

# Anti-Helminthics

**3<sup>rd</sup> Year Pharmacology and  
Toxicology-  
Biomedical Sciences  
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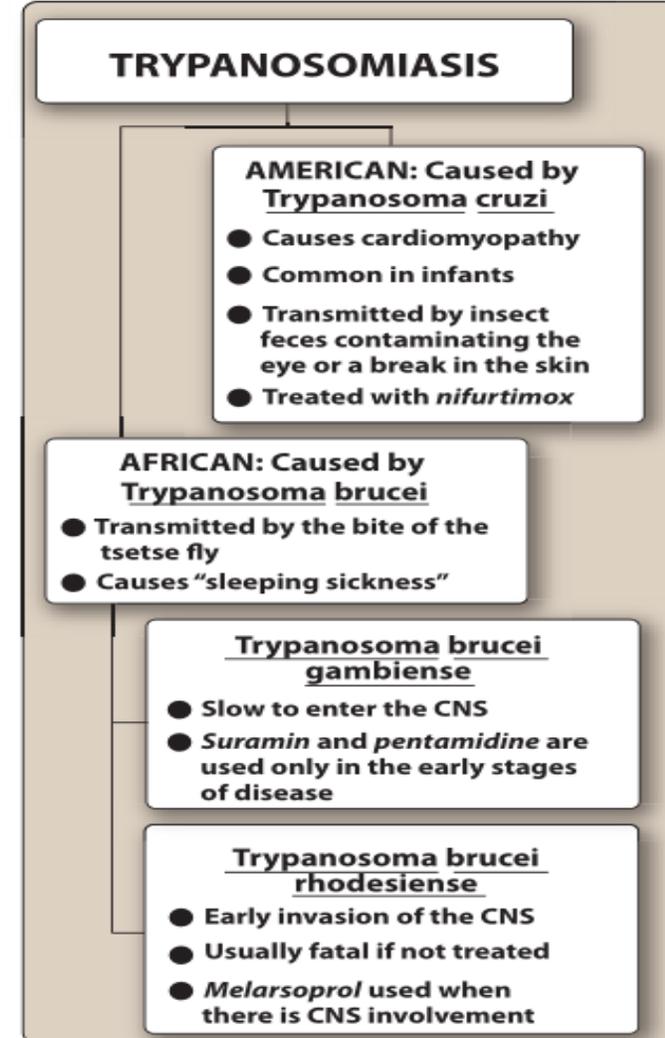
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# Introduction

- Due to human travel and migration, worms (helminthes) can spread to geographic locations that previously had been free of a particular organism
- Three groups of worms: roundworms (nematodes), flukes (trematodes), and tapeworms (cestodes)
- Anthelmintics are drugs that act either locally to expel worms from the GIT or systemically to eradicate adult helminthes or developmental forms that invade organs or tissues
- As with antibiotics, the anthelmintic drugs are aimed at metabolic targets that are present in the parasite
- The geographic distribution of helminthiasis is cosmopolitan. Eradicate: destroy

# Trypanosomiasis

- Trypanosomiasis refers to African sleeping sickness and American sleeping sickness
- Chronic and, eventually, fatal diseases caused by species *Trypanosoma*
- African sleeping sickness, the causative organisms, *T. brucei gambiense* and *T. brucei rhodiense*, initially live and grow in the blood.



# Trypanosomiasis

- The parasite invades the CNS, causing an inflammation of the brain and spinal cord that produces the characteristic lethargy and, eventually, continuous sleep.
- Chagas disease (American sleeping sickness) is caused by *T. cruzi* and occurs in South America.

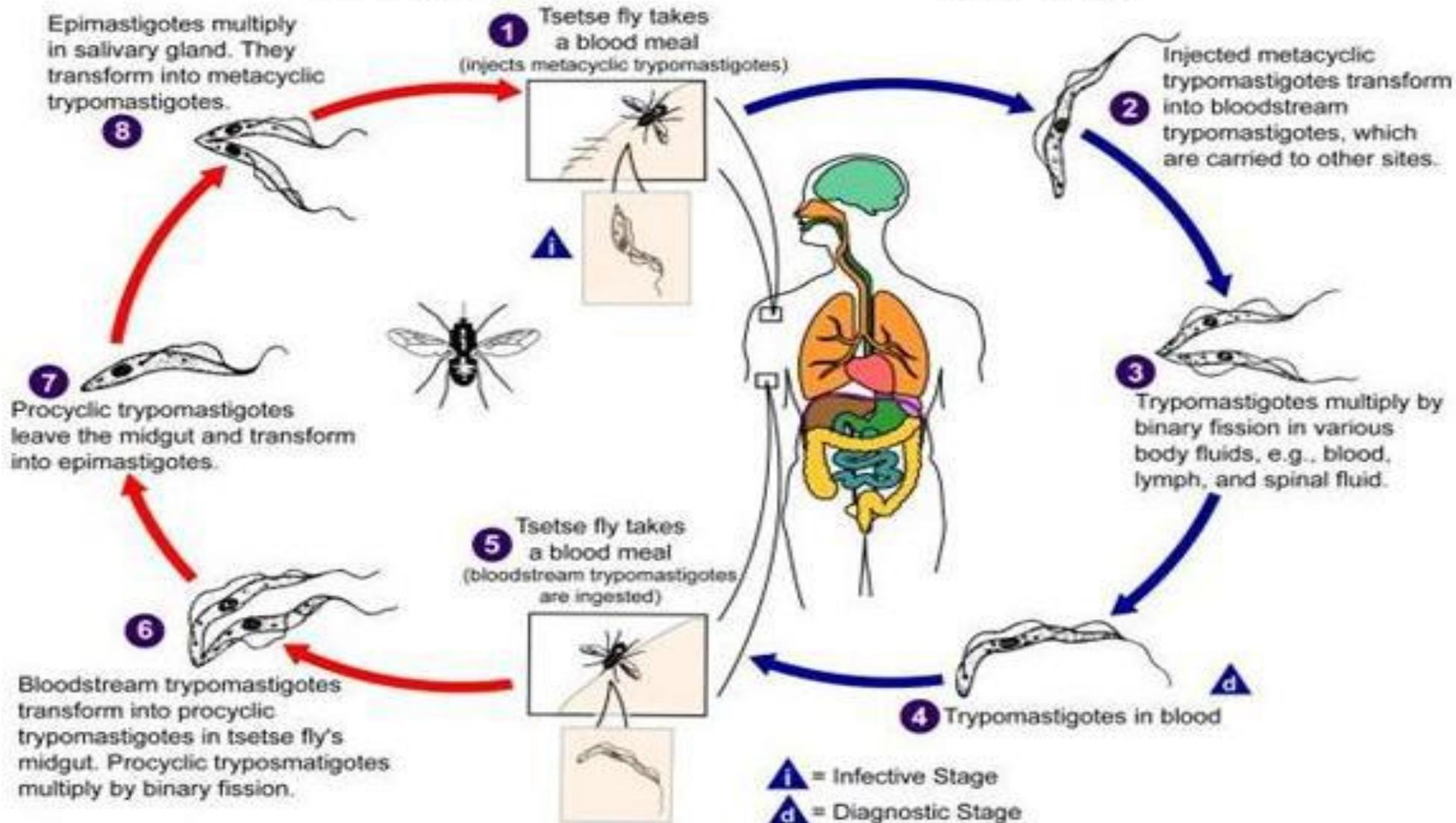
# Sleeping Sickness, African (African trypanosomiasis)

(*Trypanosoma brucei gambiense*)

(*Trypanosoma brucei rhodesiense*)

## Tsetse fly Stages

## Human Stages



# Melarsoprol

- Melarsoprol is a derivative of mers alyl oxide, a trivalent arsenical.
- Its use is limited to the treatment of trypanosomal infections (usually in the late stage with CNS involvement), and it is lethal to these parasites.

## **Mechanism of action:**

- The drug reacts with sulfhydryl groups of various substances, including enzymes in both the organism and host. The parasite's enzymes may be more sensitive than those of the HOST.

# Melarsoprol

- Melarsoprol usually is slowly administered intravenously through a fine needle
- Melarsoprol is, therefore, the agent of choice in the treatment of *T. brucei rhodesiense*, which rapidly invades the CNS, as well as for meningo encephalitis caused by *T. brucei gambiense*.
- The host readily oxidizes melarsoprol to a relatively nontoxic,
- Pentavalent arsenic compound. The drug has a very short half-life and is rapidly excreted in urine

# Adverse Effects

- CNS toxicities are the most serious side effects of melarsoprol treatment.
- Encephalopathy may appear soon after the first course of treatment but usually subsides. In rare cases, however, it may be fatal.
- Hypersensitivity reactions may also occur, and fever may follow injection.
- Gastrointestinal disturbances, such as severe vomiting and abdominal pain, can be minimized if the patient is in the fasting state during drug administration and for several hours thereafter.

# Other Drugs

- **Pentamidine** is active against a variety of protozoal infections
- **Nifurtimox** has found use only in the treatment of acute *T. cruzi* infections (Chagas disease), although treatment of the chronic stage of such infections has led to variable results. [Note: Nifurtimox is suppressive, not curative.]
- **Suramin** is used primarily in the early treatment and, especially, the prophylaxis of African trypanosomiasis.

# Leishmaniasis

- There are three types of leishmaniasis: **cutaneous, mucocutaneous, and visceral.**
- In the visceral type (liver and spleen), the parasite is in the bloodstream and can cause very serious problems.
- Leishmaniasis is transmitted from animals to humans (and between humans) by the bite of infected sandflies.
- The diagnosis is established by demonstrating the parasite in biopsy material and skin lesions.

# Leishmaniasis

- The treatments of leishmaniasis and trypanosomiasis are difficult, because the effective drugs are limited by their toxicities and failure rates.
- Pentavalent antimonials, such as sodium stibogluconate, are the conventional therapy used in the treatment of leishmaniasis, with pentamidine and amphotericin B as backup agents.
- Allopurinol has also been reported to be effective (it is converted to a toxic metabolite by the amastigote form of the organism)

# Sodium stibogluconate

- Sodium stibogluconate is not effective in vitro.
- Therefore, it has been proposed that reduction to the trivalent antimonial compound is essential for activity.
- The exact mechanism of action has not been determined.
- Evidence for inhibition of glycolysis in the parasite at the phosphofructokinase reaction<sup>8</sup> has been found.

# Sodium stibogluconate

- Because it is not absorbed on oral administration, sodium stibogluconate must be administered parenterally, and it is distributed in the extravascular compartment.
- Metabolism is minimal, and the drug is excreted in urine
- Adverse effects include pain at the injection site, gastro-intestinal upsets, and cardiac arrhythmias. Renal and hepatic function should be monitored periodically.

# Toxoplasmosis

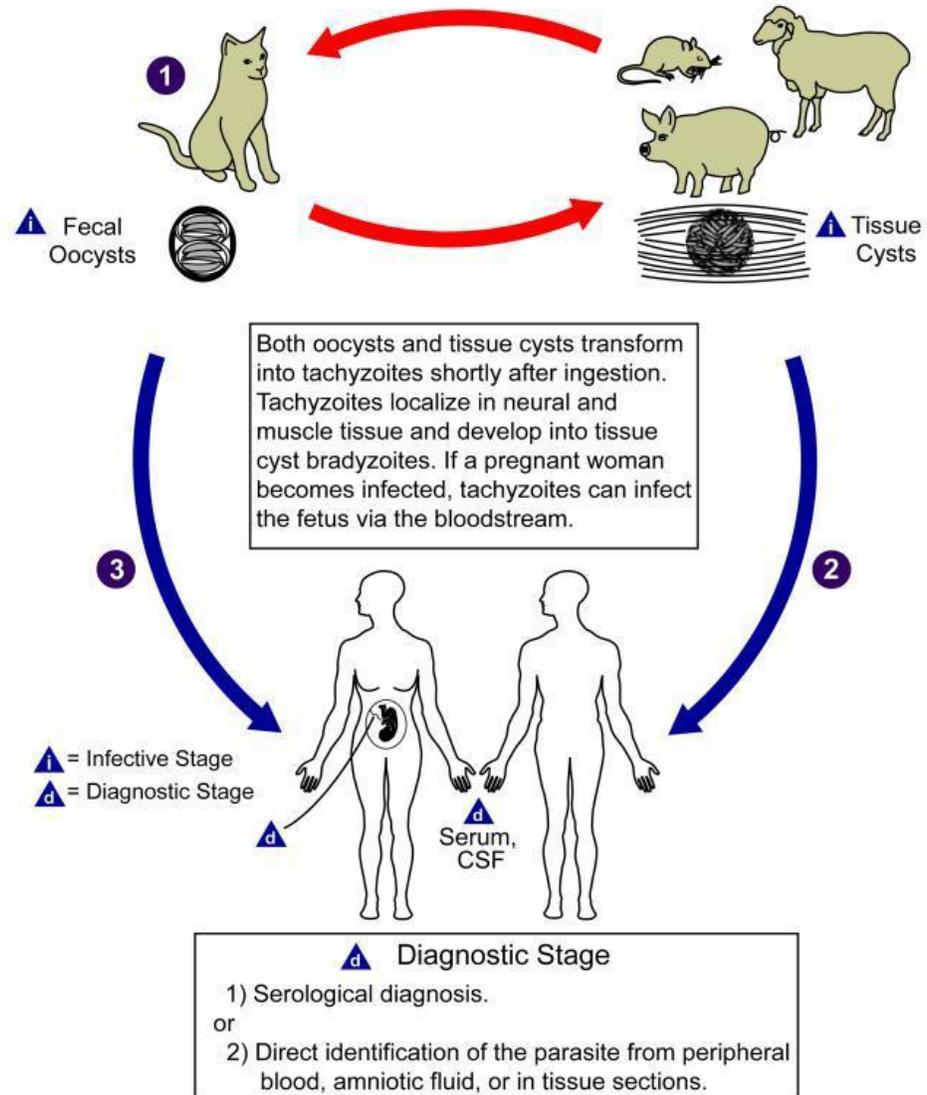
- *Toxoplasma gondii*, which is transmitted to humans when they consume
- raw or inadequately cooked infected meat.
- An infected pregnant woman can transmit the organism to her fetus.
- One of the most common infections in humans is caused by the protozoan

# Toxoplasmosis

- The treatment of choice for this condition is a combination of sulfadiazine and pyrimethamine.
- Leucovorin is commonly administered to protect against folate deficiency.
- Other inhibitors of folate biosynthesis, such as trimethoprim and **sulfamethoxazole, are without therapeutic efficacy in toxoplasmosis.**
- At the first appearance of a rash, pyrimethamine should be discontinued, because hypersensitivity to this drug can be severe

# Toxoplasmosis

(*Toxoplasma gondii*)



# Giardialamblia

- Giardialamblia is the most commonly diagnosed intestinal parasite
- It has only two life-cycle stages: the binucleate trophozoite with four flagellae and the drug-resistant, four-nucleate cyst Ingestion, usually from contaminated drinking water, leads to infection.
- Occasionally, cysts are formed that pass out in stools.
- Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immune-suppressed patients.

# Giardialamblia

- The treatment of choice is metronidazole for 5 days. One alternative agent is tinidazole, which is equally effective as metronidazole in the treatment of giardiasis but with a much shorter course of therapy (2 grams given once).
- Nitazoxanide a nitrothiazole derivative structurally similar to aspirin, was recently
- approved for the treatment of giardiasis. Nitazoxanide is also equally efficacious as metronidazole and, in comparison, has a two-day-shorter course of therapy.

# Helminths

- Three major groups of helminths(worms), nematodes, trematod, and cestodes, infect humans.
- As in all antibiotic regimens, the anthelmintic drugs are aimed at metabolic targets that are present in the parasite
- but are either absent from or have different characteristics than those of the host

**CHEMOTHERAPY OF HELMINTIC  
INFECTIONS: FOR NEMATODES**

*Diethylcarbamazine* **BANOCIDE**

*Ivermectin* **STROMEKTOL**

*Mebendazole* **VERMOX**

*Pyrantel pamoate* **NEMEX**

*Thiabendazole* **MINTEZOL**

**CHEMOTHERAPY OF HELMINTIC  
INFECTIONS: FOR TREMATODES**

*Praziquantel* **BILTRICIDE**

**CHEMOTHERAPY OF HELMINTIC  
INFECTIONS: FOR CESTODES**

*Albendazole* **ALBENZA**

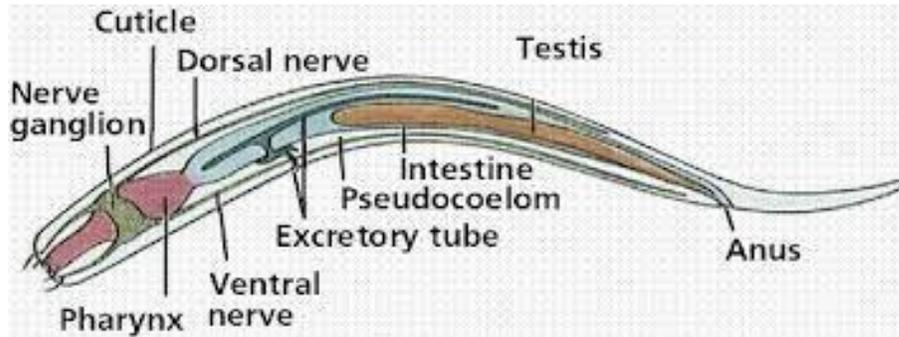
*Niclosamide* **NICLOCIDE**

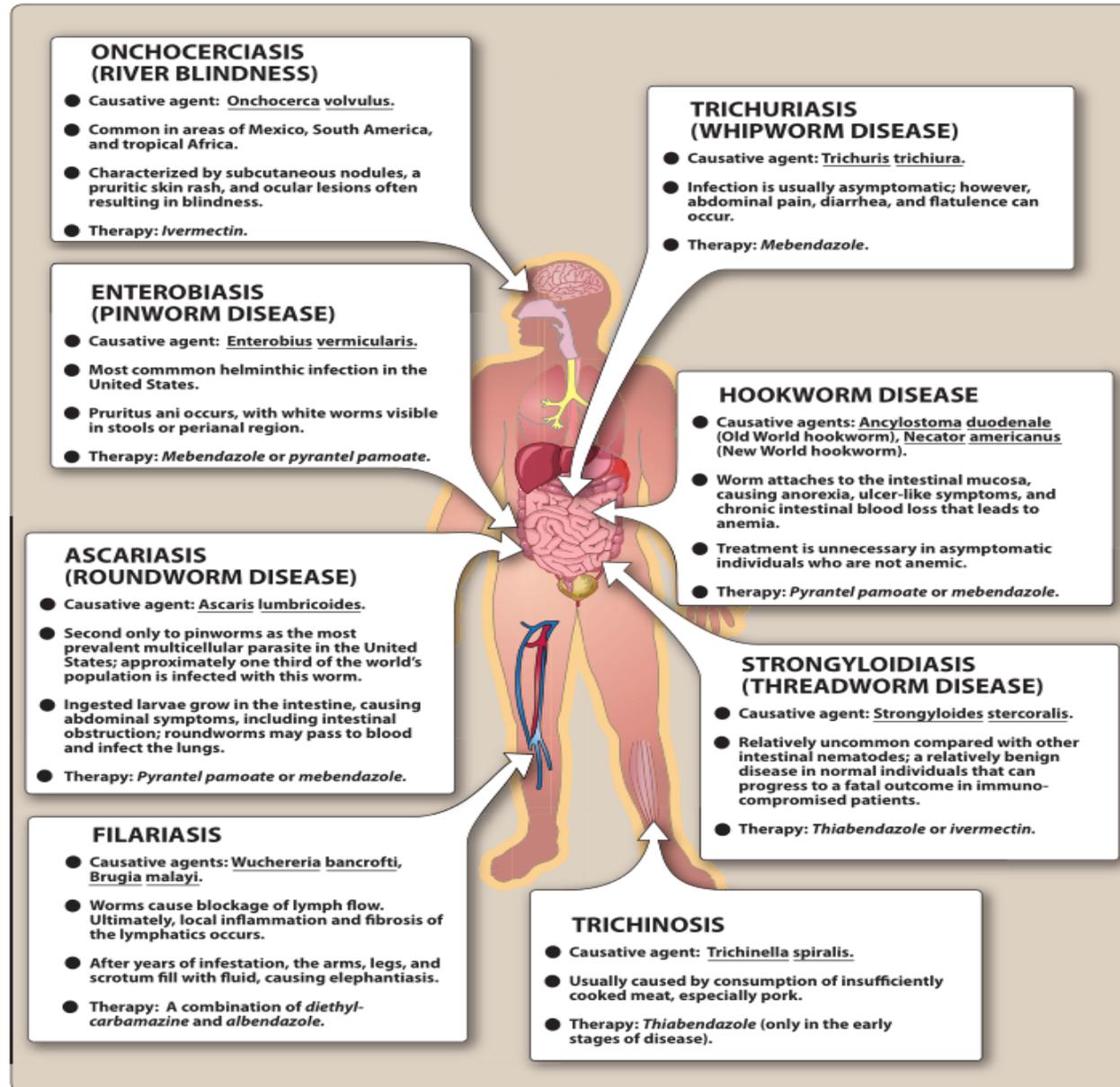
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**Figure 37.1**  
Summary of anthelmintic agents.

# Nematodes

- Nematodes are elongated roundworms that possess a complete digestive system, including both a mouth and an anus.
- They cause infections of the intestine as well as the blood and tissues





**Figure 37.4**  
Characteristics of and therapy for commonly encountered nematode infections.

# Mebendazole

- Mebendazole is a synthetic benzimidazole compound, its effective against a wide spectrum of nematodes.
- It is a drug of choice in the treatment of infections by whipworm (*Trichuris trichiura*), pinworm (*Enterobius vermicularis*), hookworms (*Necator americanus* and *Ancylostoma duodenale*), and roundworm (*Ascaris lumbricoides*).
- Mebendazole acts by binding to and interfering with the assembly of the parasites' microtubules and also by decreasing glucose uptake.

# Mebendazole

- Affected parasites are expelled with feces. Mebendazole is nearly insoluble in aqueous solution.
- Little of an oral dose (that is chewed) is absorbed, unless it is taken with a high-fat meal. It undergoes first-pass metabolism to inactive compounds.
- Mebendazole is relatively free of toxic effects, although patients may **complain of abdominal pain and diarrhea.**

# Thiabendazole

- Thiabendazole another synthetic benzimidazole, is effective against strongyloidiasis caused by *Strongyloides stercoralis* (threadworm), cutaneous larva migrans, and early stages of trichinosis (caused by *Trichinella spiralis*);
- Thiabendazole, like the other benzimidazoles, **affects microtubular aggregation.**
- Although nearly insoluble in water, the drug is readily absorbed on oral administration.

# Thiabendazole

- It is hydroxylated in the liver and excreted in urine.
- The adverse effects most often encountered are dizziness, anorexia, nausea, and vomiting.
- There have been reports of central nervous system (CNS) symptomatology.
- There have been a number of fatalities among the cases of **erythema multiformation** and **Stevens-Johnson syndrome reportedly caused by thiabendazole.**
- Its use is contraindicated during pregnancy.

# Pyrantel Pamoate

- Pyrantel pamoate along with mebendazole, is effective in the treatment of infections caused by roundworms, pinworms, and hookworms
- Pyrantel pamoate is poorly absorbed orally and exerts its effects in the intestinal tract.
- It acts as a depolarizing, neuromuscular-blocking agent, causing persistent activation of the parasite's nicotinic receptors.
- The paralyzed worm is then expelled from the host's intestinal tract.
- Adverse effects are mild and include nausea, vomiting, and diarrhea.

# Ivermectin

- Ivermectin is the drug of choice for the treatment of onchocerciasis (river blindness) caused by *Onchocerca volvulus* and for cutaneous larva migrans and strongyloidiasis.
- Ivermectin targets the parasite's glutamate-gated chloride channel receptors.
- Chloride influx is enhanced, and hyperpolarization occurs, resulting in paralysis of the worm.

# Ivermectin

- The drug is given orally. It does not cross the blood-brain barrier and has no pharmacologic effects in the CNS.
- However, it is contraindicated in patients with meningitis, because their blood-brain barrier is more permeable, making CNS effects possible. Ivermectin is also contraindicated in pregnancy.
- The killing of the microfilaria can result in a Mazotti-like reaction (fever, headache, dizziness, somnolence, and hypotension).

# Diethylcarbamazine

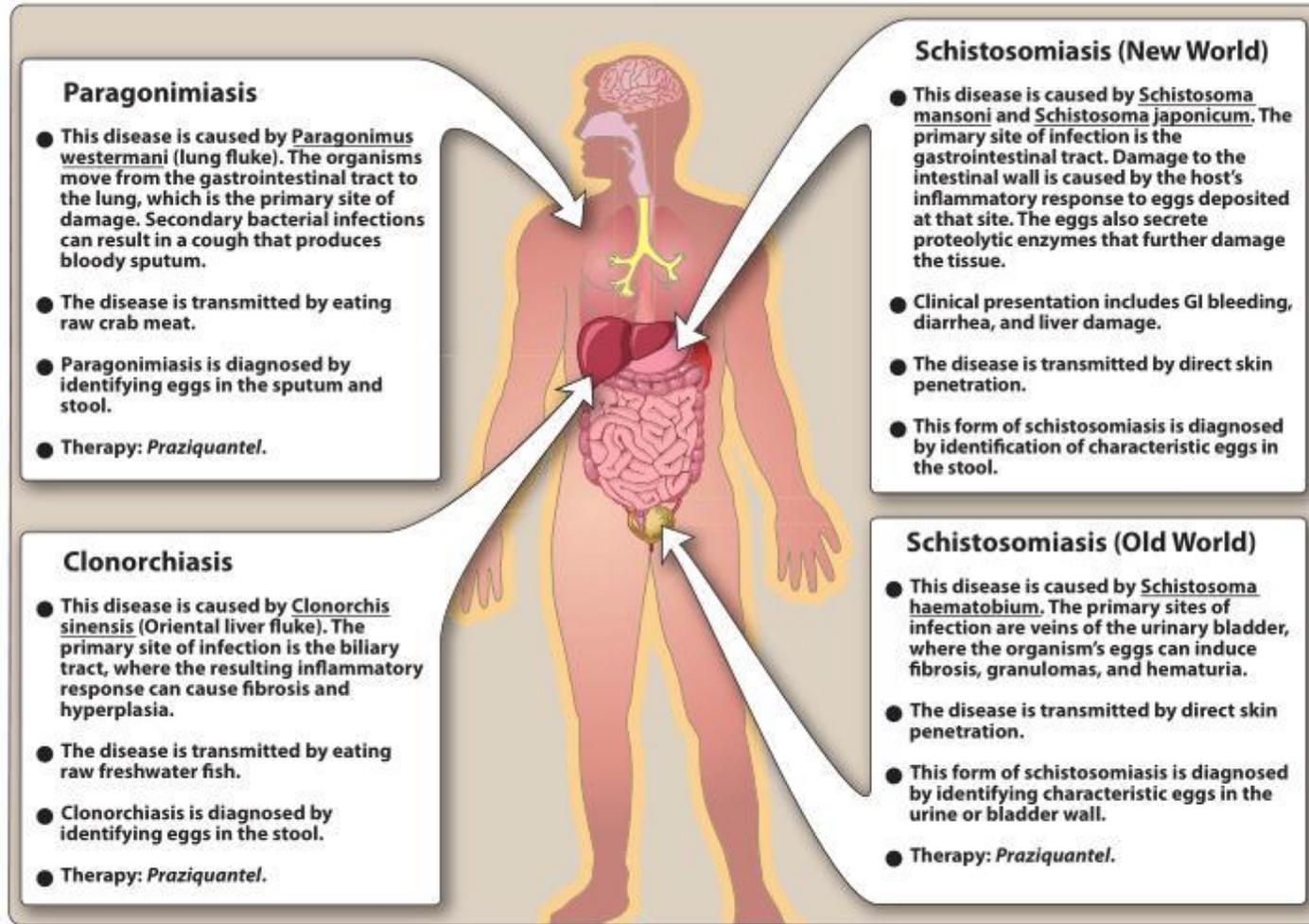
- Diethylcarbamazine is used in the treatment of filariasis because of its ability to immobilize microfilariae and render them susceptible to host defense mechanisms.
- Combined with albendazole, diethylcarbamazine is effective in the treatment of *Wuchereria bancrofti* and *Brugia malayi* infections.
- It is rapidly absorbed following oral administration with meals and is excreted primarily in urine.

# Diethylcarbamazine

- Urinary alkalosis and renal impairment may require dosage reduction. Adverse effects are primarily caused by host reactions to the killed organisms.
- Symptoms include fever, malaise, rash, myalgias, arthralgias, and headache, and their severity is related to parasite load.
- Most patients have leukocytosis.
- Antihistamines or steroids may be given to ameliorate many of the symptoms.

# The trematodes (flukes)

- The trematodes (flukes) are leaf-shaped flatworms that are generally characterized by the tissues they infect.
- For example, they may be categorized as liver, lung, intestinal or blood
- Trematode infections are generally treated with Praziquantel
- Praziquantel is an agent of choice for the treatment of all forms of schistosomiasis and other trematode infections and for cestode infections like cysticercosis.



**Figure 37.5**  
Characteristics of and therapy for commonly encountered trematode infections.

# Praziquantel

- Praziquantel is rapidly absorbed after oral administration and distributes into the cerebrospinal fluid.
- High levels occur in bile. The drug is extensively metabolized oxidatively, resulting in a short half-life.
- Permeability of the cell membrane to calcium is increased, causing contracture and paralysis of the parasite.
- The metabolites are inactive and are excreted through urine and bile.
- Common adverse effects include drowsiness, dizziness, malaise, and anorexia as well as gastrointestinal upsets.

# Praziquantel

- The drug is not recommended for pregnant women or nursing mothers.
- Drug interactions due to increased metabolism have been reported with dexamethasone, phenytoin, and carbamazepine.
- Cimetidine, which inhibits cytochrome P450 isozymes, causes increased praziquantel levels.
- Praziquantel is contraindicated for the treatment of ocular cysticercosis, because destruction of the organism in the eye may damage the organ

# Chemotherapy cestodes

- The cestodes, or —true tapeworms,|| typically have a flat, segmented body and attach to the host's intestine.
- Like the trematodes, the tapeworms lack a mouth and a digestive tract throughout their life cycle.

# Albendazole

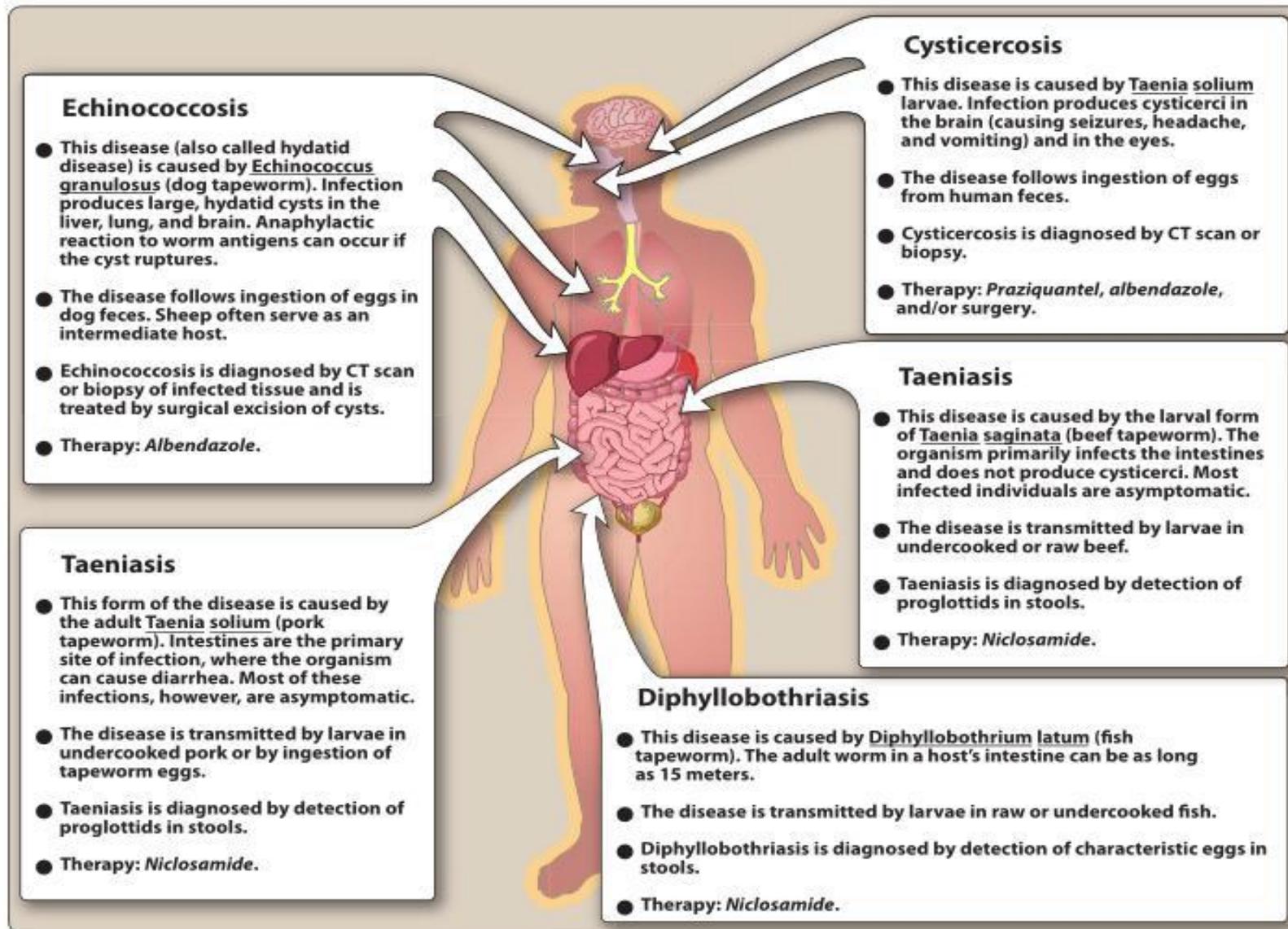
- **Albendazole** is a benzimidazole that, like the others, inhibits microtubule synthesis and glucose uptake in nematodes.
- Its primary therapeutic application, however, is in the treatment of cestodal infestations, such as **Neurocysticercosis (caused by Taenia solium larvae) and Hydatid disease (caused by Echinococcus granulosus)**

# Albendazole

- Albendazole is erratically absorbed after oral administration, but absorption is enhanced by a high-fat meal.
- It undergoes extensive first-pass metabolism, including formation of the sulfoxide, which is also active.
- Albendazole and its metabolites are primarily excreted in urine.
- When used in short-course therapy (1–3 days) for nematodal infestations, adverse effects are mild and transient and include headache and nausea.

# Albendazole

- Treatment of hydatid disease (3 months) has a risk of hepatotoxicity and, rarely, agranulocytosis or pancytopenia.
- Medical treatment of neurocysticercosis is associated with inflammatory responses to dying parasites in the CNS, including headache, vomiting, hyperthermia, convulsions, and mental changes.
- The drug should not be given during pregnancy or to children under 2 years of age.



**Figure 37.6**  
 Characteristics of and therapy for commonly encountered cestode infections.

THANK YOU

GOOD DAY