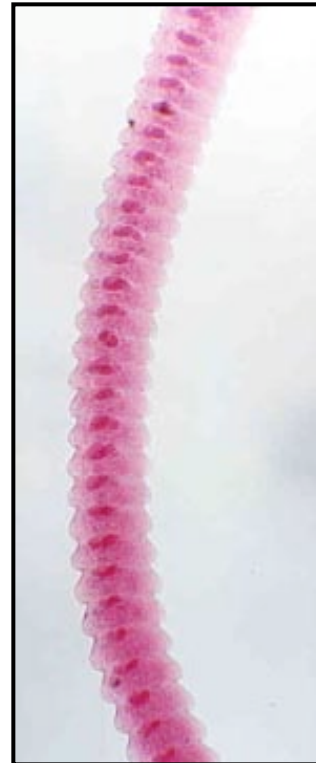


Hymenolepis nana

- Dwarf tapeworm
- **Definitive Host:** Humans, rodents
 - Most common tapeworm of humans in the world
 - 1% rate of infection in the southern U.S.
 - 97.3% rate of infection in Moscow, Russia
- **Intermediate Host:** Larval and adult beetles (but optional)
 - Larval stage, cysticercoid, can develop in D.H. if it eats the eggs
 - Probably a recent evolutionary event?!?



Hymenolepis nana

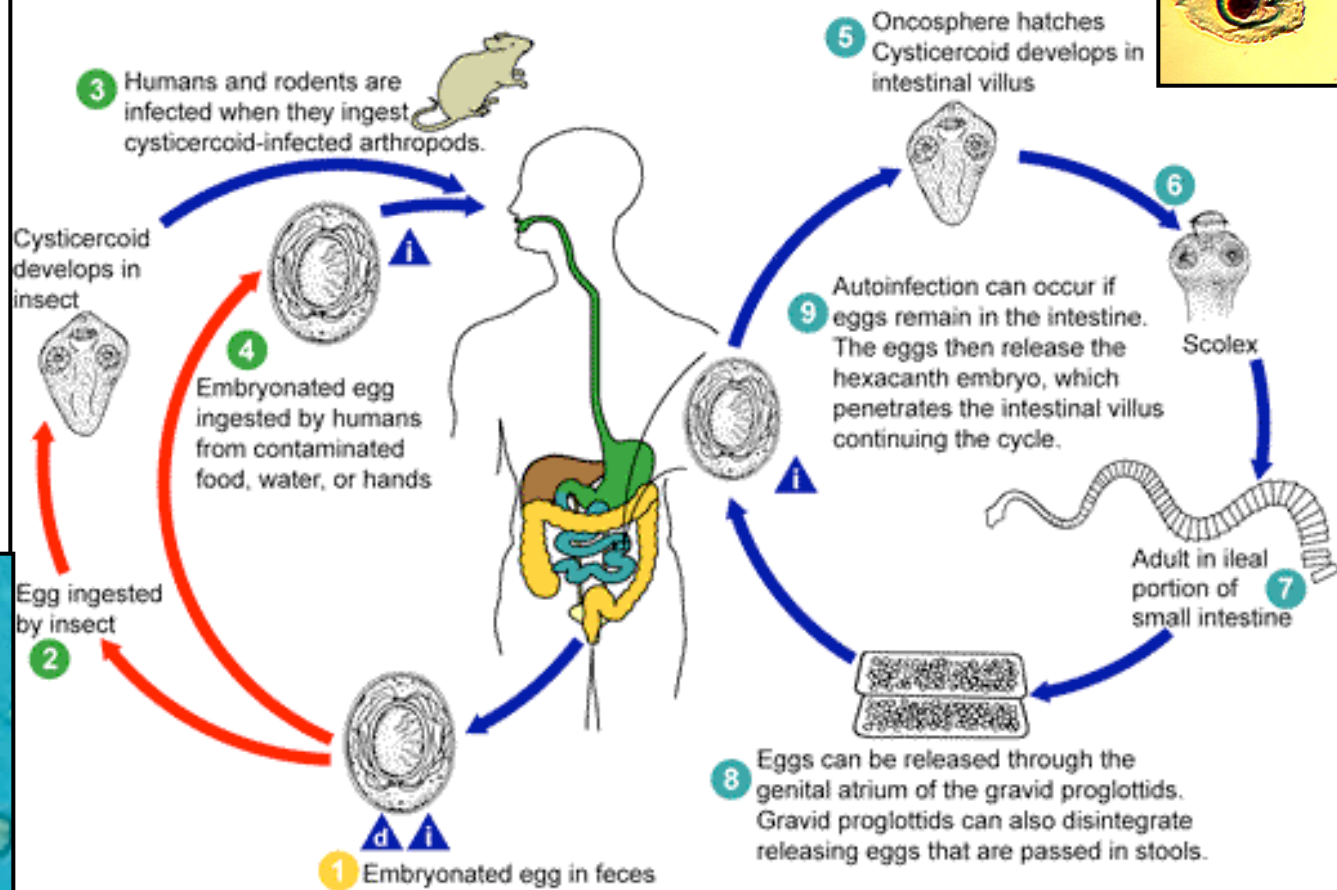
- **Geographic distribution:**
Cosmopolitan.
- **Mode of Transmission:**
 - Ingestion of infected beetle
 - Ingestion of food contaminated with feces (human or rodent)
 - Fecal/oral contact
- **Control:**
remove rodents from house
- **Pathology and Symptoms:**
Generally none because worm is so small (about 40 mm).



Cysticercoid

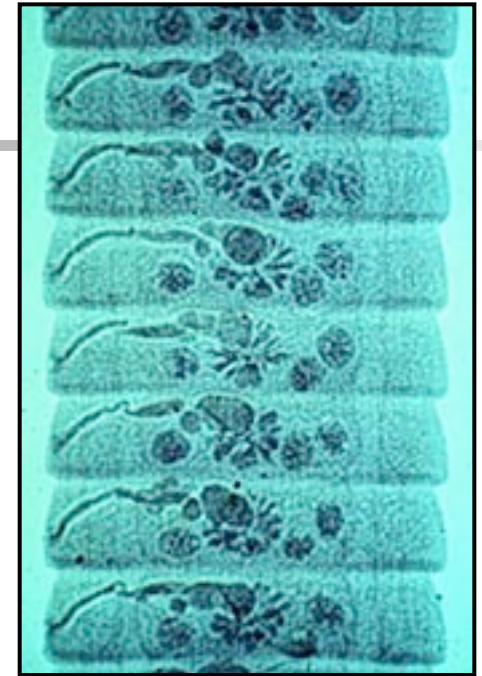
Hymenolepis nana life cycle

i = Infective Stage
d = Diagnostic Stage



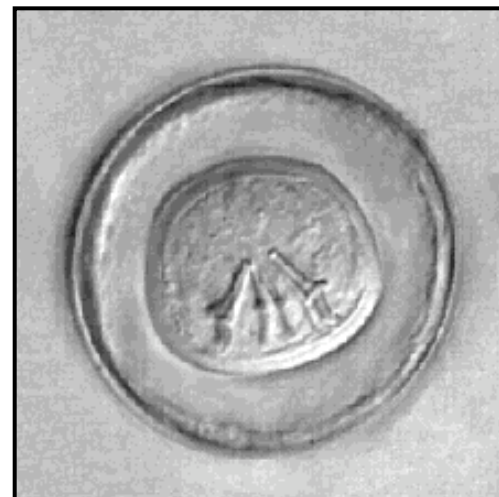
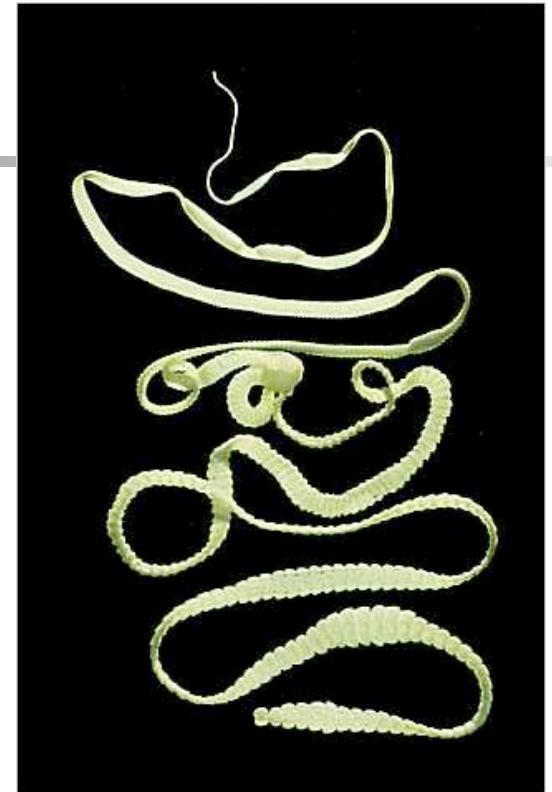
Hymenolepis diminuta

- Rat tapeworm
- **Definitive Host:** Humans and rats
 - Human infections are uncommon
- **Intermediate Host:** grain beetles (*Tribolium*)
 - Required
- **Geographic Distribution:** Cosmopolitan
- **Mode of Transmission to D.H.:** Ingestion of infected beetle.

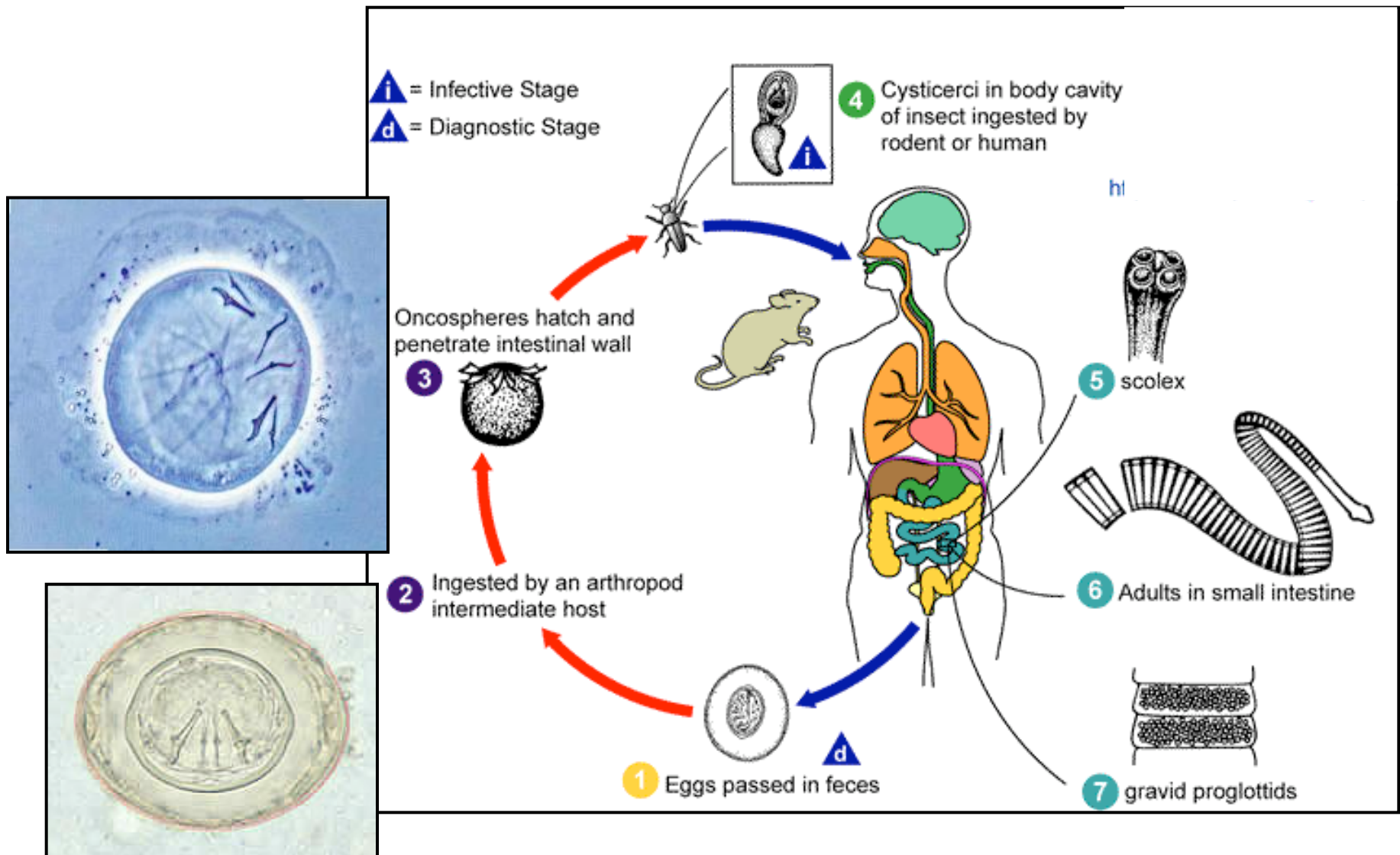


Hymenolpeis diminuta

- **Pathology:** Usually asymptomatic
 - because worms are relatively small (90 cm maximum).
- Heavy infections are rare.
 - No fecal/oral infection
- **Diagnosis:** Eggs in feces. Eggs do not have polar filaments.
- **Treatment:** Praziquantel
- **Prevention:** Remove rats from home.
- **Notes:** Easily maintained in laboratories so has been used as the “model” tapeworm to study metabolism, reproduction, genetics, physiology, etc.



H. diminuta human infections are rare

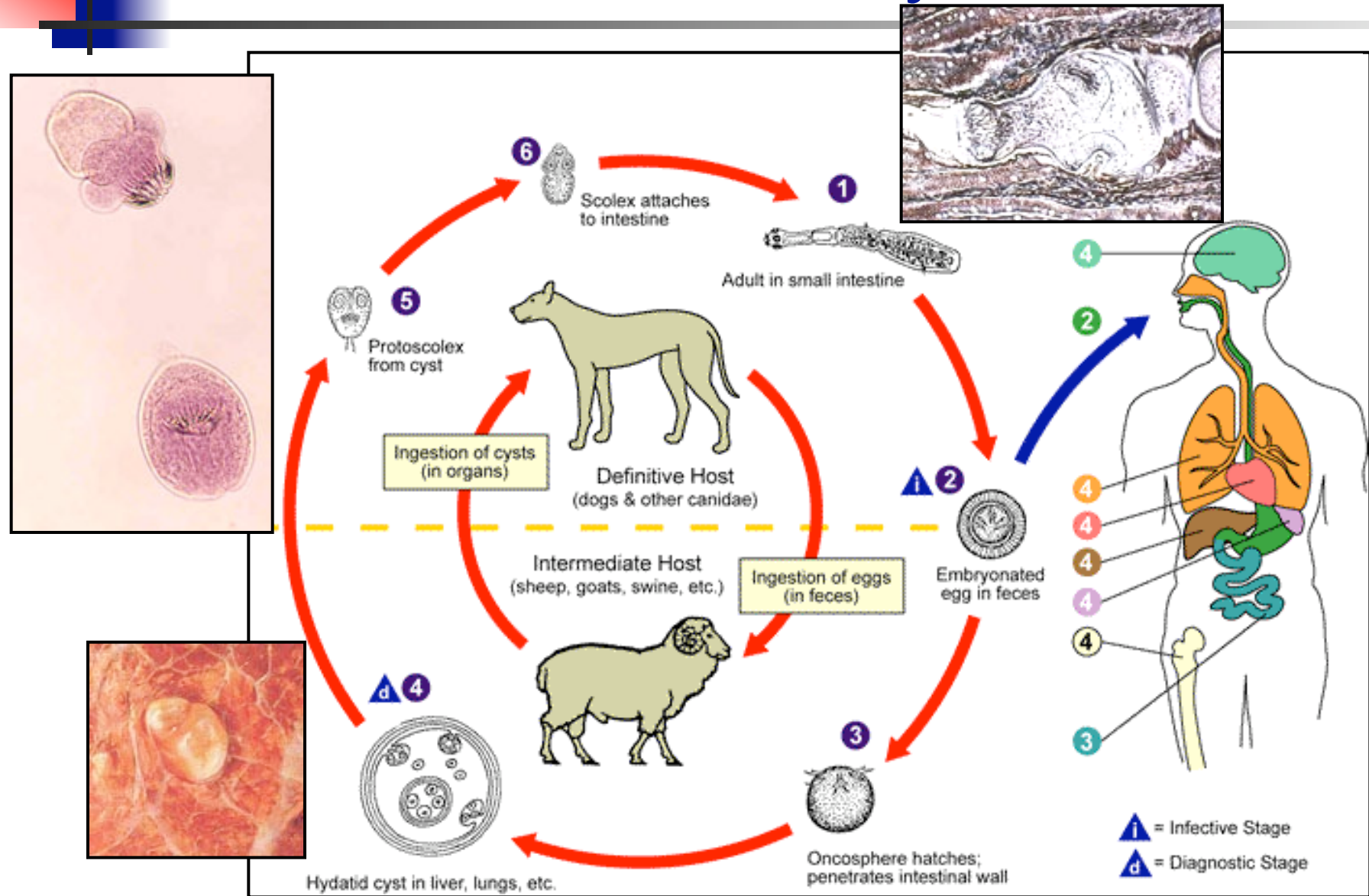


Echinococcus granulosus

- A.K.A – Sheep Tapeworm
- **Definitive Host:** Carnivores including dogs, wolves, and coyotes
- **Intermediate Host:** Herbivores including sheep and mice.
- **Geographic Distribution:**
Most common in sheep raising countries
 - New Zealand and Australia highest incidence

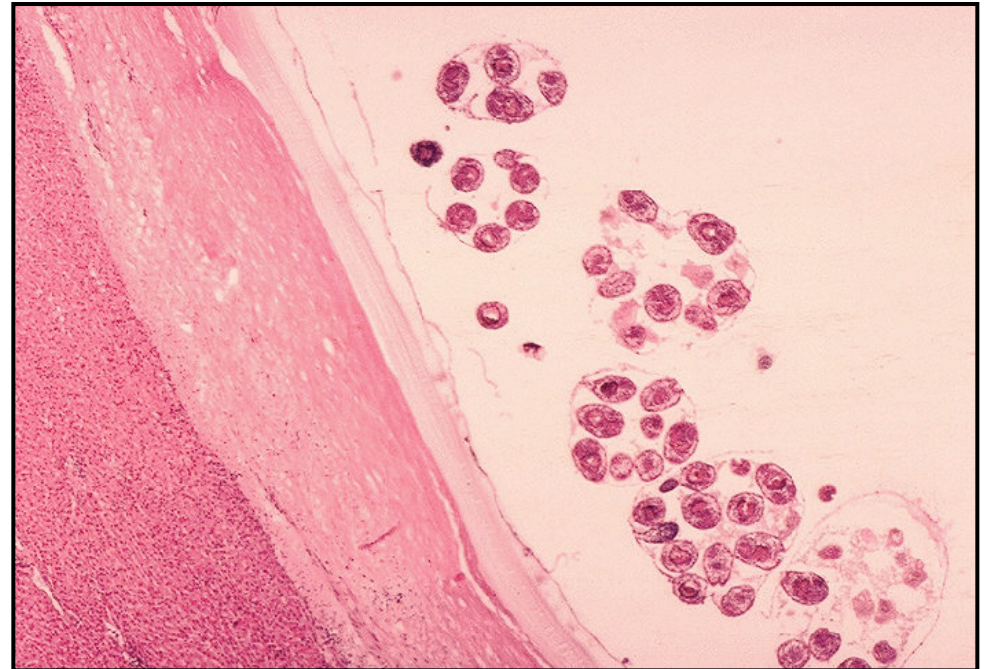
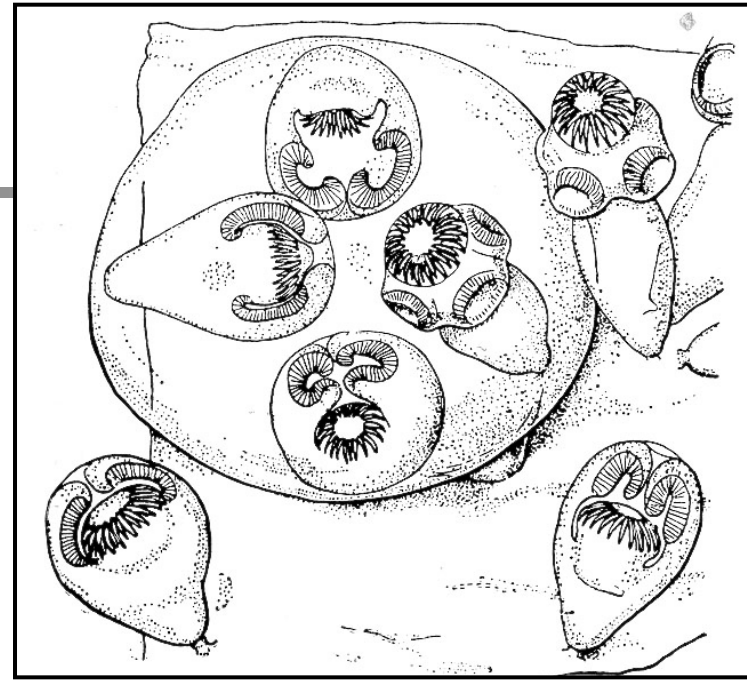


Echinococcus Life Cycle

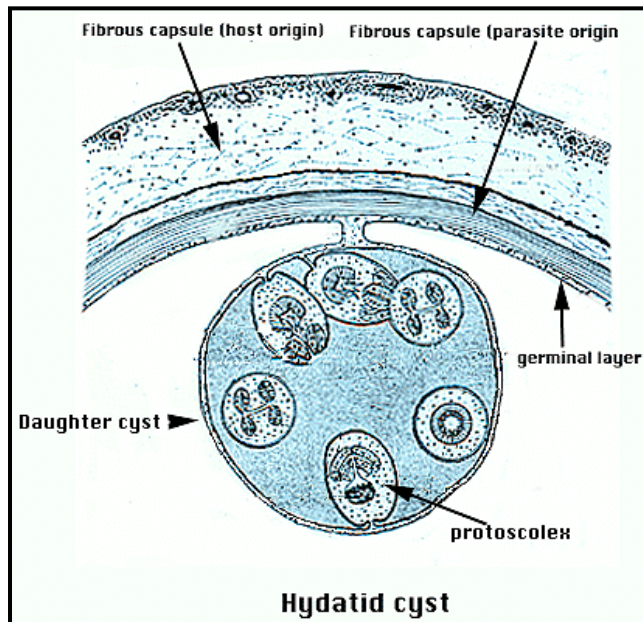


Hydatidosis

- Caused by the larval stage.
 - After egg hatches, oncosphere leaves intestines and goes to another location
 - Divides to create more worms
 - Forms a hydatid cyst.
 - Single chamber filled with fluid and larvae
 - Tough, outer wall
- Grows very slowly.
 - May take 20 years for symptoms to start



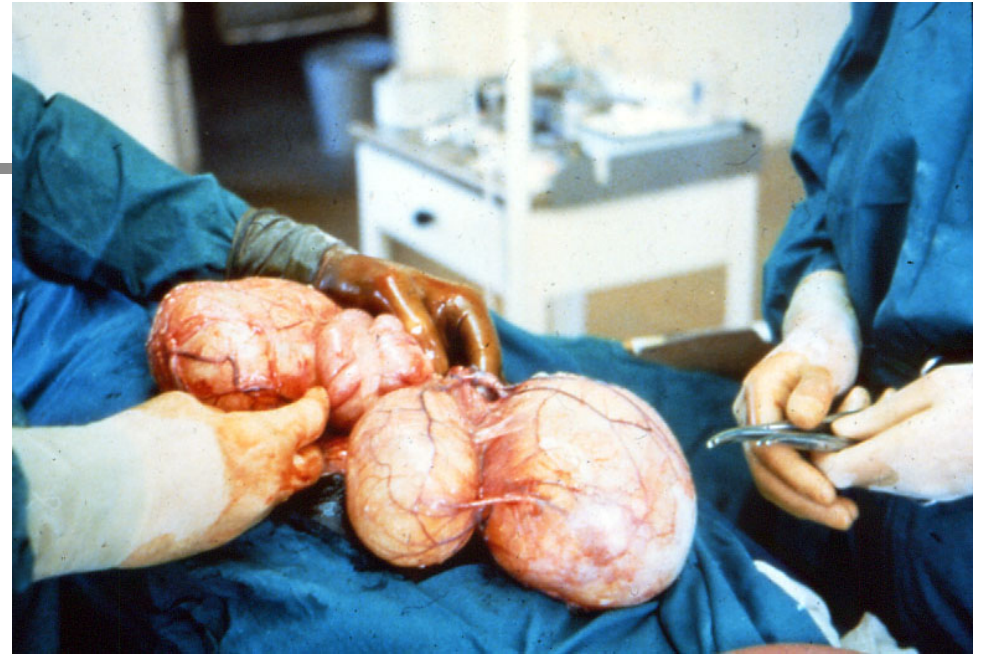
The Hydatid Cyst



- The cyst is lined by a multilayer parasite tissue with the innermost layer being the **germinal layer**
- This layer is an undifferentiated “**stem cell**” layer that can spawn the formation of “brood capsules” which are themselves lined by GL
- The **daughter cysts** (the encircled body) “bud” into the center of the fluid-filled cyst.
- Thousands of **protoscolices** can fill the hydatid (hydatid sand)
- Protoscolices are the infective stage for dogs (each one will grow into an adult worm)
- Hydatides usually grow slowly but steadily (1-5 cm per year)
- They are usually well tolerated until their size becomes a problem or they rupture
- Cyst rupture or leakage can result in allergic reactions and metastasis

Hydatidosis

- Cyst can reach large size
 - Holds up to 15 quarts of fluid
 - Fluid contains remains of dead larvae and worm waste
- **Symptoms:** Depends on location.
 - Most common location are lungs, liver, abdominal cavity
 - Asymptomatic
 - CNS – causes problems very quickly
 - If cyst ruptures, host dies of anaphylactic shock

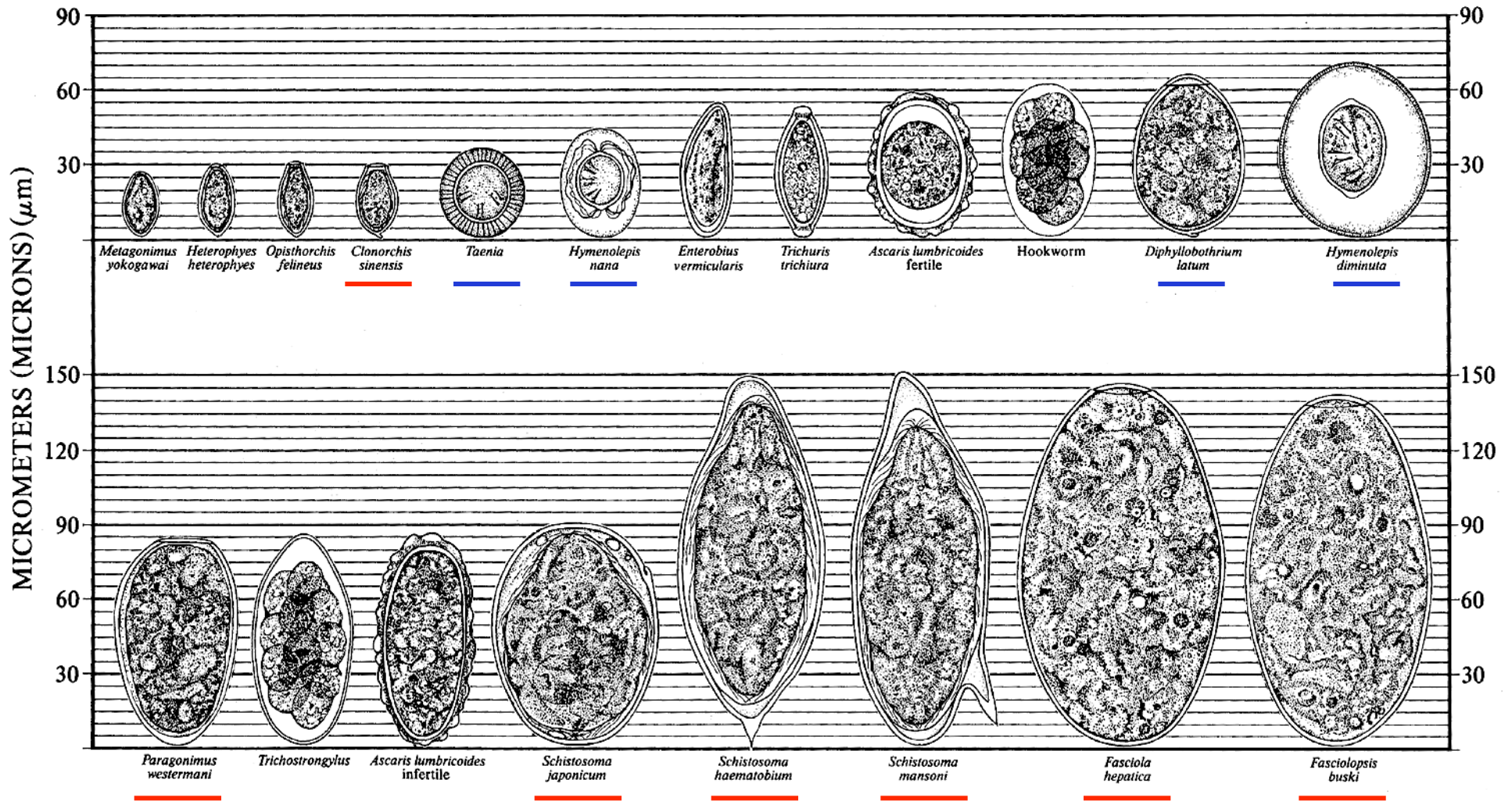


Hydatidosis

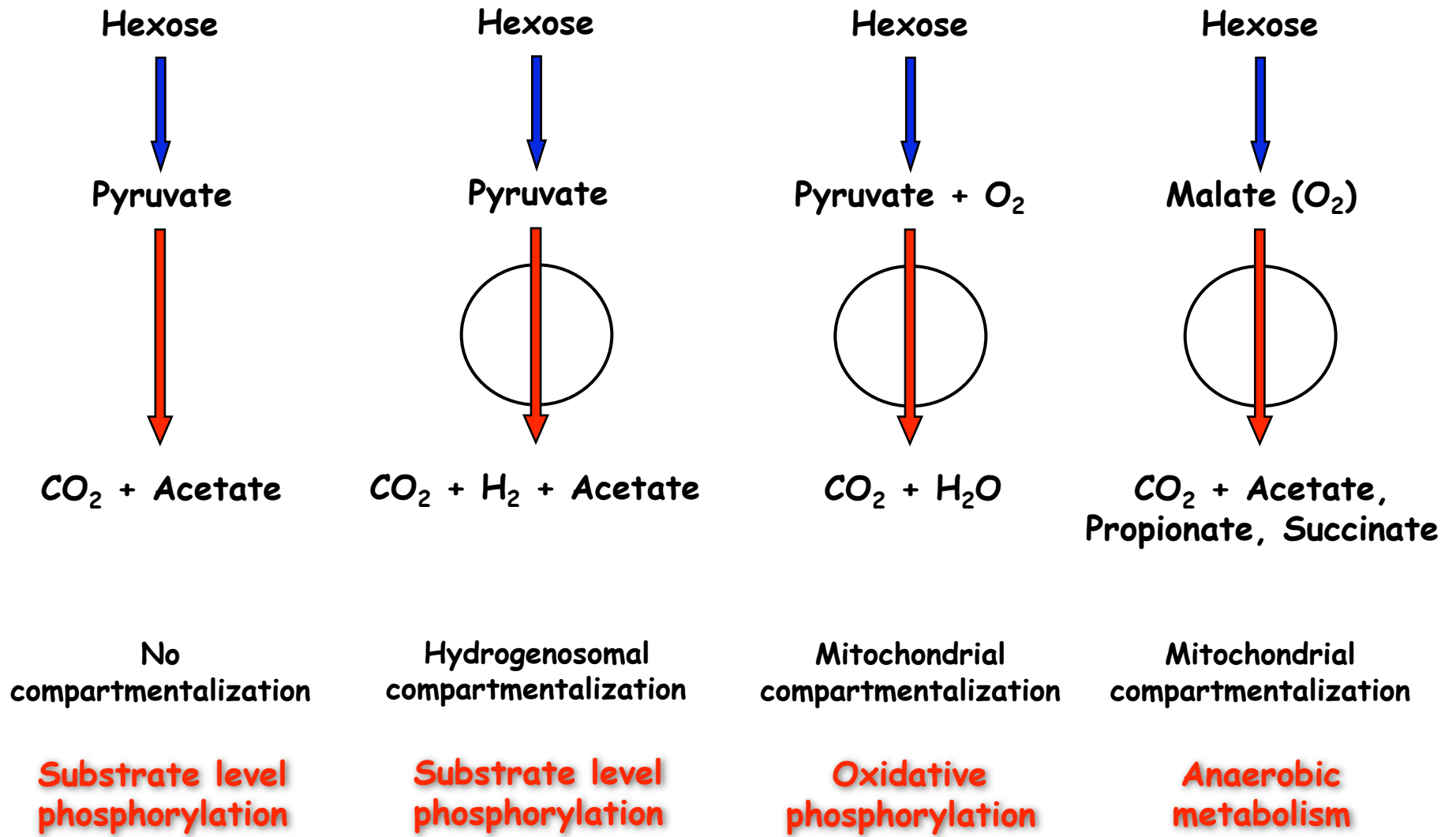
- **Prevention:** Most U.S. cases are from improper handling of dog feces or accidental egg ingestion while handling dog.
- In Kenya, transmission between humans and dogs are frequent.
 - Humans become intermediate host by eating roasted dog intestines.
- In Lebanon, most human cases in leather workers.
 - Dog feces are used in tanning solutions.



Comparative Egg Size

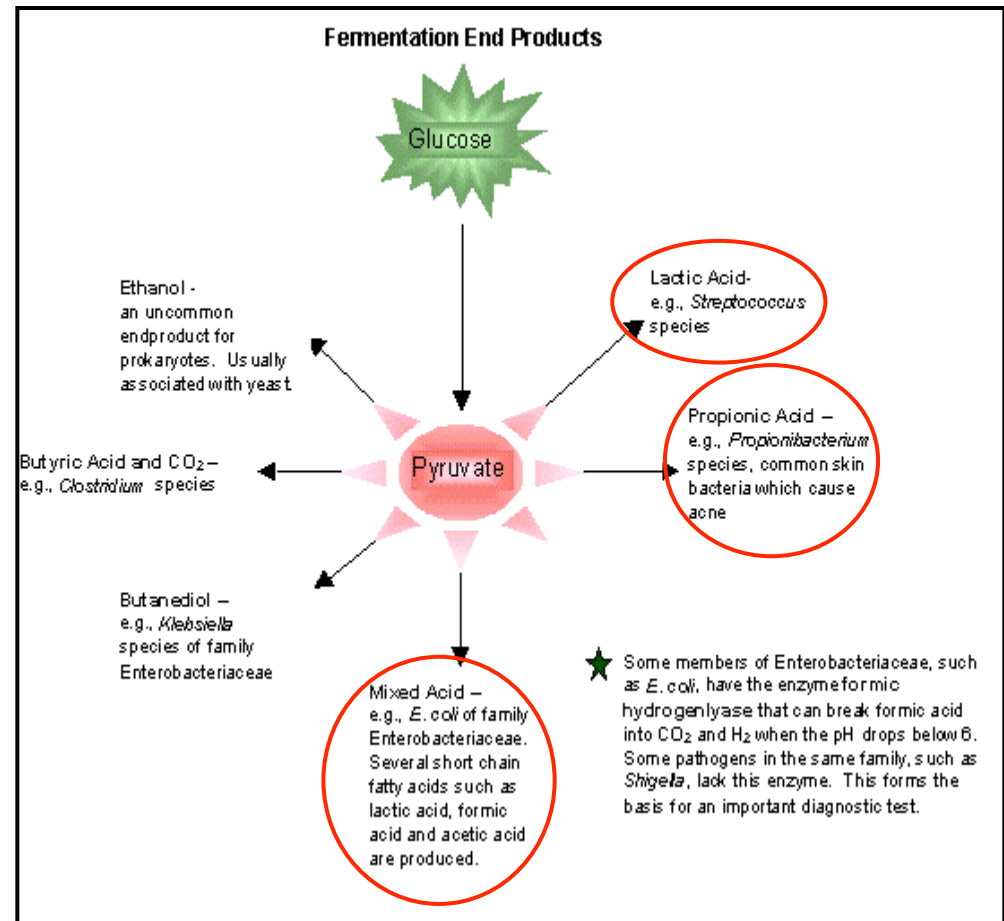


Carbohydrate Metabolism in Eukaryotes

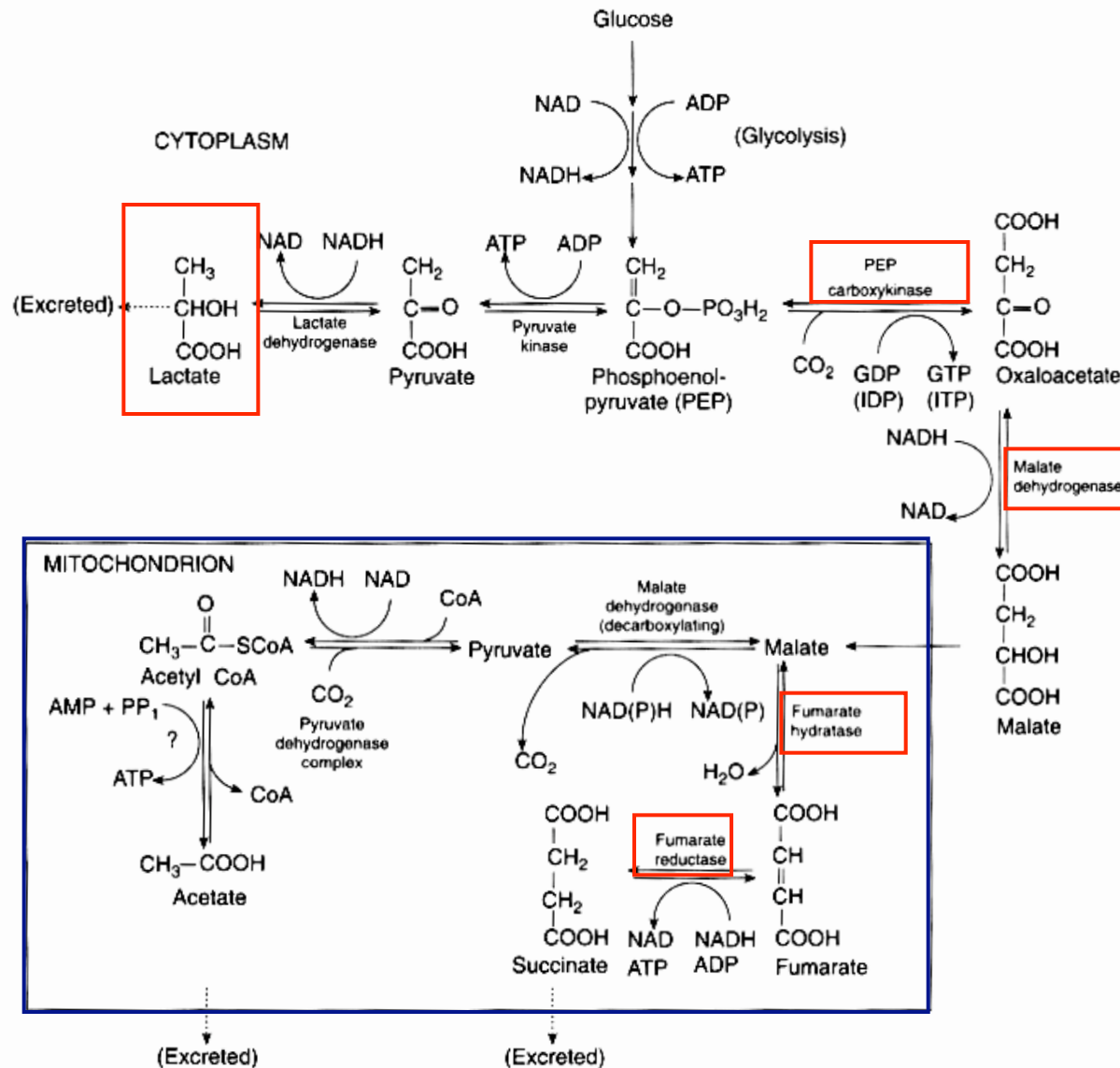


Helminth Carbohydrate Metabolism

- **Homolactate fermentors** - Schistosomes and Filarial worms
 - Production of lactic acid by anaerobic glycolysis and excretion of lactic acid
 - 2 moles of ATP formed per mol of glucose
- **Mixed fermentation** - adult worms, later larval stages
- **Respiration** - free-living and early larval forms



General Platyhelminth Metabolism



- **Facultative Anaerobes**

- glucose is main energy source

- Glucose is taken down to pyruvate and PEP through **glycolysis** (NAD is recycled by reduction of pyruvate to lactate, succinate and acetate)

- **Malate dismutation**

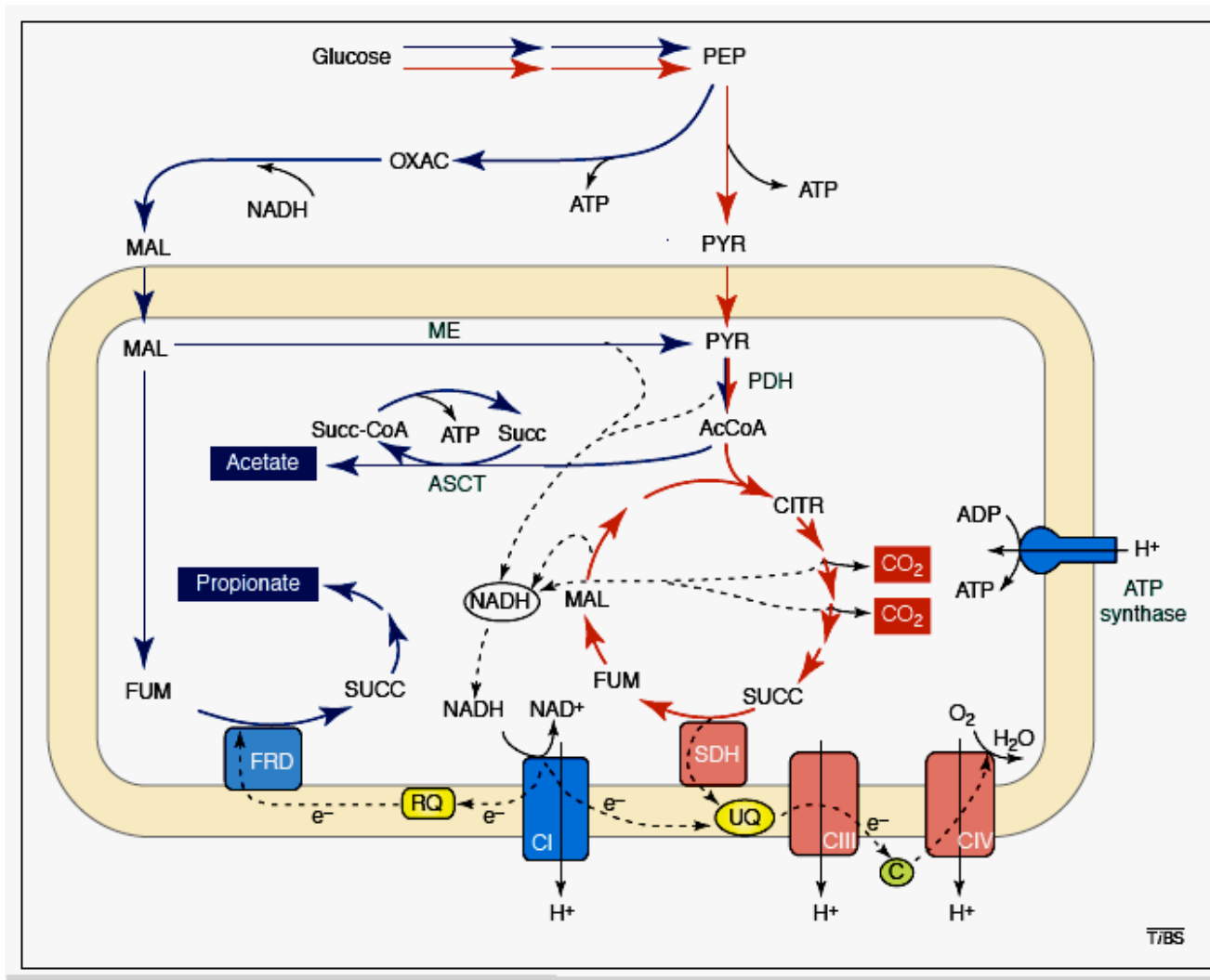
CO₂ fixation step - PEPCK

3 enzymes in common

MDH FH FR

- The adult cestode store large amounts of **GLYCOGEN** to provide energy between host meals

Aerobic to Anaerobic transitions



Anaerobic Mitochondria!

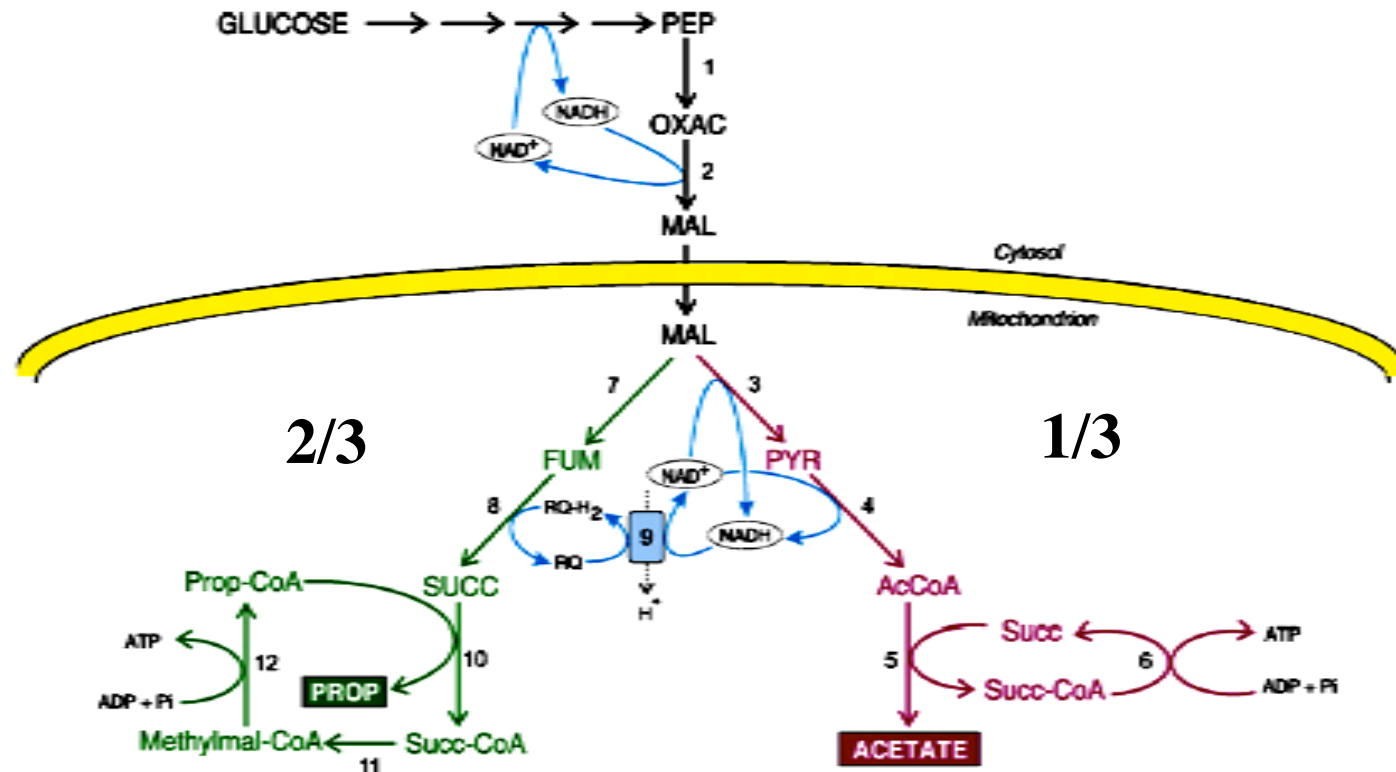


Fig. 1. Anaerobic fumarate-respiration in the mitochondria of *Fasciola hepatica*. The oxidative branch of malate dismutation is indicated in purple and the reductive branch in green. Electron transport to and from NAD⁺/NADH and rhoquinone is indicated in blue. Note that the enzyme complexes 8 and 9 are part of the electron transport chain and in fact located in the mitochondrial inner membrane. The dashed arrow through enzyme complex 9 is symbolic for proton translocation over the mitochondrial inner membrane. The numbers indicate the following enzymes: (1) phosphoenolpyruvate carboxykinase, (2) malate dehydrogenase, (3) malic enzyme, (4) pyruvate dehydrogenase, (5) acetate:succinate CoA-transferase, ASCT, (6) succinyl-CoA synthetase, (7) fumarase, (8) fumarate reductase, (9) NADH-dehydrogenase, Complex I, (10) propionate:succinate CoA-transferase, PSCT, (11) methylmalonyl-CoA mutase + methylmalonyl-CoA epimerase, (12) propionyl-CoA carboxylase. Abbreviations: AcCoA, acetyl-CoA; FUM, fumarate; MAL, malate; Methylmal-CoA, methylmalonyl-CoA; OXAC, oxaloacetate; PEP, phosphoenolpyruvate; PROP, propionate; prop-CoA, propionyl-CoA; PYR, pyruvate; RQ, rhoquinone; RQ-H₂; reduced rhoquinone; SUCC, succinate; Succ-CoA, succinyl-CoA.



Platyhelminth Treatments

- Quinoline derivatives

- Praziquantel
- Oxamniquine

- Benzimidazole derivatives

- Mebendazole
- Albendazole
- Thiabendazole

- Other drugs

- Niclosamide
- Metrifonate

- Why Praziquantel?

- Early 20th century relied heavily on antimonials
- Effective against a number of species
- Most widely used drug
- Safe, fairly cheap to make

Common agents for helminth infestations

<u>Helminth</u>	<u>Drug(s) of choice</u>	<u>Alternative(s)</u>
CESTODES		
<i>Taenia saginata</i> (beef tapeworm)	Niclosamide or Praziquantel	Albendazole or Mebendazole
<i>Taenia solium</i> (pork tapeworm)	Niclosamide or Praziquantel	Albendazole or Mebendazole
<i>Cysticercosis</i> (pork tapeworm larval stage)	Praziquantel or Albendazole	
<i>Diphyllobothrium latum</i> (fish tapeworm)	Niclosamide or Praziquantel	
<i>Hymenolepis nana</i> (dwarf tapeworm)	Praziquantel	Niclosamide
<i>Echinococcus granulosus</i>	Surgery	
<i>Echinococcus multilocularis</i> (hydatid disease)	Albendazole	Mebendazole
TREMATODES		
<i>Schistosoma haematobium</i>	Praziquantel	Metriphonate
<i>Schistosoma mansoni</i> (bilharzia)	Praziquantel	Oxamniquine

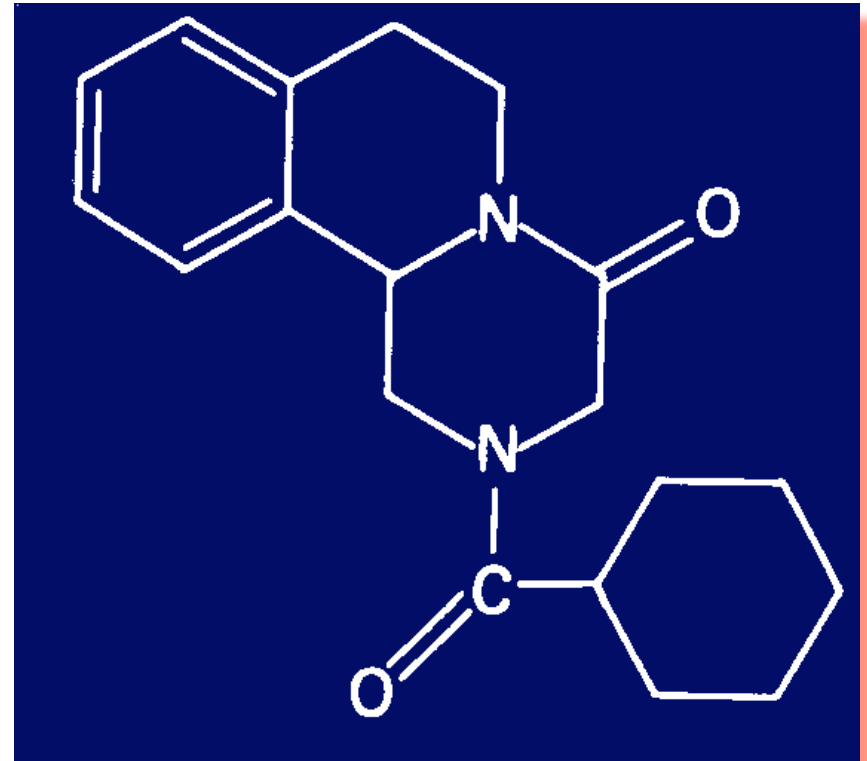


A little history on praziquantel

- Large number of pyrazino isoquinoline compounds were synthesized by Merck as potential tranquilizers (~late 1960s)
- Partnership between Merck and Bayer led to the first screening of the compounds as possible anthelmintics (mid-1970s)
- EMBAY 8440 - now known as praziquantel - was an effective antitremitode and anticestode compound.
- First human volunteers tested in 1978, by 1980 praziquantel had become the drug of choice to treat schistosomiasis as well as a number of other worm infections

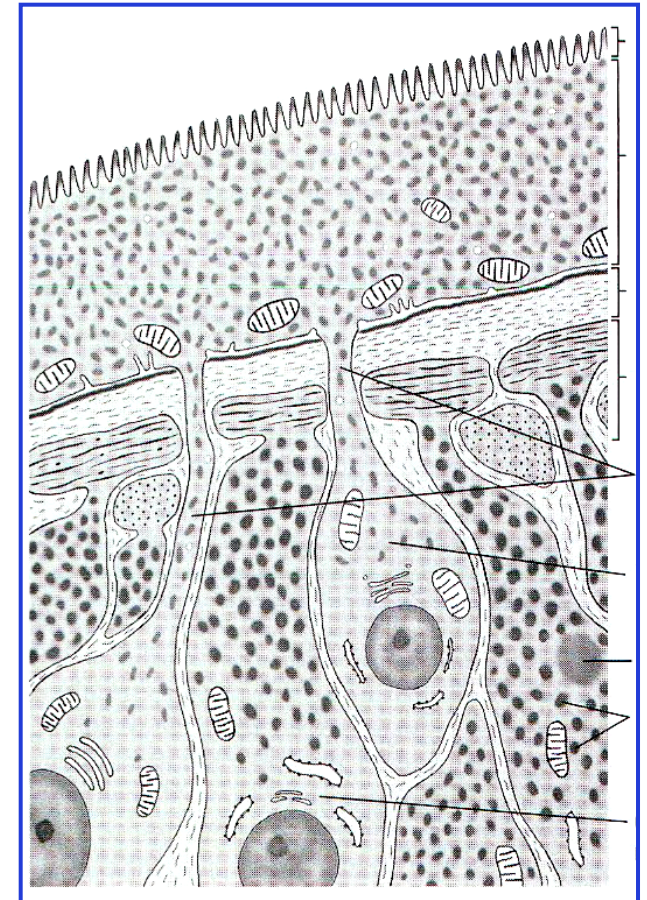
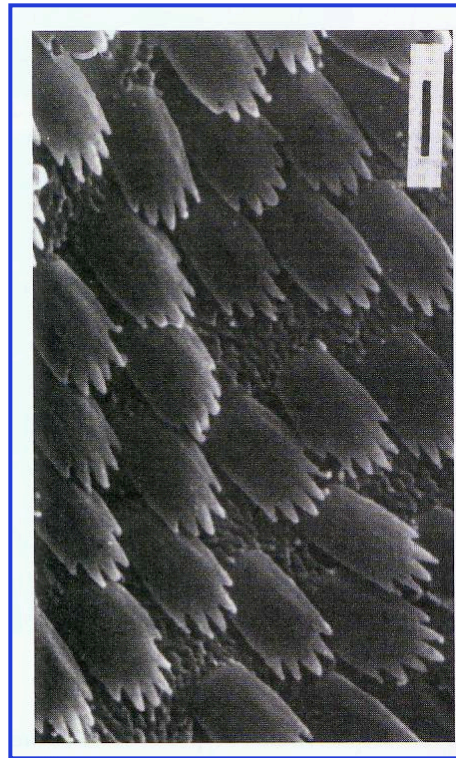
Praziquantel (Biltricide)

- Broad spectrum helminth chemotherapeutic
- Drug of choice for treating Cestode and Trematode infections
- Effective single dose treatment
- Inexpensive - ~\$0.25/dose
 - Decreasing still - \$0.075/tablet
- Minimal side effects
 - Nausea, vomiting, abdominal pain - brief period



Tegument is a syncytium

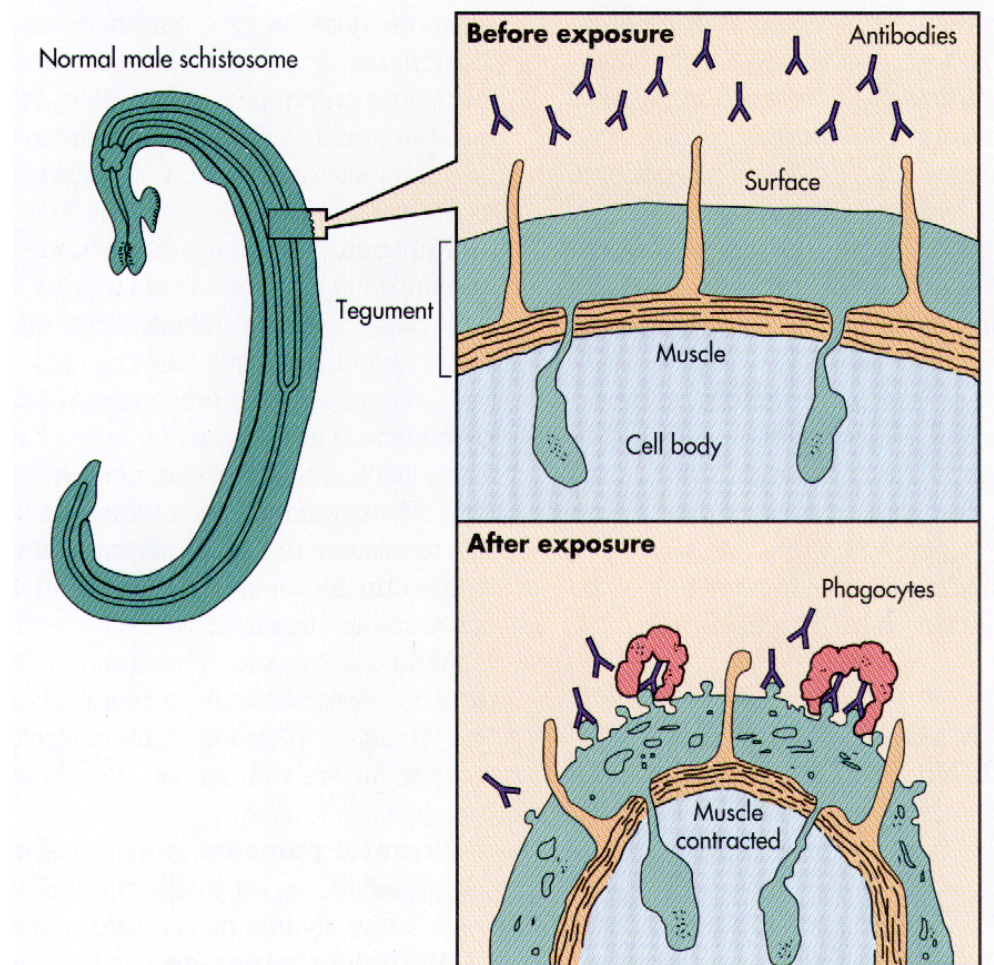
- absorb nutrients (drugs) through the **tegument**
- praziquantel causes vacuolization of the syncytial distal tegument
- Processes can be observed in flukes or tapeworms, both in vivo and in vitro
- The tegumental vacuoles finally burst leading to parasite death



Trematode and Cestode tegument structure is similar (not identical)

Praziquantel - mode of action

- Influx of Ca^{2+} results in muscle contractions of entire body
 - Appears non-selective
- Spastic contraction of musculature
- Vacuolization and blebbing of the tegument
- Increased exposure of worm antigens
- Leads to changes in glucose uptake
- Accelerated depletion of energy stores
- Host-immune response is necessary for complete activity of PZQ



vacuolization

Surface blebbing

Widespread use



Eastern Nishikigoi

GINRIN SHOWA

Breeder: SHINODA

Size: 28 inches

Sex: Female

Price: \$14000.00

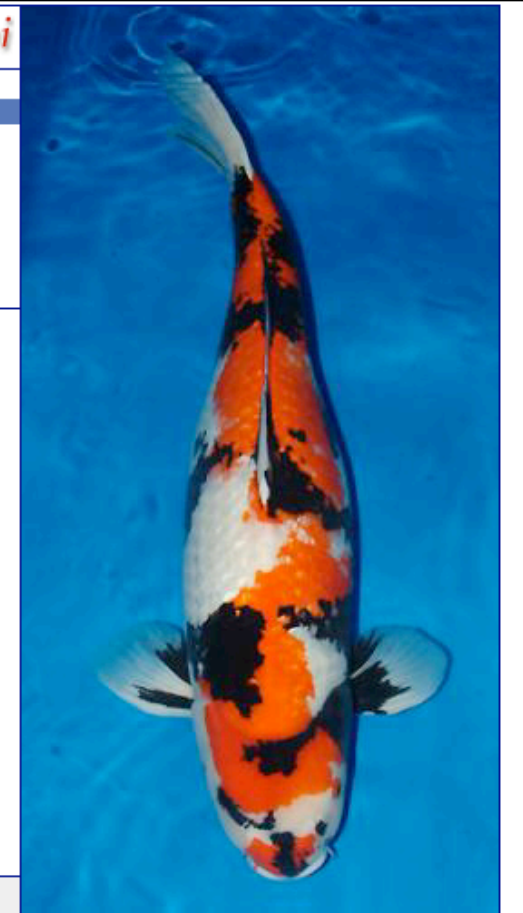
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or ordering information.

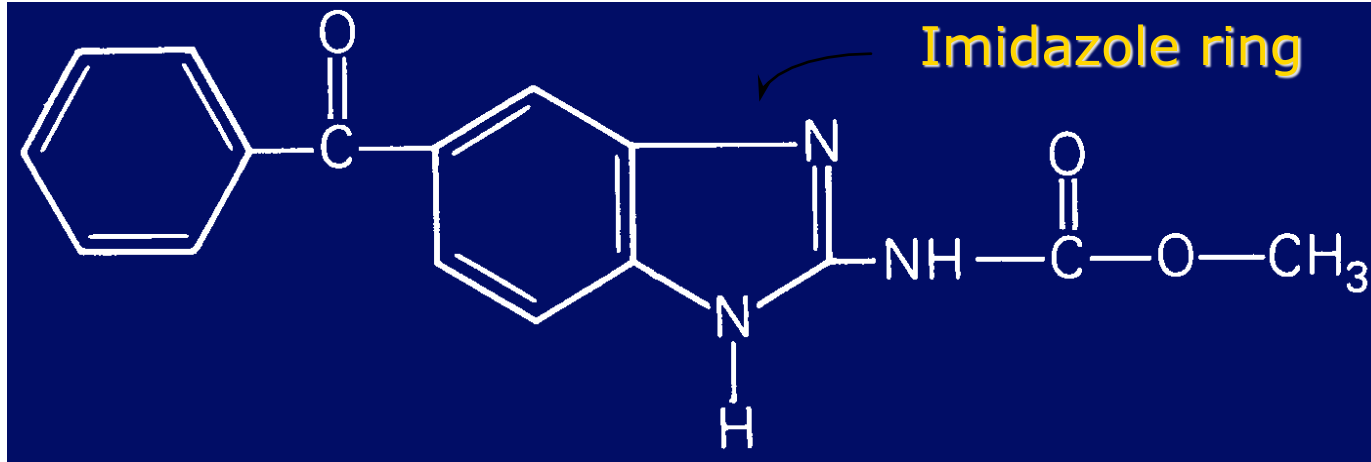
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14700 Goldenwest Street
Westminster, CA 92683
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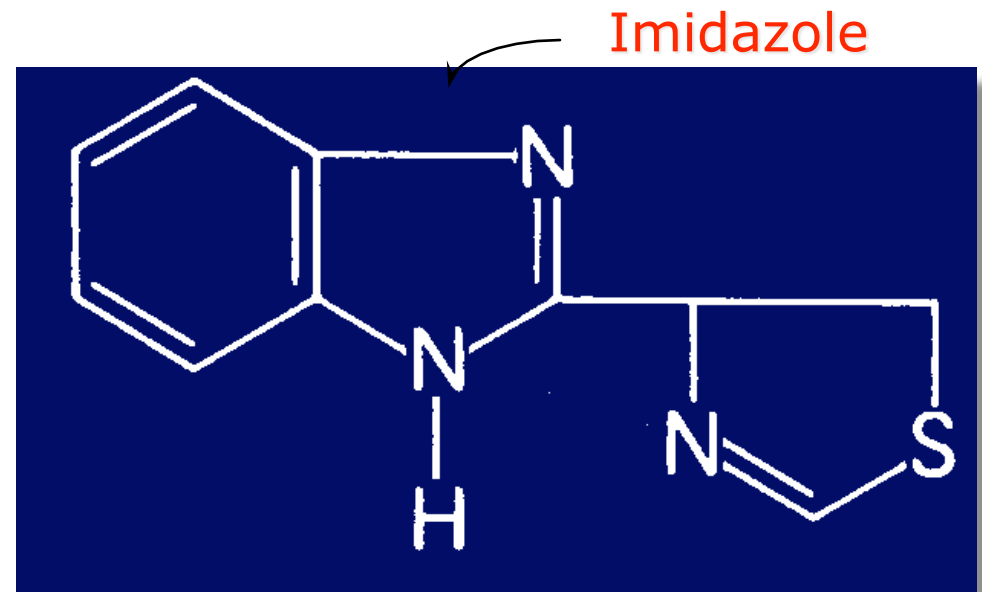
Mebendazole



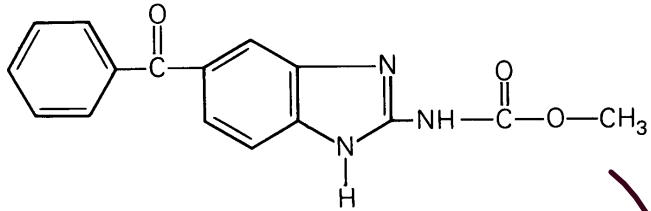
- Broad spectrum
- Binds tubulin and disrupts microtubules
- Low toxicity, however poorly absorbed

Thiabendazole

- Introduced in 1961
- Blocks fumarate reductase
- Also binds tubulin
- High incidence of nausea, vomiting, anorexia



Mebendazole & Thiabendazole



Mebendazole

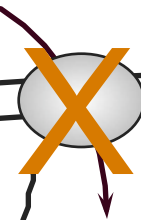
High affinity binding
effectively irreversible



Tubulin α, β

Fumarate
reductase

Glucose

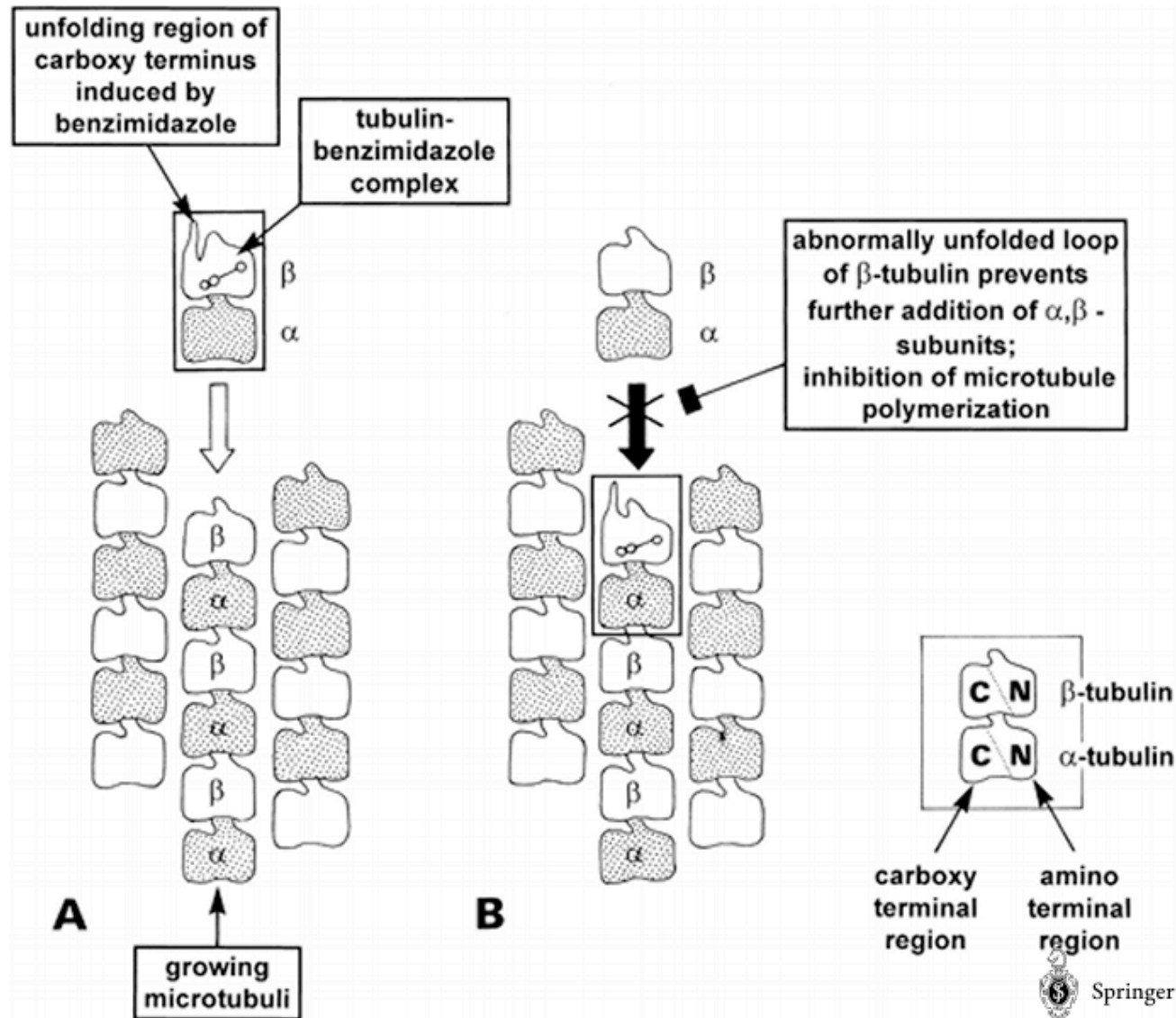


Microtubules

MTOC

Nucleus

Benzimidazole binding to tubulin



Applied Parasitology

Applied parasitology:



During the Paris olympics, sprinter Gilbert Velox was disqualified for "illegal use of his tapeworm".

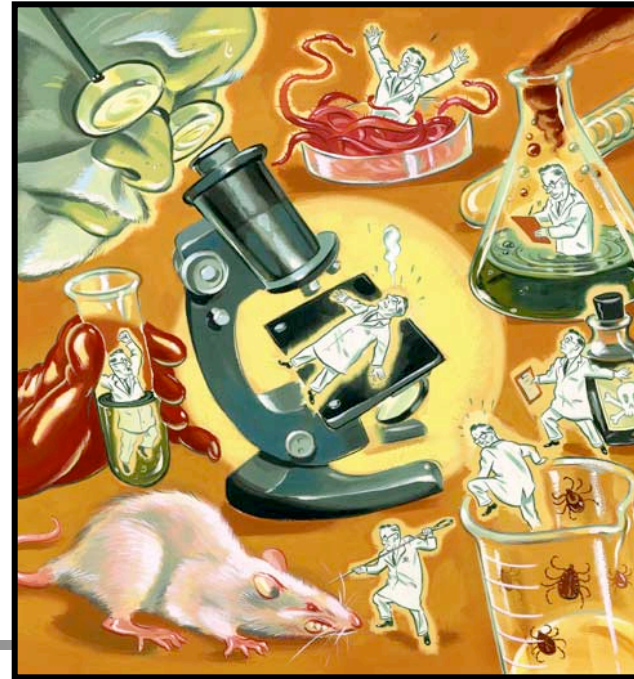
(c)1999 Benoit Leblanc

One of the worst jobs in science?

Worm Parasitologist By William Speed Weed

Certainly, studying worm parasites isn't nearly as bad as playing host to them. But here's an essential distinction: The medicos who go into this line—God bless 'em—do it by choice. Supported by the World Health Organization and various international charities, they travel to the tropics to eradicate diseases that afflict millions of people. Yet although we're regularly treated to tales of Ebola warriors, we rarely hear about the tribulations of the worm docs.

For instance . . . [consider these ellipses a pause to enable the faint of stomach to flee the page] . . . Ascaris lumbricoides eggs hatch in the small intestine, then migrate to the lungs; they're coughed into the mouth and swallowed back to the gut, where each worm will grow as long as 16 inches and where each female will lay billions of eggs to be defecated forth so that a new cycle of life can begin. (The adults can exit this way too, in a large bolus that resembles a tangle of spaghetti.) The Wuchereria bancrofti worm sometimes settles in the scrotum, where it blocks the flow of lymph. This can result in elephantiasis, a wretched condition that features scrotal swelling to jack-o'-lantern proportions and an infection that reeks of death. Moving right along . . . [see helpful ellipsis-related note, supra] . . . the female Dracunculus medinensis migrates from the gut to a point just under the skin of, say, a leg, where she then



commences growth to a length of as great as three feet, and where, ultimately, she lays her eggs. When the thousands of babies make their joyous arrival, they blister the skin and pop through, leaving Mom behind. The traditional way to get rid of her is to wrap her head around a stick and twist very slowly—one turn of the stick per day—for weeks or months, depending on how long she is. (This treatment is so old that it inspired the ancient snake-and-pole aesculapius symbol of medicine.) And so worm parasitologists are unsung heroes—and decorum dictates that unsung they shall remain. "We can't show pictures or even really talk about these diseases," says parasitologist Eric Ottesen of Emory University. "Society just isn't ready for it."