ANTIMALARIALS

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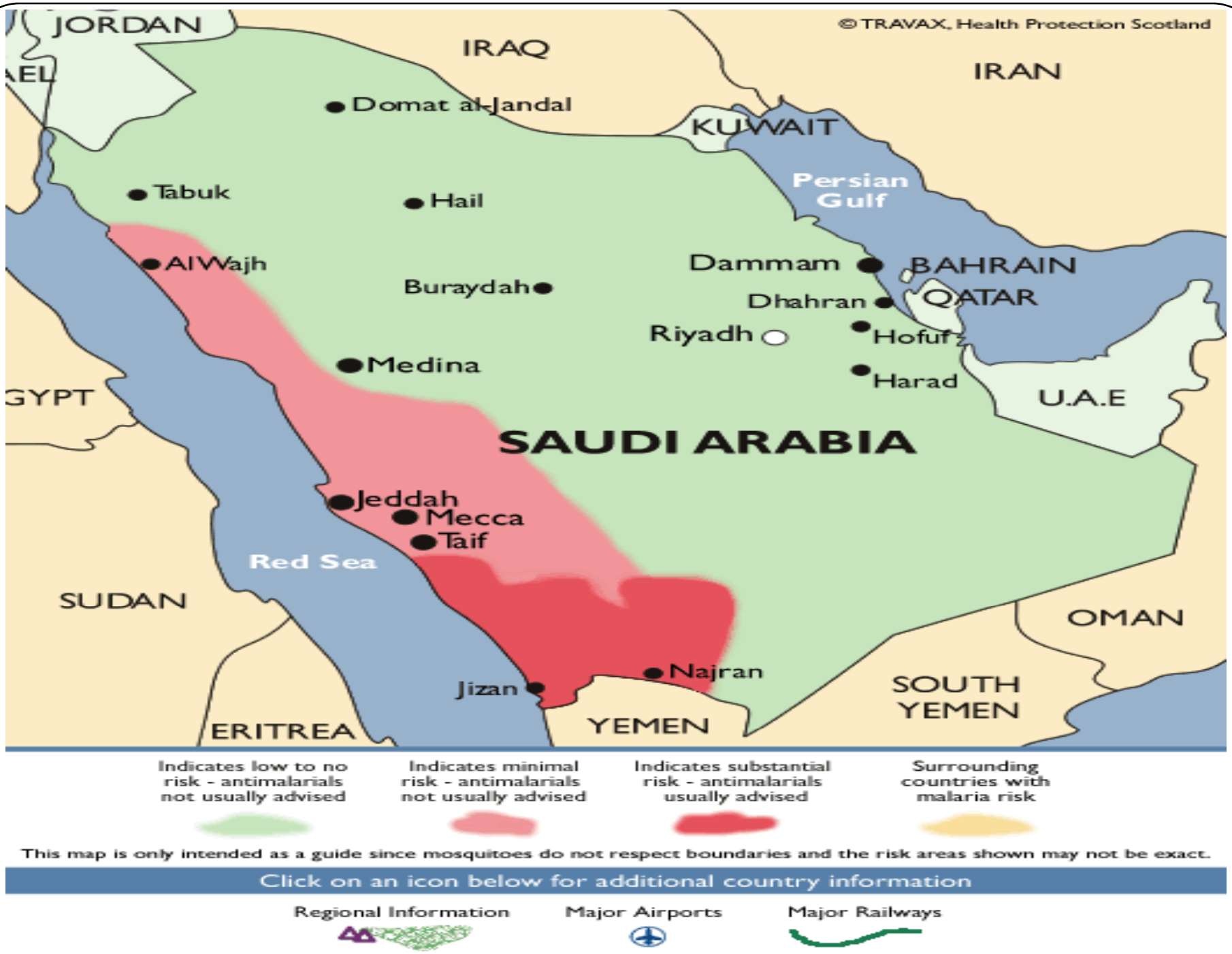
MALARIA

- Major killer diseases of the world
- Loss of life especially in children < 5 years age
- Endemic disease of tropical & sub tropical regions (Southeast Asia, south America, Africa, Middle East)

Incidence

About 300-500 million clinical cases /year (90% in Africa)

Mortality rate= 3 million/year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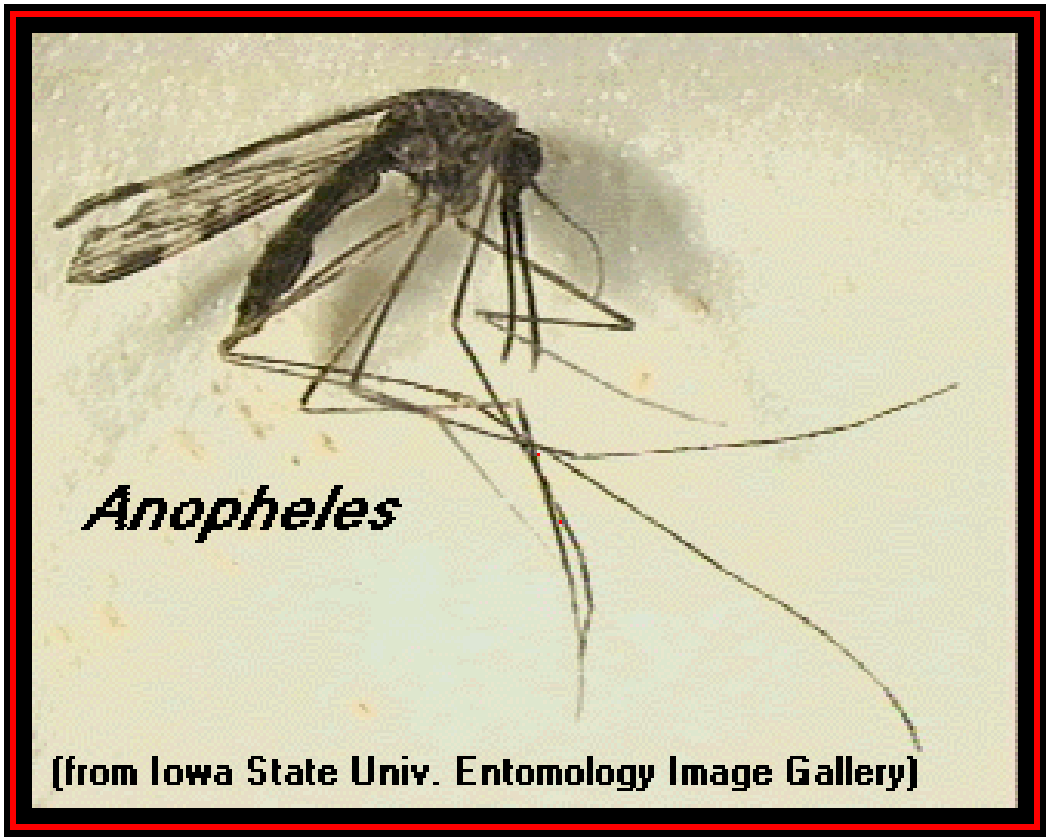
JORDAN
IRAQ
IRAN
Domat al-Jandal
KUWAIT
Persian Gulf
Tabuk
Hail
AlWajh
Dammam
BAHRAIN
Buraydah
Dhahran
QATAR
Riyadh
Hofuf
Medina
Harad
U.A.E
SAUDI ARABIA
Jeddah
Mecca
Taif
Red Sea
SUDAN
OMAN
Najran
Jizan
SOUTH YEMEN
YEMEN
ERITREA
Indicates low to no risk - antimalarials not usually advised
Indicates minimal risk - antimalarials not usually advised
Indicates substantial risk - antimalarials usually advised
Surrounding countries with malaria risk
This map is only intended as a guide since mosquitoes do not respect boundaries and the risk areas shown may not be exact.
Click on an icon below for additional country information
Regional Information
Major Airports
Major Railways

Vector (carrier) of Malaria



Cause

- Malaria is caused by protozoa (plasmodium)
- Spiking Fever occurs with chills

Species of Plasmodium

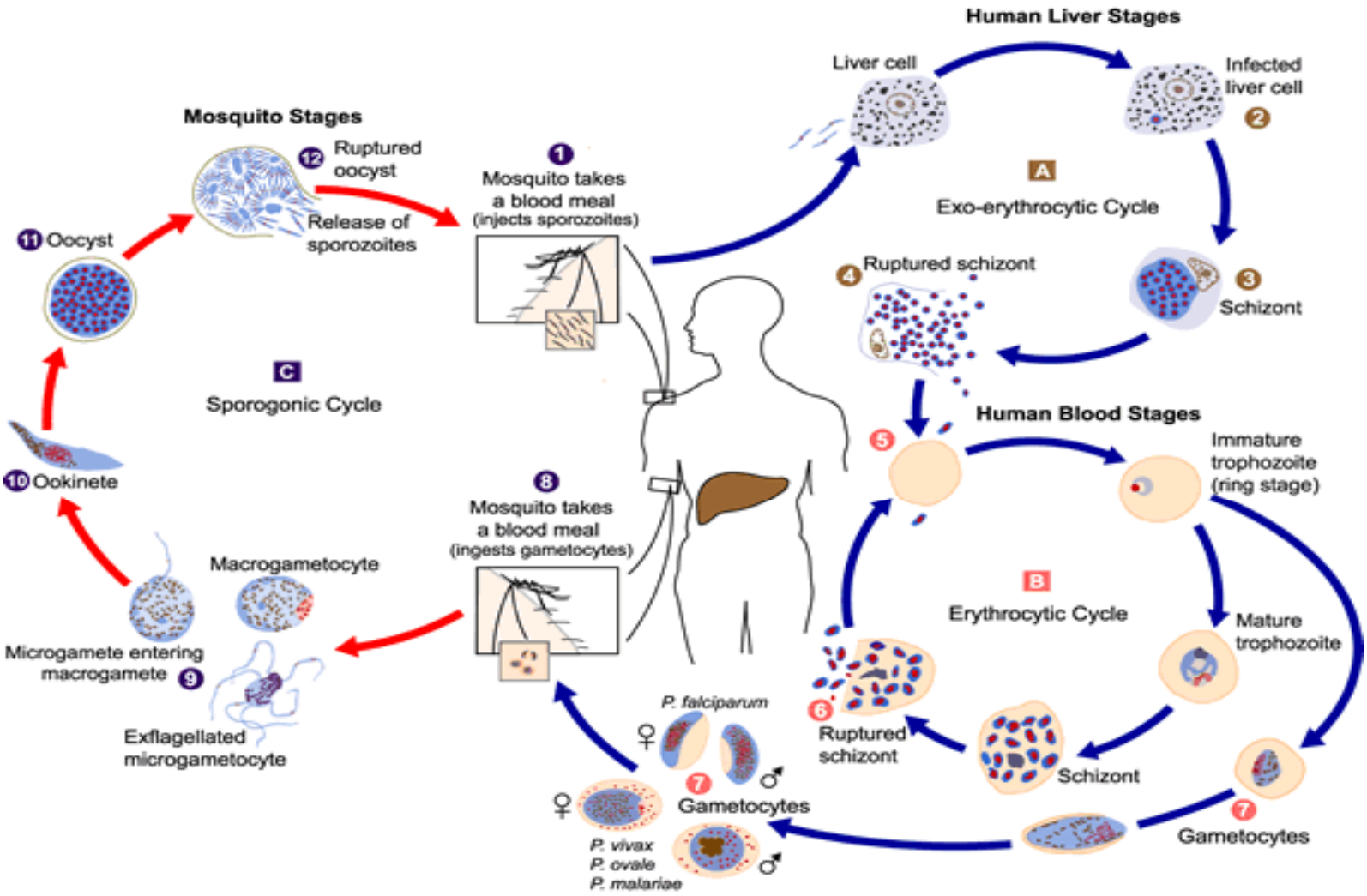
P. falciparum (periodic malaria; malignant; dangrous)

P. vivax (tertian malaria; mild, benign)

P. malariae (quartan)

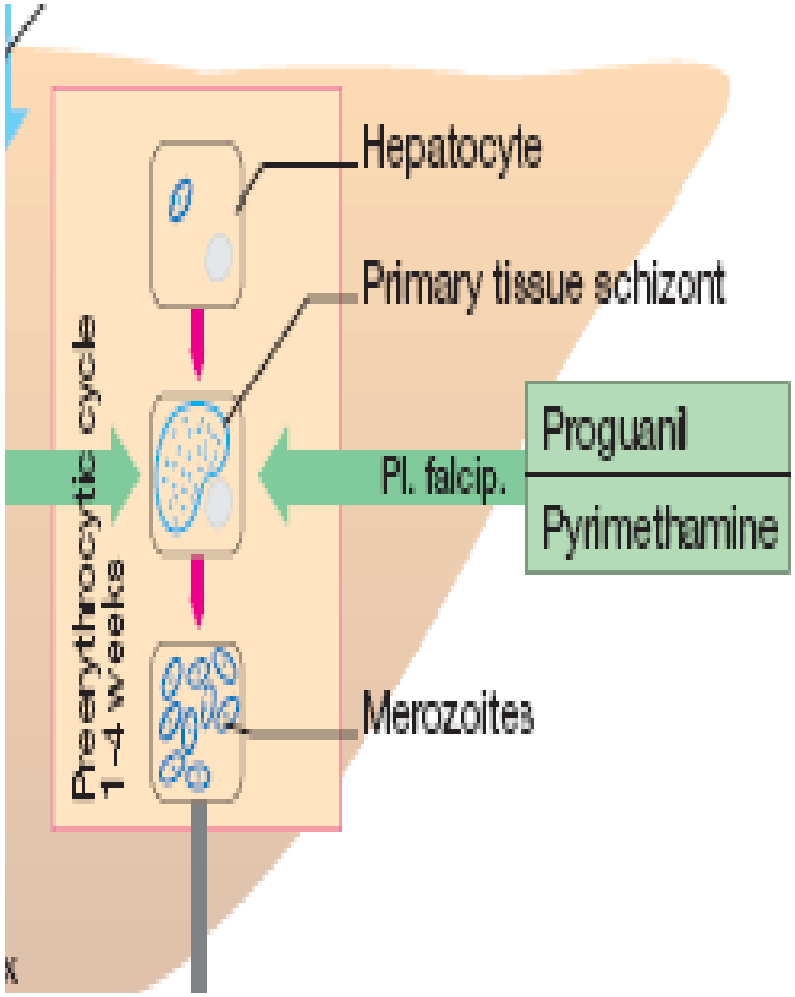
P. ovale (tertian malaria; rare)

LIFE CYCLE OF MALARIAL PARASITE



Classification of Antimalarials

- **Tissue schizonticides:-**
  .Drugs that eliminate dormant liver forms
- E.g., **Primaquine** (P.vivax, P. ovale)



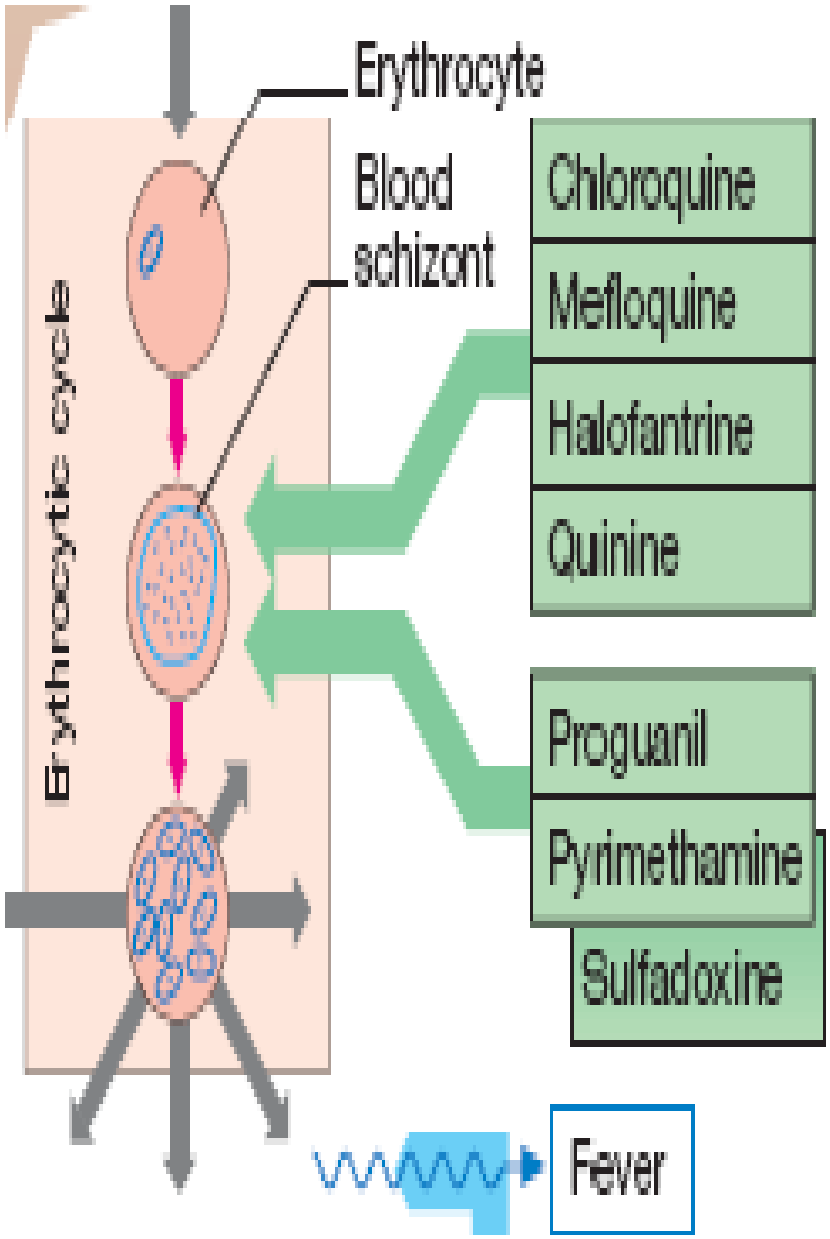
Blood schizonticides:-.

- Drugs acting on erythrocytic parasites also c/d **suppressive agents**

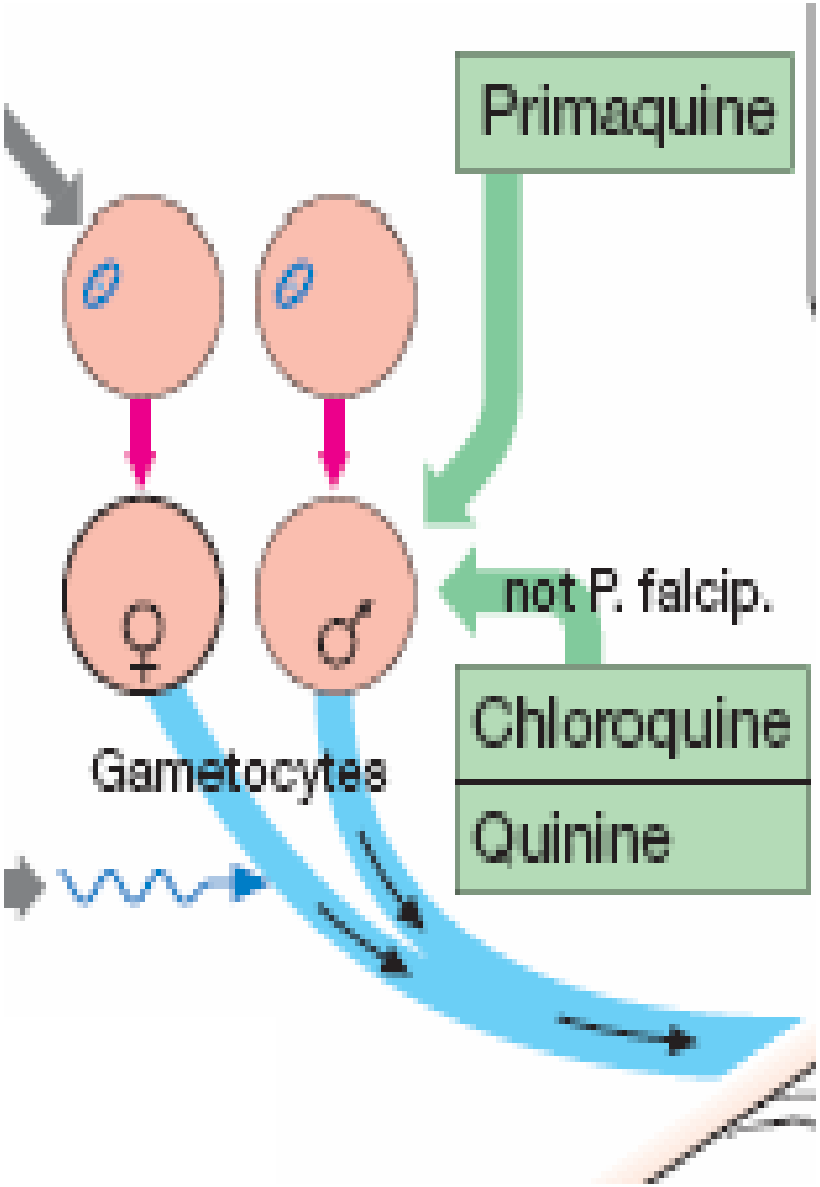
Two groups

i) **Rapid acting** (chloroquine, quinine, halofantrine)

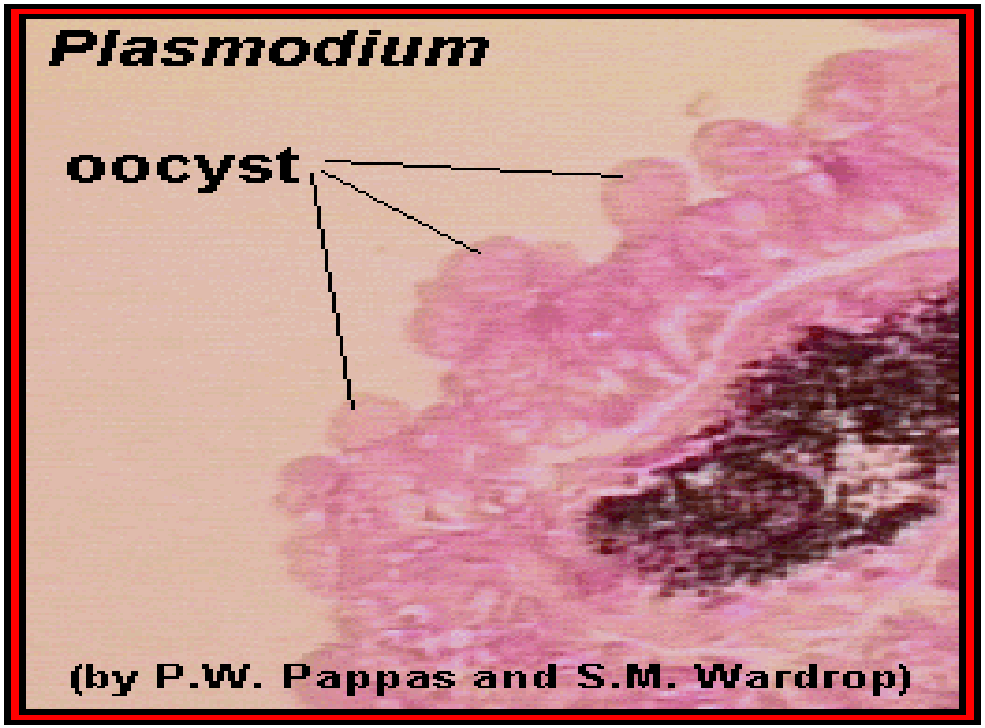
ii) **Slower acting** (folate inhibitors & antibiotics)



- Gametocides:- destroy the sexual forms of the parasite.
- Prevent transmission of malaria to mosquito

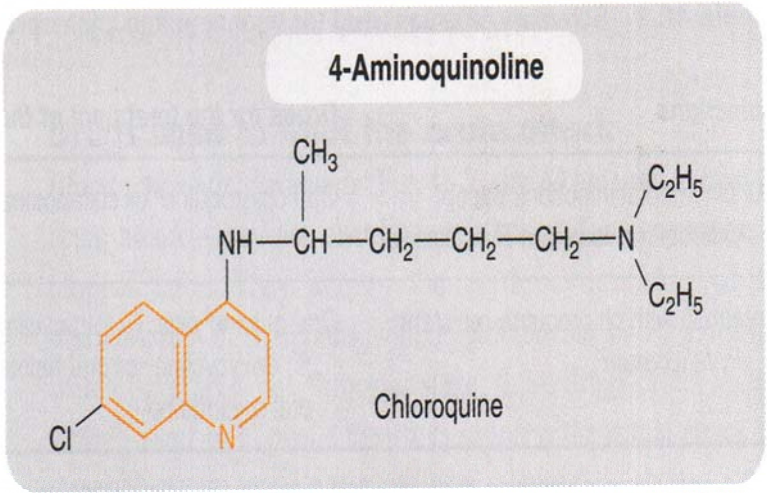


- Sprontocides:- interupt development of sporogonic phase in mosquitoes .



Chloroquine

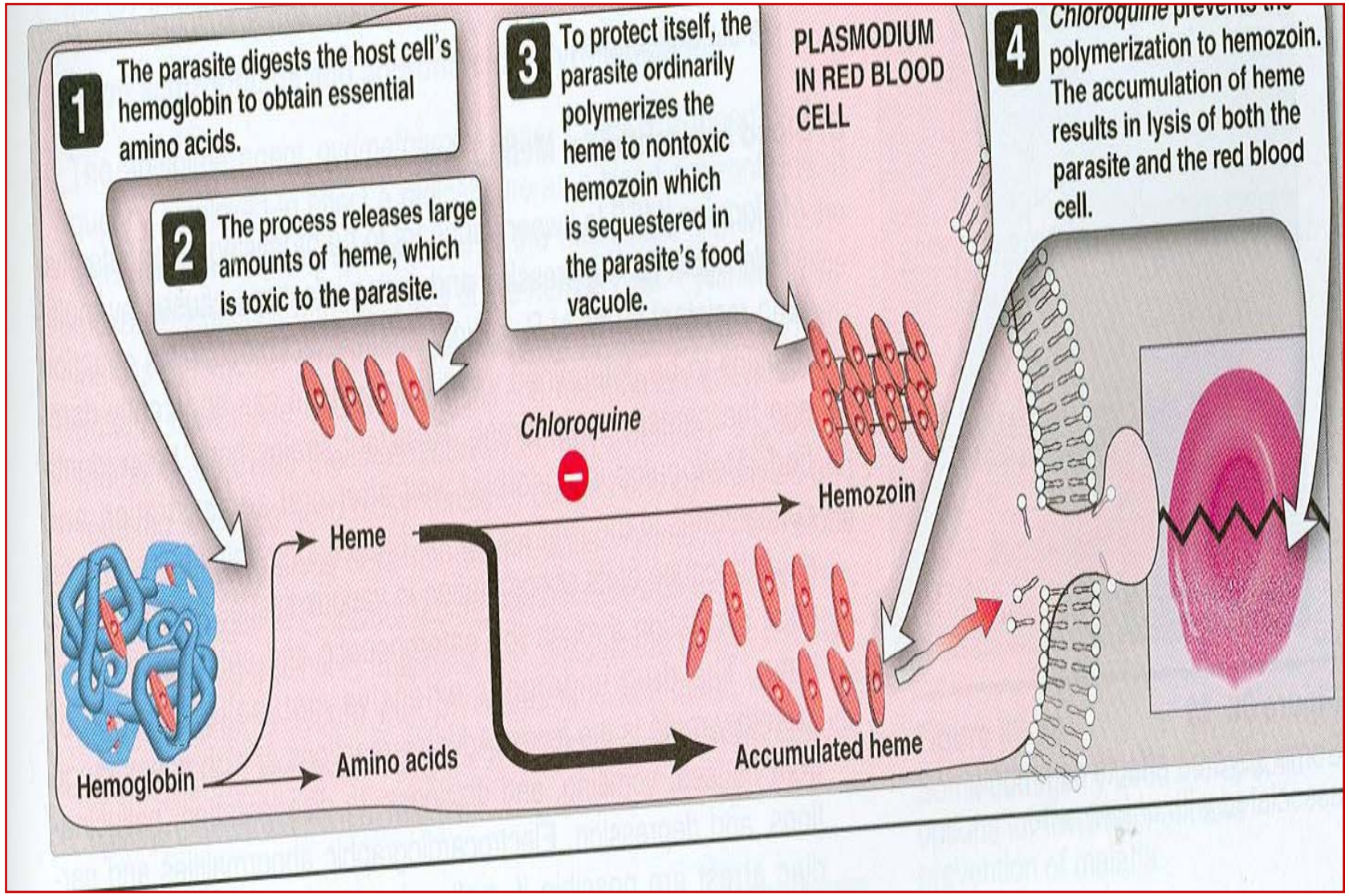
- Synthetic 4-aminoquinoline
- Rapidly & completely absorbed from GIT
- Rapid distribution to tissues
- Large Vd= 100-1000 L/kg
- Excreted in urine



Antimalarial Action

- Highly effective blood schizonticide
- Moderately effective against gametocytes of *P.vivax, P.ovale* & *P. malaria*
- Not effective for liver stage
- Drug of choice for treatment + chemoprophylaxis

Mechanism of Action of Chloroquine



Resistance

- Resistance to Chloroquine = very common among *P. falciparum*
- Uncommon (increasing) for *P. vivax*

Mechanism of resistance

Not clear; but mutation (genetic change) in structure of a chemical transporter of chloroquine into the malarial parasite is responsible for this resistance

Clinical Uses

A- Treatment

Chloroquine-Drug of choice for non falciparum & sensitive falciparum malaria

- Rapidly terminates fever (24-48 h)+ parasitemia (48-72 h)
- Still used in many areas (resistance) b/c of low price & safety

B-Chemoprophylaxis

- Chloroquine is preferred chemoprophylaxis agent in malarious regions without resistant falciparum malaria

- For eradication of *P. vivax & P. ovale* = **Primaquine** (course)

C- Amebic Liver Disease

- Chloroquine (liver ↑ conc.)+ Metronidazole = hepatic abscess

Adverse Effects

Common effects

- Pruritis, nausea, vomiting, abdominal pain, headache, anorexia, malaise, blurring of vision, urticaria
- Cont.

Rare adverse effects

- Hemolysis (G-6PD deficient person), impaired hearing, confusion, psychosis, seizures, agranulocytosis, dermatitis, alopecia, bleaching of hair, hypotension & ECG changes (QRS widening, T wave abnormalities)
- Ototoxicity, retinopathy, myopathy & peripheral neuropathy (long term use for rheumatologic disease)
- Severe hypotension, respiratory & cardiac arrest (large i.m or i.v injection)

Contraindication & Cautions

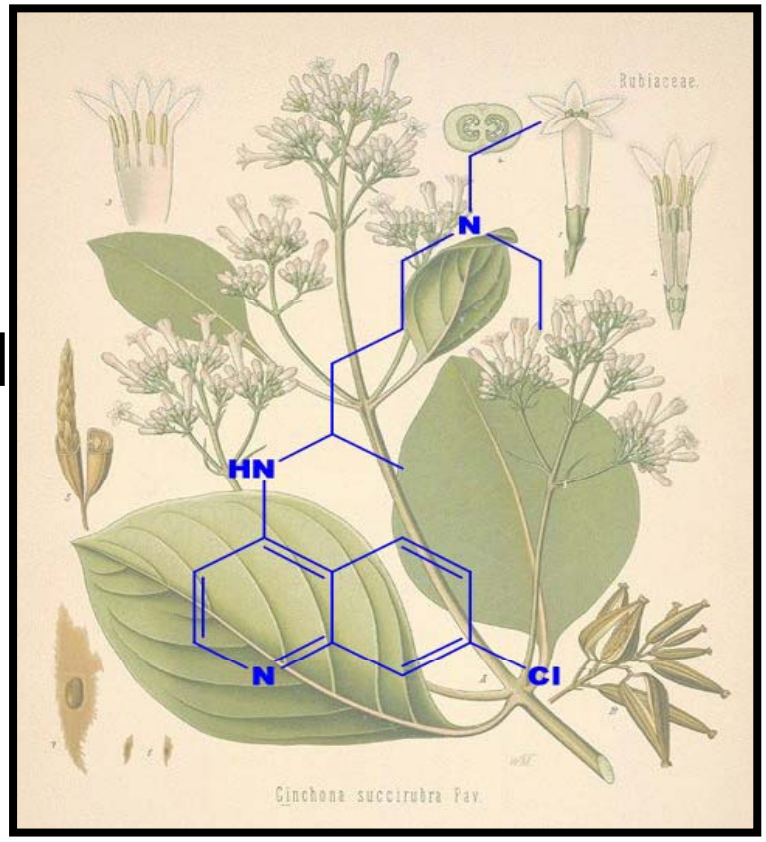
- Contraindicated in psoriasis or porphyria
- Not used in retinal or visual field abnormalities or myopathies
- Used with caution in a history of liver disease or neurologic or hematologic disorders
- Chloroquine not taken with antidiarrheal agent (Kaolin) + antacids (Mg or Ca) ⇒interfere absorption
- Chloroquine ----safe in pregnancy

Amodiaquine (4 aminoquinolone)

- Closely related to chloroquine
- Shares same MOA of chloroquine
- Used in many countries b/c of low cost, limited toxicity, effectiveness against chloroquine resistant strains of P. falciparum

Quinine & Quinidine

- First line therapy for Falciparum malaria with chloroquine resistance
- (especially) severe disease



Source

- Quinine (alkaloid) is derived from bark of cinchona tree

Quinidine

- Dextrorotatory stereoisomer of quinine

Pharmacokinetics

Quinine

- Rapidly absorbed after oral
- Reaches peak plasma level in 1-3 h
- Widely distributed; ↑ protein binding; ½ life = 18h

Quinidine

- Shorter half life than quinine
- Metabolized in liver
- Excreted in urine

Antimalarial action

Quinine = rapidly acting highly effective blood schizonticide against four species of human malaria parasites

- Gametocidal against *P.vivax* & *P.ovale* but not *P. falciparum*
- Not active against liver stage parasite
- MOA of quinine is unknown
- Resistance to quinine is very common

Clinical Uses

A. Parenteral treatment of severe Falciparum Malaria

- Quinine dihydrochloride or quinidine gluconate = treatment of choice for severe falciparum malaria

- Given as slow i.v or i.m $\Rightarrow$oral therapy

B. Oral treatment of Falciparum Malaria

- Quinine sulfate= first line therapy for uncomplicated falciparum malaria (with chloroquine resistance)
- Quinine is commonly used with second drug (doxycycline)

C. Babesiosis

Quinine + clindamycin = *Babesia microti* or other human babesial infections

Adverse Effects

Therapeutic doses (quinine & quinidine)

- Tinnitus, headache, nausea, dizziness, flushing & visual disturbances (Cinchonism), hypoglycemia

Prolonged therapy

- More marked visual & auditory problems, vomiting, diarrhea, abdominal pain, hypersensitivity reaction (skin rashes, urticaria, angioedema & bronchospasm), hemolysis, leukopenia, agranulocytosis, thrombocytopenia,
- Cont.

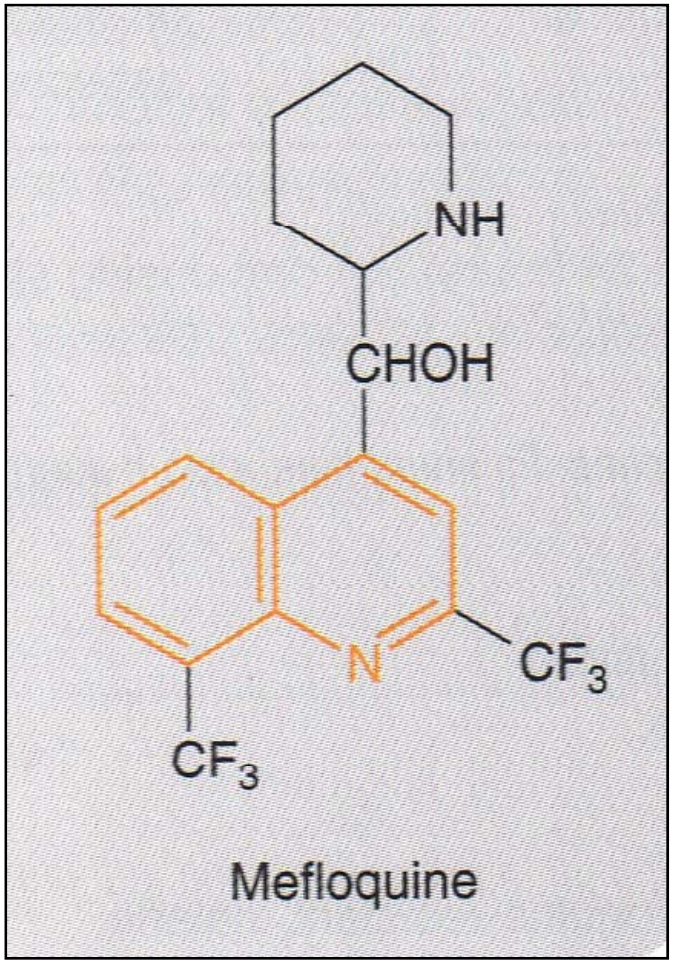
- Quinine can stimulate uterine contraction but mild (especially in 3rd trimester)
- Quinine & quinidine =drug of choice for severe falciparum malaria during pregnancy
- Rapid i.v. infusion= sever hypotension, ECG abnormalities
- Black water fever = rare severe illness (marked hemolysis & hemoglobinemia)

Contraindications & Cautions

- Quinine or quinidine is discontinued in severe cinchonism, hemolysis, hypersensitivity
- Avoided in underlying visual or auditory problems
- Used with caution in cardiac abnormalities
- Quinine should not be given with mefloquine
- Absorption blocked by Al-containing antacids
- Quinine can ↑ plasma level of warfarin & digoxin
- Dosage must be reduced in renal insufficiency

Mefloquine

- Blood schizontocide active against *P.vivax & P.falciparum,* but no effect on hepatic form of the parasite.
- Inhibits haem polymerase.
- Effective mainly as **prophylactic** agent for many chloroquine-resistant strains of *P. falciparum*
- Resistance has occurred in southeast Asia.



Mefloquine

- Given only orally (not parenteral b/c severe local irritation)
- Well absorbed, slow onset of action, t½=30d→ enterohepatic recycling or tissue storage.
- ADR:-GIT disturbances, transient CNS toxicity, confusion, dizziness, leukocytosis, thrombocytopenia & insomnia.
- May provoke neuropsychiatric disorder.
- Contra-indicated in pregnant women, epilepsy, psychiatric disorders, arrhythmia

Halofantrine

- Blood schizontocide
- Effective against all four human malarial species
- Rapidly effective against most chloroquine-resistant strains of *P. falciparum*

PK

Variable oral absorption; ↑ with food

½ life= 4d; excretion is in feces

MOA= unknown

- ADR:-abdominal pain, headache, transient ↑in hepatic enzymes, cough, pruritus, lengthening of Q-T interval & PR intervals
- May cause haemolytic anaemia & convulsions.
- Dangerous arrhythmia & some deaths (rare)
- **Contraindicated** with mefloquine.
- Patients with cardiac conduction defects.
- In pregnancy → embryotoxic in animals

Artemisinin

- Derived from the herb qing haosu [Artemisia].
- Artemisinin is poorly soluble in water & fast acting blood schizontocide.
- Effective in treating acute attack , including chloroquine –resistant & cerebral malaria.

Artemesia annua

Artemisinin Derivatives

i) Artesunate

- A water- soluble derivative, iv, im & oral

ii) Artemether & artether

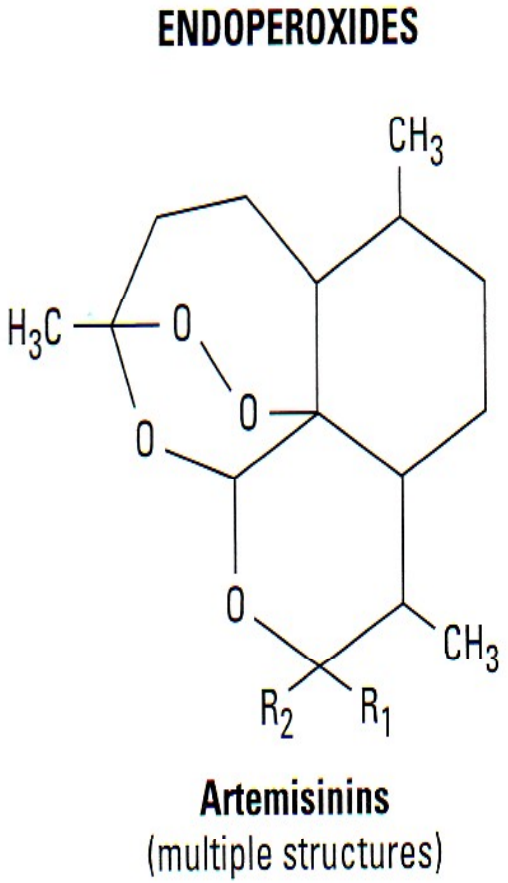
- [synthetic analogues, lipid soluble] have higher activity & are better absorbed.

MOA

- Damages the parasite membrane by carbon-centered free radicals.

PK= Rapidly absorbed , widely distributed,

- Converted in the liver to the active metabolite dihydroartemisinin.
- t½ of artemisinin 4h,artesunate=45min, artemether 4-11h.
- **ADR:-** transient heart block, ↓neutrophil count, brief episodes of fever.
- Neurotoxic in animal , no reported resistance against P.falciparum



- Artesunate & artemether= important in multidrug – resistant P. falciparum malaria
- Efficacy is limited by short plasma half lives
- Not used in prophylaxis

Slower acting blood Schizonticides

A) Inhibitors of folate synthesis (antifolates)

- E.g., Sulphonamides, sulphones, Pyrimethamine, proguanil

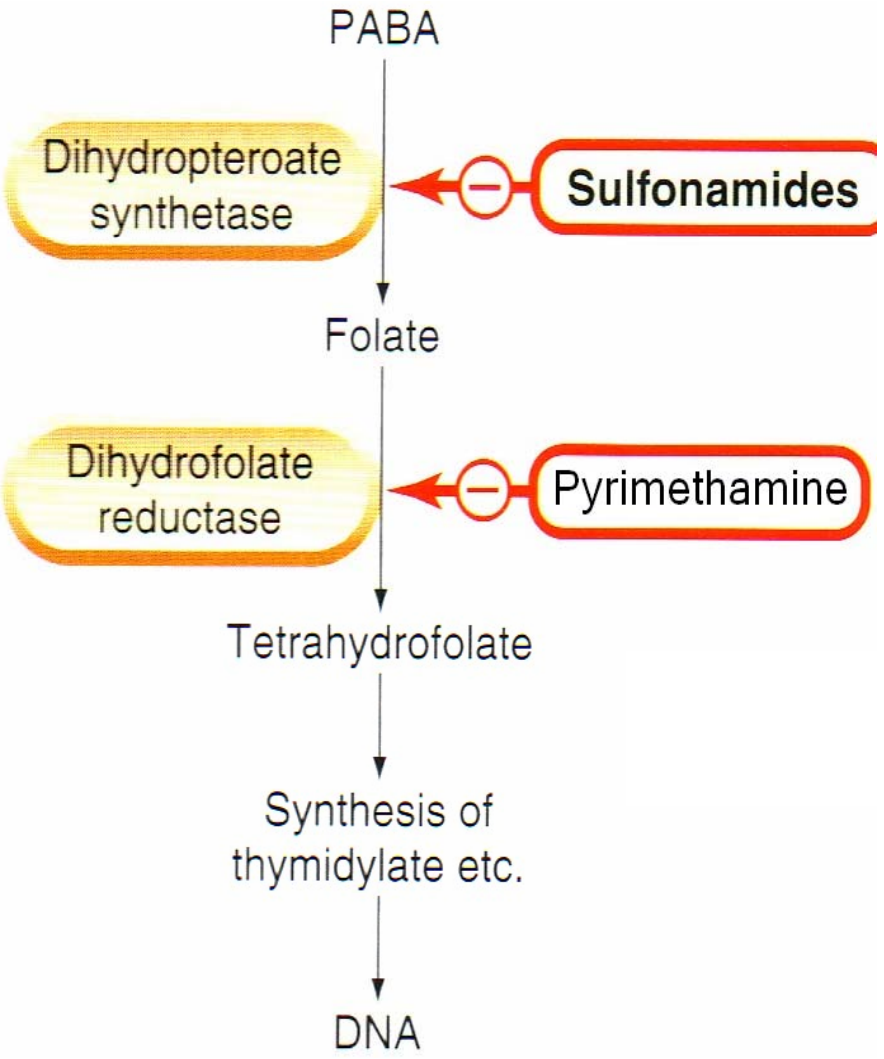
B) Antibiotics

- Tetracyclines, clindamycin

A) Antifolates

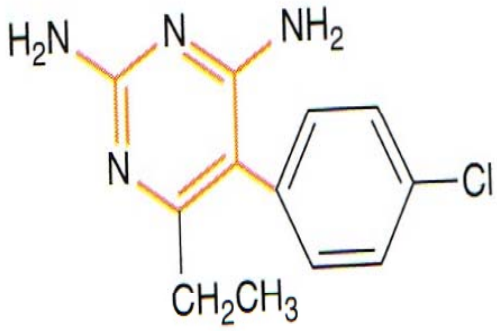
- **Type 1** antifolates sulphonamides & sulphones , competes with PABA.

- **Type 2** ,pyrimethamine & proguanil→↓ dihydrofolate reductase.

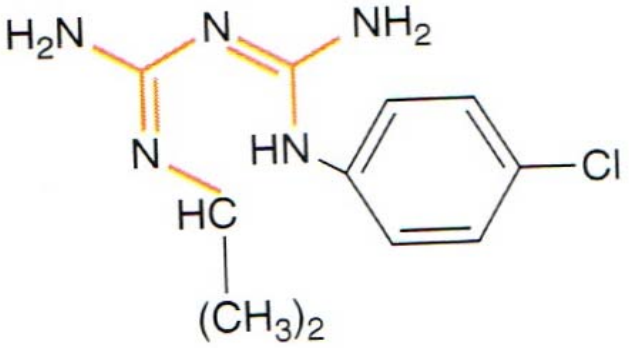


Pyrimethamine & Proguanil

- Have slow action against the erythrocytic forms of the parasite (all four).
- **Proguanil** has activity for hepatic form
- **Pyrimethamine** is used in combination with either dapsone or sulfadoxine.



Pyrimethamine



Proguanil

Pharmacokinetics

- Pyrimethamine -sulfodoxine (Fansidar) is used for chloroquine –resistant malaria.
- Pyrimethamine & proguanil are absorbed orally slowly.
- t½ of pyrimethamine =4d, proguanil=16h.
- Proguanil is metabolized to an active metabolite , cycloguanil which is excreted in urine.

Clinical Uses

A-Chemoprophylaxis

- Combination of chloroquine + proguanil

B-Treatment of chloroquine resistant falciparum malaria

Fansidar (sulfadoxine+pyrimethamine)

C-Probable treatment of Malaria in travelers

D- Toxoplasmosis

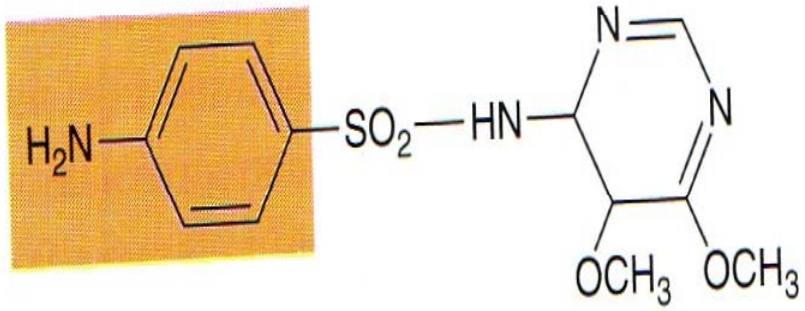
Pyrimethamine + sulfadiazine

Adverse effects

- GIT symptoms, skin rashes & itching----rare
- Proguanil= mouth ulcers & alopecia
- Large doses of pyrimethamine-dapsone combination causes haemolytic anaemia, agranulocytosis.
- In high doses pyrimethamine ↓ mammalian dihydrofolate reductase → megaloblastic anaemia
- Use of folate antagonist =cautious in renal or hepatic dysfunction
- **Proguanil**= safe in pregnancy (with folate supplementation)

Sulfonamides & sulfones

- Weakly active against erythrocytic schizonts but not against liver stages or gametocytes
- Not used alone but are effective in combination with other agents



Sulfadoxine

B) Antibiotics

- **Tetracyclines, clindamycin, azithromycin**
- None of antibiotic should be used as single agents for the treatment of malaria b/c their action is much slower than action of standard antimalarials
- Active (slow) against erythrocytic schizonts
- Not active against liver stage

Tetracyclines

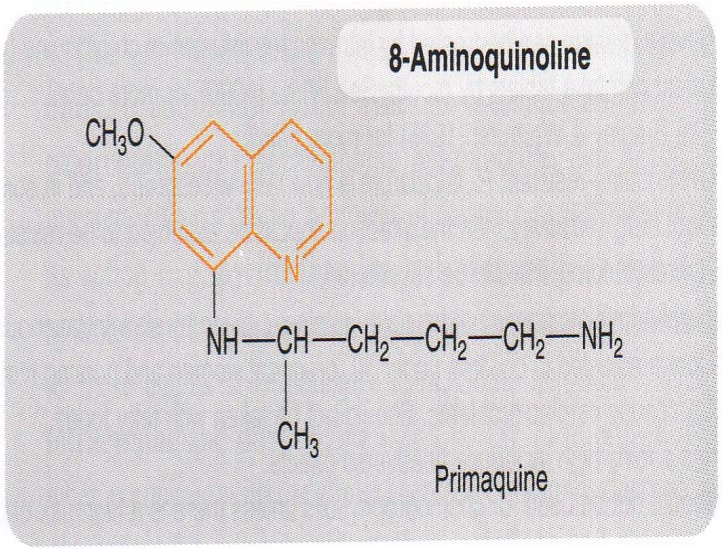
- Doxycycline + quinidine or quinine = falciparum malaria
- Standard chemoprophylactic agent

Clindamycin

- Used in combination with quinine or quinidine
- Used for children & pregnant women

Primaquine

- Active against liver hypnozoites, produces radical cure for parasites which have dormant stage in the liver [P.ovale &P.vivax].
- Has gametocytcide action , most effective for preventing transmission of the disease.
- Combined with chloroquine, mechanism unknown, resistance rare.



PK

- Given orally, rapidly metabolized to etaquine & tafenoquine which are more active & slowly metabolized, t½=3-6h

Clinical Uses

- For radical cure of acute vivax and oval malaria":- chloroquine is given to eradicate erythrocytic forms and then primaquine(30mg daily for 14 days) to eradicate liver hypnozoites
- Chemoprophylaxis of malaria

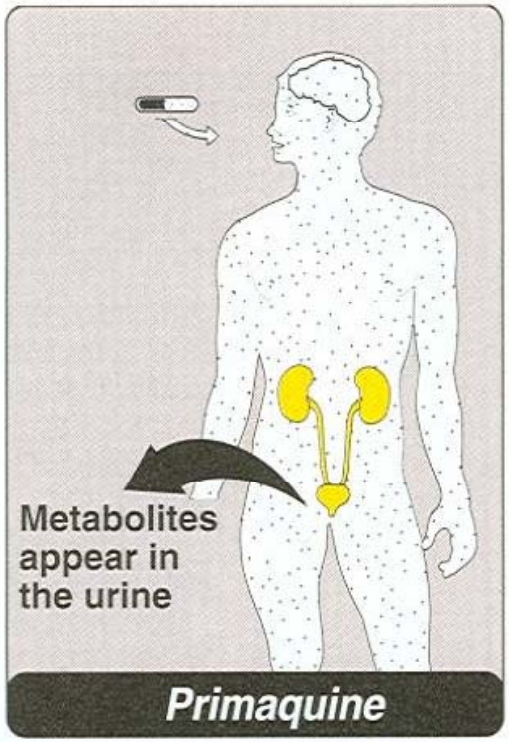


Figure 36.8
Administration and fate of *primaquine*.

Adverse Effects

Infrequent

- Nausea, epigastric pain, abdominal cramps, headache

Rare but serious

- Leukopenia, agranulocytosis, leukocytosis & cardiac arrhythmias, hemolysis (G6PD deficiency)

Contraindications & Cautions

- Avoided in granulocytopenia or methemoglobinemia
- Never given parenterally b/c it may cause hypotension
- Patients should be tested for G6PD deficiency (b/c of risk of hemolysis)
- Avoided in pregnancy

Prophylaxis

Travelers to areas endemic for chloroquine-susceptible disease	Chloroquine
Travelers to areas endemic for chloroquine-resistant disease	Mefloquine

Q1

- What is the best choice of drug therapy?