Agents antiparasitaires

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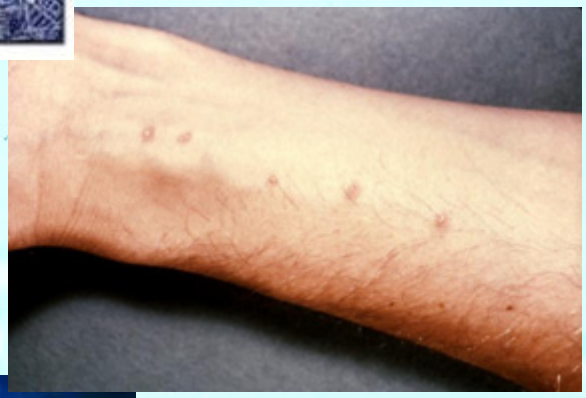
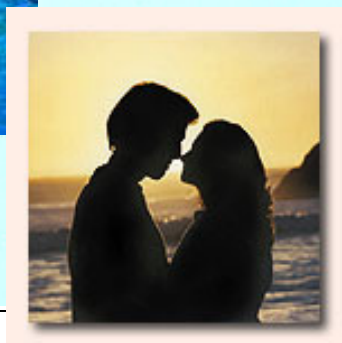
Ces diapositives sont reprises en partie de documents des Prof. I. Lambev (Université de Sofia, Bulgarie) et K. Larson (Southern Methodist University, Dallas, TX)

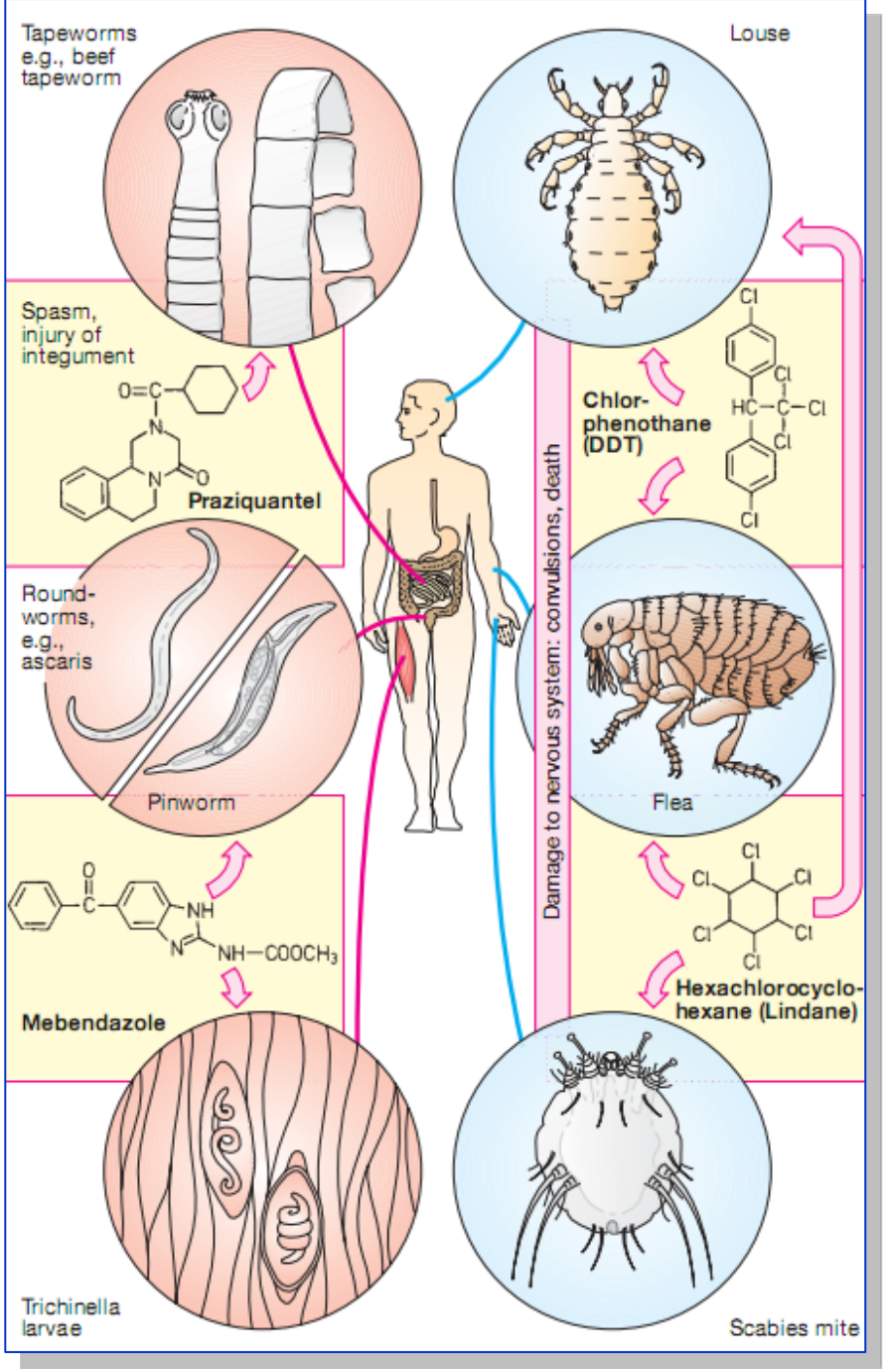
Modes of Transmission of parasitic diseases

- Four main mechanisms for parasitic transfer:
  - Ingestion of eggs from the fecal material of an infected individual
    - Ascaris lumbricoides
  - The larva of the parasite can burrow into the skin of a person
    - Schistosomes
  - The larva of the parasite can move from person to person through an insect vector
    - Trypanosomes
    - Plasmodia
  - Sexual transmission
    - Trichomonas vaginalis

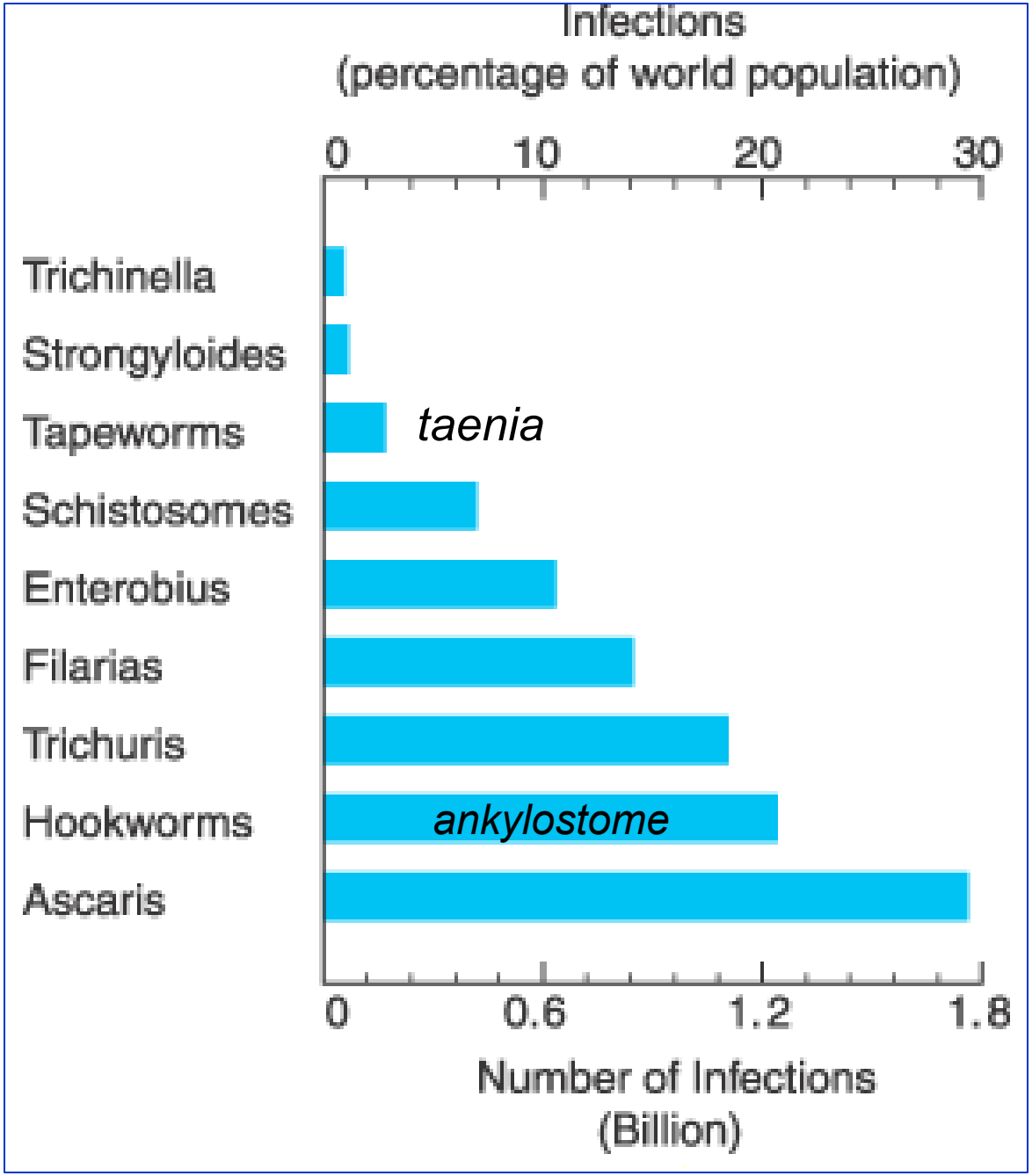




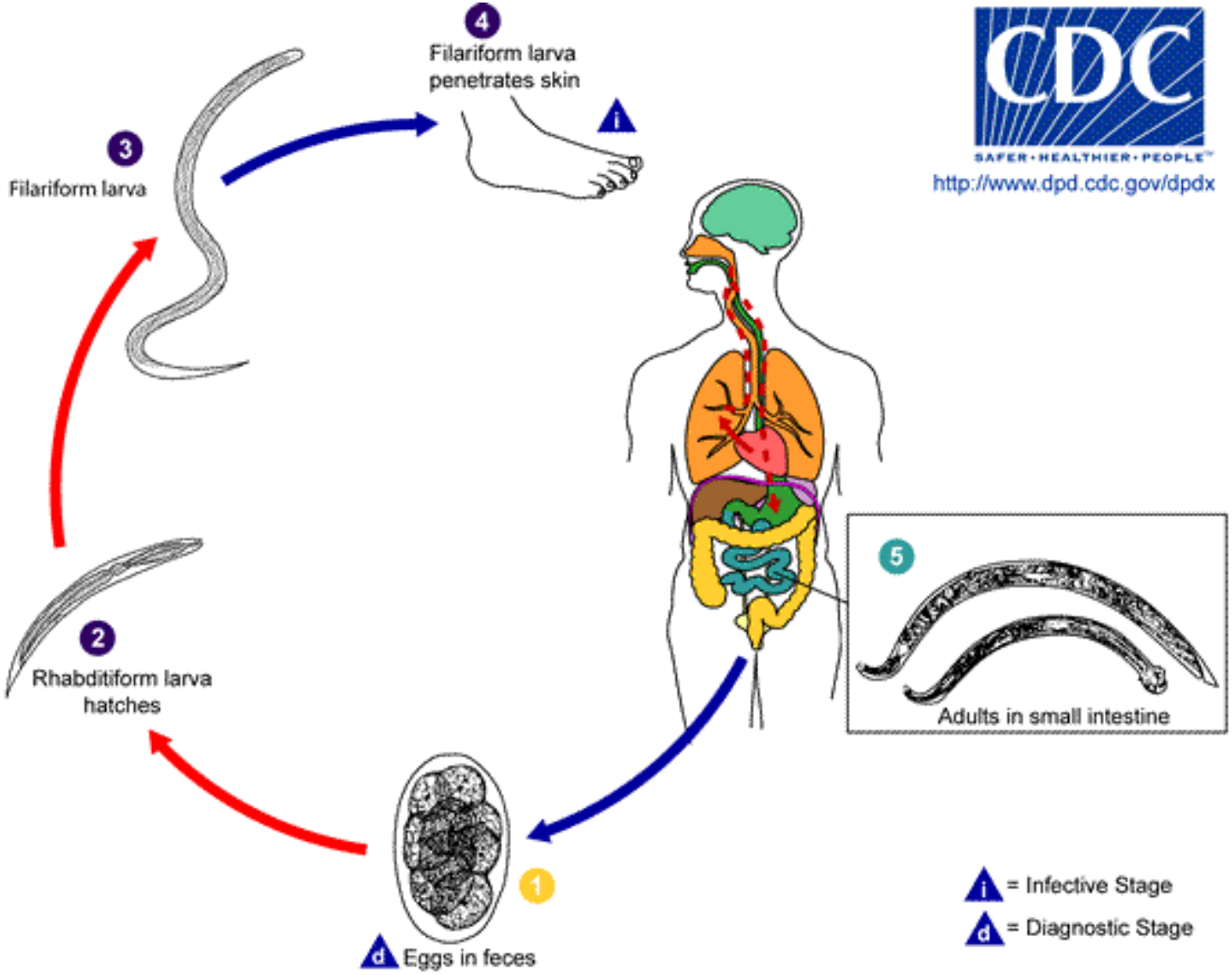
Antihelmintic drugs



Relative incidence of helminth infections worldwide



Ankylostome (hookworm)



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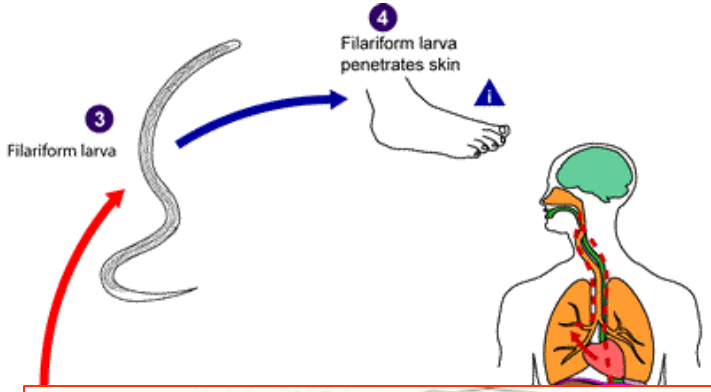

CDC
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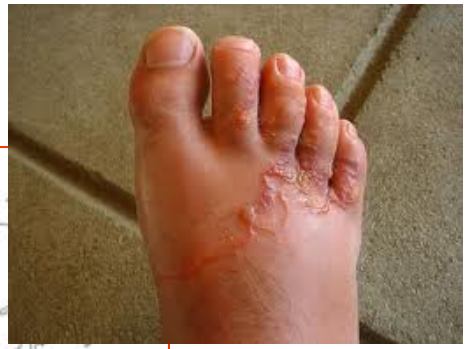
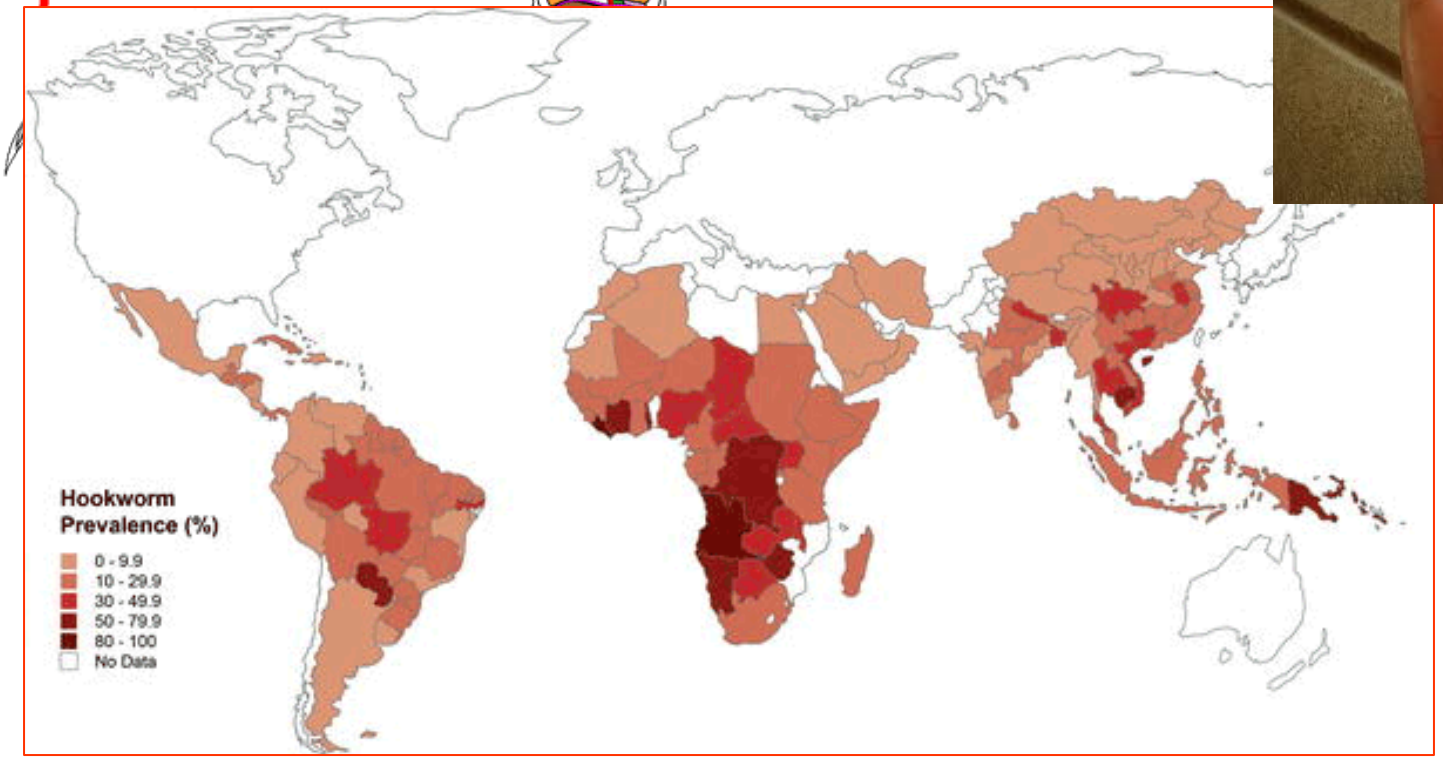
http://www.dpd.cdc.gov/dpdx





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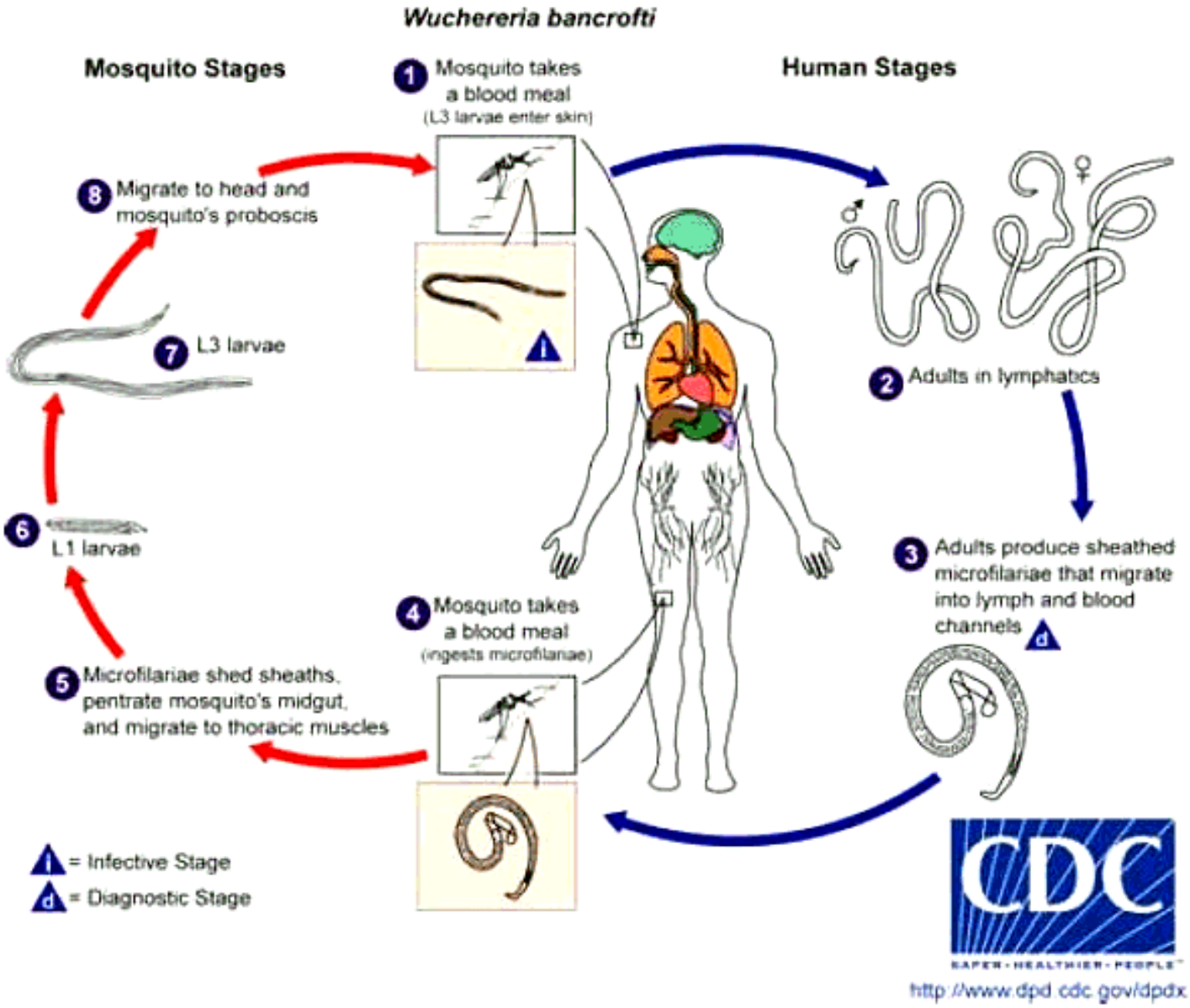

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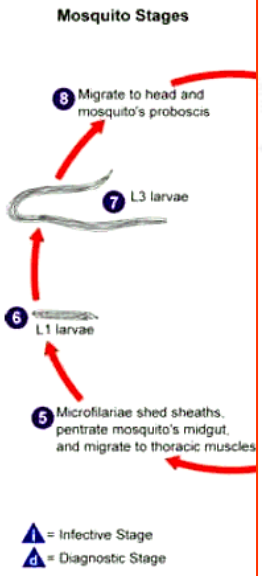
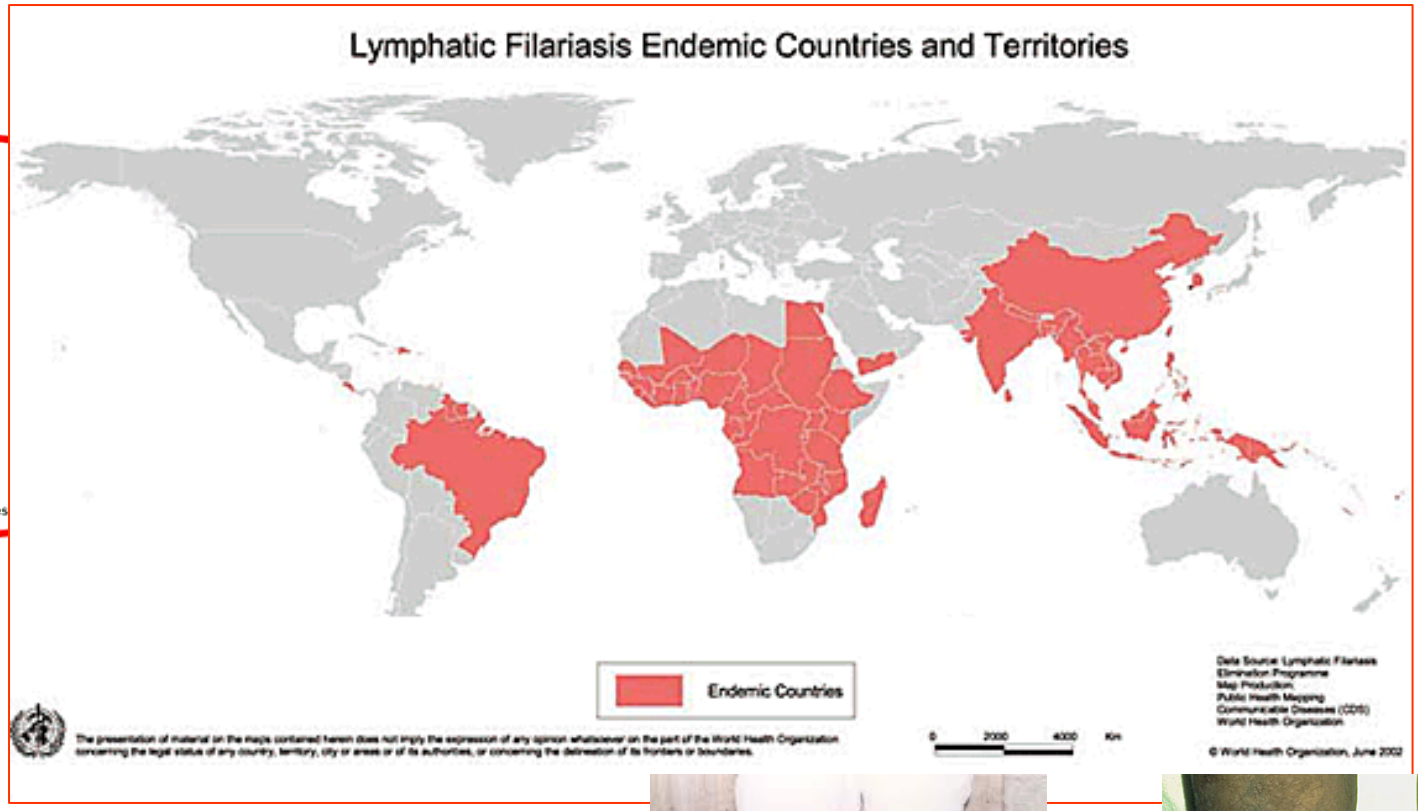
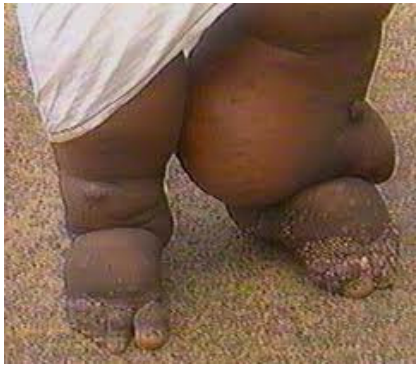
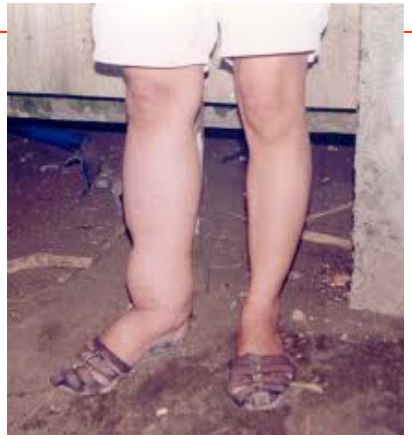
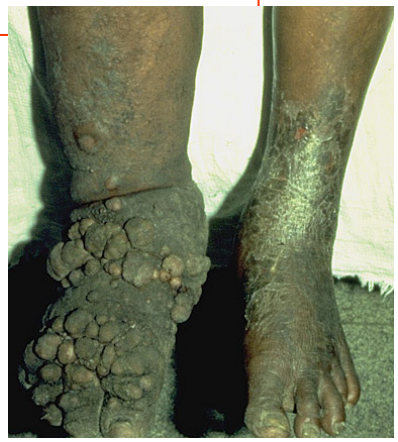


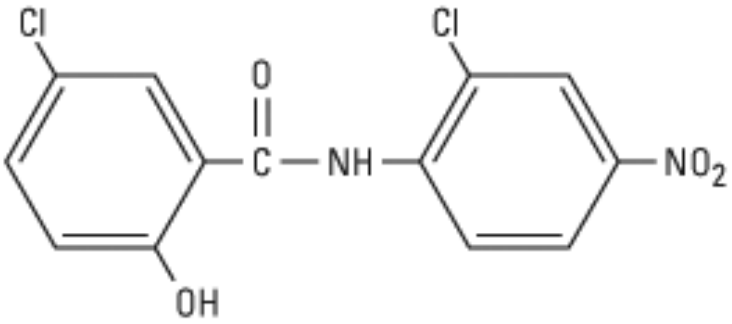




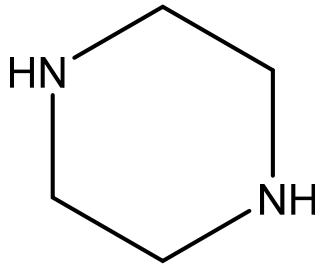




Antihelmintic drugs: niclosamide et pipérazine



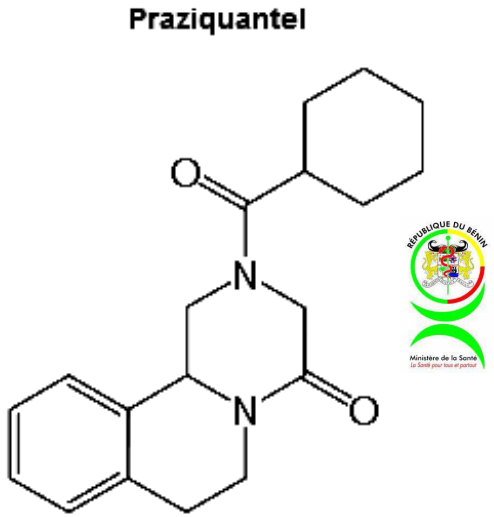
Niclosamide



piperazine

- **Niclosamide** *blocks glucose uptake* by intestinal tapeworms. It may cause some mild GI symptoms.
- **Piperazine** paralyses the helminth because of agonist effect on the GABA receptor (local activity [intestine of the host] and differences in isoforms). May cause hypersensitivity reactions, *neurological symptoms* (including "worm wobble") and may precipitate epilepsy.

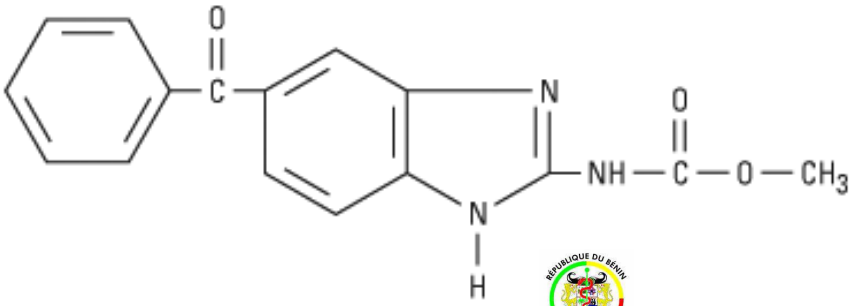
Antihelmintic and antischistosoma drugs: praziquantel



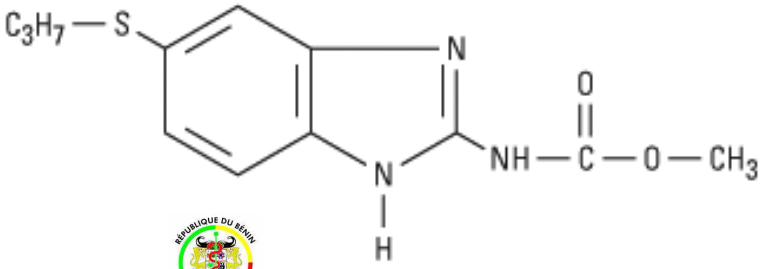
Praziquantel

- paralyses both adult worms and larvae by increasing Ca^{++} membrane permeabiliy
- paralyzed helmints are digested...
- cures with a single dose (or divided doses in one day)
- oral administration but first pass effect (loss)
- may cause nausea, headache, dizziness, and drowsiness

Antihelmintic drugs: bendazoles



Mebendazole



Albendazole

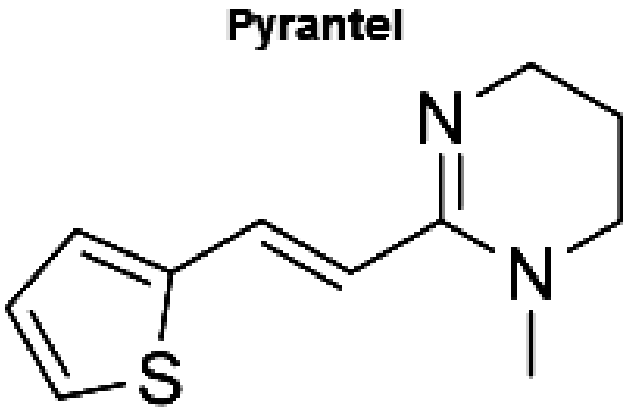
Mebendazole

- selectively inhibits the synthesis of microtubules in the intestinal cells of parasitic worms, thereby *blocking glucose uptake* by nematodes.
- causes mild GI disturbances, nut otherwise non-toxic
- should not be used in pregnancy (embryotoxic and teratogenic) or in children under the age of 2

Flubendazole is mebendazole with a F on position para of the benzene ring

Albendazole is similar to mebendazole and often used in conjunction with ivermectin In sub-Saharan Africa.

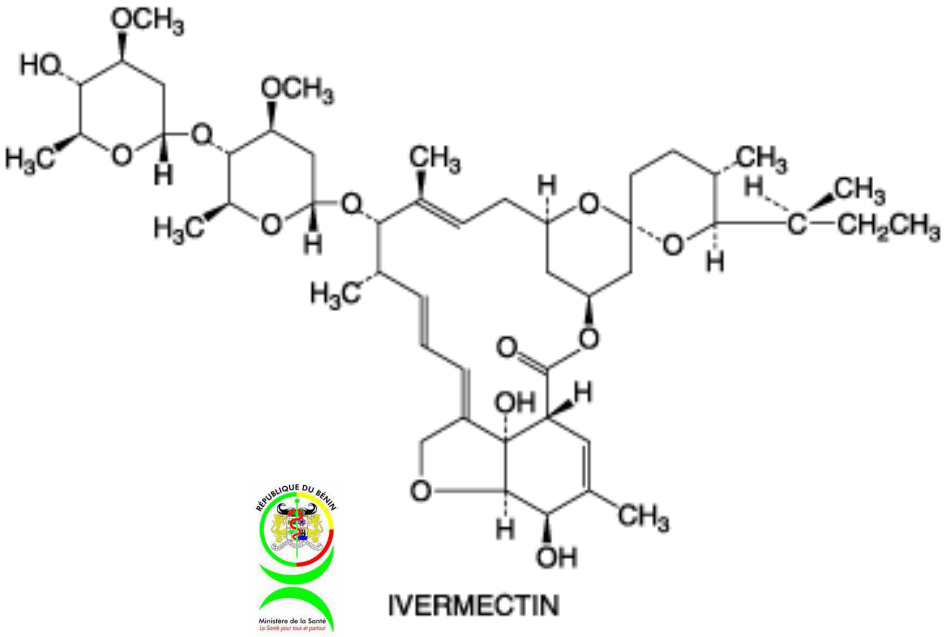
Anti-helmintic drugs: pyrantel



Pyrantel

- nicotinic receptor agonist, causing spastic muscle paralysis by ***depolarising neuromuscular junctions*** of susceptible nematodes which are then expelled in the faeces.
- cures with a single dose.
- may induce GI disturbance, headache, dizziness, drowsiness, and insomnia.

Anti-filariasis drug: ivermectin



- binds and activates glutamate-gated chloride channels (GluCls; invertebrate-specific members of the Cys-loop family of ligand-gated ion channels present in neurons and myocytes).
- active against onchocerciasis, but also strongyloidiasis, ascariasis, trichuriasis, filariasis, enterobiasis, and some epidermal parasitic skin diseases, including scabies (la gale)

- causes immediate reactions due to the death of the *microfilaria (early stage in the life cycle of certain parasitic nematodes)*.
- is toxic for the CNS of the host if passing accross the blood-brain-barrier (PgP deficiency; dogs)
- can be effective in a single dose, but it works best if repeated at 6–12-month intervals

Antimalarials

- Symptoms of malaria infection:
  - Fever, rigors, headaches, sweating, tiredness, myalgia (limbs and back), abdominal pain, diarrhea, lost of appetite, orthostatic hypotension, nausea, slight jaundice, cough, enlarged liver and spleen, vomiting

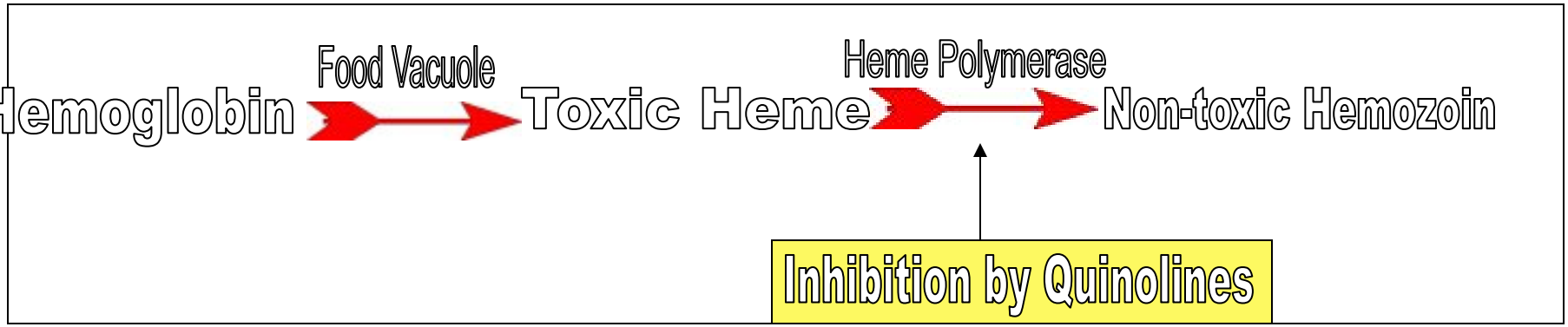
- Infections affect more than 200 million people and kill more than 3 million every year

- Drugs that are active against the four species of Plasmodia
  - Quinolines, artemisinin, mefloquine, halofantrine, pyrimethamine, proguanil, sulfonamides, tetracycline

Antimalarials: Quinolines

- Quinolines and related compounds: quinine, chloroquine, halofantrine, mefloquine, lumefantrine, amodiaquine, amodiaquine, pyronaridine, piperaquine, primaquine, tafenoquine

- Mechanism of action:
  - Quinolines concentrate in the food vacuole of the parasite, where human hemoglobin is digested, which releases heme
  - Heme by itself kills the parasite through oxidative damage to membranes, digestive proteases, and other critical biomolecules
  - To prevent this, the toxic heme is sequestered as an unreactive malarial pigment termed hemozoin to prevent toxic side effects
  - Quinolines sequester the heme so that it cannot be made unreactive, resulting in the death of the parasite



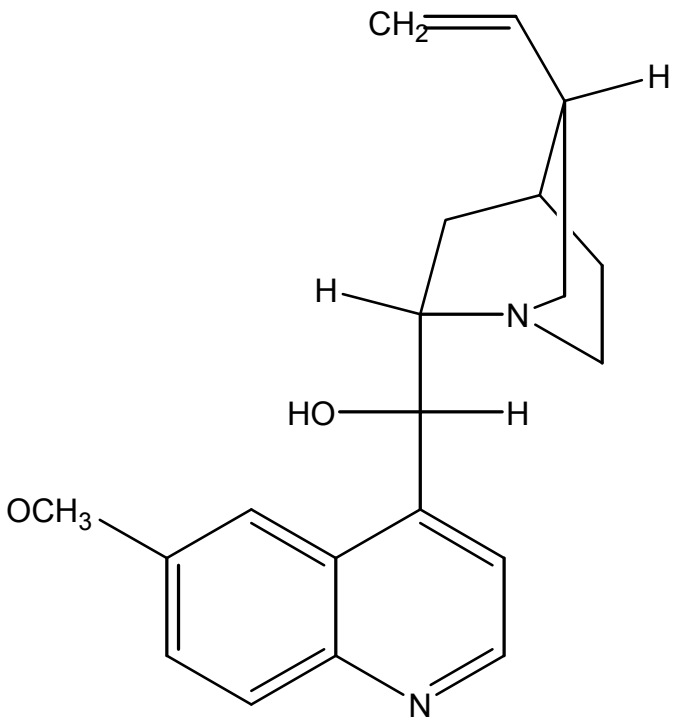
Antimalarials: History of the Quinolines

- The first quinoline that was used medicinally was quinine
  - The chief alkaloid of cinchona- powdered bark of the South American cinchona tree
  - Cinchona was used to treat fevers and shivers for over 350 years in South America
  - Jesuit monks took cinchona to Europe in the 1640s
  - Quinine isolated in 1820 by Pelletier and Caventou

- The Japanese capture of cinchona plantations early in WWII caused a shortage of quinine in the United States, resulting in a sudden surge of research dedicated to the discovery of synthetic antimalarials

Antimalarials: Quinine

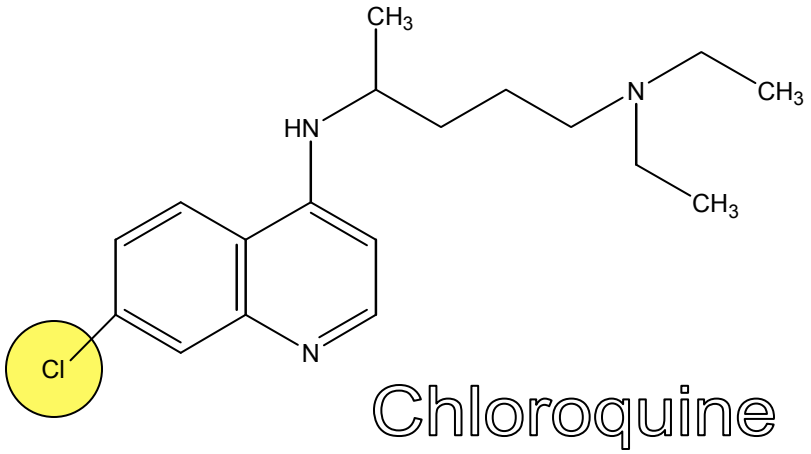
- Cinchona contains a mixture of more than 20 structurally related alkaloids—the most important are quinine and quinidine
- Quinine and quinidine differ only in the steric configuration at two of the three asymmetrical centers
- Hard to synthesize: still obtained from natural sources
- Quinidine is more toxic and more potent as an antimalarial than quinine



Quinine

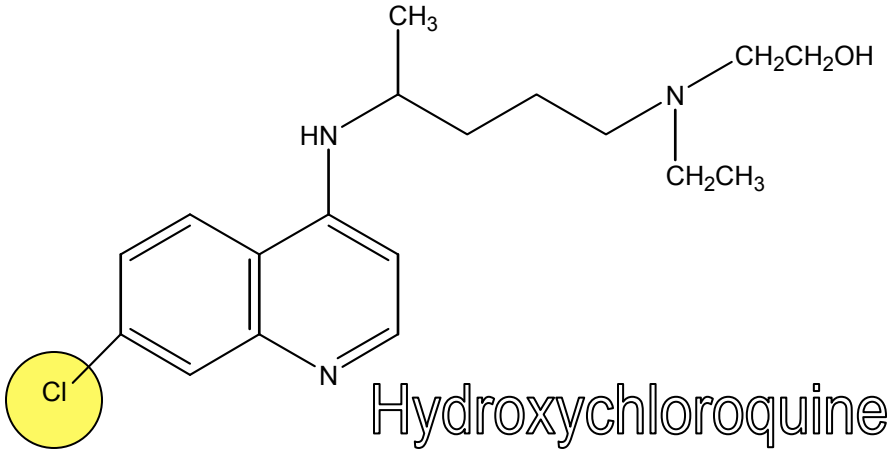
Antimalarials: Chloroquine and Hydroxychloroquine

- Chloroquine
  - The chlorine atom attached to position 7 of the quinoline ring confers the greatest antimalarial activity



Chloroquine

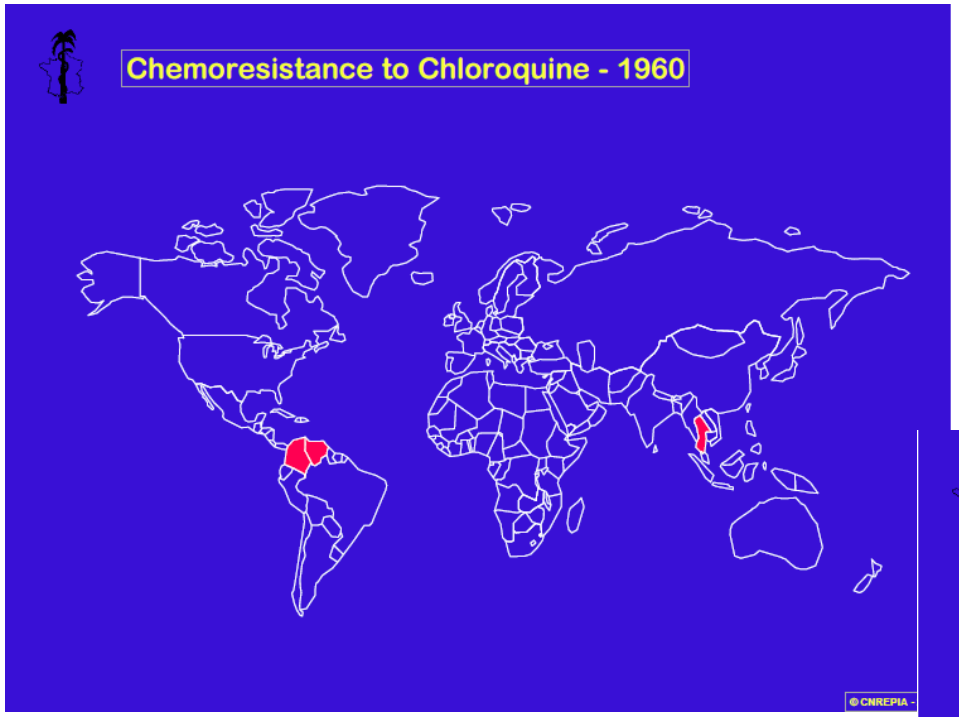
- Hydroxychloroquine
  - One of the *N*-ethyl substituents of chloroquine is beta-hydroxylated

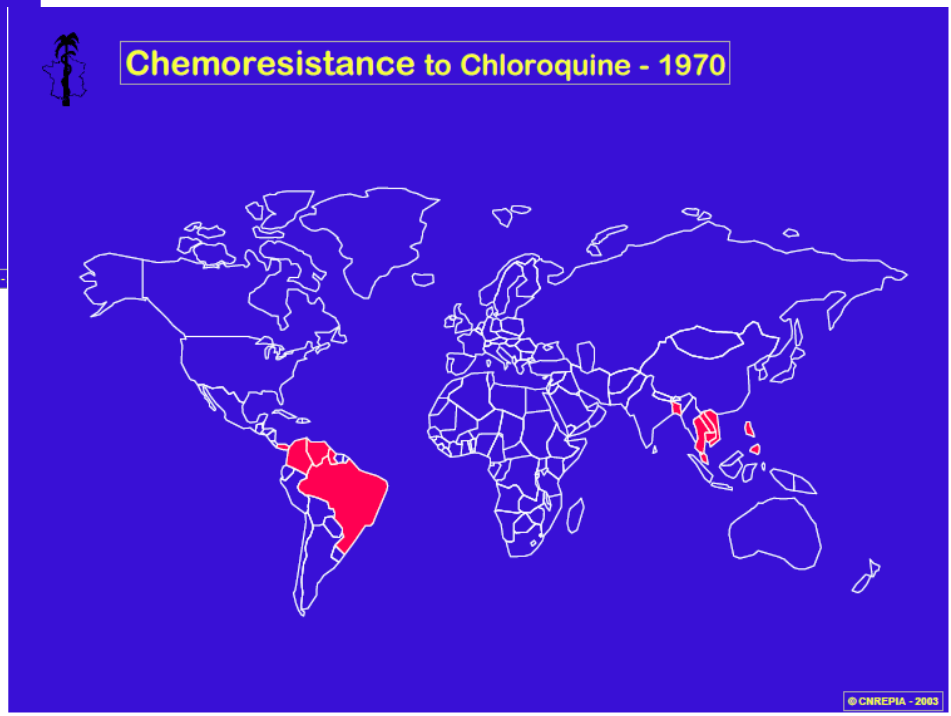


Hydroxychloroquine

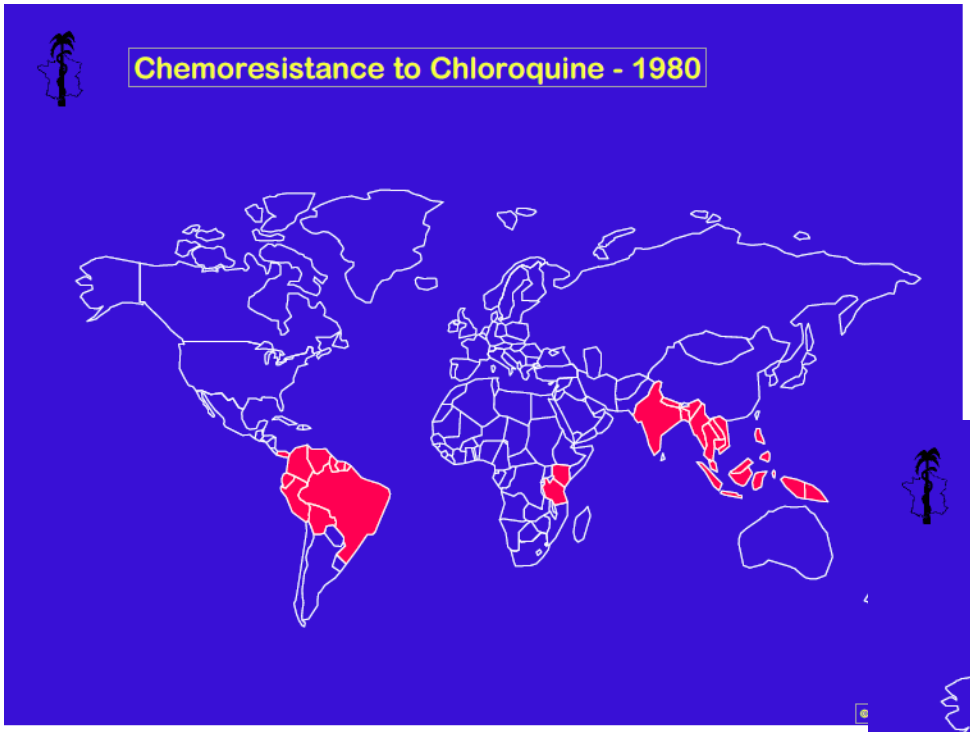
Résistance importante en Afrique

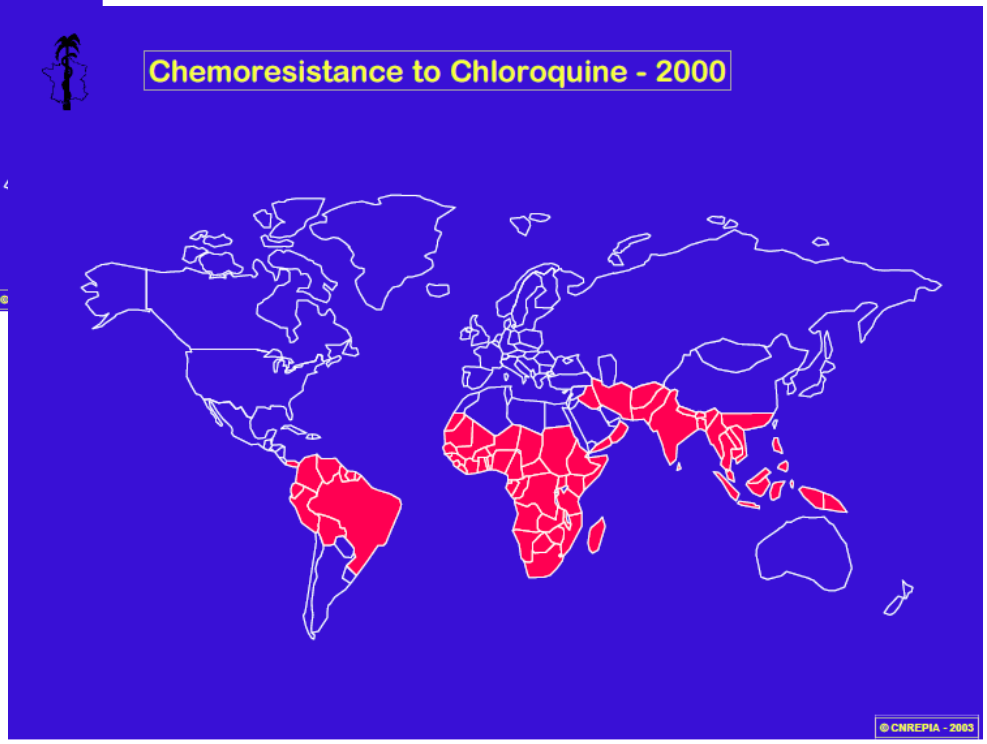
Resistance to chloroquine: 1960-1970





Resistance to chloroquine: 1980 - 2000



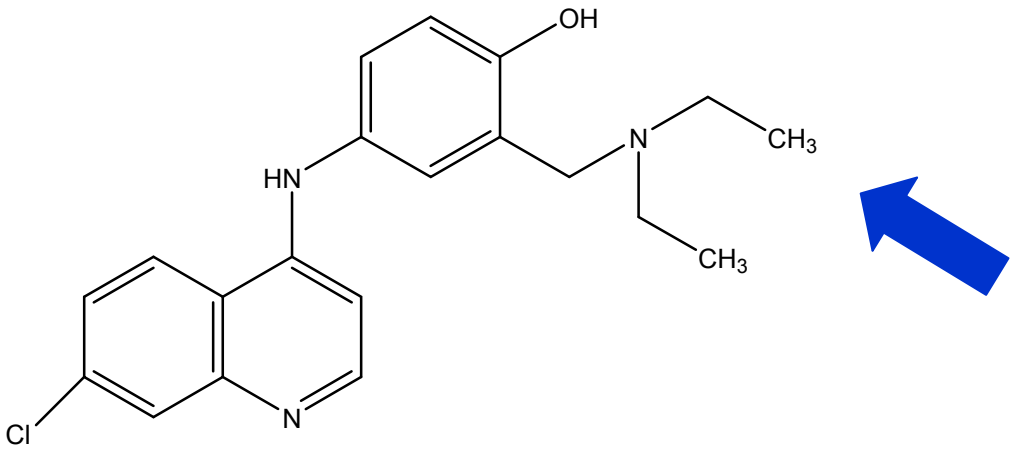


Antimalarials: Amodiaquine

- related to chloroquine but more effective against chloroquine-resistant *Plasmodium falciparum* malaria infections
- must be activated to N-desethylamodiaquine by the cytochrome p450 enzyme CYP2C8 to become active
- CYP2C8*2, *3 and *4 (about 4% of the African population) show a range of “poor metabolizer” phenotypes
  → lower treatment efficacy against malaria and increased toxicity.

Note: Amodiaquine is also a histamine N-methyltransferase inhibitor.

amodiaquine



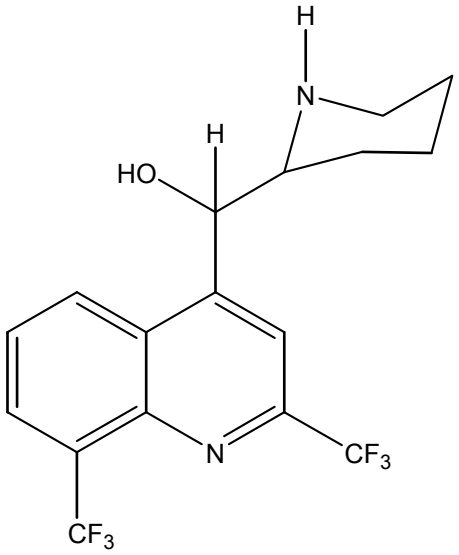
Antimalarials: Mefloquine and Halofantrine

- Mefloquine
  - A product of the Malaria Research Program established in 1963 by the Walter Reed Institute for Medical Research
  - Inhibits heme polymerization during hemoglobin digestion in the parasite food vacuole
  - Most effective for the treatment of **chloroquine-resistant falciparum** malaria with lw, transient CNS toxicity

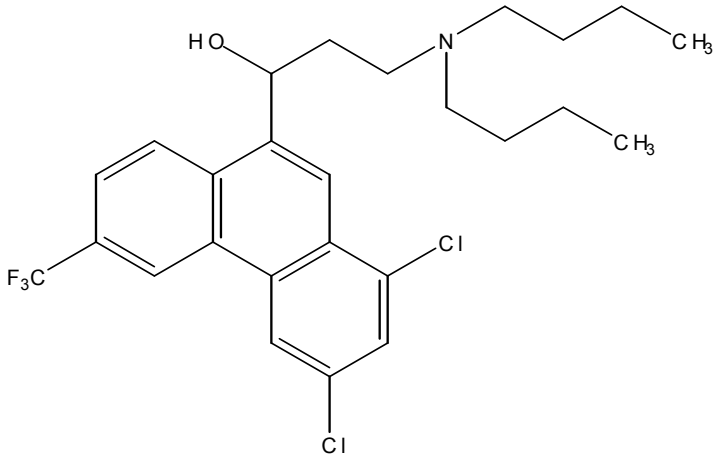
- Halofantrine
  - Originally discovered in the 1940s by the Walter Reed Army Institute but forgotten because of side effects (cardiac [Qc prolongation and sudden death... to come back because of resistance
  - Schizonticidal
  - **Most effective when mefloquine is ineffective**

- **Lumefantrine**
  - analogue of holofantrine
  - most often associated with artemether (voir dias artemisine)

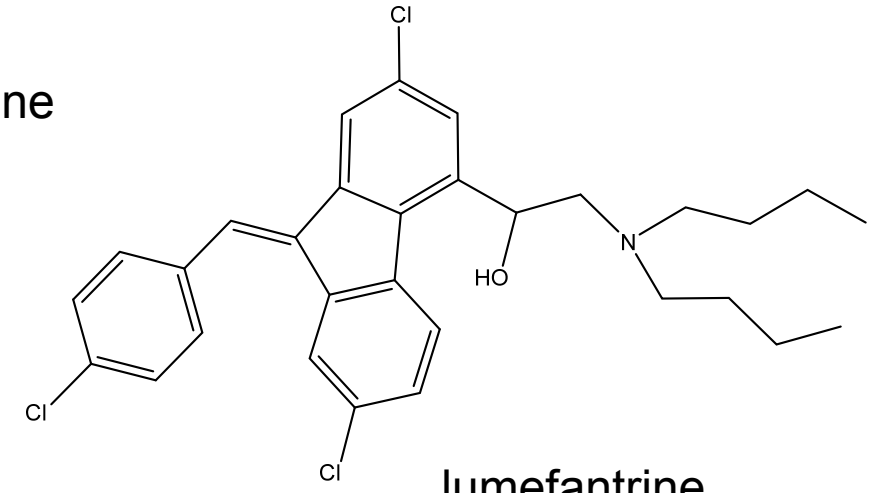
Antimalarials: mefloquine, halofantrine, and lumefatrine



mefloquine



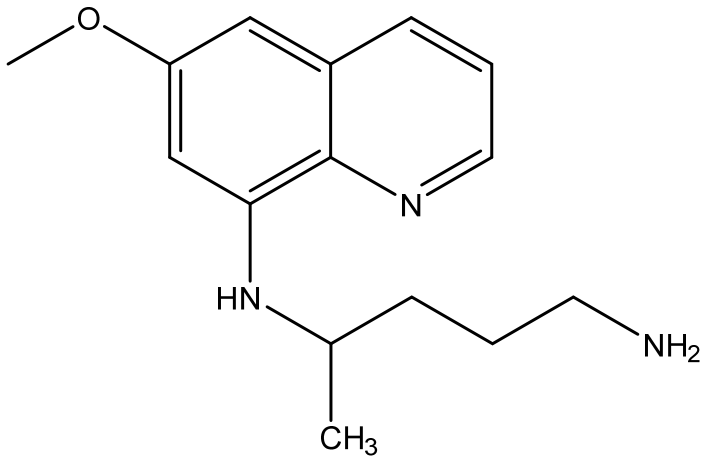
halofantrine



lumefantrine

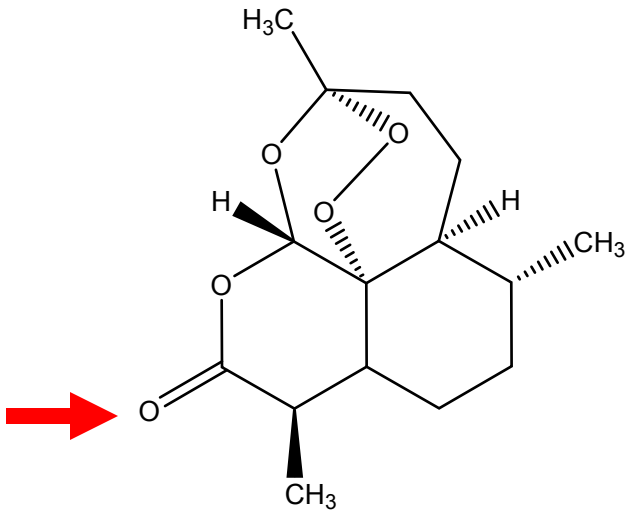
Antimalarials: Primaquine

- kills the parasites dormant in the liver tissues of the host
- frequently **administered with other quinolines** so that all of the Plasmodia in the body are eliminated
- Side effects include
  - nausea, vomiting and stomach cramps, visual disturbances and intense itching.
  - hemolysis in patients with G6PD deficiency (Africans or Caucasians of Mediterranean descent).



Antimalarials: Artemisinin

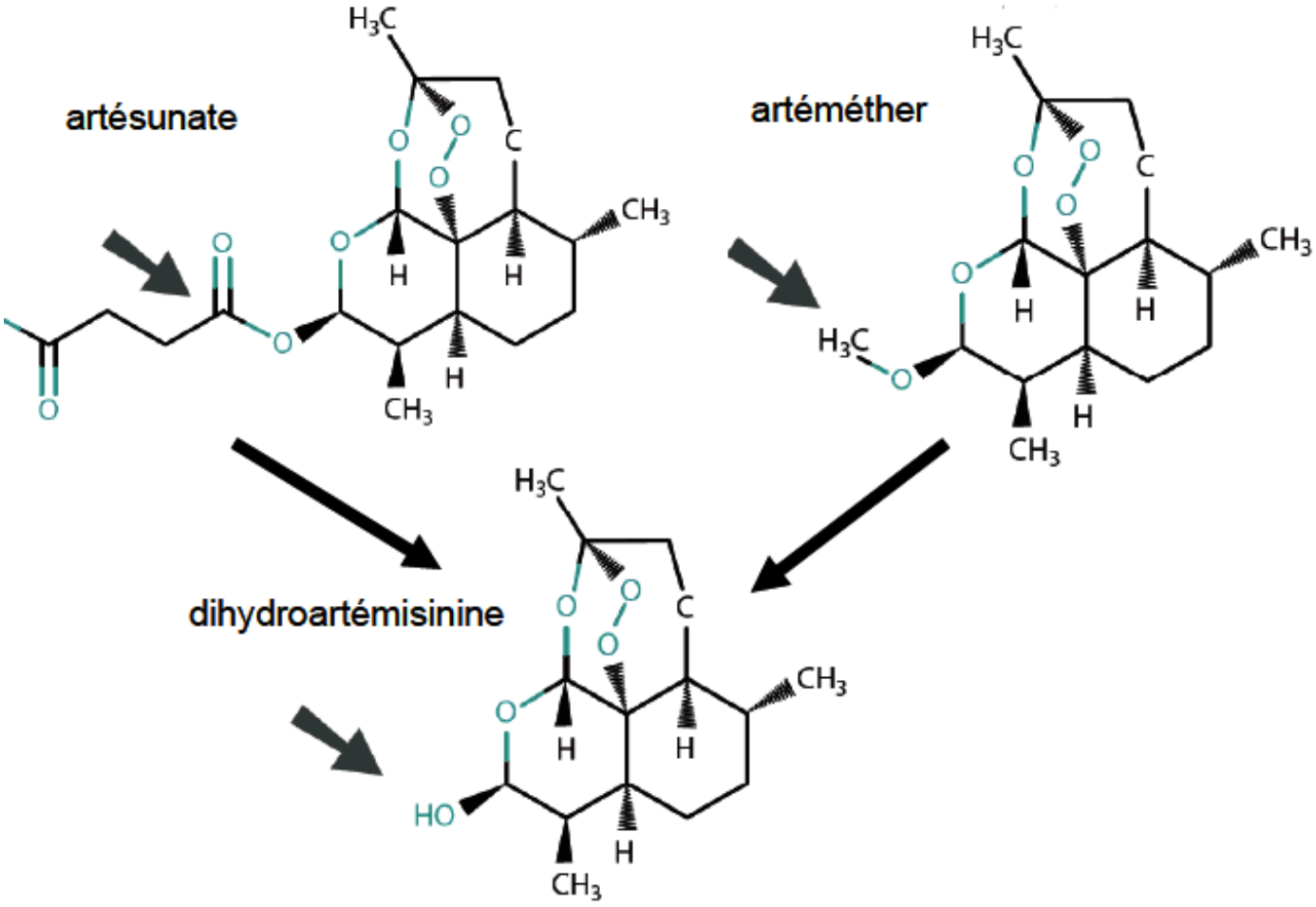
- History
  - Obtained from the shrub called Artemesia annua (sweet wormwood) or qing- hao
  - Has been used in China for over 200 years to treat fever and chills
  - In 1967 the government of the People's Republic of China purified and crystallized Qinghaosu (Artemisinin)



- A sequiterpene- One of a few naturally occurring compounds containing a peroxide

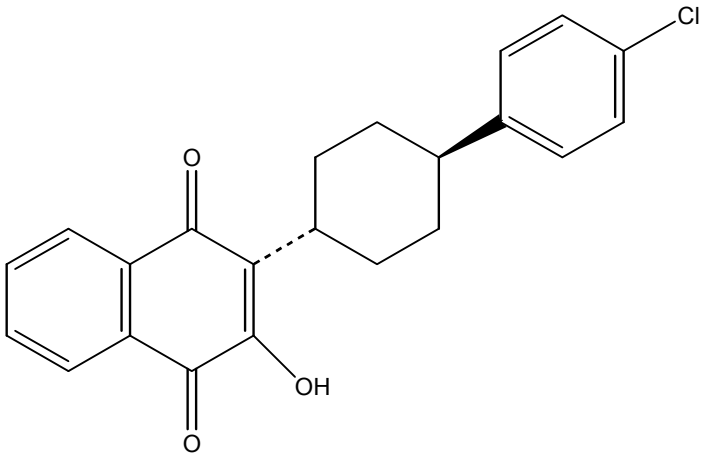
- Mechanism of action
  - Highly hydrophobic, so binds to various parasitic membranes
  - Activated by heme/ molecular iron to produce carbon centered free radicals- the endoperozxide bridge is necessary for this action
  - Free radicals cause membrane damage

Antimalarials: Artemisin derivatives

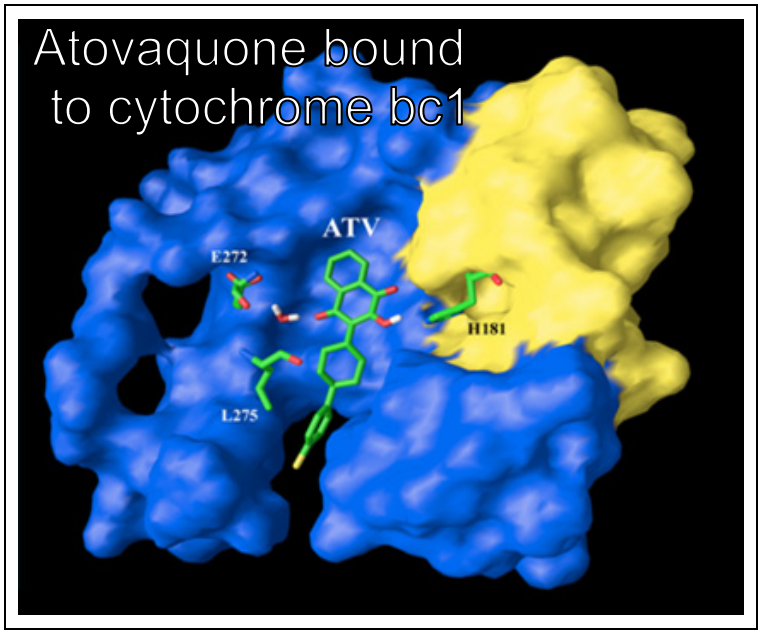


Dérivés de l'artémisinine (sesquiterpène lactone peroxyde),
par hémi synthèse d'extraits d'une plante : l'armoise *Artemisia annua*

Antimalarials: Atovaquone



- interferes with mitochondrial function (ATP and pyrimidine biosynthesis)
  - Compound acts at the cytochrome bc1 complex of malaria mitochondria to inhibit electron transport and collapse the mitochondrial membrane potential
  - Proguanil enhances the membrane-collapsing activity of atovaquone **(atovaquone+ proguanil= Malarone)**
  - Without this gradient, the energy required for processes such as ATP synthesis, ion transport, and flagellar movement is not produced
- Resistance is rapide (should never be administered alone
- few side effects except, in combination with proguanyl, headache and sleep disturbances (nightmares)a possibility of



Antimalarials: Proguanil, Diaminopyrimidines, Sulfonamides

- Mechanism of action:
  - All of these drugs act by inhibiting a step in the pathway of the biosynthesis of folate in the Plasmodia
  - Without the necessary folate, DNA synthesis is inhibited and the folate cofactors are depleted

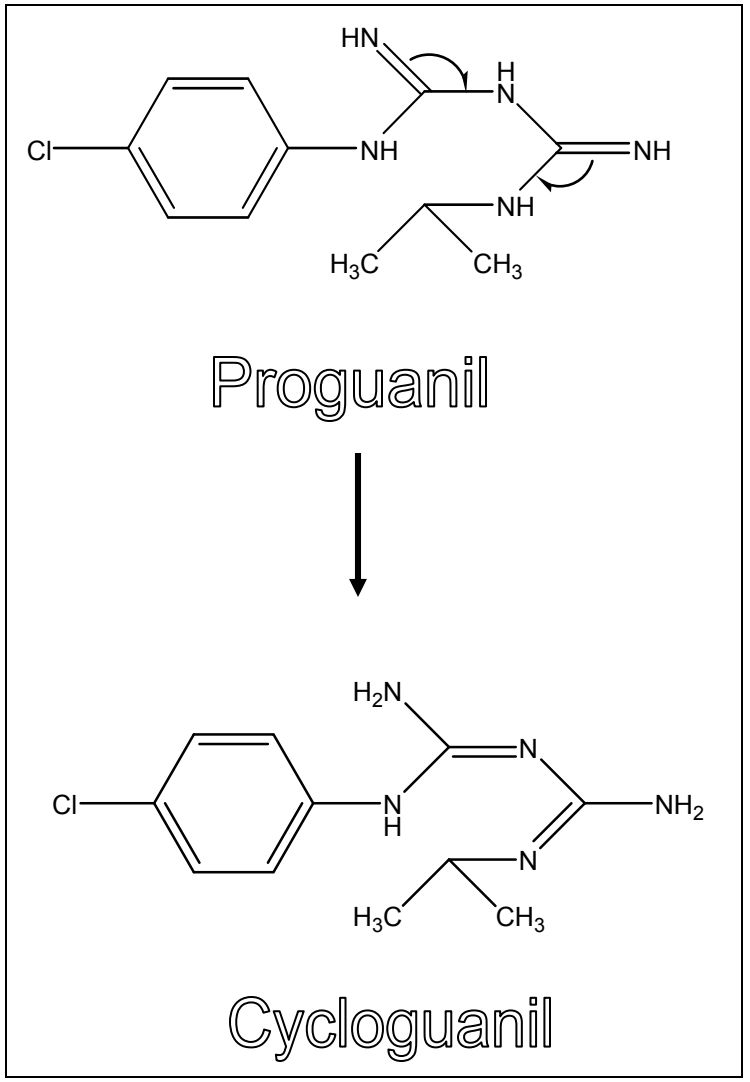
- **Proguanil**: bifunctional plasmodial dihydrofolate reductase-thymidylate synthetase

- **Diaminopyrimidines**: dihydrofolate reductase

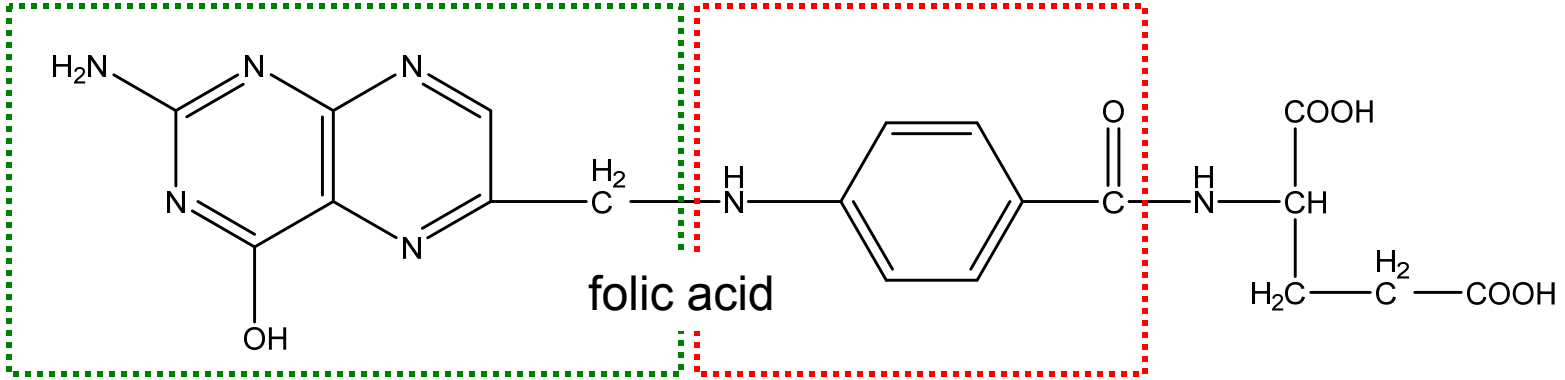
- **Sulfonamides**: dihydropteroate synthase

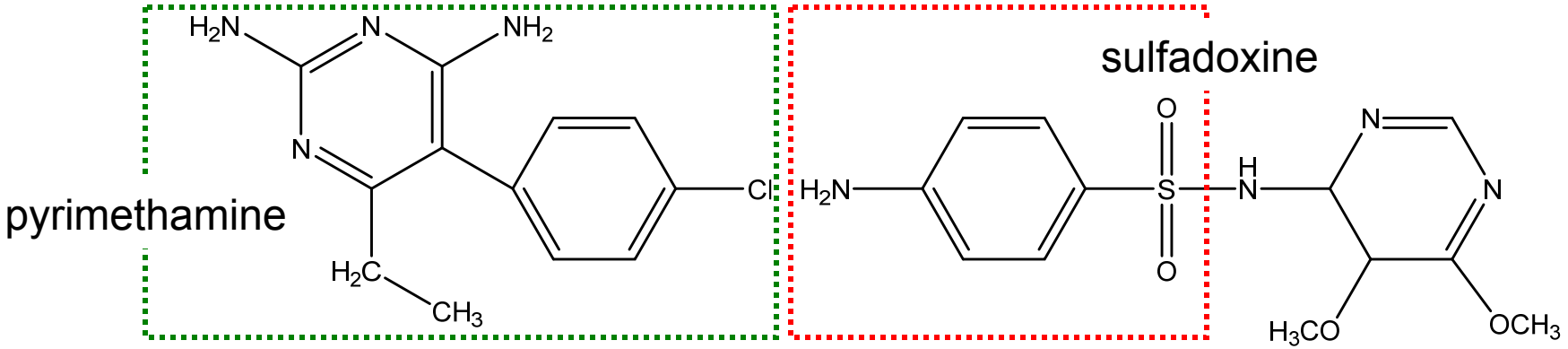
Antimalarials: Proguanil

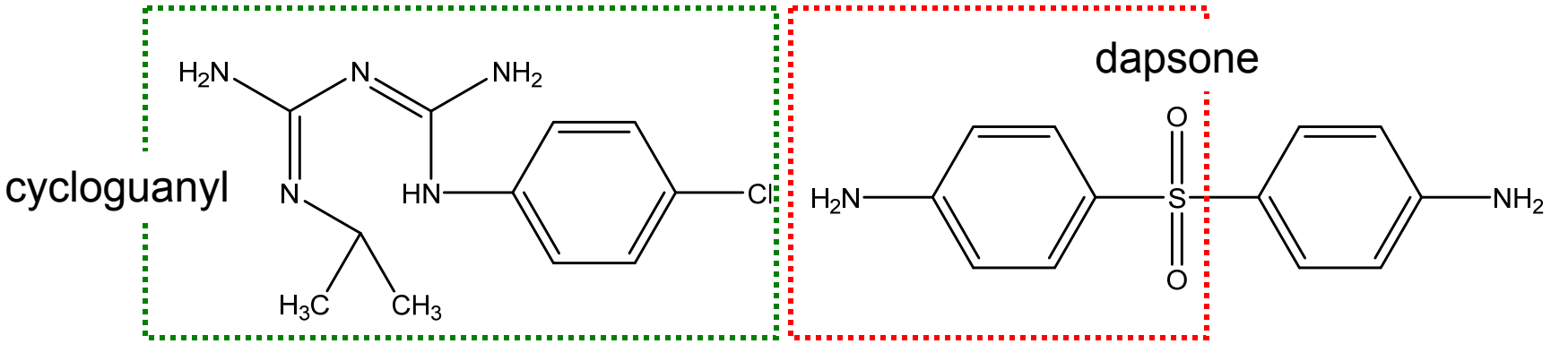
- Common name for chloroguanide
- Proguanil is rearranged to form **cycloguanil**
  - Cycloguanil = selective inhibitor of the bifunctional plasmodial dihydrofolate reductase-thymidylate synthetase (configuration siilar to pyrimethamine) → Inhibition of DNA synthesis and depletion of folate cofactors
- always used in combination with dapsone or a sulfonamide for treatment or with atavaquone for prohylaxis
- very few side effects (best tolerated antimalarial drug)



Folic acids and inhibitors



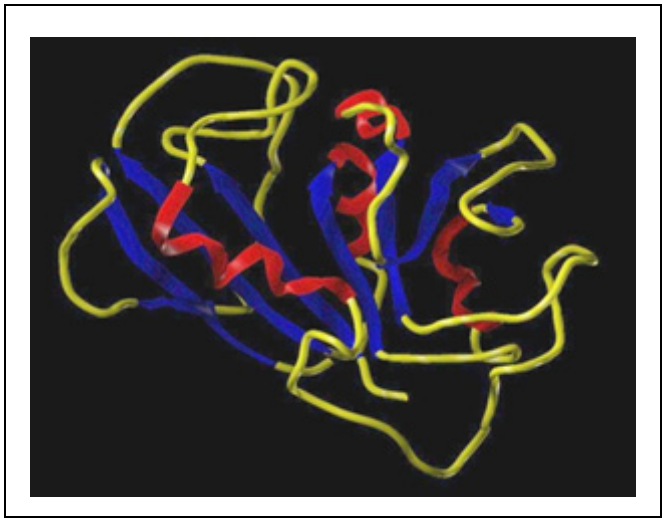




Antimalarials: Diaminopyrimidines

- In the late 1940's a large number of 2,4-diaminopyrimidines were tested based on the success of proguanil (similarly structured)

- Inhibits the dihydrofolate reductase of plasmodia at a much higher rate than the comparable inhibition of mammalian enzymes → the necessary folate is not produced



Dihydrofolate reductase (DHFR) from the parasite Plasmodium falciparum has been constructed by homology building

Antimalarials: Sulfonamides and Sulfones

- Sulfonamides do not give a complete cure- given with other antimalarials
  → a combination of pyrimethamine and sulfadoxine

- Competitively inhibit the dihydropteroate synthase of *P. falciparum*
  - This enzyme has been X-ray crystallized
  - Prevents the folate pathways from taking place

- Used together with and inhibitor of parasite dihydrofolate reductase to enhance antiplasmodial action

Antimalarials: Tetracyclines

- A broad spectrum antibiotic
- Works by inhibiting protein synthesis by binding to the 30 S ribosome subunit
- Work slowly to kill Plasmodia
  → should be given with a faster acting drug, ie. quinine

Protozoa-cides

- Drugs that are active against protozoan infections such as:
  - Giardiasis, trichomoniasis, trypanosomiasis, leishmaniasis, pneumocystosis and balantidiasis

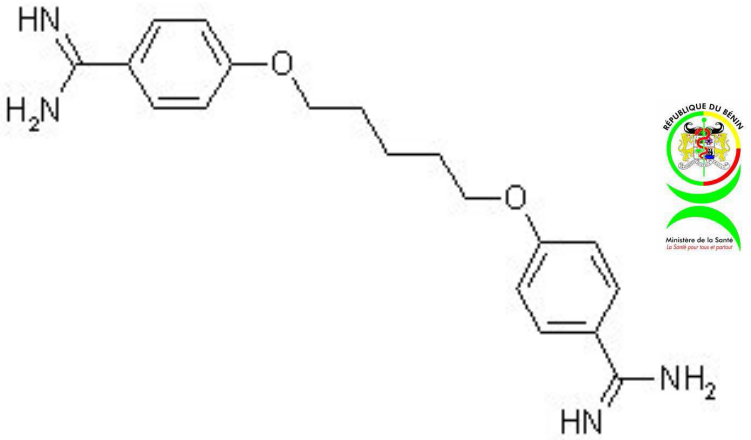
- Pentamidine, suramin, melarsoprol, amphotericin, eflornithine, benznidazole, aminosidine

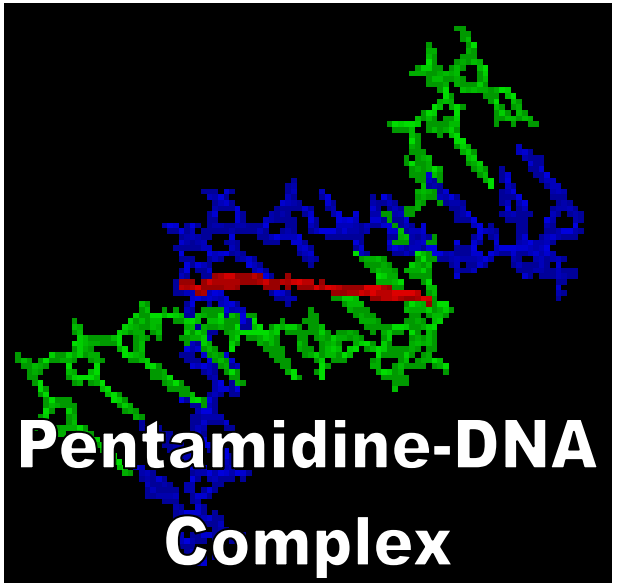
Human Trypanosomiasis

- Human African Trypanosomiasis
  - Pentamidine (a diamidine) and suramin (a sulphonated napththylamine)
    - Used to treat early stages of infection
  - Melarsoprol
    - Used to treat the CNS stages of the infection
    - Inhibits the trypanothione reductase at the reduced (necessary for binding) disulfide binding site
- Human American Trypanosomiasis
  - Benznidazole

Protozoacides: Pentamidine

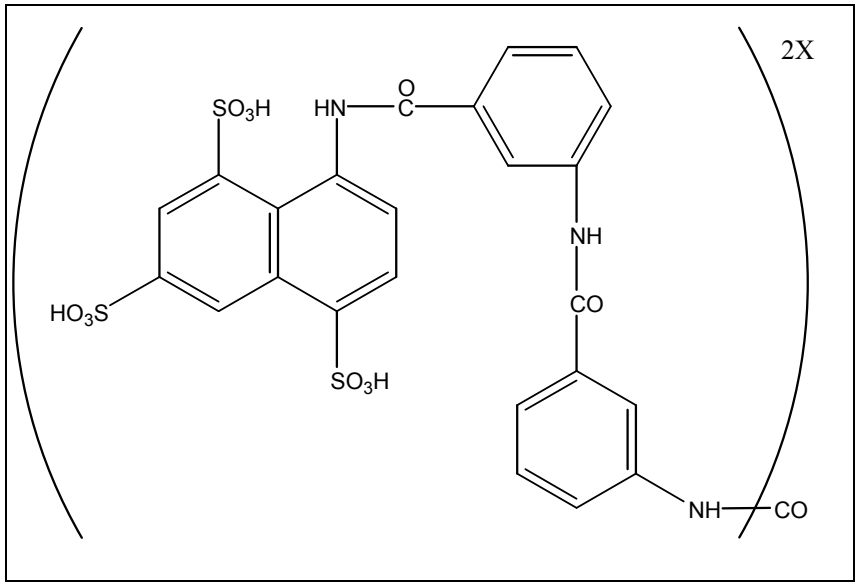
- Mechanism of action:
  - May interfere with the incorporation of nucleotides into DNA and RNA
  - May inhibit oxidative phosphorylation and the biosynthesis of DNA, RNA, proteins, and phospholipids
  - May have folate-antagonist actions
- Does not cross BBB
  - Only used in early stages of infections, while the parasite is still in the blood
- Limited by its toxicity (hypotension, tachycardia, nephrotoxicity, hepatotoxicity, hypoglycemia





Protozoacides: Suramin

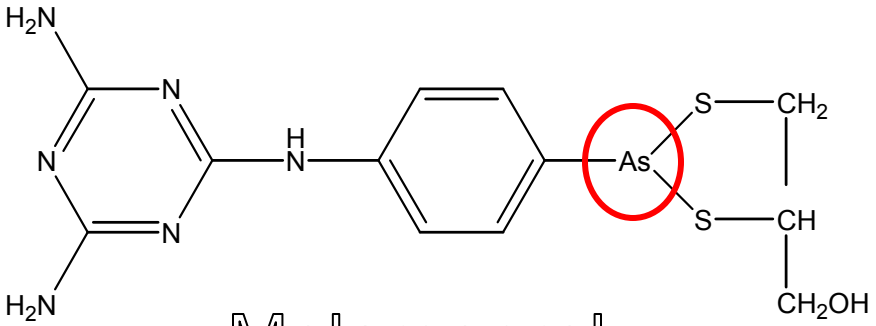
- Synthesized in 1916 as a product of the German dye industry
- Sulfonic acid and structurally related to dyes
- A highly negatively charged compound- does not cross the BBB
  - Six negative charges
- Mechanism of action unknown but affects many proteins in the parasite



Protozoacides: Melarsoprol and Eflornithine

Melarsoprol

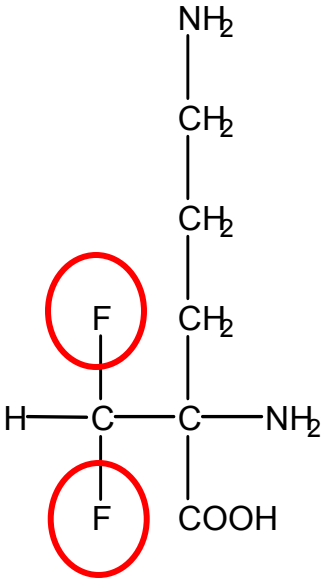
- Has been used to treat trypanomiasis since 1947
- Melarsoprol is a prodrug that is metabolized into melarsen oxide
- Inhibits the many enzymes, including the trypanothione reductase
- Can have severe side effects, including death in 5% of patients



Melarsoprol

Eflornithine

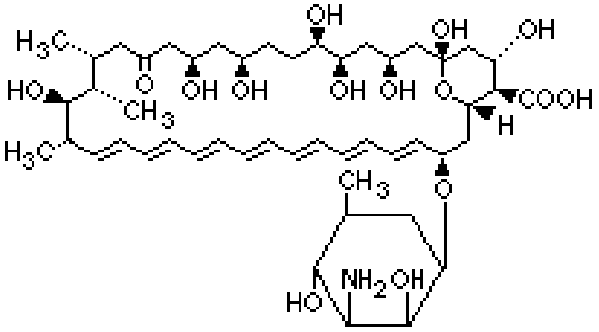
- Less toxic than melarsoprol
- An ornithine analogue that inhibits the enzyme ornithine decarboxylase, the first enzyme in the synthesis of polyamines
- These polyamines are essential for cell division, cellular differentiation, and in the protection against oxidative stress
- hematological and ototoxicity !



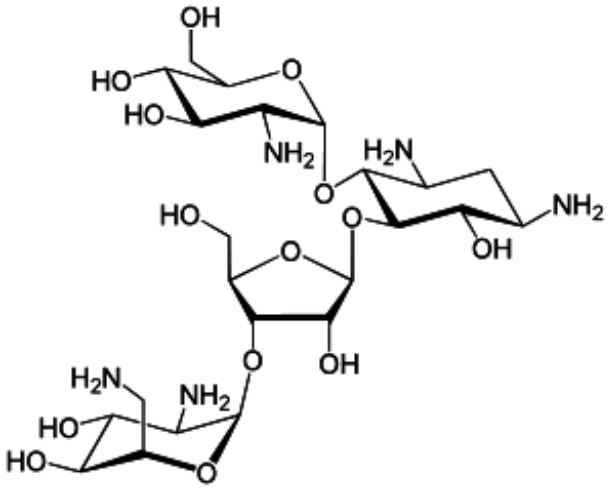
Eflornithine

Protozoacides: Leishmaniasis

- Lipid Amphotericin B
  - In 1997 the FDA approved liposomal amphotericin B (Ambisome) for the treatment of leishmaniasis
  - Less toxic than the antifungal amphotericin B
  - Amphotericin complexes with ergosterol precursors in the cell membrane, forming pores that allow ions to enter the cell



- Paromomycine (aminosidine)
  - An aminoglycoside antibiotic
  - Inhibits initiation and elongation during protein synthesis



Business Implications of Antiparasitic Agents

- Most areas that still have problems with parasites are the poor, underdeveloped countries
  - Not much research going on for the development of new drugs because pharmaceutical companies would not make a profit on drugs, much less break even

- Strategies for combating this problem:
  - Develop drugs that have both commercial markets in the west, as well as applications against a neglected parasite disease in poorer areas
  - Develop new drugs at academic institutions with federal support
  - Or military research