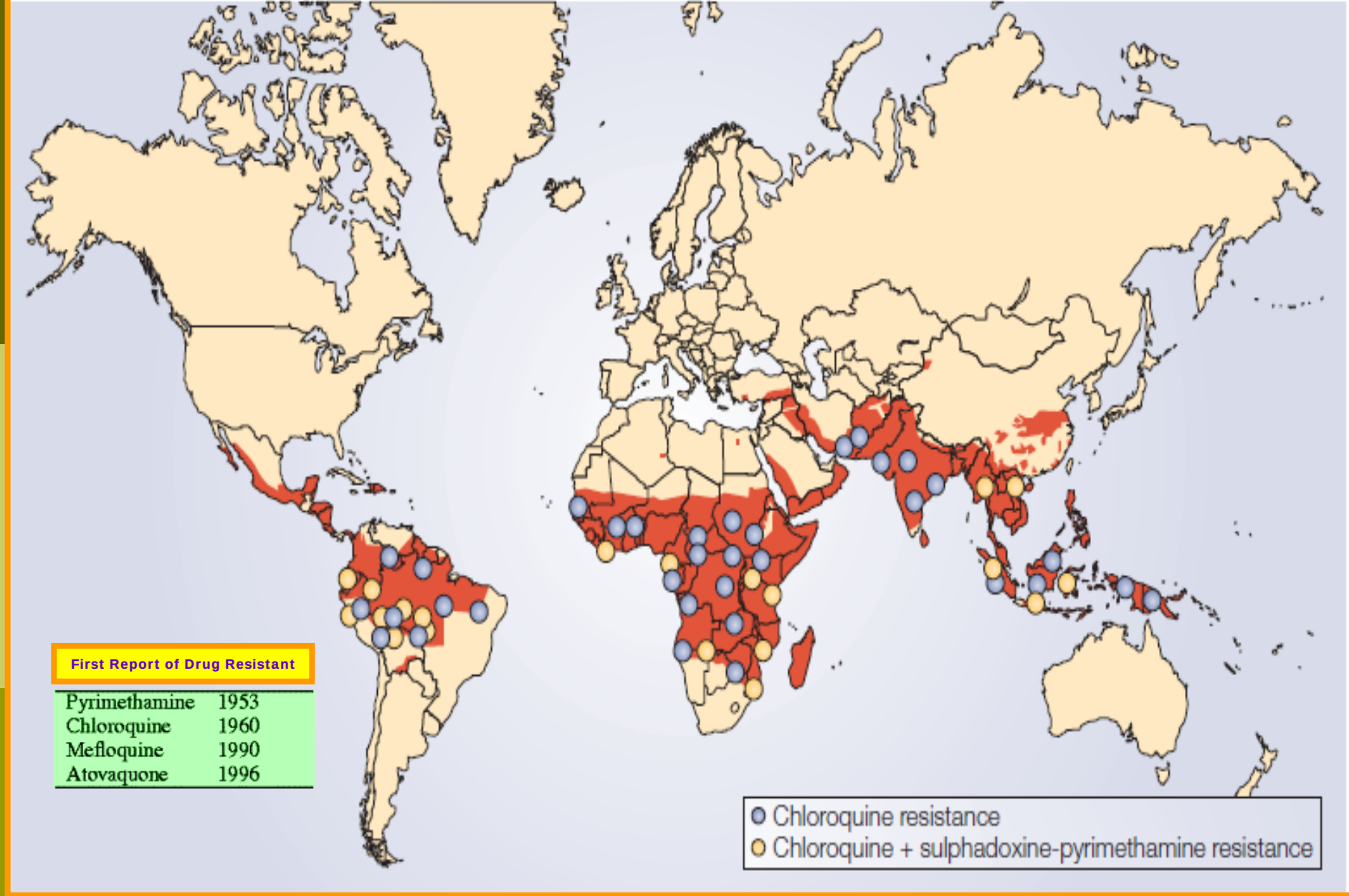
PfCRT actively pumps drug molecules out of the target area, rendering them ineffective

PfCRT Mutations in Chloroquine Resistance



Malaria: Big killer and big advancesThomas Wellems (NIAID) and John Robbins (NICHD)

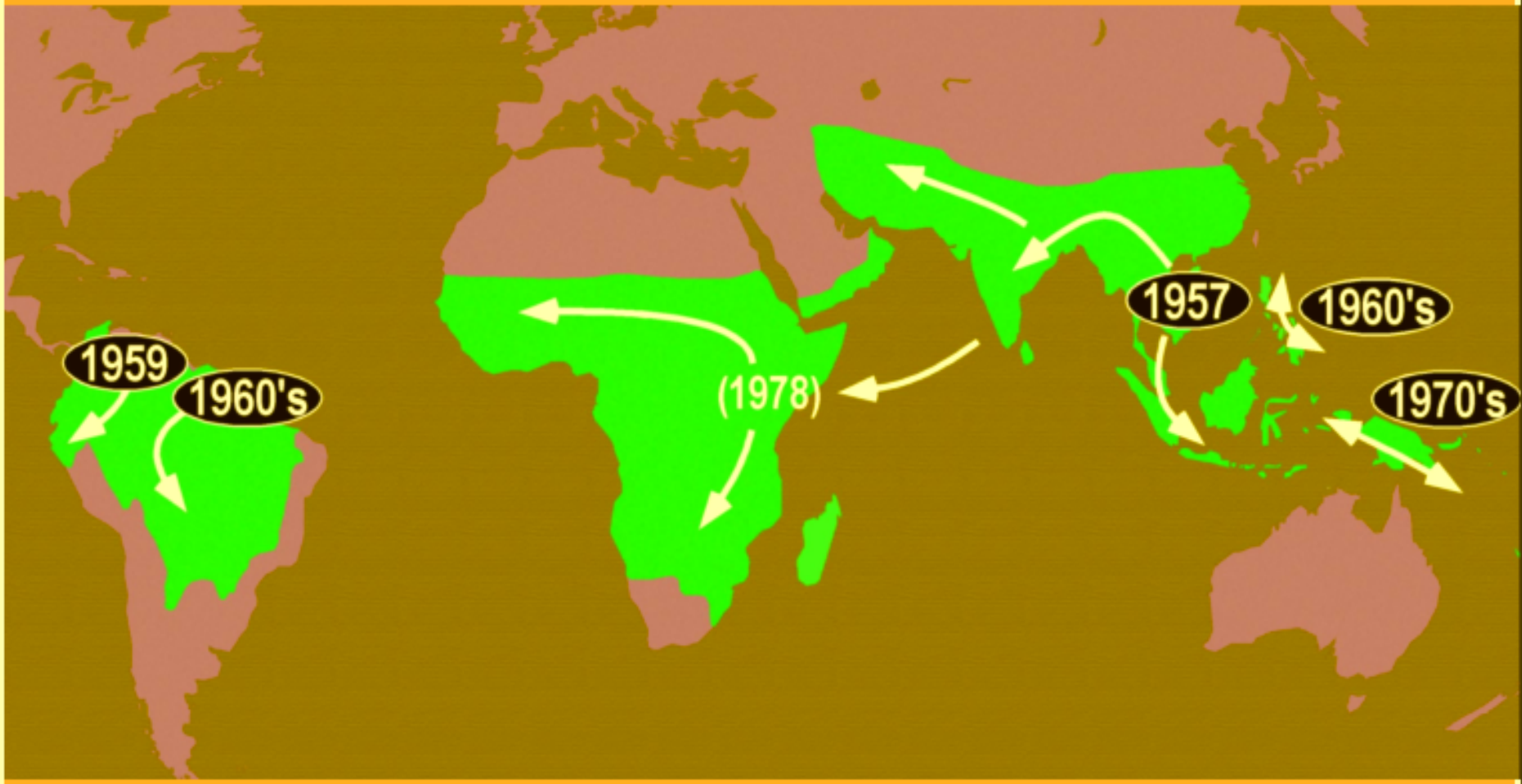
Fidock *et al.* (2000) *Mol. Cell* 6:861-871
Carlton *et al.* (2001) *Curr. Opin. Microbiol.* 4:415-420



The global distribution of malaria, showing areas where *Plasmodium falciparum* resistance to the most commonly used antimalarial drugs, chloroquine and sulphadoxine-pyrimethamine

Five Independent Foci of Chloroquine Resistance

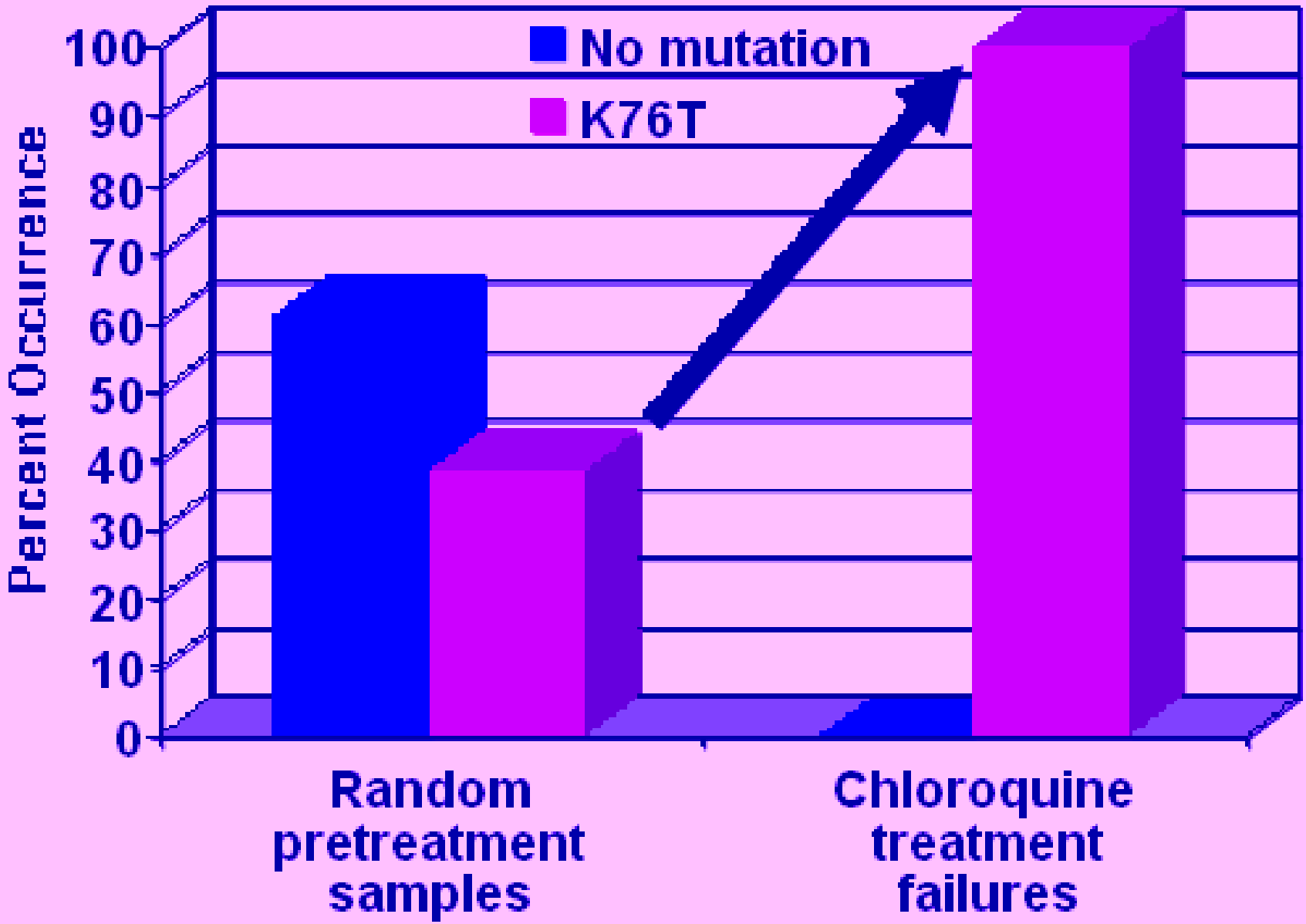
Malaria: Big killer and big advancesThomas Wellems (NIAID) and John Robbins (NICHD)



Gene cg2
PfCRT mutation

Wellems & Plowe (2001) *J. Infect. Dis.* 184:770-776; Wootton et al. (2002) *Nature* 418:320-323; Chen *et al.* (2003) *Antimicrob. Agents Chemother.* 47:3500-3505

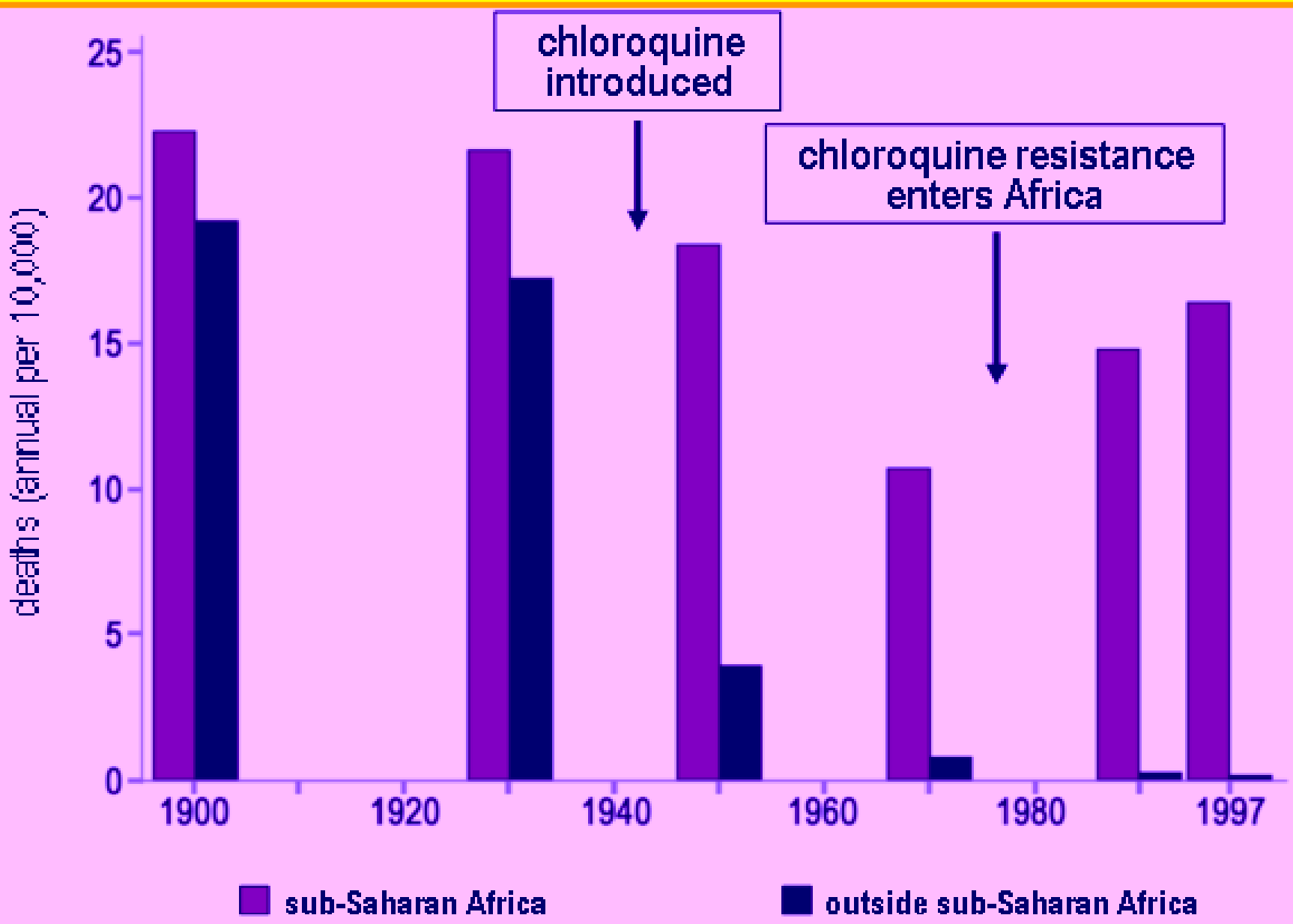
100% Selection of K76T mutant



Djimde et al. N Engl J Med 2001;344(4):257-263

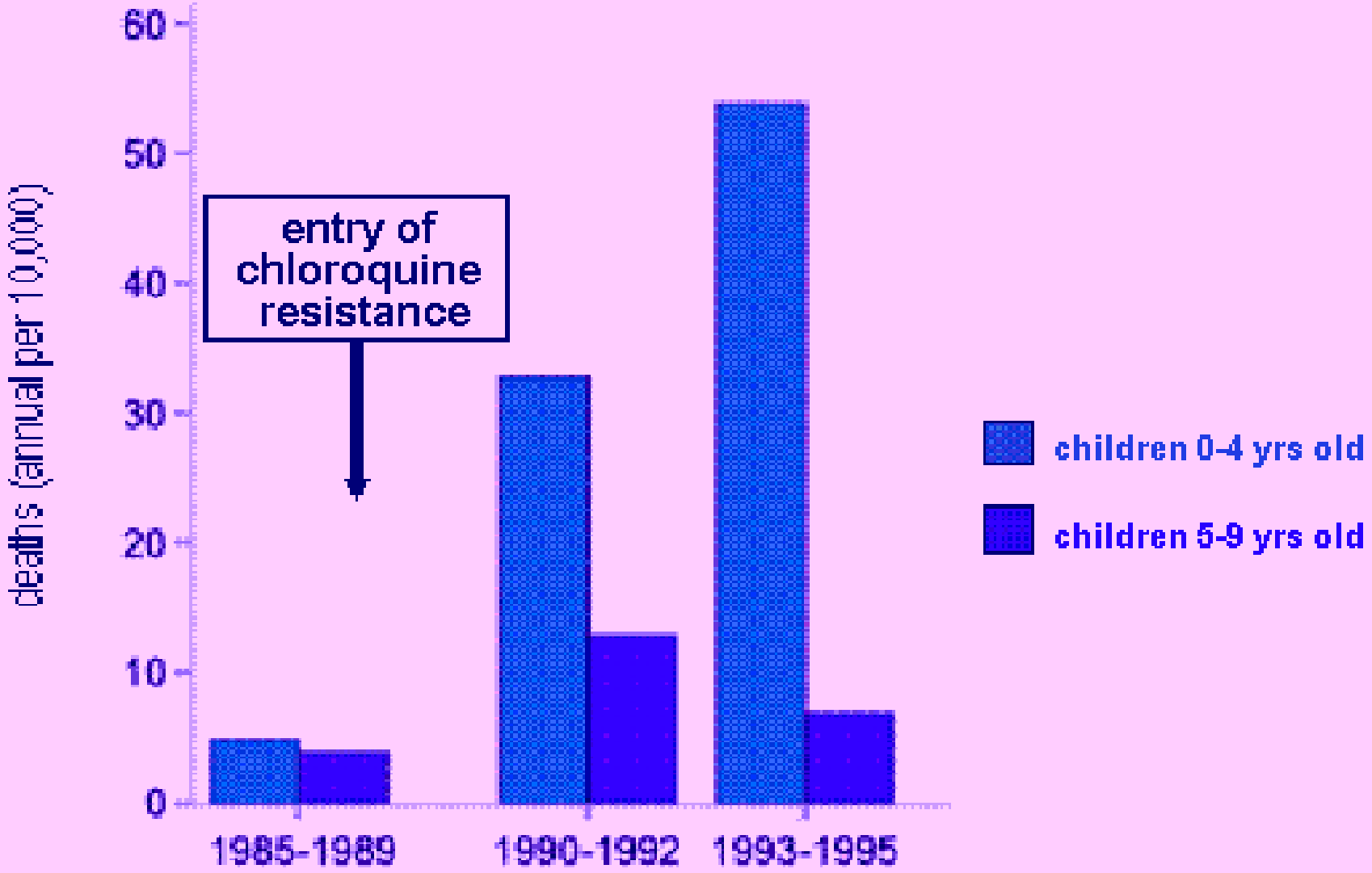
Evolutionary and Historical Aspects of the Burden of Malaria

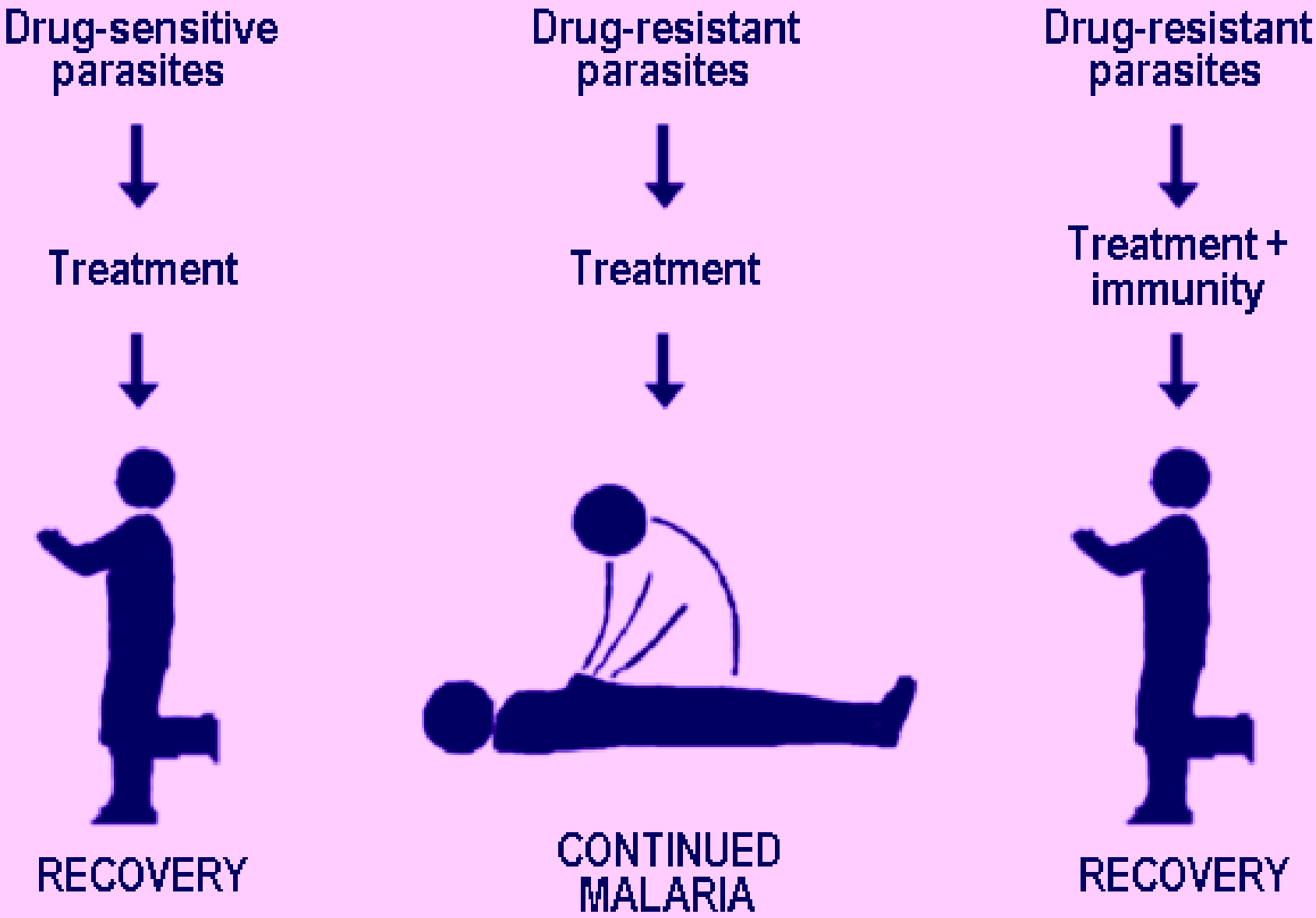
Richard Carter1* and Kamini N. Mendis2 Clinical Microbiology Reviews, October 2002, p. 564-594, Vol. 15, No. 4



Impact of chloroquine resistance on malaria mortality

C R Acad Sci III 1998, 321:689-697 Sokhna CS, Molez JF, Ndiaye P, Sane B, Trape JF



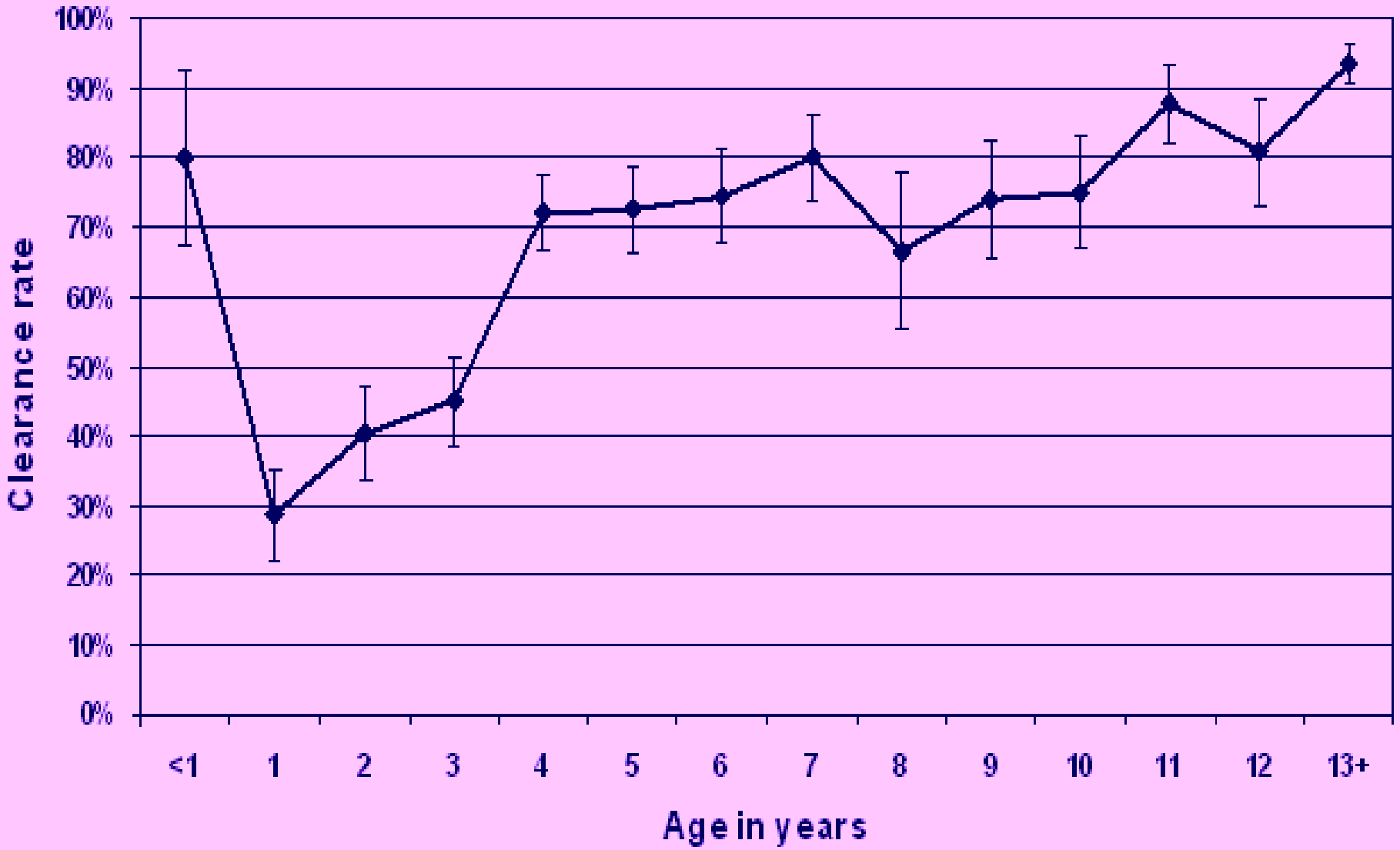


Immunity and Chloroquine Treatment Outcome

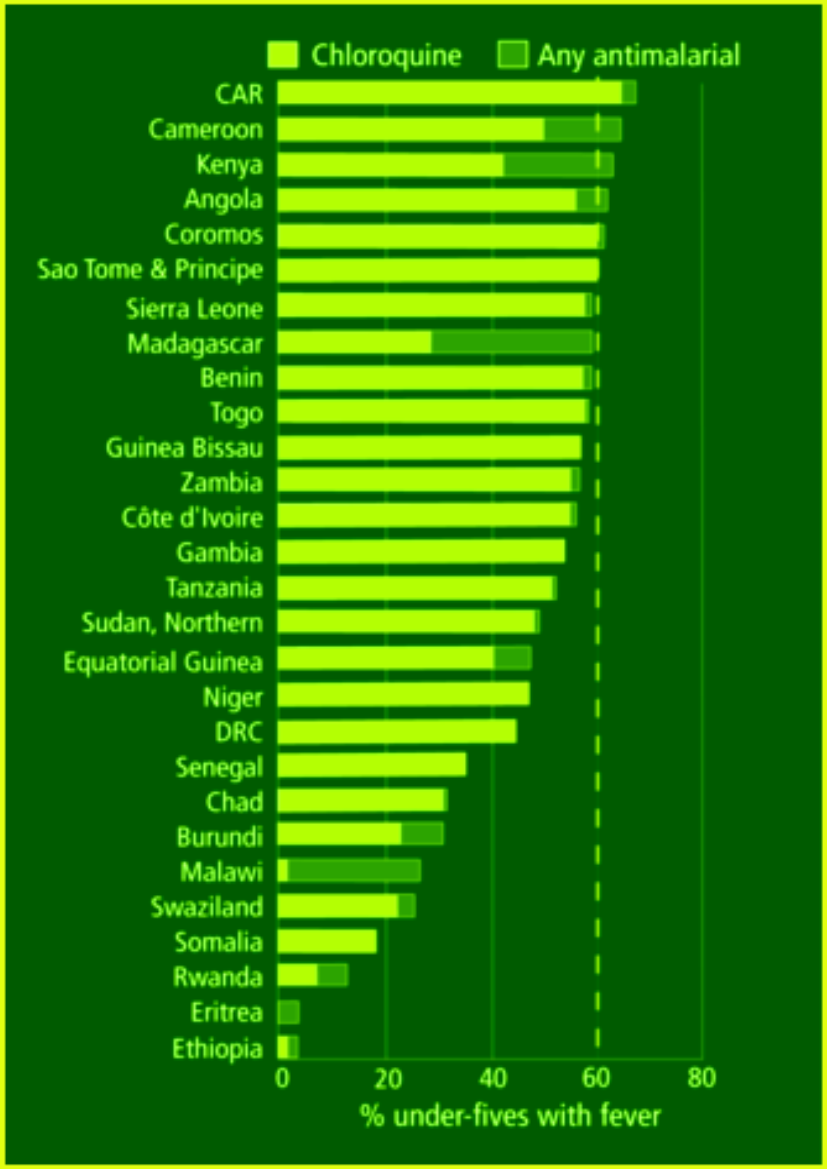
Chloroquine-resistant malaria 2001: Wellems T E; Plowe C V The Journal of infectious diseases 2001;184(6):770-6.

CLEARANCE OF DRUG-RESISTANT PARASITES AS A MODEL FOR PROTECTIVE IMMUNITY IN PLASMODIUM FALCIPARUM MALARIA

ABDOULAYE A. DJIMDÉ Am. J. Trop. Med. Hyg., 69(5), 2003, pp. 558-563



Continued Use of Chloroquine in Africa



- Almost half of the febrile children under the five years of age are treated with an antimalarial drug.
- Most treatments are with chloroquine, despite the risk of chloroquine resistance.

WHO (2003) The Africa Malaria Report

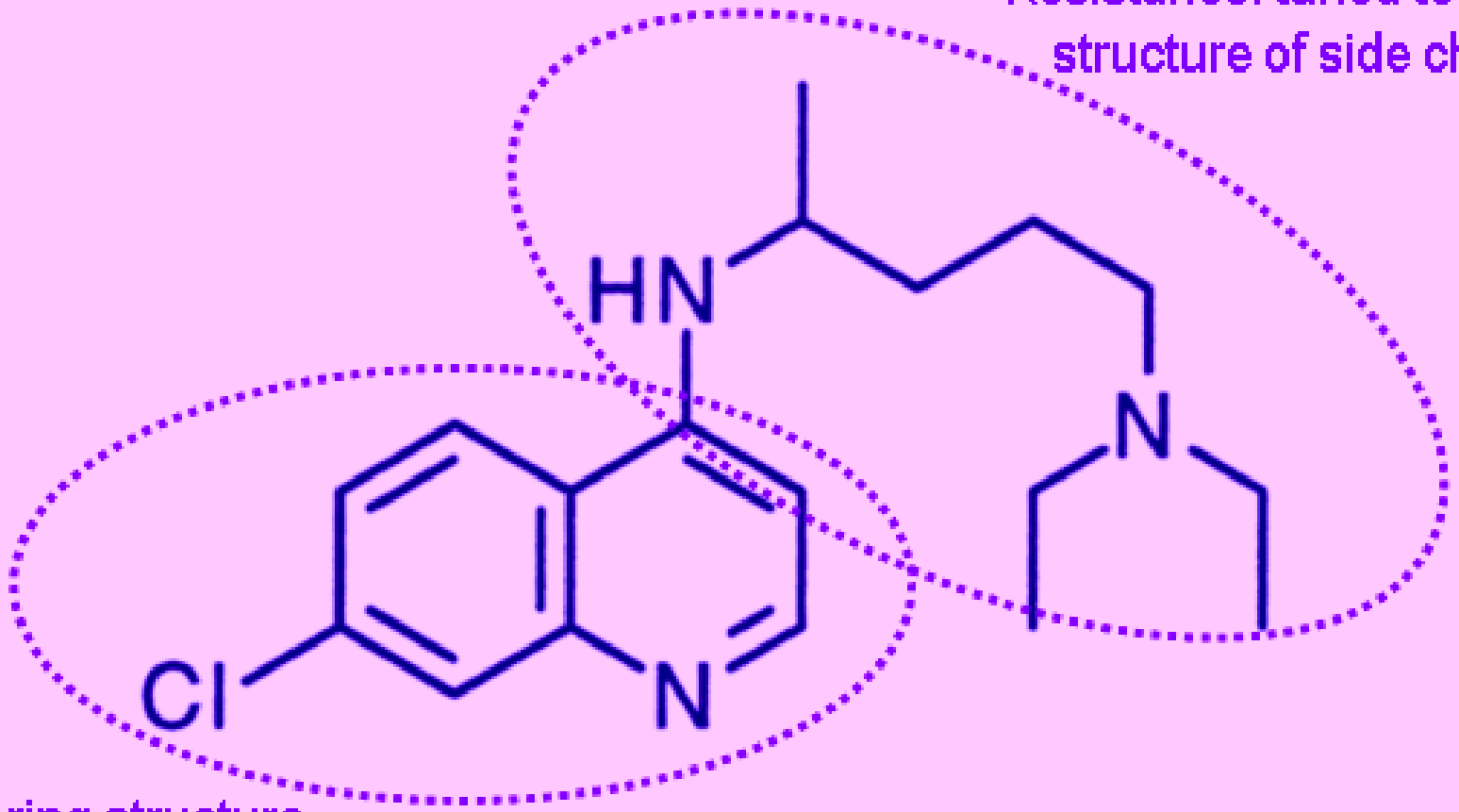
Problem of Chloroquine Resistance in Africa

- **Consequences of chloroquine failure:**
  - Surges in mortality & morbidity
  - Increased demands on medical services
  - Lost confidence in system after unsatisfactory treatment outcomes
- **Costs of alternative drugs:**

• Chloroquine	$ 0.37
• Fansidar (tablets)	1.90
• Mefloquine	13.55
• Halofantrine	20.33
• Quinine (injection)	30.96
* Artemisinin derivatives	> 2.00
* Amodiaquine	1.10

Chloroquine Structure and Activity Relationship

Resistance: tuned to structure of side chain



Action: ring structure sandwiches with hematin