Protozoal infections

1. Amebiasis
2. Malaria
3. Giardiasis
4. Leshmaniasis
5. Toxoplasmosis
6. Trypanosomiasis

Protozoal infections

1. Protozoal cells (Eukaryotes) have metabolic processes closer to human host than prokaryotic bacterial pathogens.
2. Difficult to be treated than bacterial infections.
3. Many of antiprotozoal drugs cause toxic effects on the host.
4. Cells with high metabolic processes in the host are susceptible.
5. Bone marrow, renal tubular, intestinal, neuronal.
6. Antiprotozoal are not safe during pregnancy.

Antiprotozoal Drugs

1. Chemotherapy for amebiasis
2. Chemotherapy for malaria
3. Chemotherapy for giardiasis
4. Chemotherapy for leshmaniasis
5. Chemotherapy for toxoplasmosis
6. Chemotherapy for trypanosomiasis

AMOEBIASIS

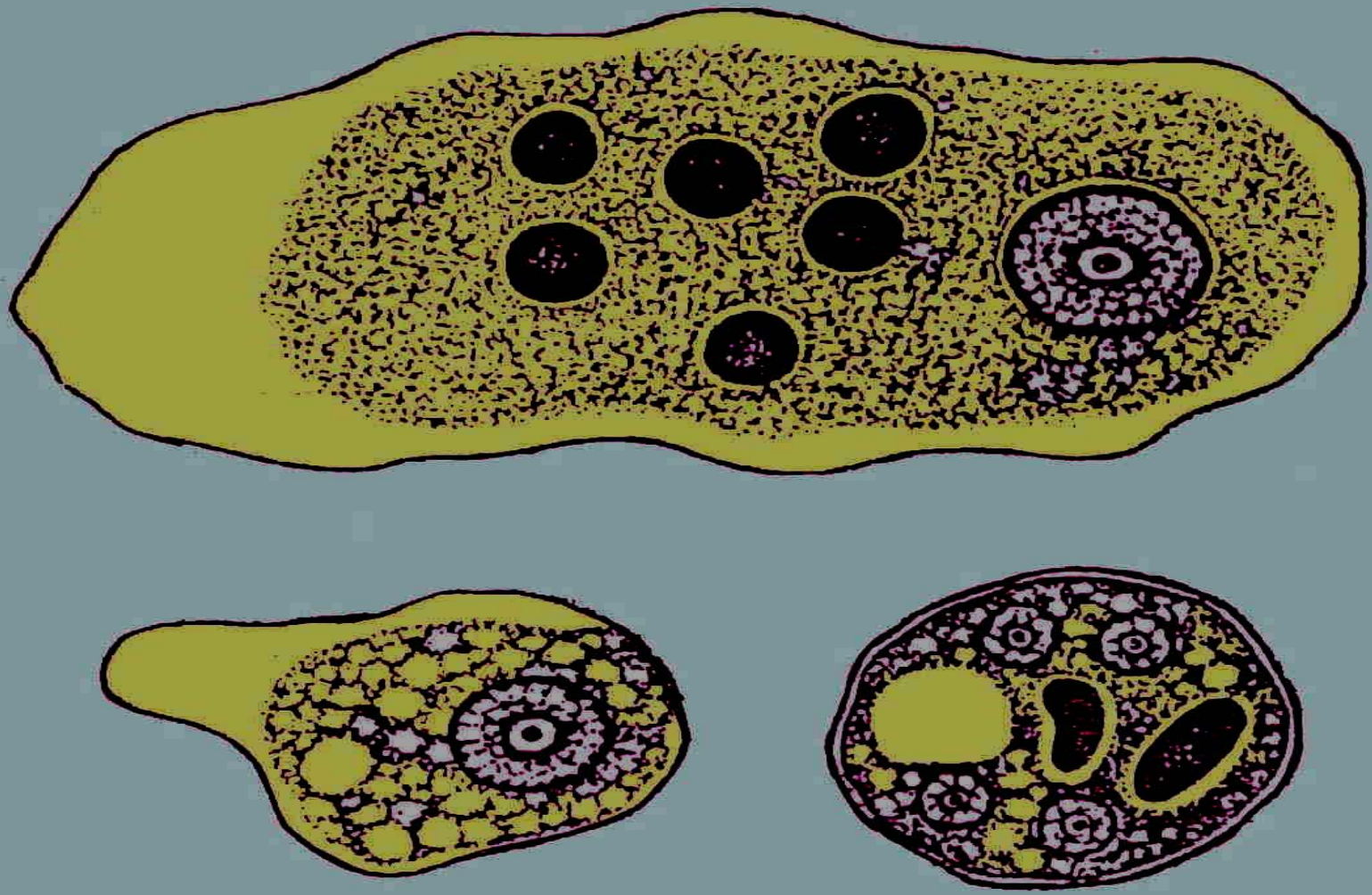


Fig. 46.—Amoebiasis. *E. histolytica*. Trophozoite with ingested erythrocytes to cysts. (*From an original drawing by B. Jobling*)

Amebiasis occurs due to ingestion of foods contaminated with **Entameba Histolytica cysts**

LIFE CYCLE

Entamoeba histolytica exists in two forms:

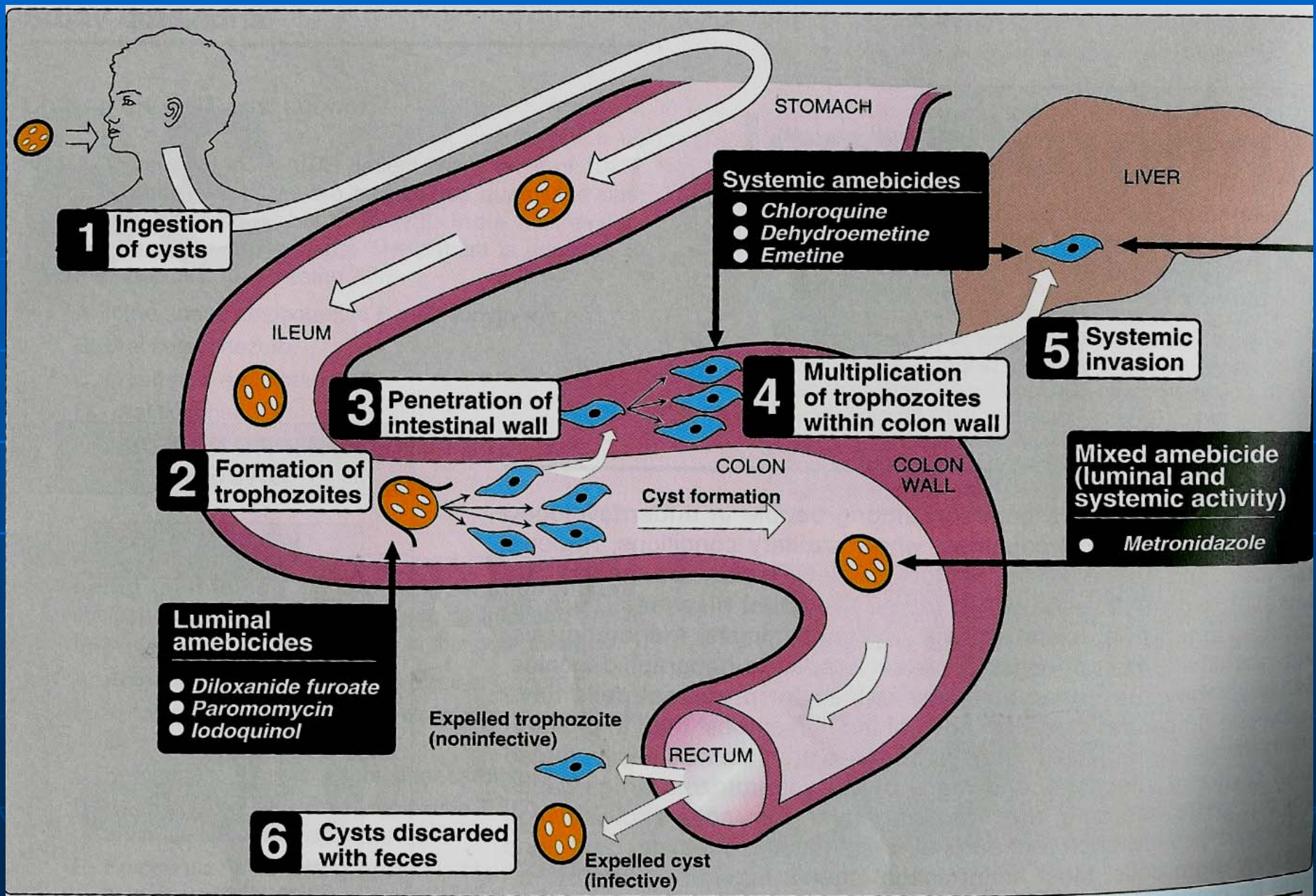
1. Cysts (infective):

- can survive outside the human body.
- transform to trophozoites.

2. Trophozoites (non-infective; invasive):

- Reproduce
- invade wall of large intestine, causing ulceration and may migrate to other tissues, especially the liver.
- transform to cysts which are excreted in feces.

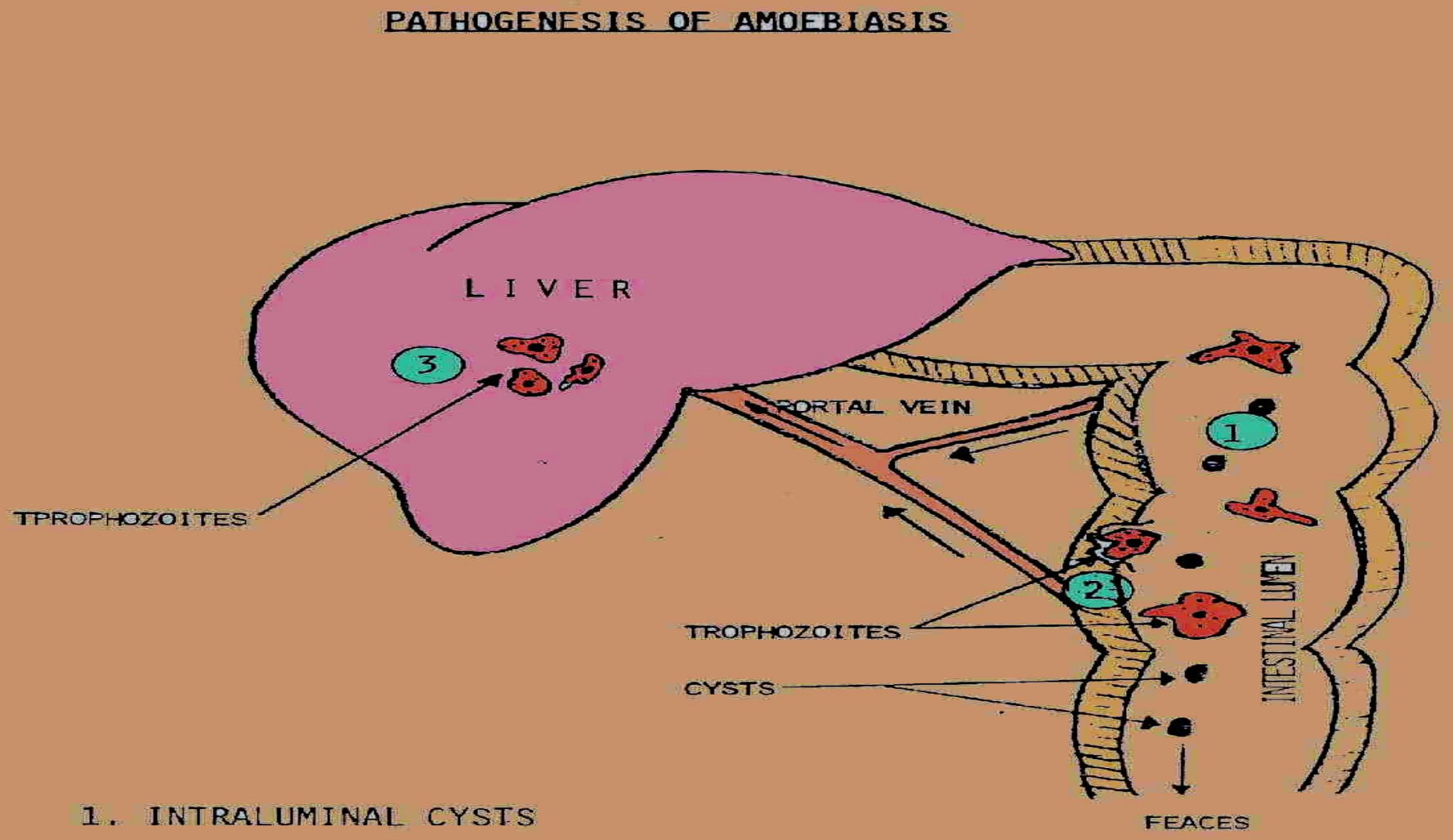
LIFE CYCLE


STOMACH
LIVER
1 Ingestion of cysts
Systemic amebicides
Chloroquine
Dehydroemetine
Emetine
ILEUM
5 Systemic invasion
3 Penetration of intestinal wall
4 Multiplication of trophozoites within colon wall
2 Formation of trophozoites
COLON
COLON WALL
Cyst formation
Mixed amebicide (luminal and systemic activity)
Metronidazole
Luminal amebicides
Diloxanide furoate
Paromomycin
Iodoquinol
Expelled trophozoite (noninfective)
RECTUM
6 Cysts discarded with feces
Expelled cyst (infective)

Life Cycle

1. Cysts ingestion.
2. Formation of trophozoites
3. Penetration of intestinal wall
4. Multiplication of trophozoites within colon wall.
5. Systemic invasion.
6. Cyst formation in rectum and excretion in feces.

PATHOGENESIS OF AMOEBIASIS



CLINICAL PRESENTATIONS

- Asymptomatic Intestinal infection (Carriers, passing cysts)
- Mild to moderate intestinal disease (Nondysenteric Colitis)
- Severe Intestinal infection (Dysentery)
- Hepatic abscess
- Ameboma (localized granulomatous lesion of colon)
- Extraintestinal disease (other than hepatic abscess).

ANTIAMEBIC DRUGS

- Luminal Amebicides
- Tissue or systemic amebicides
- Mixed Amebicides

LUMEN AMOEBICIDES

- **Acts on the parasites in the lumen of the bowl.**
- **used for treatment of asymptomatic amebiasis.**

Include

- **Diloxanide Furoate**
- **Halogenated Hydroxyquinolines**
  - **Iodoquinol**
- **Antibiotics**
  - **Tetracyclines**
  - **Paramomycin**
  - **Erythromycin**

Tissue Amoebicides (systemic)

- **acts principally in the intestinal wall and liver (or any other extra-intestinal tissue).**
- **Used for treatment of systemic form of the disease (liver absesses or intestinal wall infection).**
- **Emetine**
- **Dehydroemetine**
- **Chloroquine (liver only)**

Luminal amebicides

- **Acts on the parasites in the lumen of the bowl.**
- **Should be used for treatment of asymptomatic amebiasis.**
- **Include**
  - **Iodoquinol**
  - **Diloxanide furoate**
  - **Paromomycin**

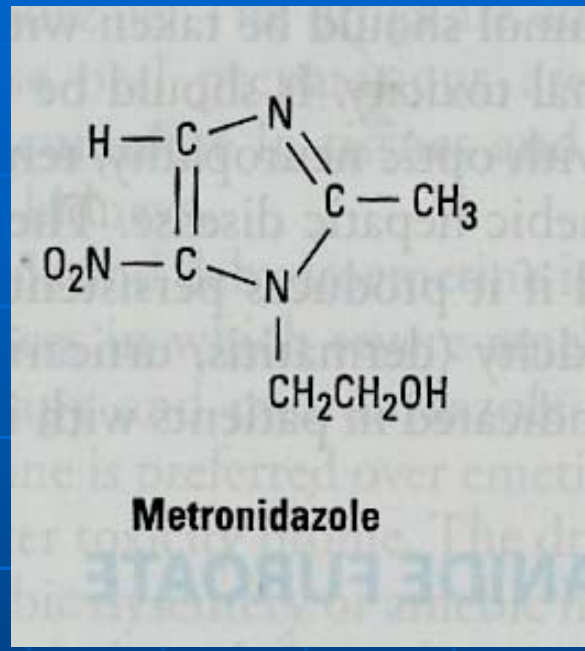
Mixed AMOEBICIDES

Effective against both luminal and systemic forms of the disease. Although luminal concentration is too low for single drug – treatment.

- **Metronidazol**
- **Tinidazole**

METRONIDAZOLE

- Mixed amoebicide.
- Drug of choice for intestinal & extraintestinal amoebiasis.
- Acts on trophozoites.
- Has no effect on cysts.
- Nitro group of metronidazole is reduced by protozoan leading to cytotoxic reduced product that binds to DNA and proteins resulting into parasite death.



Metronidazole

Pharmacokinetics

- Given orally or IV.
- Absorption is rapid and complete.
- Due to rapid absorption from GIT, less effective against parasites in the lumen.
- Wide distribution to all tissues and body fluids (CSF, saliva, milk).
- Plasma protein binding is low (< 20%).
- Plasma half life is 8 h

Pharmacokinetics

- Metabolized by oxidation in liver by mixed function oxidase followed by glucouronylation.
- Excreted in urine as unchanged drug plus metabolites.
- Clearance is decreased in liver impairment.

Clinical Uses

- Amoebiasis (with luminal amebicide).
- Giardiasis (Giardia intestinalis)
- Trichomoniasis (trichomonas vaginalis)
- Broad spectrum of Anaerobic bacteria e.g.,
  - Helicobacter pylori infection (H Pylori)
  - Pseudomembranous colitis (Clostridium defficile).

Adverse effects

Tinidazole has better toxicity profile than metronidazole, but is equally active

1. GIT:

- **Nausea**
- **Vomiting**
- **Dry mouth**
- **Metallic taste**
- **Diarrhoea**
- **Oral Thrush (Moniliasis, yeast infection).**

Adverse effects

2. CNS: Neurotoxicological effect

- **Insomnia**
- **Dizziness**
- **peripheral neuropathy**
- **Numbness or paresthesia in peripheral nervous system**
- **ataxia, encphalopathy, convulsion (rare).**

3. Dysuria, dark urine.

4. Neutropenia

5. Disulfiram-like effect if taken with alcohol.

disulfiram like -effect

When metronidazole is given with alcohol abdominal distress, nausea, vomiting, flushing, or headache, tachycardia, hyperventilation

Drug interactions:

- Enzyme inhibitors (cimetidine, ketoconazole)
- Inducers (phenytoin and phenobarbitone, rifampin).
- inhibits CYP family 2C9 & 3A4
- Potentiate anticoagulant effect of warfarin.
- potentiates lithium toxicity.
- disulfiram --- confusional & psychotic states

CONTRAINDICATIONS / PRECAUTIONS:

- Pregnancy and nursing women.
- Alcohol intake
- CNS diseases
- Severe hepatic disease
- Severe renal disease

EMETINE AND DEHYDROEMETINE

Chemistry:

- Emetine hydrochloride is a plant alkaloid derived from ipeca.
- Dehydroemetine is a synthetic analogue

Pharmacokinetics:

- Erratic oral absorption.
- Given preferably subcutaneously but could be given by IM, NEVER I.V.
- Plasma half life is 5 days.

EMETINE

- Concentrated in Liver, Lungs, Spleen, Kidney, Cardiac muscle and Intestinal wall.
- Metabolized & Excreted slowly via kidney so it has a **cumulative effect.**
- Trace amounts could be detected in urine 1-2 month after last dose.
- Should not be used for more than 10 days (usually 3-5 days).

Pharmacological Actions

- Act on trophozoites causing irreversible block of protein synthesis.
- Depress cardiac conduction & contraction arrhythmia, heart failure and death.
- Antiadrenergic action may lead to hypotension.
- Nausea & vomiting of central origin.
- Decreases serum potassium.

Clinical Uses

- Amoebic liver abscess.
- Intestinal wall infections.
- Severe forms of **acute amoebic dysentery** dehydroemetine + tetracycline for a short period followed by metronidazole.

Adverse Effects

- Dehydroemetine is less toxic than emetine
- pain at site of injection, abcesses.
- GIT: nausea, vomiting, diarrhoea.
- Neuromuscular weakness
- Serious toxicities: cardiotoxicity
  - cardiac arrhythmias,
  - Hypotension
  - congestive heart failure

Contraindications

- Heart disease
- Kidney disease
- Pregnancy
- Children

Chloroquine

- Antiamebic drug
- Antimalarial drug
- Used in combination with metronidazole and diloxanide furoate for amebic liver diseases.

LUMEN AMOEBICIDES

- **Acts on the parasites in the lumen of the bowl.**
- **used for treatment of asymptomatic amebiasis.**

Include

- **Diloxanide Furoate**
- **Halogenated Hydroxyquinolines**
  - **Iodoquinol**
- **Antibiotics**
  - **Tetracyclines**
  - **Paramomycin**
  - **Erythromycin**

LUMEN AMOEBICIDES

DILOXANIDE FUROATE

Chemistry

- Dichloroacetamide
- Ester of diloxanide + furoic acid .

Pharmacokinetics

- Given orally.
- Split in the intestine, most of diloxanide is absorbed, conjugated to form a glucoronide which is excreted in urine (90%).
- The unabsorbed moiety being the amoebicidal agent (10%).

Pharmacodynamics:

- Unkown mechanism of action
- Direct amoebicidal action against luminal forms.
- Not active against tissue trophozoites.

Therapeutic Uses

- Drug of choice for **asymptomatic Intestinal infection**
- For eradication of infection given along with tissue amoebicide (metronidazole).
- Dose:500 mg three times/day for 10 days.

Adverse Effects

- Flatulence
- Nausea, vomiting, abdominal cramps.
- No serious adverse effects

Contraindications:

- Pregnancy
- Children (less than 2 years).

Paromomycin Sulphate

- Aminoglycoside, not absorbed.
- Effective against luminal forms of ameba

Mechanism of action

- Direct amebicidal action (causes leakage by its action on cell membrane of parasite).
- Indirect killing of bacterial flora essential for proliferation of pathogenic amoebae.

Kinetics

- Orally
- Not significantly absorbed from the GIT
- Small amount absorbed is excreted unchanged in urine (may accumulate with renal insufficiency).

Adverse effects

- Gastrointestinal distress and diarrhea.

Precautions

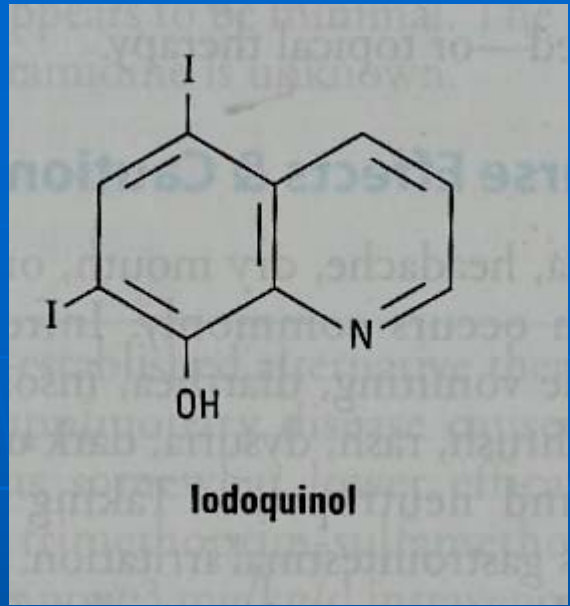
- Severe renal disease
- patients with GIT ulceration

Tetracyclines

- Very weak direct amoebicidal action.
- Mainly act indirectly on bacterial flora.
- Used in severe cases of amoebic dysentery not responding to metronidazole combined with dehydroemetine.

HALOGENATED HYDROXYQUINOLINES

- **Iodoquinol**
- **Cliquinol**



Iodoquinol

Mechanism of action

- **Unknown**
- **Effective against organisms in GIT only Not intestinal wall or liver.**

Pharmacokinetics

- **Absorption is poor (90%), excreted in feces.**
- **10% enter circulation, excreted as glucouronide in urine.**
- **Half life is 11-14 h**

Uses

- lumen amoebicide.
- For eradication of infection given along with tissue amoebicide (metronidazole).

Adverse Effects

- Peripheral neuropathy including optic neuritis
- GIT: Nausea, vomiting, diarrhoea.
- Enlargement of the thyroid gland.
- Agranulocytosis.
- Iodine sensitivity.
- Drug interfere with thyroid function tests (increase protein-bound serum iodine, decrease in measured ^{131}I uptake).

Contraindications

- Optic neuropathy
- Thyroid disease
- Sensitivity to iodine
- Severe liver disease
- Severe kidney disease
- **discontinued** if it produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticaria, pruritus, fever)

CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	*Iodoquinol* or *Paromycin* or *Diloxanide furoate*
Diarrhea/dysentery Extraintestinal	*Metronidazole* plus *Iodoquinol* or *Paromycin* or *Diloxanide furoate*
Amebic liver absess	*Chloroquine* plus *Metronidazole* or *Emetine*

Table 53–4. Treatment of amebiasis.[1]

Clinical Setting	Drugs of Choice and Adult Dosage	Alternative Drugs and Adult Dosage
Asymptomatic intestinal infection	Luminal agent: Diloxanide furoate,[2] 500 mg 3 times daily for 10 days *or–* Iodoquinol, 650 mg 3 times daily for 21 days *or–* Paromomycin, 10 mg/kg 3 times daily for 7 days	
Mild to moderate intestinal infection	Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days *plus–* Luminal agent (see above)	Luminal agent (see above) *plus either–* Tetracycline, 250 mg 3 times daily for 10 days *or–* Erythromycin, 500 mg 4 times daily for 10 days
Severe intestinal infection	Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days *plus–* Luminal agent (see above)	Luminal agent (see above) *plus either–* Tetracycline, 250 mg 3 times daily for 10 days *or–* Dehydroemetine[3] or emetine,[2] 1 mg/kg SC or IM for 3–5 days
Hepatic abscess, ameboma, and other extraintestinal disease	Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days *plus–* Luminal agent (see above)	Dehydroemetine[3] or emetine,[2] 1 mg/kg SC or IM for 8–10 days, followed by (liver abscess only) chloroquine, 500 mg twice daily for 2 days, then 500 mg daily for 21 days *plus–* Luminal agent (see above)