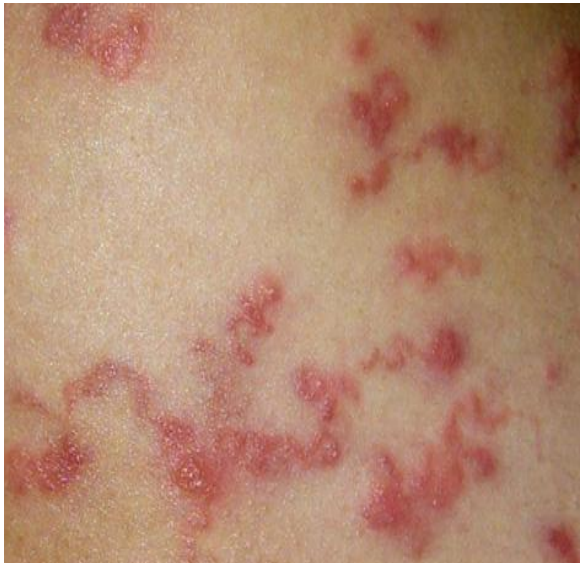
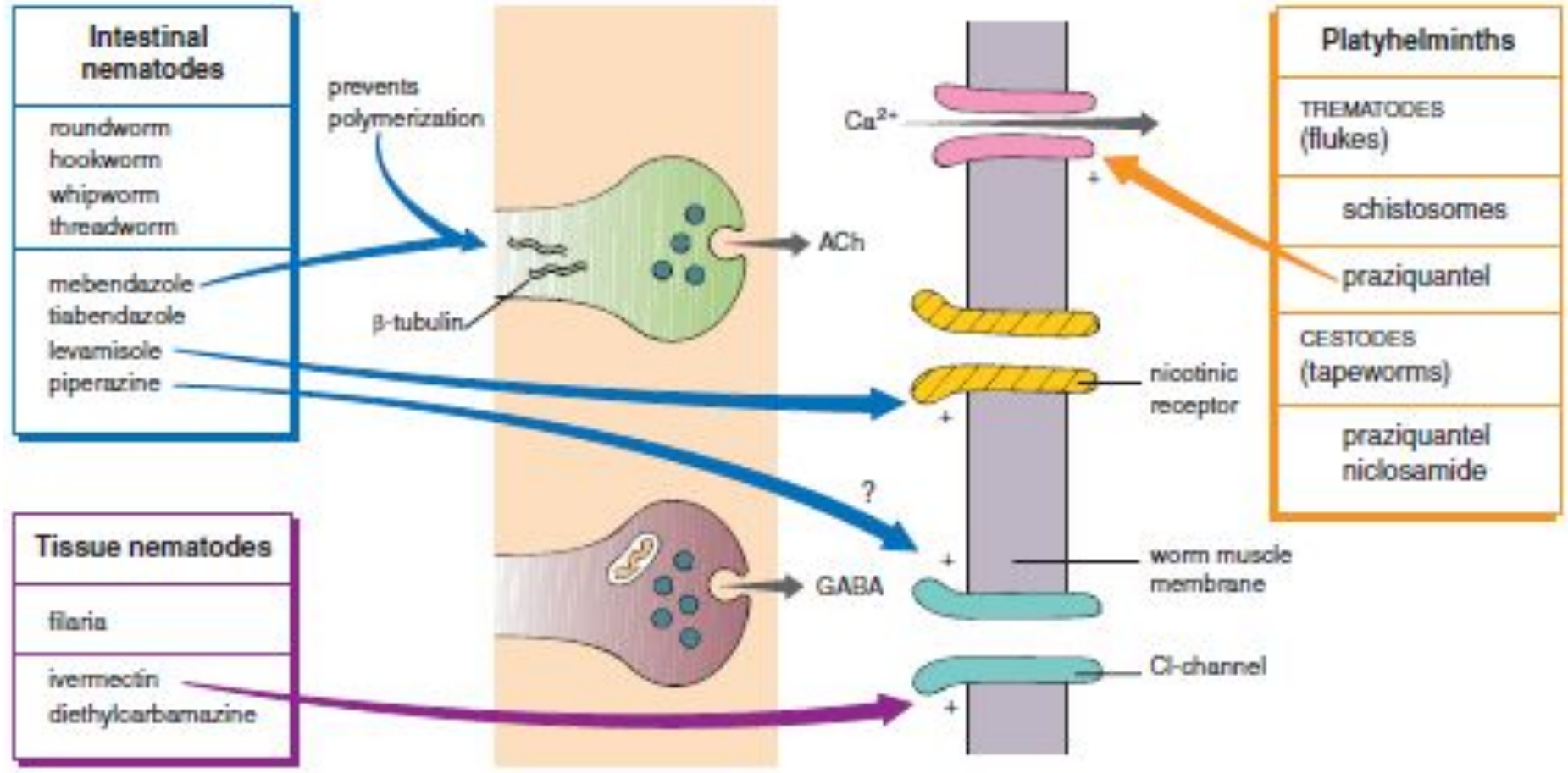
ANTIHELMINTHIC AND ANTIPROTOZOAL DRUGS



- Antihelmintics are drugs that either kill (vermicide) or expel (vermifuge) infesting helminths.
- Nematodes, trematodes, and cestodes are three major groups of helminthes (worms) that infect humans.
- Nematodes are elongated roundworms that possess a complete digestive system. They cause infections of the intestine as well as the blood and tissues.
- We use: mebendazole, albendazole, pyrantel, levamisol, piperazine.


Intestinal nematodes
roundworm
hookworm
whipworm
threadworm
mebendazole
tiabendazole
levamisole
piperazine
Tissue nematodes
filaria
ivermectin
diethylcarbamazine
prevents polymerization
β-tubulin
ACh
GABA
?
Ca2+
+
+
+
+
nicotinic receptor
worm muscle membrane
Cl-channel
Platyhelminths
TREMATODES (flukes)
schistosomes
praziquantel
CESTODES (tapeworms)
praziquantel
niclosamide

Mebendazole

- **Uses:** whipworms (Trichuris trichiura), pinworms (Enterobius vermicularis), hookworms (Necator americanus and Ancylostoma duodenale), and roundworms (Ascaris lumbricoides);

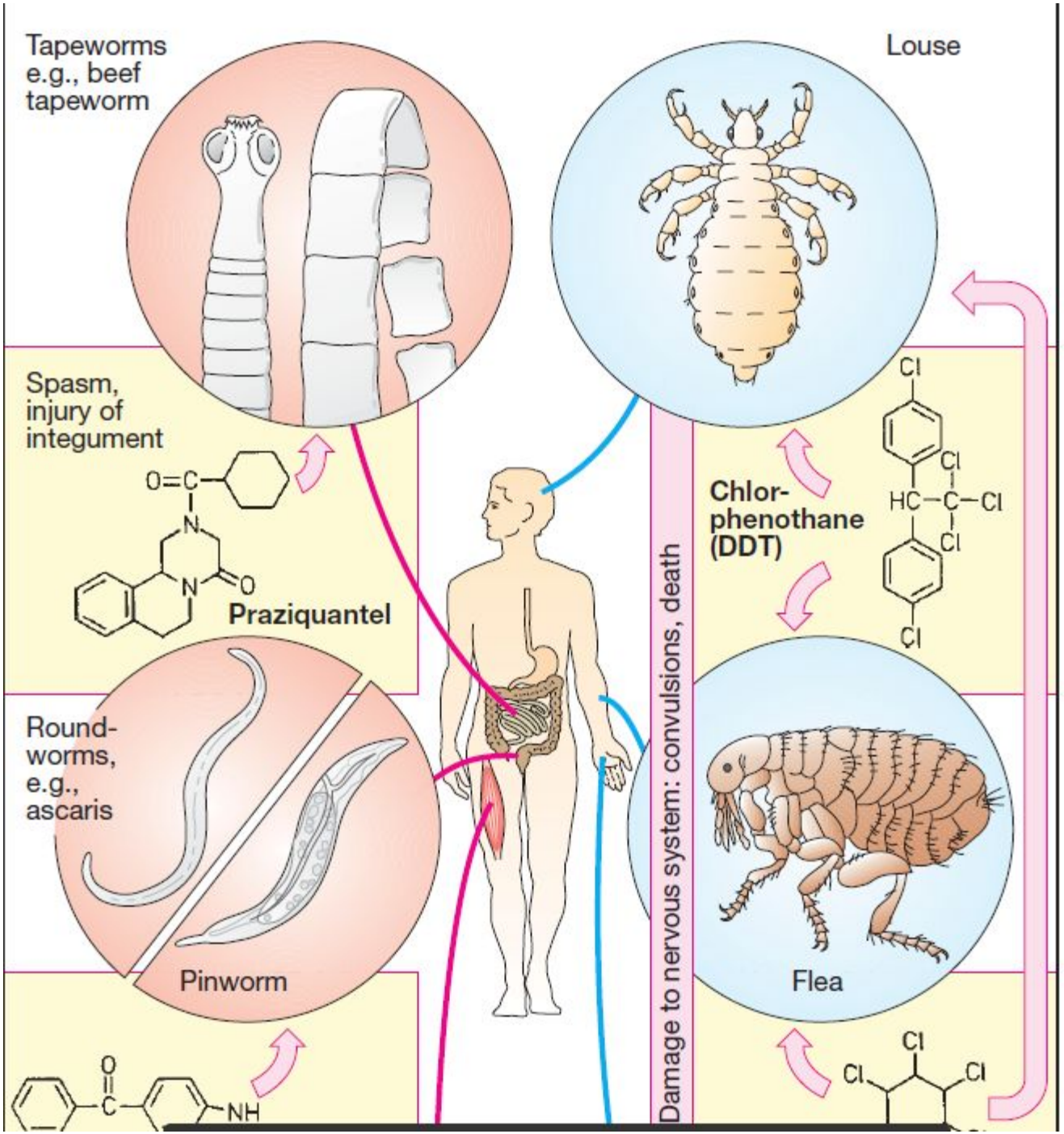
  in high doses: extraintestinal helminthiasis (trichinellosis and echinococcosis)
- It inhibits the assembly of the microtubules and glucose utilization in helminthes and paralyses them. It kills ova and larvae of Ascaris.
- Absorption from intestines – 10-15%
- Adverse effects: abdominal pain, diarrhea, headache, allergic reactions

Albendazole

- Uses: ascariasis, hookworms and enterobiasis (a single dose) , toxocariasis, filariasis, cysticercosis, echinococcosis (long-term therapy).
- It is absorbed from GIT, metabolized in the liver.
- Adverse effects: headache, diarrhea, dizziness, leucopenia, skin rashes, abdominal pain, vomiting.

Levamisole

- Uses: a single dose – ascariasis, less effective – ankylostomiasis, strongyloidiasis, filariasis.
- Mechanism: stimulation of ganglia, drug-induced paralysis of helminthes due to depolarization of their muscles, inhibition of fumarate reductase and metabolism.
- Adverse effects: abdominal pain, diarrhea, nausea

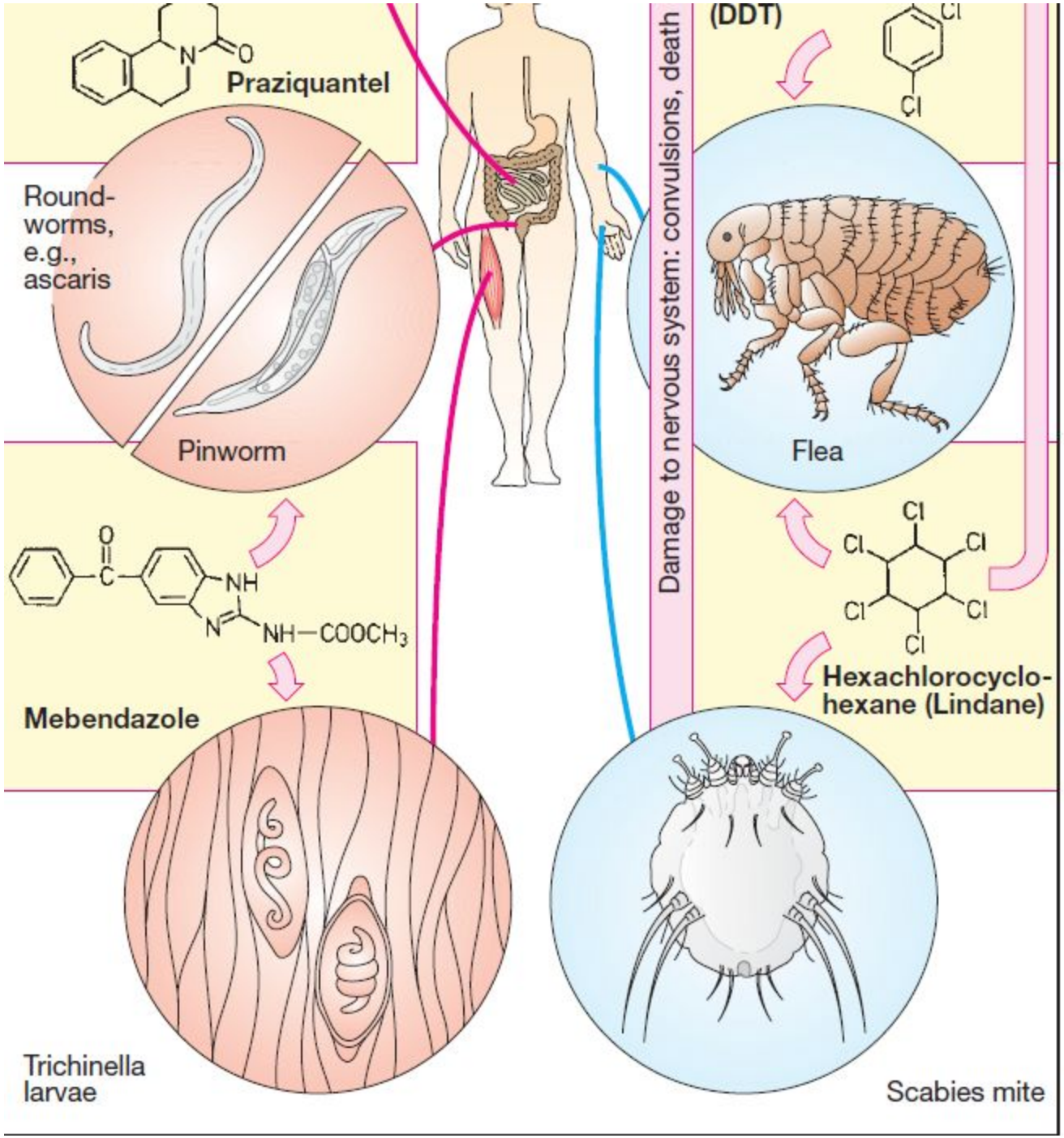

Tapeworms
e.g., beef
tapeworm
Louse
Spasm,
injury of
integument
Praziquantel
Chlor-
phenothane
(DDT)
Round-
worms,
e.g.,
ascaris
Pinworm
Flea
Damage to nervous system: convulsions, death

- **Pyrantel** is active against Ascaris, Enterobius, Ancylostoma, Necator, Strongyloides
- Mechanism: activation of nicotinic cholinergic receptors in the worms → persistent depolarization → slowly developing contracture and spastic paralysis.
- Absorption from GIT – 10-15%.
- Adverse effects: nausea, vomiting, abdominal pain, headache and dizziness

- **Diethylcarbamazine citrate** is microfilaricidal. It has a highly selective effect on microfilariae and against adult worms.
- It is rapidly absorbed following oral administration with meals and is excreted mainly in the urine.
- Adverse effects may include fever, nausea, vomiting, arthralgia, and headache.

Niclosamide

- Uses: Taenia saginata, Diphyllobothrium latum and Hymenolepis nana.
- It inhibits the mitochondrial phosphorylation of adenosine diphosphate (ADP). Anaerobic metabolism may also be inhibited.
- In cases of *T. solium,* digestion of the dead segments can be hazardous, because the ova released from them may develop into larvae in the intestine, penetrate its wall and cause visceral cysticercosis.
- It is minimally absorbed from GIT.
- Adverse effects: dyspepsia, allergic reactions.

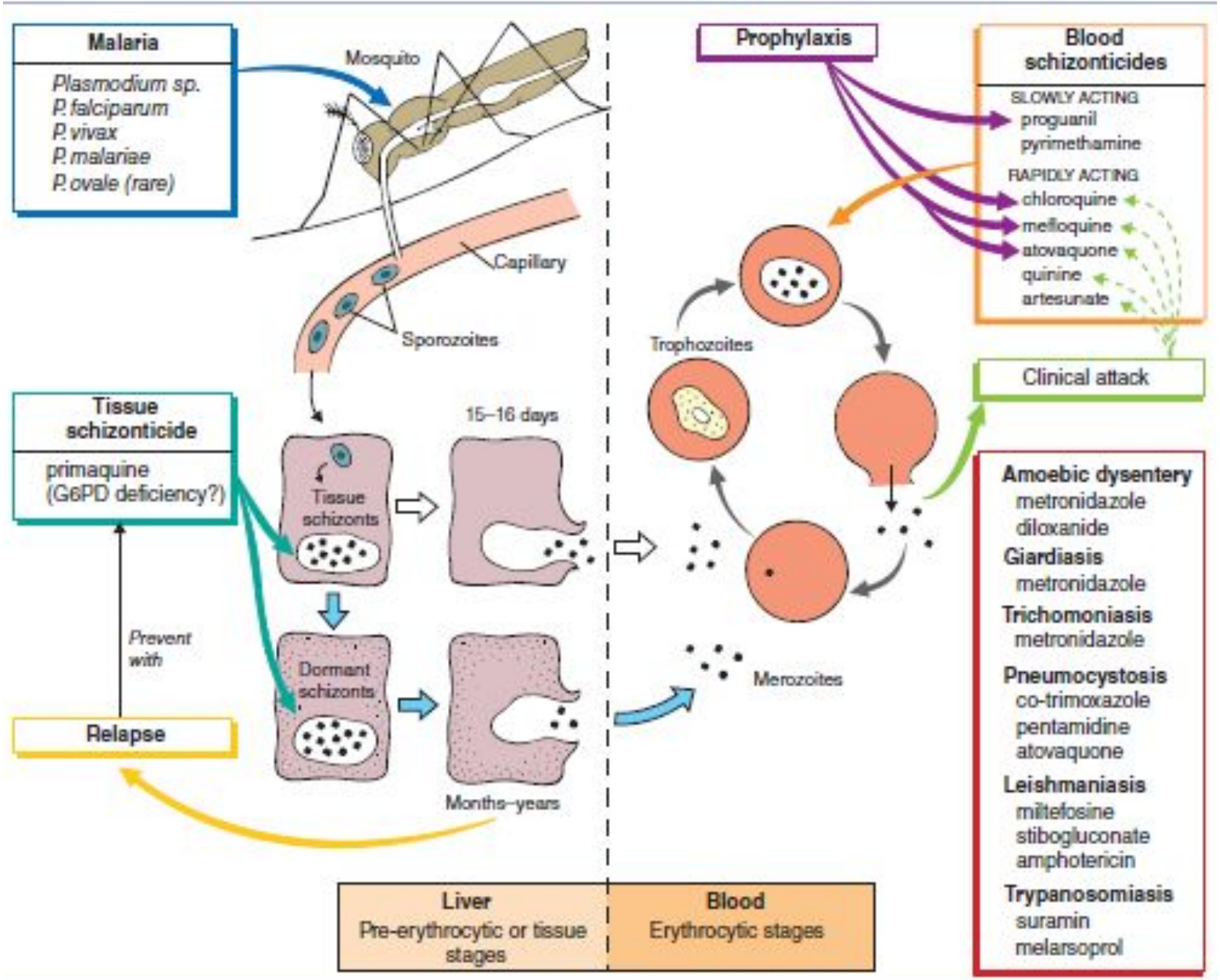

Praziquantel
Round-worms, e.g., ascaris
Pinworm
Damage to nervous system: convulsions, death
(DDT)
Flea
Mebendazole
Hexachlorocyclo-hexane (Lindane)
Trichinella larvae
Scabies mite

Praziquantel

- Uses: all forms of schistosomiasis, other trematode infections, cestode infections such as taeniasis, cysticercosis (caused by Taenia solium larvae)
- Mechanism: leakage of intracellular calcium from the membranes → contracture and paralysis.
- It is rapidly absorbed after oral administration and distributes into the cerebrospinal fluid (CSF). It is extensively metabolized, and the inactive metabolites are excreted primarily in the urine.
- Adverse effects: dizziness, malaise, headache

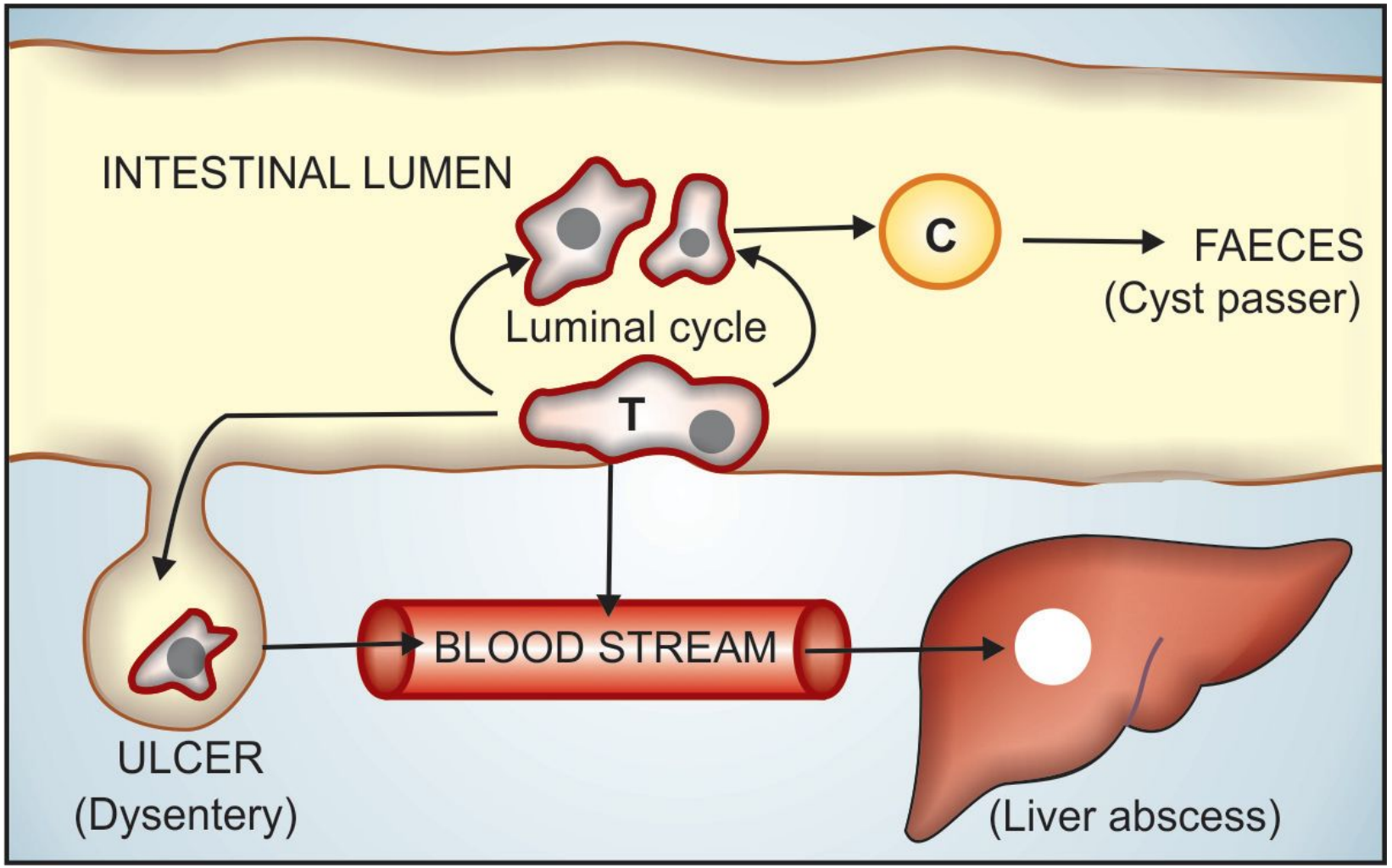
Antiprotozoal drugs are used for the treatment and prophylaxis of:

- Malaria
- Amebiasis
- Giardiasis (Metronidazole, furazolidone)
- Trixomoniasis (Metronidazole, furazolidone, Diiodohydroxyquin rect.)


Malaria
Plasmodium sp.
P. falciparum
P. vivax
P. malariae
P. ovale (rare)
Mosquito
Capillary
Sporozoites
Tissue schizonticide
primaquine
(G6PD deficiency?)
Prevent with
Relapse
15–16 days
Tissue schizonts
Dormant schizonts
Months–years
Prophylaxis
Blood schizonticides
SLOWLY ACTING
proguanil
pyrimethamine
RAPIDLY ACTING
chloroquine
mefloquine
atovaquone
quinine
artesunate
Trophozoites
Merozoites
Clinical attack
Amoebic dysentery
metronidazole
diloxanide
Giardiasis
metronidazole
Trichomoniasis
metronidazole
Pneumocystosis
co-trimoxazole
pentamidine
atovaquone
Leishmaniasis
miltefosine
stibogluconate
amphotericin
Trypanosomiasis
suramin
melarsoprol
Liver
Pre-erythrocytic or tissue stages
Blood
Erythrocytic stages

- Toxoplasmosis (pyrimethamine, sulfadimidine)
- Balantidiasis (tetracyclines, monomycin, quiniofone)
- Leishmaniasis (solusurmine, stibogluconate, amphotericin B, paromomycin)
- Trypanosomiasis (melarsoprol, primaquine, suramin)

- **Antiamoebic drugs - d**rugs useful in infection caused by the anaerobic protozoa *Entamoeba histolytica.*



CLASSIFICATION

1. **Tissue amoebicides**

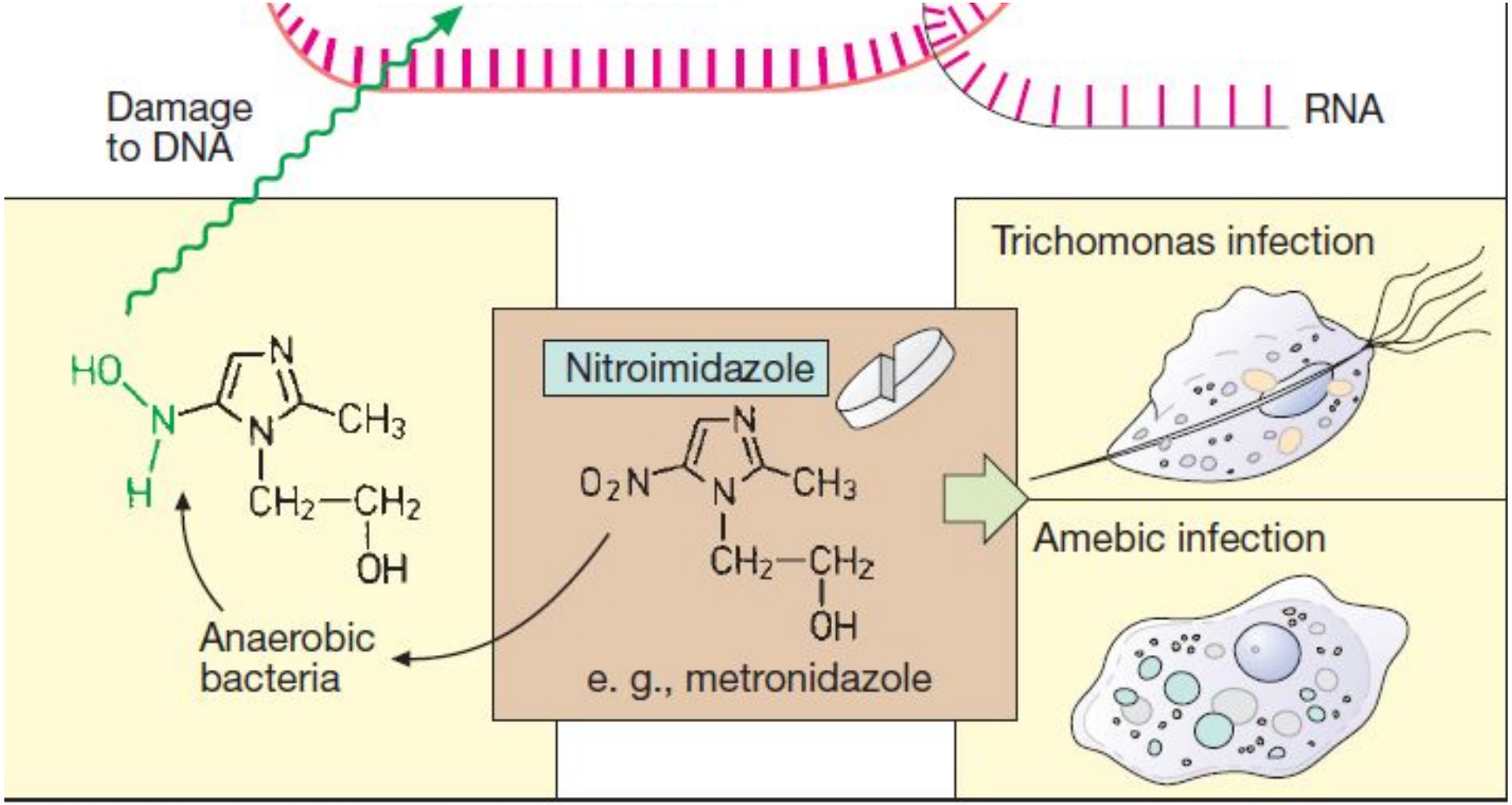
For both intestinal and extraintestinal amoebiasis:

Nitroimidazoles: **Metronidazole, Tinidazole, Ornidazole**

For extraintestinal amoebiasis only: **Chloroquine**

2. *Luminal amoebicides:* **Tetracyclines**

- **Nitroimidazoles** (Metronidazole) is used for the treatment of infections caused by:
- Entamoeba histolytica,
- Giardia lamblia,
- Trichomonas vaginalis,
- anaerobic cocci, and anaerobic gram-negative bacilli (Bacteroides species),
- for the treatment of pseudomembranous colitis caused by the anaerobic, gram-positive bacillus Clostridium difficile.



A. Antibacterial drugs acting on DNA

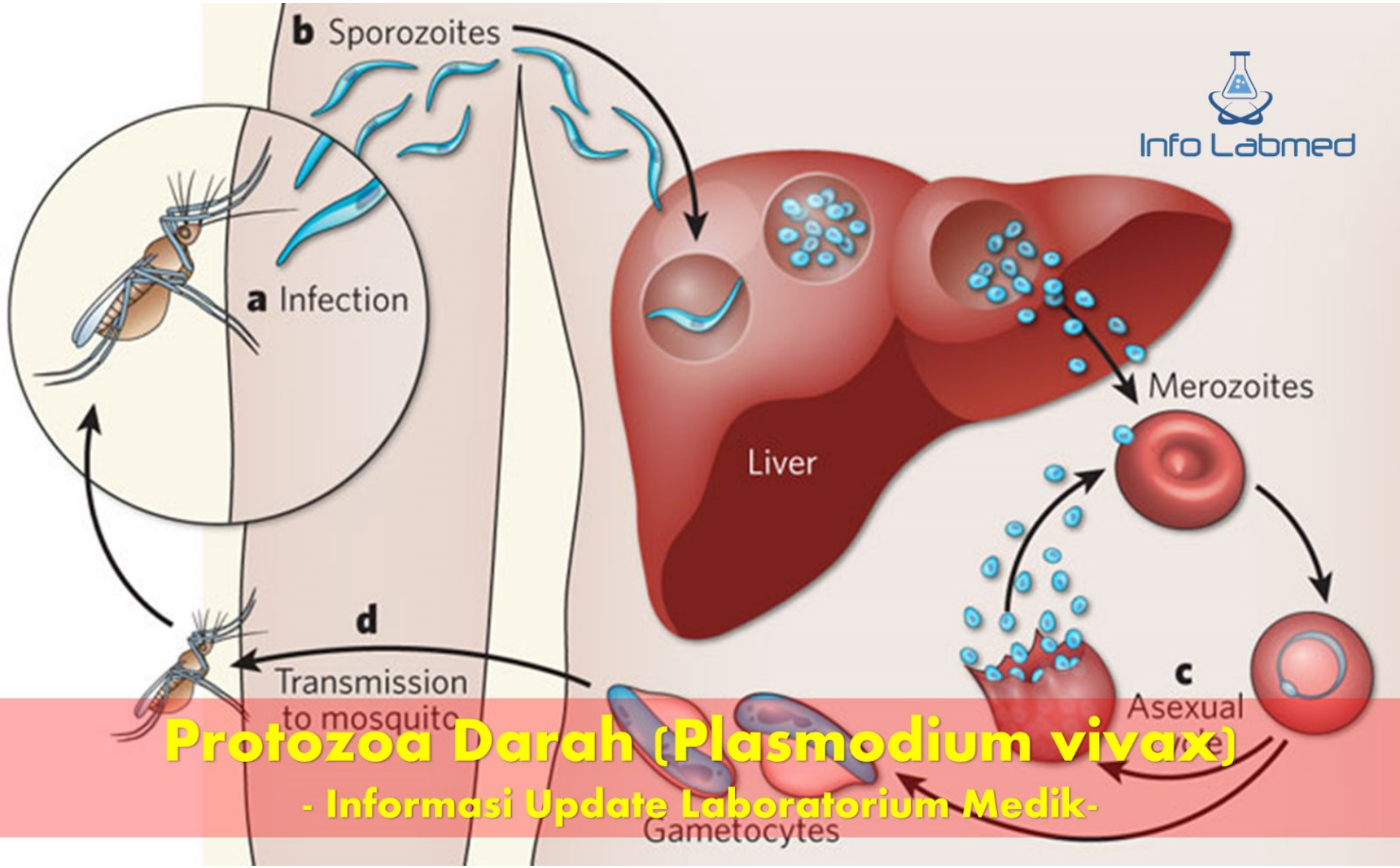
- The nitro group of **Nitroimidazoles** is able to serve as an electron acceptor, forming reduced cytotoxic compounds that bind to proteins and DNA. The drugs disrupt metabolism and cause death of microorganisms.
- They are absorbed well from GIT, distribute well throughout body tissues and fluids. Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF).
- Tinidazole and ornidazole are well absorbed from GIT, accumulated in the plasma in higher concentrations than Metronidazole and provide longer effect than it.

Adverse effects:

- nausea, vomiting, epigastric distress, and abdominal cramps, an unpleasant, metallic taste,
- oral moniliasis (yeast infection of the mouth),
- neurotoxicity (dizziness, vertigo, and numbness or paresthesia),
- a *disulfiram-like reaction* (if taken with alcohol).

- Malaria is one of the most common diseases worldwide and a leading cause of death. *Plasmodium species that infect humans* (*P falciparum, P malariae, P ovale, P vivax) undergo a primary* developmental stage in the liver and then parasitize erythrocytes. *P falciparum and P malariae have only 1 cycle of liver* cell invasion. The other species have a dormant hepatic stage responsible for recurrent infections and relapses. Primary **tissue schizonticides (eg, primaquine) kill schizonts in the liver,** whereas **blood schizonticides (eg, chloroquine, quinine) kill** these parasitic forms only in the erythrocyte. **Sporonticides** (proguanil, pyrimethamine) prevent sporogony and multiplication in the mosquito.

DRUGS FOR MALARIA



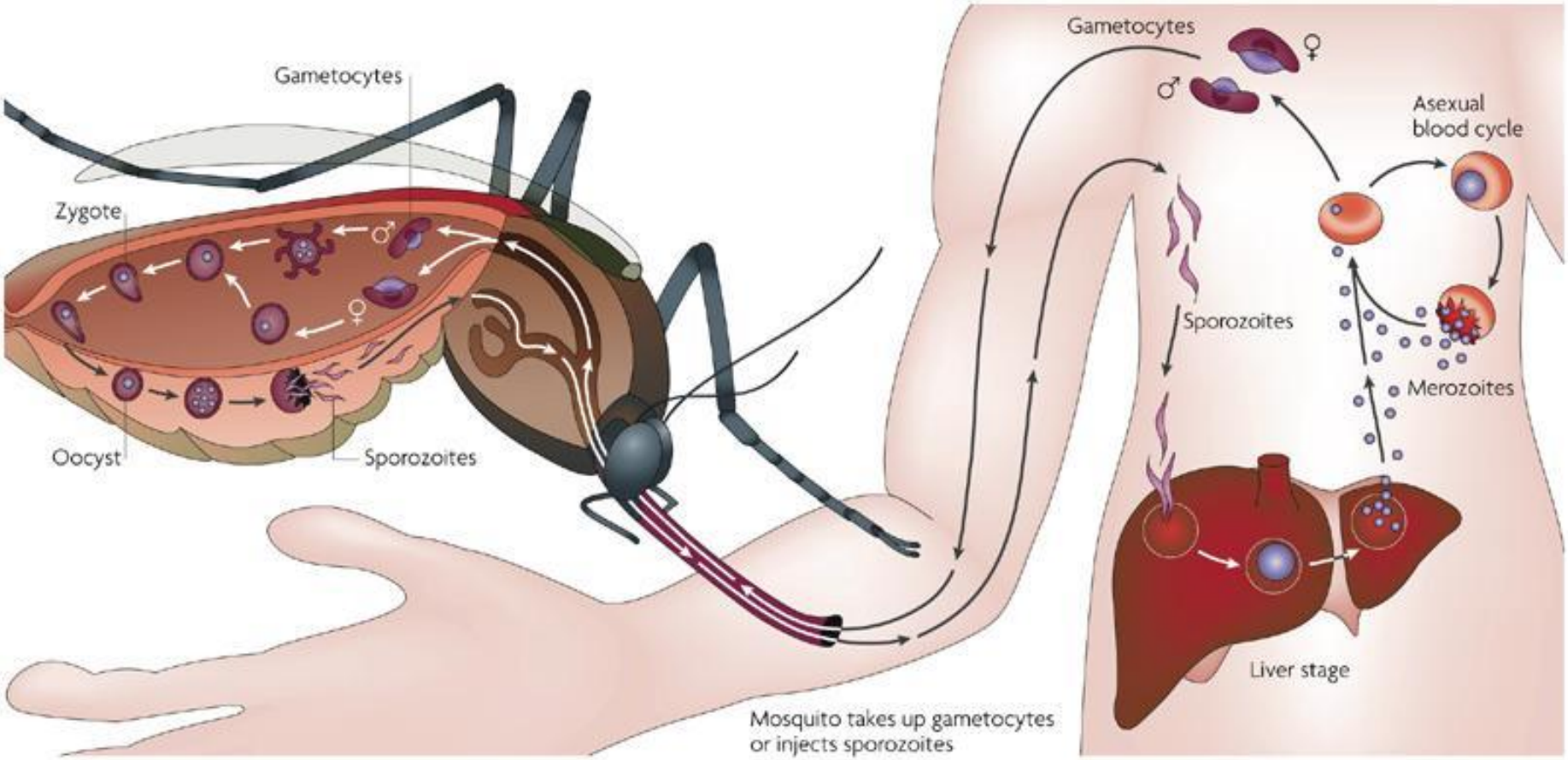
Protozoa Darah (Plasmodium vivax)

- Informasi Update Laboratorium Medik-

Principals of antimalarial drugs use

1. Individual chemoprophylaxis: prevention of the development of malaria in men during the time of residency in a area which has a high risk of malaria. We can use drugs influencing on preerythrocytic forms or hematoshizotropic drugs (pyrimethamine, chloroquin)
2. The treatment: oral administration of hematoshizotropic drugs, which influence erythrocytic forms of plasmodia. These drugs are used to cure the acute attacks of M.

3. Prevention of delayed relapses: administration of drugs which have tropism towards paraerythrocytic forms (primaquine).
4. Social chemoprophylaxis: prevention of the transmission of the infection by a sick person. We use gametotropic drugs (primaquine, pyrimethamine).



Nature Reviews | Genetics

- **Chinine (**Quinine) complexes with doublestranded DNA and prevents strand separation, blocks DNA replication and transcription to RNA. It is solely a blood schizonticide.
- It is rapidly absorbed orally and is metabolized before renal excretion. Intravenous administration of quinine is possible in severe infections.
- It is used in the treatment of severe or complicated falciparum malaria.
- Adverse effects: **cinchonism (**gastrointestinal distress, headache, vertigo, blurred vision and tinnitus).

- **Chloroquine** is rapidly absorbed when given orally, is widely distributed to tissues.
- It accumulates in the food vacuole of plasmodia and prevents polymerization of the hemoglobin breakdown product heme into hemozoin. Intracellular accumulation of heme is toxic to the parasite.
- It is the drug of choice for acute attacks of malaria and for chemoprophylaxis.
- Side effects: gastrointestinal irritation, skin rash, and headaches; peripheral neuropathies, myocardial depression, retinal damage, auditory impairment, and toxic psychosis

- Sulfonamides act as antimetabolites of PABA and block folic acid synthesis by inhibiting dihydropteroate synthase.
- **Pyrimethamine is a** selective inhibitor of protozoan dihydrofolate reductases. The combination has synergistic antimalarial effects (**blockade of 2 steps in** folic acid synthesis).
- The antifols are blood schizonticides that act mainly against *P falciparum*.
- Adverse effects: skin rashes, gastrointestinal distress, hemolysis, kidney damage.

- **Primaquine** is a synthetic 8-aminoquinoline. It is used orally.
- It forms quinoline- quinone metabolites, which are electron-transferring redox compounds that act as cellular oxidants. The drug is a tissue schizonticide and also limits malaria transmission by acting as a gametocide.
- Uses: Eradication of liver stages of *P vivax and P ovale,* primary prevention
- Adverse effects: GI distress, methemoglobinemia, hemolysis in G6PD deficiency

Nitrofuran derivatives

Nitrofural : antiseptic

Furazolidon: intestinal infections, giardiasis, Trichomonas colpitis

Nitrofurantoin (Furadonin), Furazidin (Furagin): uroinfection.

Spectrum:

Gram-negative bacteria: Escherichia coli, Shigella, Salmonella, Klebsiella

Cocci (entero-, staphylo-,strepto-, meningo, gonorrhea)

Vibrio cholerae, Giardia, Trichomonas

Mechanism:

- The restoration of the nitro group to the amino group under the influence of reductase microbial cells.
- The formation of complexes with nucleic acids,
- Disruption of the respiratory chain of microorganisms.
- Increase in the body's resistance to infections.
- The decline in the production of toxins.

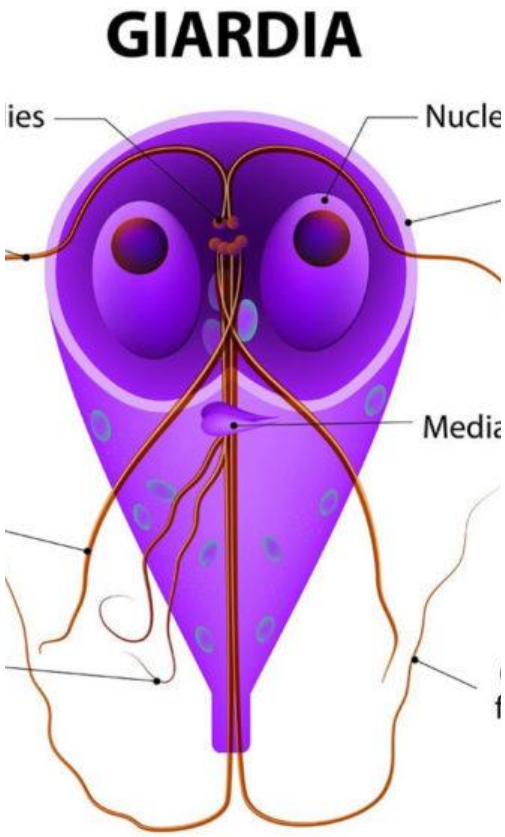
Type of action: bacteriostatic or bactericidal

Side effects

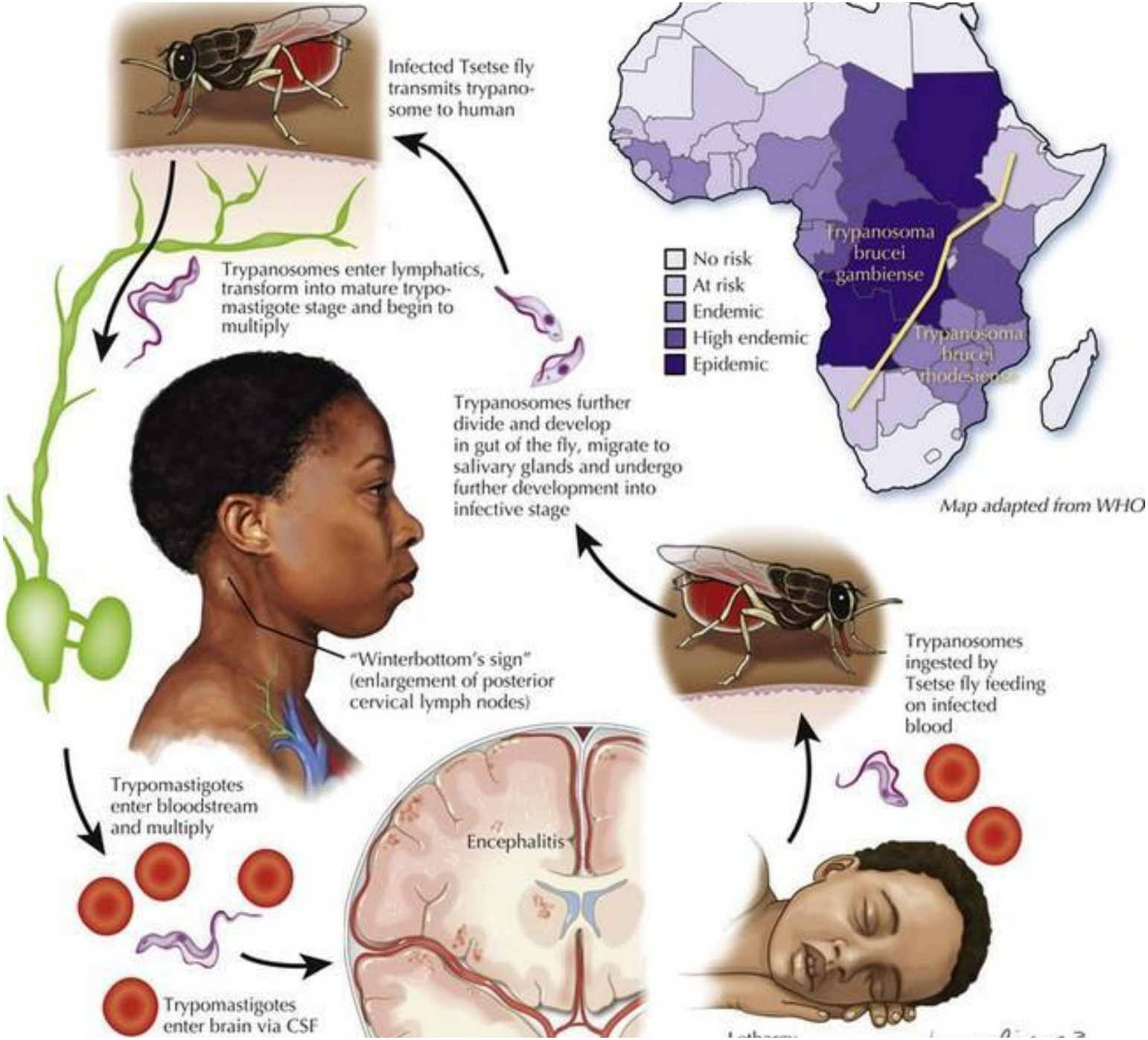
- Dyspeptic disorders: nausea, vomiting, diarrhea;
- Cholestasis; disorders of liver function;
- Allergic reaction;
- Headache, dizziness;
- Hemolytic anemia,
- Methemoglobinemia in children

up to a year;

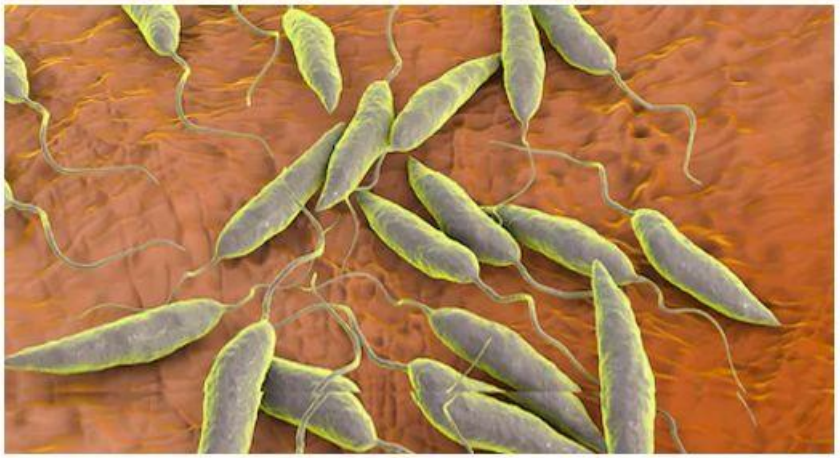
- Arterial hypertension

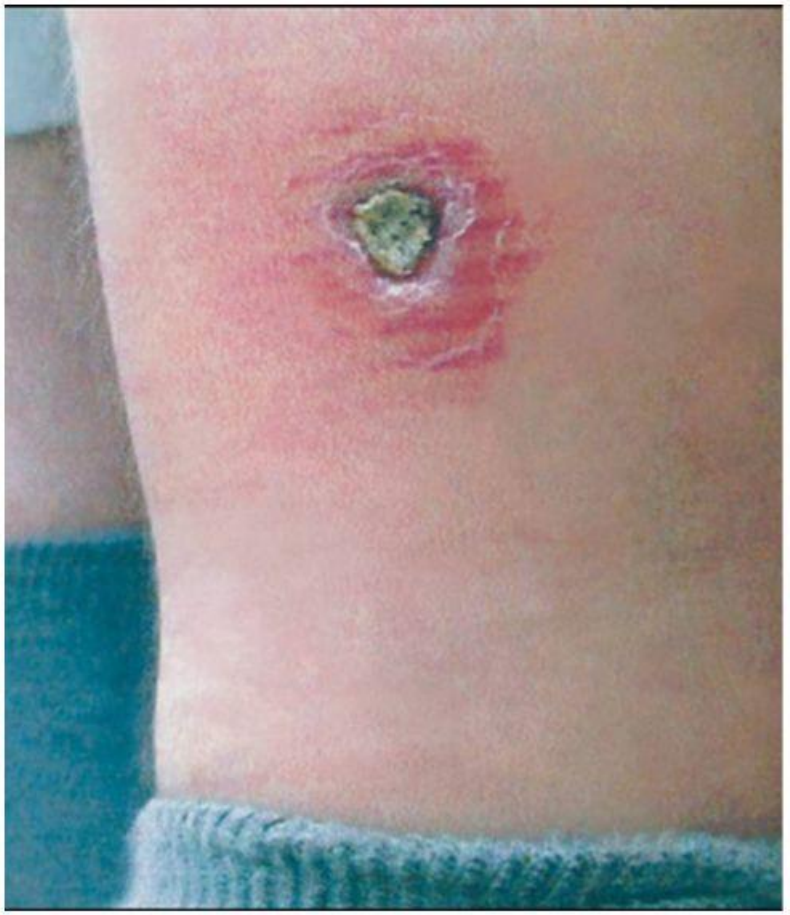


- **Melarsoprol** is used for the treatment of trypanosomal infections. The drug reacts with sulfhydryl groups of various substances, including enzymes in both the organism and host.
- It is administered by slow IV injection and has irritating effect. Adequate trypanocidal concentrations appear in the CSF. The drug has a very short half-life and is rapidly excreted in urine.
- Adverse effects: CNS toxicity, peripheral neuropathy, hypertension, albuminuria; allergy, febrile reactions; hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency.


Infected Tsetse fly transmits trypanosome to human
Trypanosomes enter lymphatics, transform into mature trypomastigote stage and begin to multiply
Trypanosomes further divide and develop in gut of the fly, migrate to salivary glands and undergo further development into infective stage
"Winterbottom's sign" (enlargement of posterior cervical lymph nodes)
Trypomastigotes enter bloodstream and multiply
Trypomastigotes enter brain via CSF
Encephalitis
Trypanosomes ingested by Tsetse fly feeding on infected blood
No risk
At risk
Endemic
High endemic
Epidemic
Trypanosoma brucei gambiense
Trypanosoma brucei rhodesiense
Map adapted from WHO

Leishmania, transmitted by flesh-eating flies, cause various diseases ranging from or mucocutaneous lesions to splenic and hepatic enlargement with fever.





- Solusurminum and Sodium stibogluconate (pentavalent antimony) kills the parasite by inhibition of glycolysis or effects on nucleic acid metabolism.
- Stibogluconate must be administered parenterally and is potentially cardiotoxic (QT prolongation). Alternative agents include fluconazole or metronidazole (for cutaneous lesions), and amphotericin (for mucocutaneous leishmaniasis).

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