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PARASITOLOGY

M1 Infectious Diseases Sequence
Vernon Carruthers
Cary Engleberg

Spring 2009

University of Michigan
Medical School

What do you need to learn for this course?

- **Recognize the names of pathogens associated with characteristic diseases** (Don't memorize names or spellings)
- **Remember the key features of the life cycles** (i.e., how do the parasite get from one host to the next?)
- **Remember the main mechanisms of disease** (i.e., how does damage to the host occur?)

Definitions

- “zoonosis”
- “enzootic” ~ “endemic”
- “epizootic ~ epidemic”
- “reservoir”
- “vector”

Major Human Parasites

Protozoan (single-celled) parasites

Low branching protozoa (*Entamoeba*)

Kinetoplastids (African trypanosomes, *Leishmania*)

Apicomplexa (*Plasmodium*, *Toxoplasma*)

Fungus-like protozoa (*Microsporidia*)

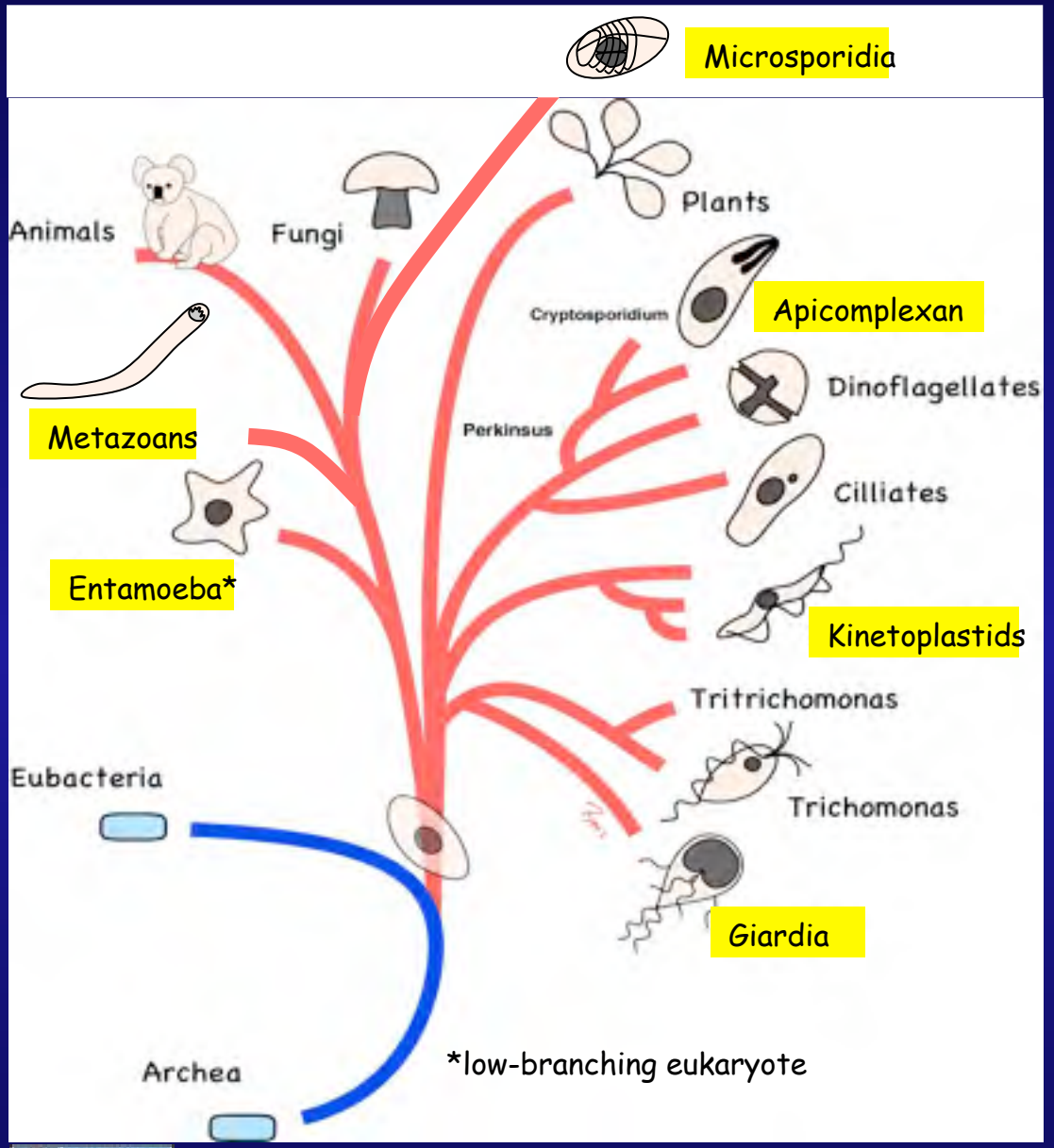
Metazoan (multicellular) parasites

Nematode (Onchocerca or hookworm)

Trematode (*Schistosoma*)

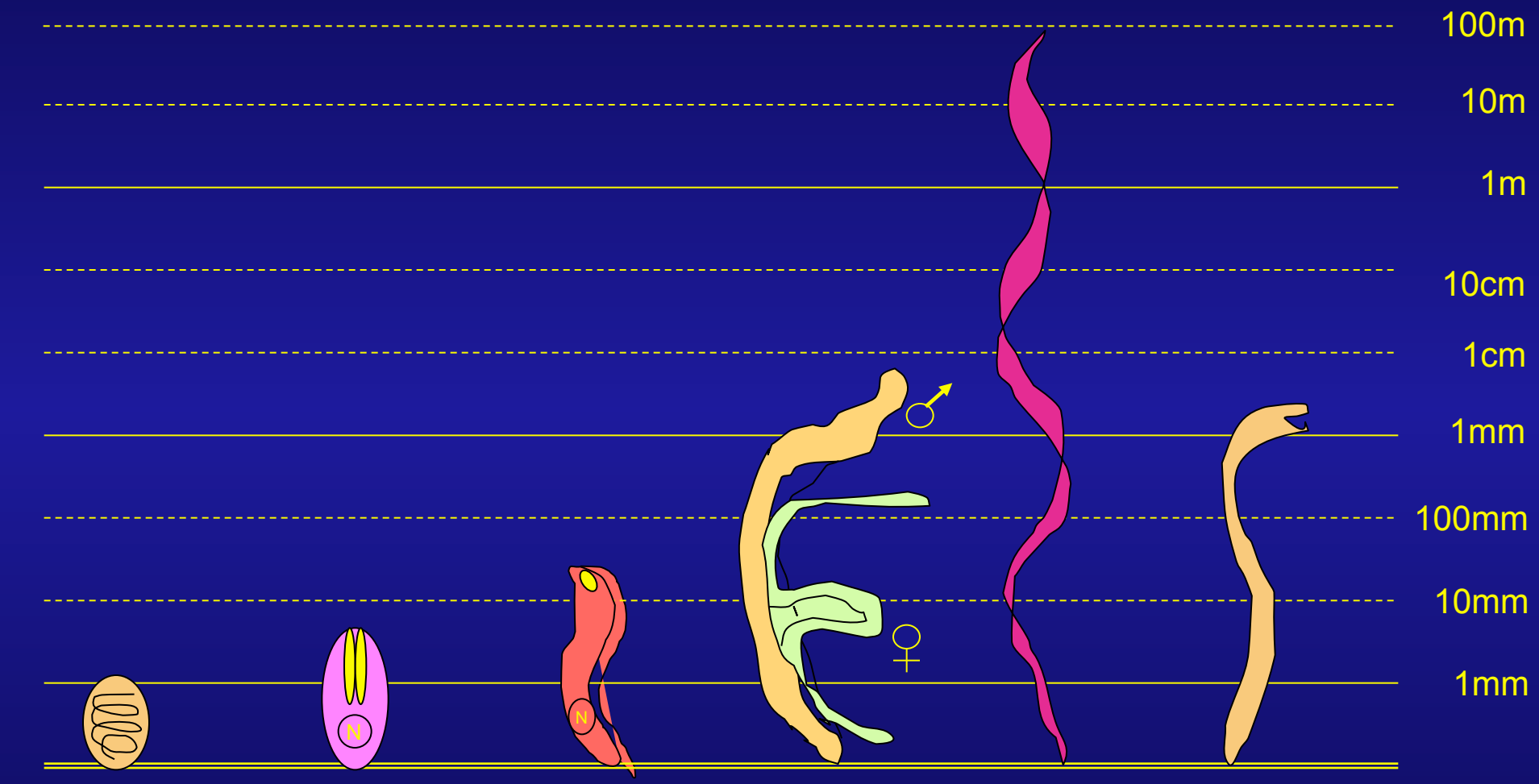
Cestode (Tapeworm e.g., Echinococcus)

Parasites on the Tree of Life



PD-INEL Sandy Baldauf / Boris Striepen

Parasite Diversity



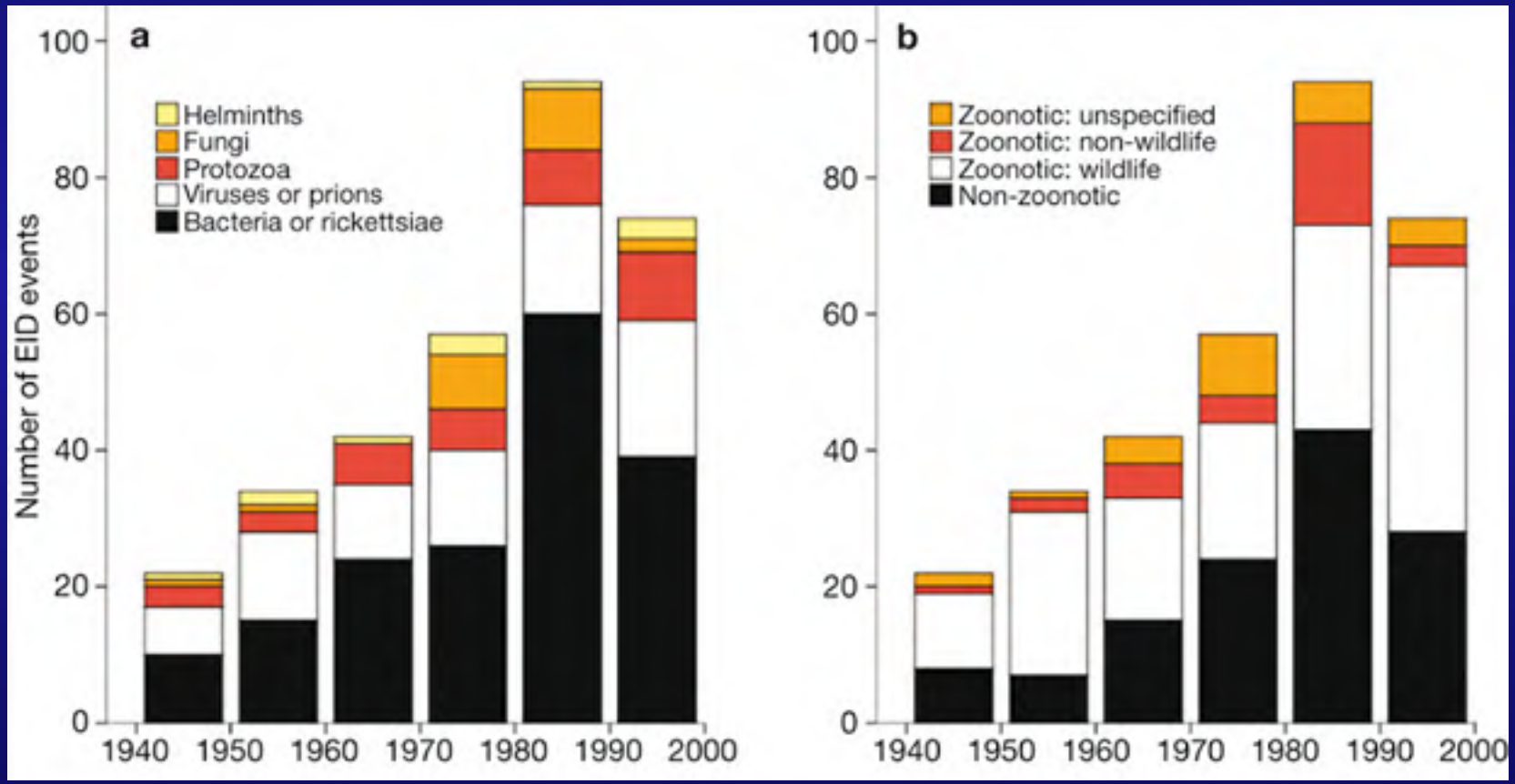
Global Morbidity and Mortality from Parasitic Diseases

		Infections* (millions)	Disease* (millions)	Deaths* (thousands)
Protozoa	malaria	800	150	1500
	amoeba	480	50	100
	toxoplasma	**1700**	40	10
	trypanosoma	24	1.2	60
Nematodes	intestinal nematodes	2400	2.6	80
	filaria	250	3	<1
	onchocerca	30	5	50
Trematodes	schistosoma	200	20	1000
Cestodes	tapeworms	2.5		

*Annual

West Nile Virus <0.5 <0.01 <0.3

New Trends in Emerging Infectious Diseases



Jones et. al., *Nature* Feb 2008

Factors influencing the geography of parasitic infections

- **Local ecology**
  - vectors
  - reservoirs (animal and human)
  - local habitats
- **Local socioeconomic conditions**
  - sanitation
  - exposure to vectors
  - untreated carriers

Protozoal Infections

Classification of protozoa

Entamoebae
(shapeless)

PD-INEL Source Undetermined

Alveolates
(sub-membrane cytoskeleton confers a fixed shape)

Flagellates

PD-INEL Source Undetermined

Apicomplexa
(Sporozoa)

PD-INEL Source Undetermined

(Ciliates)

Outline of protozoal diseases

- Intestinal protozoal infection
- Systemic protozoal infection

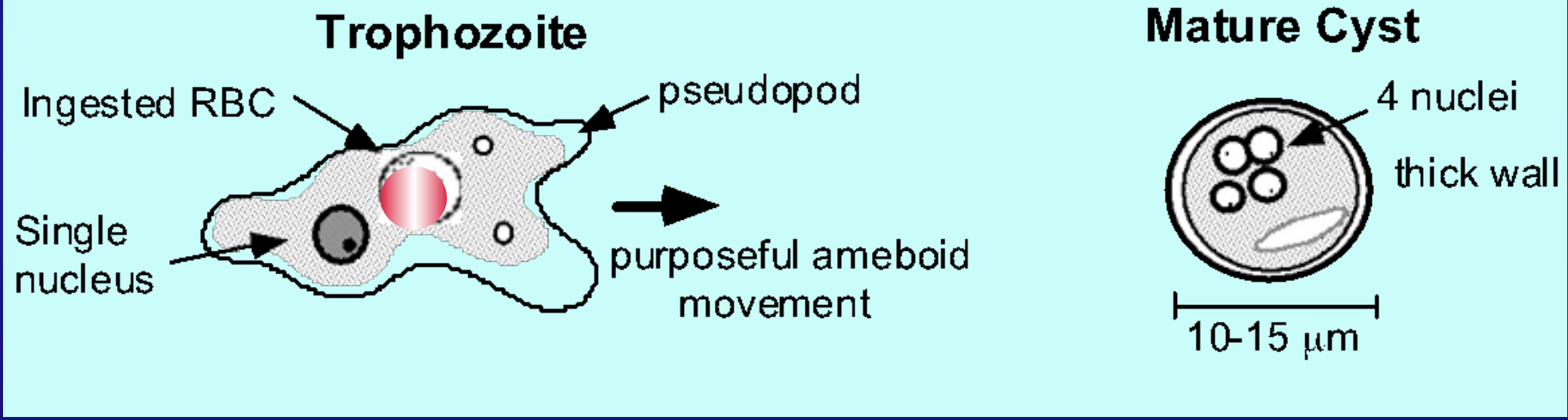
Outline of protozoal diseases

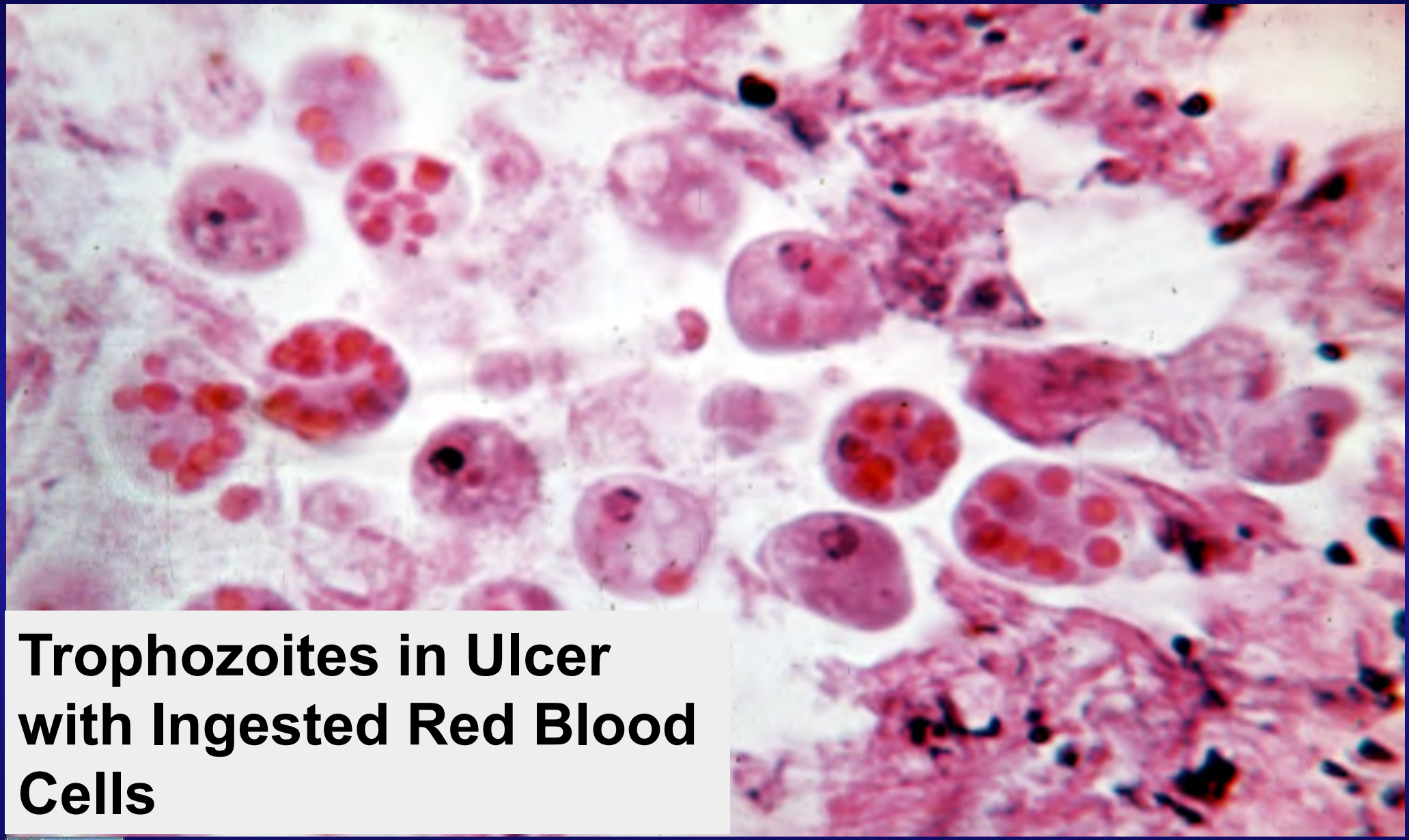
- **Intestinal protozoal infection**
  - -Invasive (dysentery/bloodstream invasion)
    - entamoeba → * *Entamoeba histolytica*
  - -Non-invasive (watery diarrhea/weight loss)
    - dinoflagellate → * *Giardia lamblia (G. intestinalis)*
    - apicomplexa → * *Cryptosporidia* and *Cyclospora*
    - * *microsporidia*
- **Systemic protozoal infection**

Amebiasis

- ***Entamoeba*** **- an enteric amoeba, i.e., not free-living.**
- ***histolytica*** **- human invasion by the parasite involves tissue lysis (histo-lytica)**

E. histolytica - parasitic forms





Trophozoites in Ulcer with Ingested Red Blood Cells

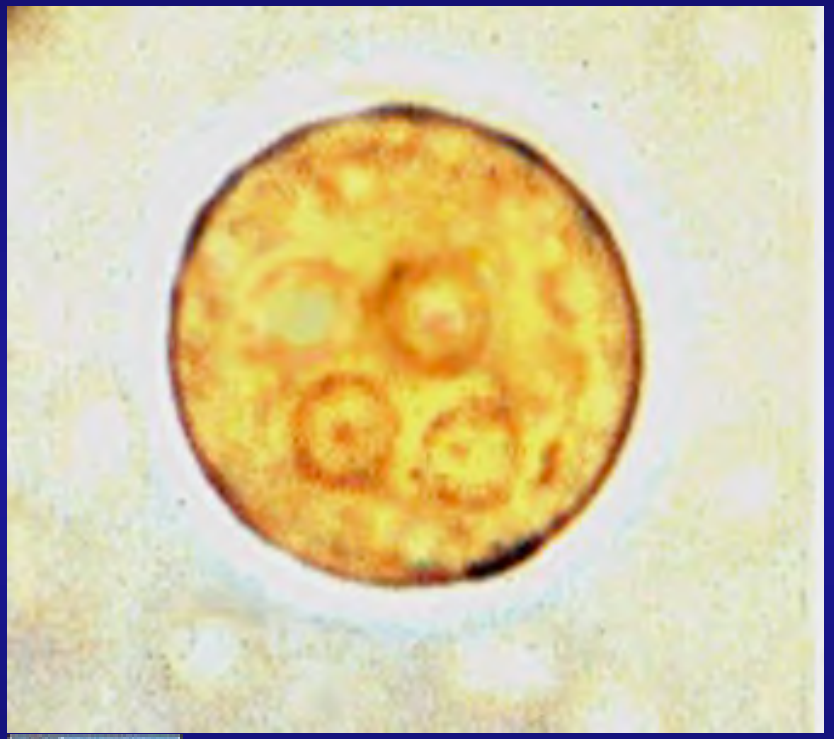
PD-INEL William Petri

Entamoeba histolytica -- life cycle

- Humans are the only reservoir excreting amoebic cysts
- Cysts resist environmental conditions
- Fecal-oral transmission (food, water)
- In response to gastric acid, ingested cysts release trophozoites in the upper intestine
- Trophozoites invade the large intestine and replicate by fission.
- Trophozoites that reach the lower colon encyst again.

PD-INEL Source Undetermined

Trophozoite in stool



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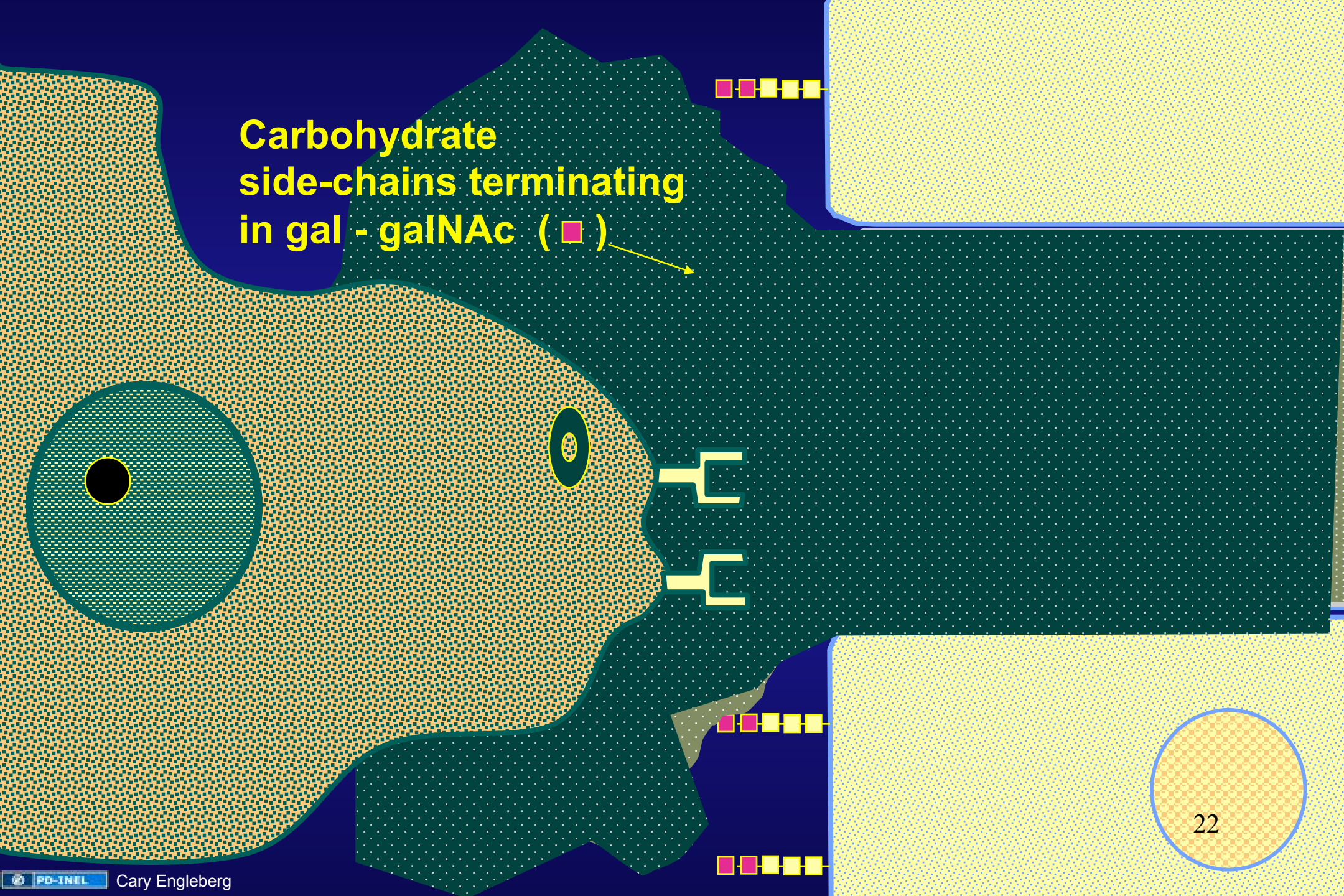
Cyst in stool

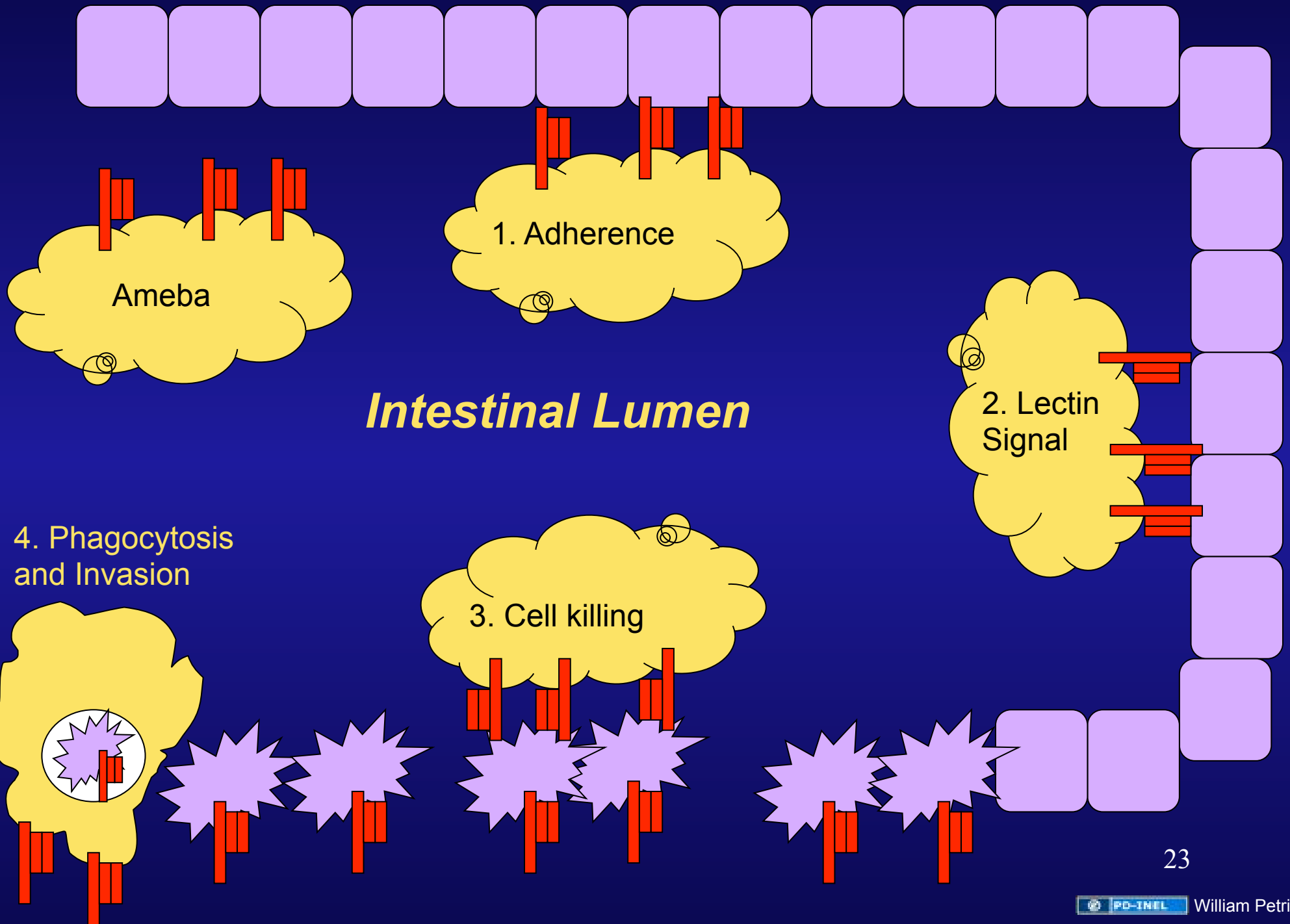
Entamoeba histolytica -- pathogenesis

- Trophozoites disrupt mucus layer
- Key virulence factors:
  - amebic lectin: binds parasite to galactose-containing sugars on host cells
  - amoebapores: adherence-dependent cytolysis
  - cysteine protease: cleaves preIL-1β to IL-1β which triggers NF-kB and pro-inflammatory cytokines; also cleaves antibodies and C3
- Trophozoites ingest human cells
- Colonic ulceration

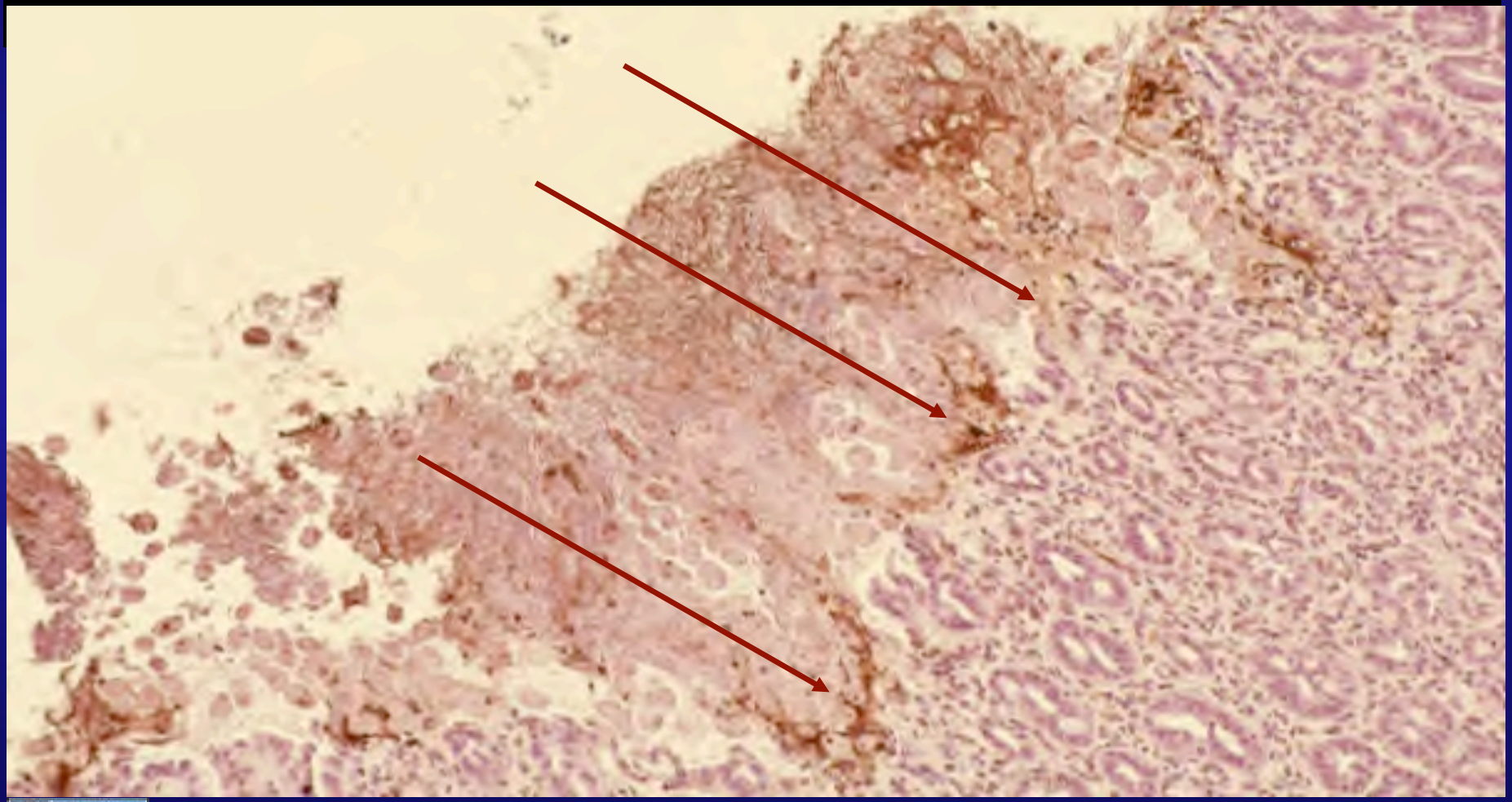
Risk Factors for Amebiasis in the United States

- **Hispanic/Asian/Pacific Islanders - 50% of U.S. cases reported to CDC**
- **Travelers - 0.3% incidence in one study**
- **Institutions for mentally retarded**
- **Men who have sex with men**
- **Men - 90% amebic liver abscesses in men (male mice also more susceptible, in part because of lower IFNγ and fewer functional NKT cells)**





TUNEL Stain Demonstrates Apoptosis at Sites of Amebic Invasion of Mouse Colon



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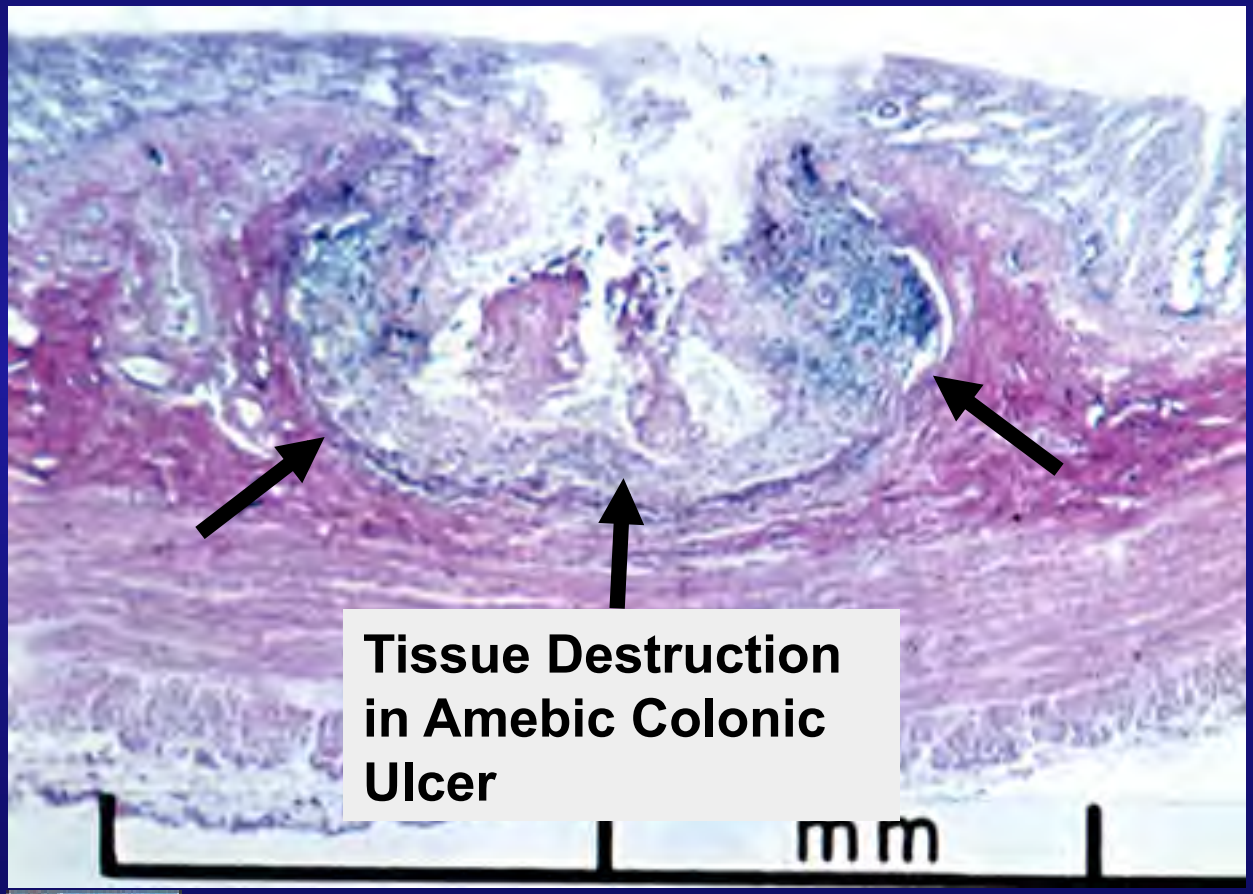
Histopathology of amebiasis



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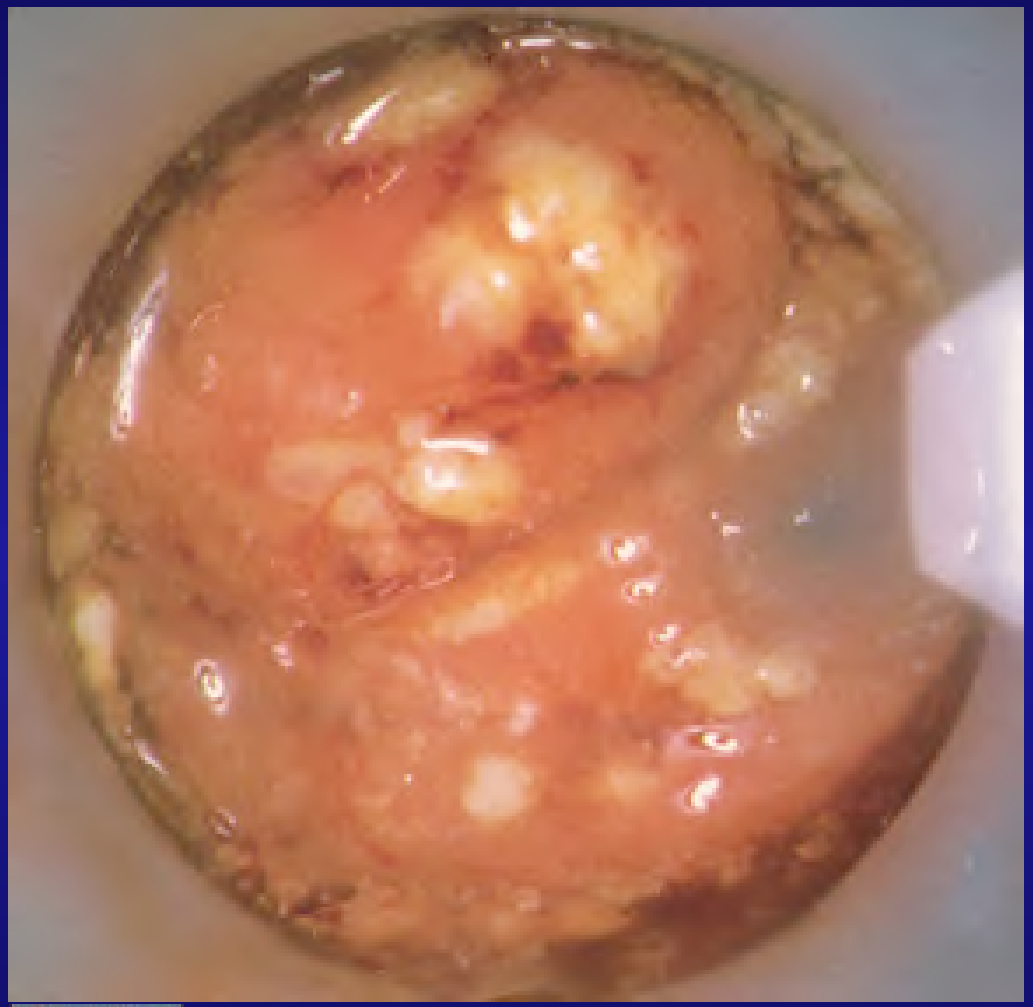
Classic Flask-Shaped Ulcers (side view)



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Amebiasis - clinical syndromes

- **Intestinal**
  - Ranges from asymptomatic to chronic diarrhea to amebic dysentery
- **Extraintestinal**
  - amebic liver abscess
  - other metastatic foci (e.g., brain)

Dx: identification of trophozoites or cysts in the stool, stool antigen tests, serology

Two microscopically indistinguishable *Entamoeba* sp.

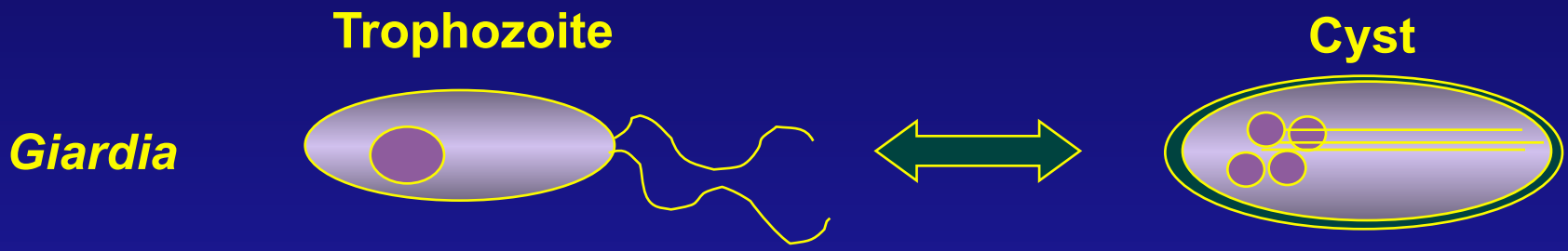
- ***E. histolytica***
  - invades tissues
  - should always be treated, even in asx patients
- ***E. dispar***
  - is non-pathogenic, even in AIDS
  - should not be treated

Treatment of amebiasis

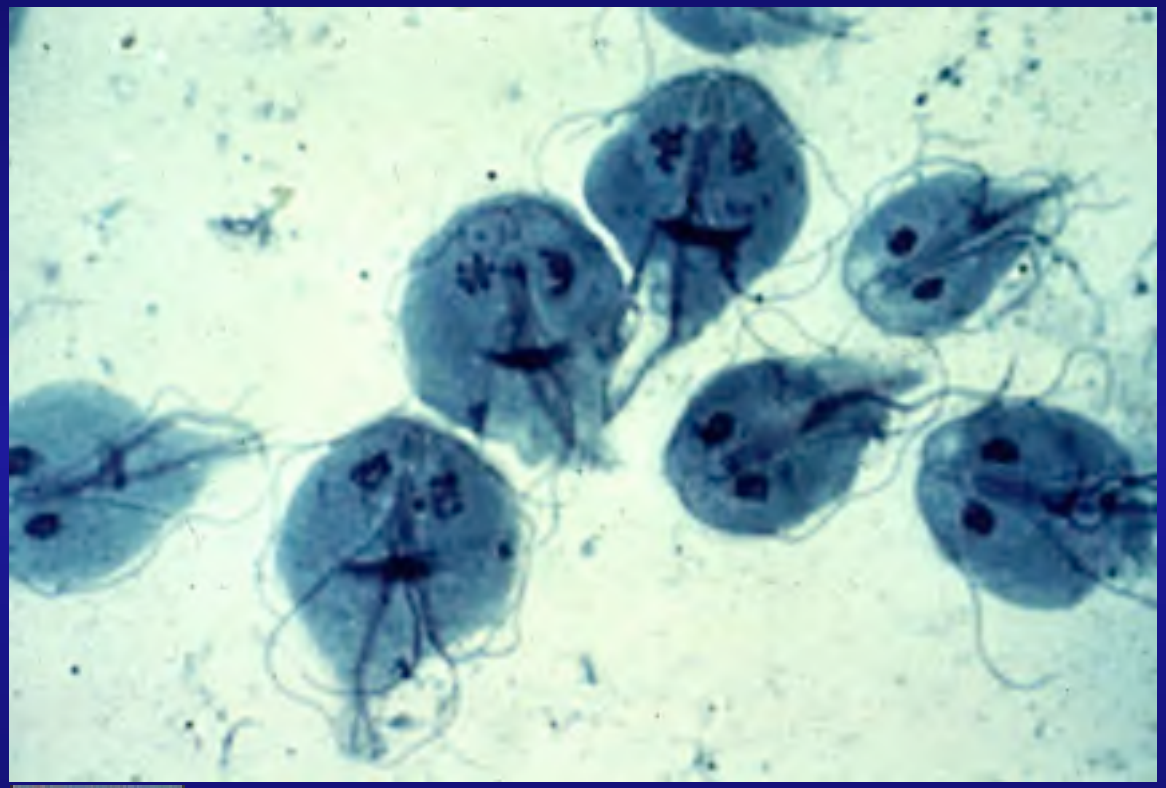
- The parasites in two locations are treated sequentially with two drugs
  - For invasive forms: **metronidazole**
  - For luminal forms: **diiodohydroxyquin, paromomycin, diloxanide furoate**
- Do not treat asymptomatic intestinal *E. dispar* infection

Giardiasis

Giardiasis - life cycle



- *G. lamblia* is a zoonosis (infected small mammals pass cysts and contaminate surface waters)
- Waterborne transmission is most common, but can also be spread person-to-person by young children (e.g., day-care centers)
- Ingested as cysts
- Excystation of the trophozoite and attachment to the mucosa occurs in the upper small intestine.



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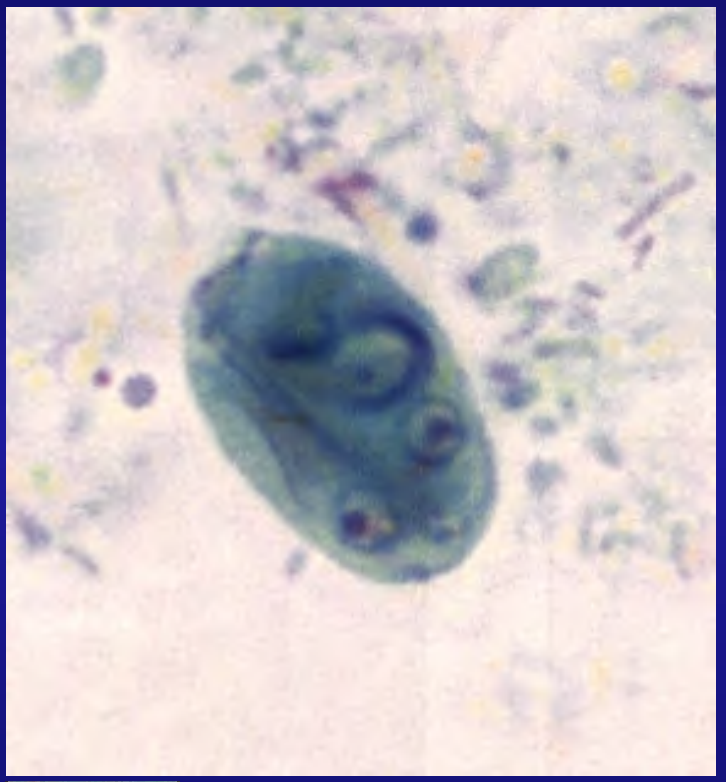
Trophozoites in duodenum



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Cyst in stool

Giardia pathogenesis

- Parasites elicits localized hypersensitivity
- Intestinal villi become blunted
- Malabsorption develops

Dorsal "Suction Disc"

Ventral

PD-INEL Source Undetermined

Giardia - clinical features

- Acute, self-limited diarrhea
- Chronic diarrhea with malabsorption, steatorrhea, and weight loss
- Chronic asymptomatic cyst passage

Dx: stool antigen testing, stool examination, duodenal aspirate.

Giardiasis - treatment

- Metronidazole (or nitazoxanide)

Giardiasis - prevention

- Filtration of water
- Heating water to >50°C
- 2% iodine x 30 minutes

Generalizations about other intestinal protozoa
(Cryptosporidium, Cyclospora, Microsporidia)

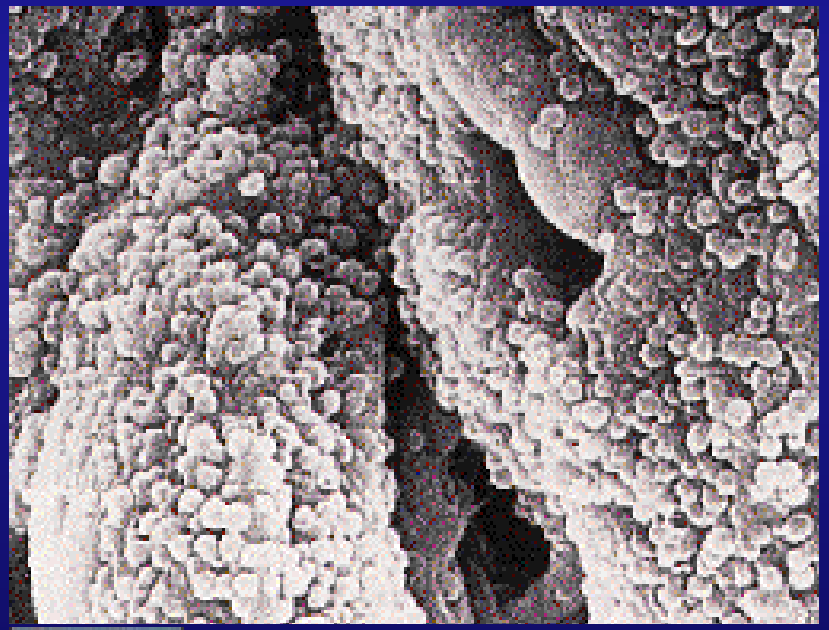
- All acquired by fecal-oral route
- All grow abundantly inside of mucosal cells
- All cause watery diarrhea, cramps, anorexia (not inflammatory) - pathogenesis uncertain
- All require special stains or examinations of stool for dx.

Cryptosporidium in tissue

Organisms attached to an intestinal villus

PD-INEL Source Undetermined

Intestinal organisms by scanning EM



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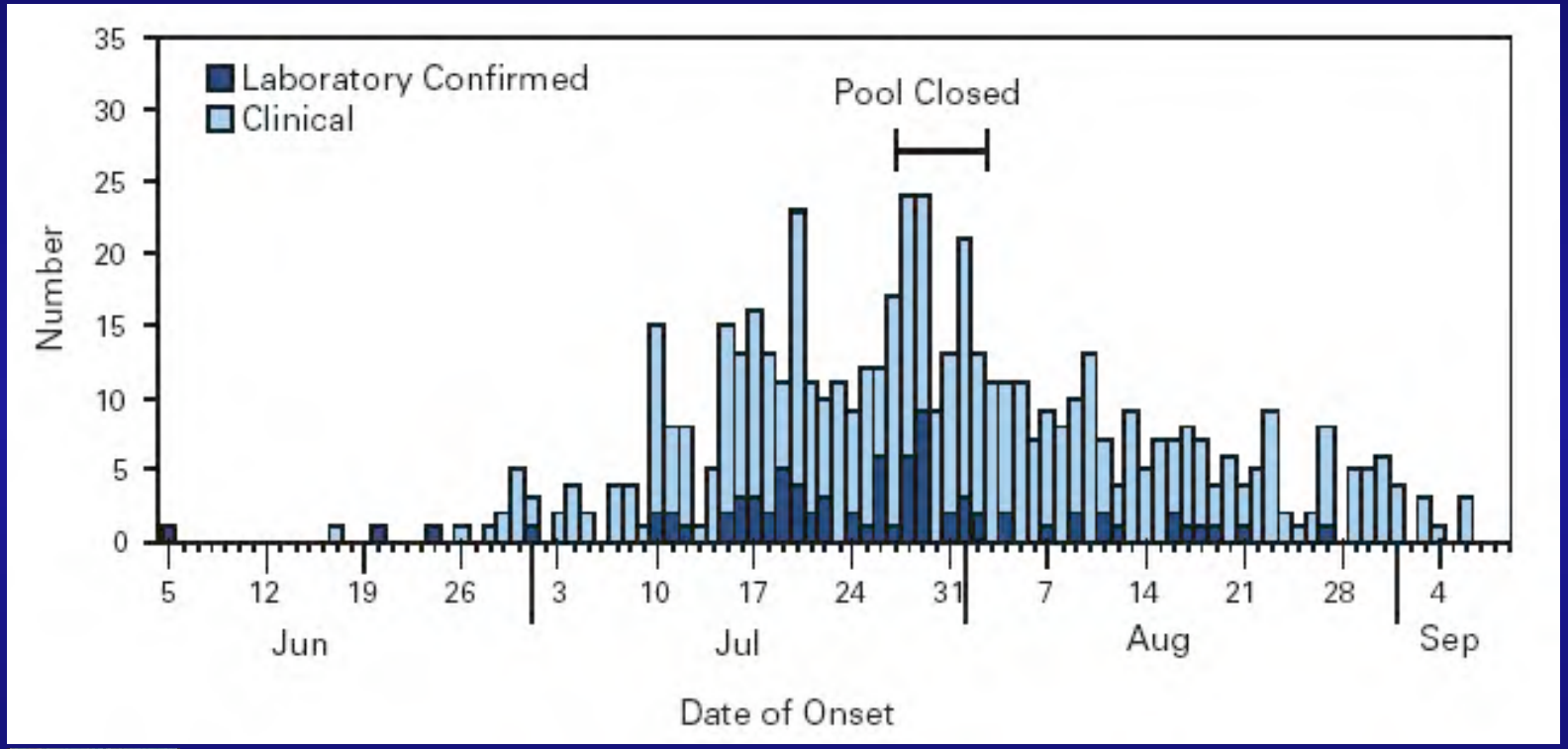
Cryptosporidium parvum

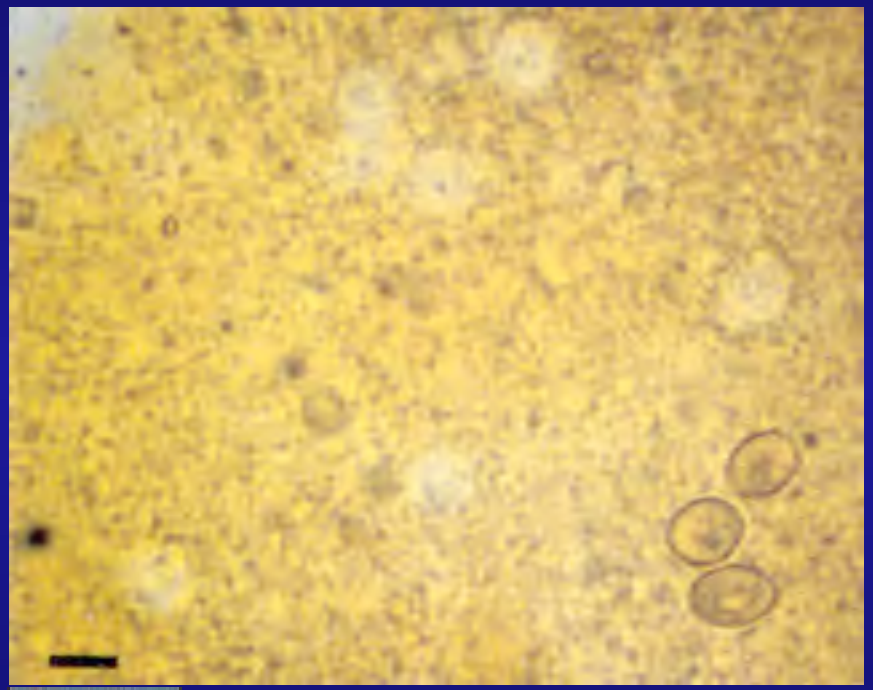
- **Associated with-**
  - **prolonged self-limited diarrhea in immunocompetent individuals**
  - **traveler's diarrhea**
  - **chronic, unrelenting diarrhea in AIDS**
- **Usual acquired from**
  - **drinking water (e.g., Milwaukee, 1993)**
  - **swimming pools**
- **Relative chlorine resistance**

Number of cryptosporidiosis cases, by date of onset, Delaware Co., Ohio, Jun–Sep 2000



- **Relative risk of swimming at a private swim club = 42.3 (12.3–144.9)**
- **At least 5 fecal accidents witnessed**

Cryptosporidium



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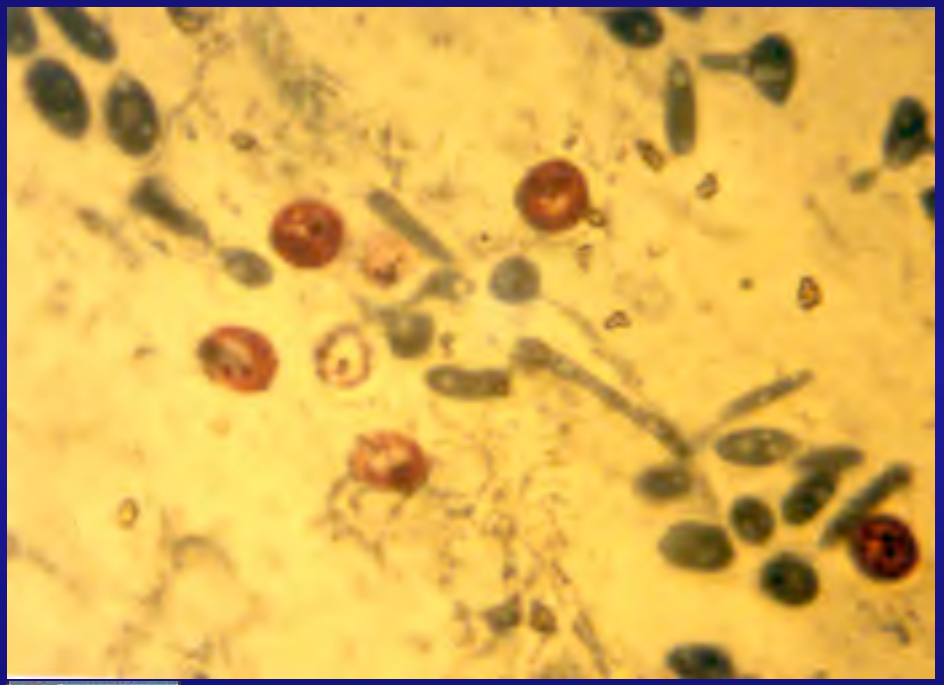
Iodine stain of stool



PD-INEL Source Undetermined

Acid-fast stain of stool

Treatment of cryptosporidiosis

- Supportive (rehydration, antimotility agents)
- No FDA-approved rx
- Nitazoxanide?

Cyclospora

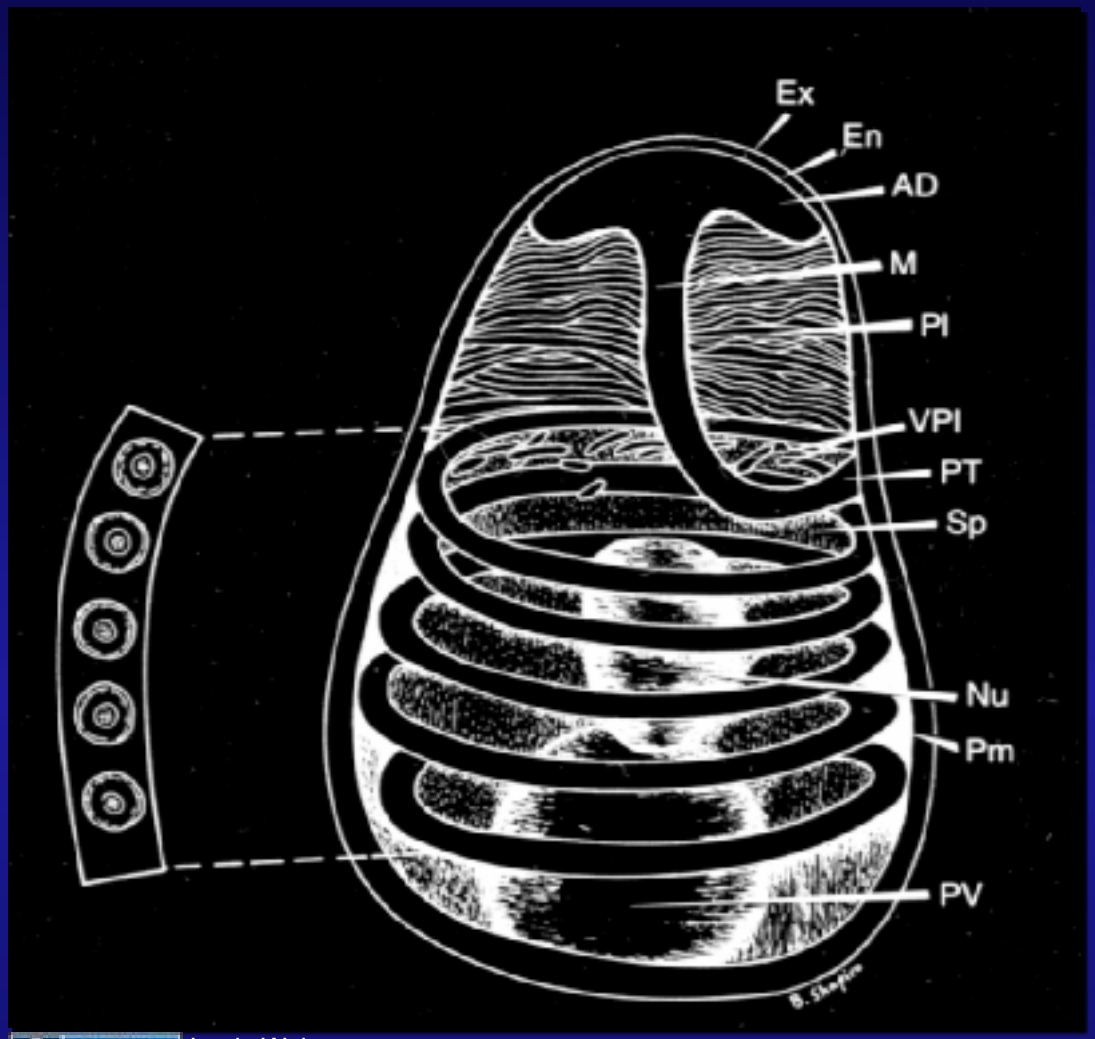
PD-INEL Source Undetermined

Cyclospora

- Food and waterborne transmission
  - 1996-97 outbreaks associated with Guatemalan raspberries shipped to U.S.
- Also replicates within mucosal cells
- Diarrhea may persist for 1-2 months without treatment
- Trimethoprim/sulfa x 7 days is effective therapy (unlike Cryptosporidium)

Microsporidia

- Primitive fungi that were initially thought to be protozoa
- Long recognized as animal pathogens
  - human cases in AIDS
  - recent human cases also seen in immunocompetent persons
- Hundreds of species identified



PD-INEL Louis Weiss

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Ex, exospore
En, endospore
AD, achoring disc
PT, polar tube
Sp, sporoplasm

Explosive Discharge of the Invasion Tube

- **4-30 coils depending on spp**
- **Stimulus varies depending on spp, can be pH shift, dehydratioin/rehydration, mucin, UV, etc**
- **Stimulus increases osmotic pressure, water influx**

Outline of protozoal diseases

- Intestinal protozoal infection
- Systemic protozoal infection

Outline of protozoal diseases

- **Intestinal protozoal infection**
- **Systemic protozoal infection**

apicomplexa:
- Malaria (*Plasmodium* sp.)
- Babesiosis (*Babesia* sp.)

(RBC infection and fever)

- Toxoplasmosis (*T. gondii*)
- Leishmaniasis

(Intracellular infections)

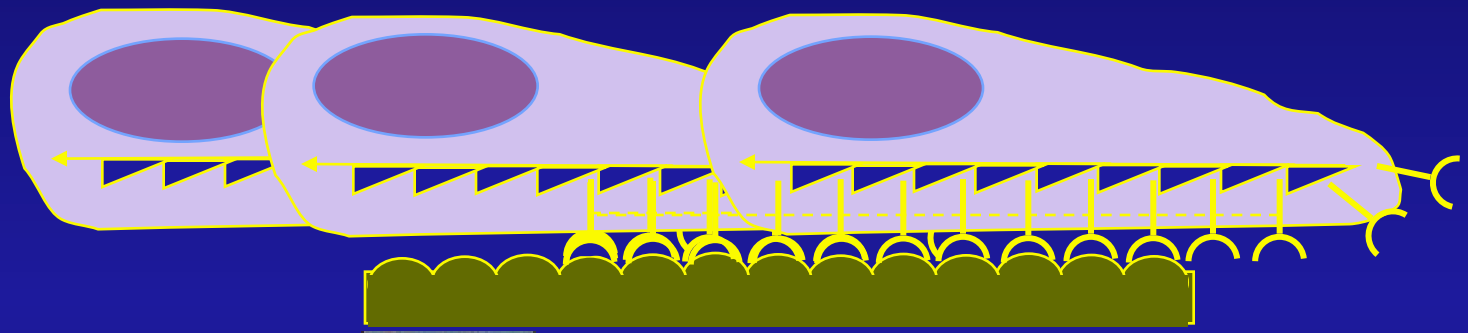
dinoflagellates:
- Others:
  - African trypanosomiasis (sleeping sickness)
  - American trypanosomiasis (Chagas' disease)

Toxoplasmosis

Toxoplasma Features

- **Apicomplexan parasite (similar to *Cryptosporidium*, *Cyclospora* and *Plasmodium*)**

Gliding Motility of Apicomplexa



PD-INEL Cary Engleberg

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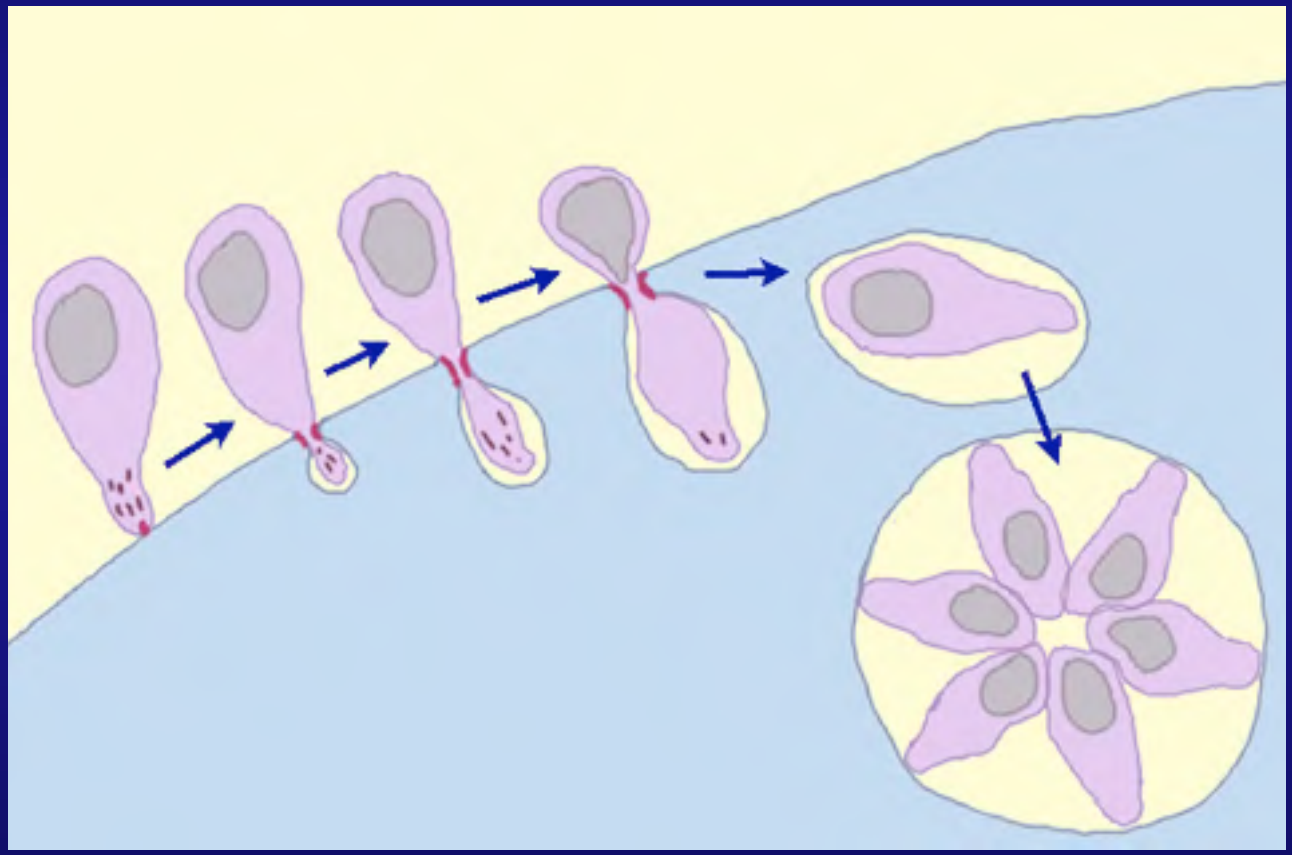
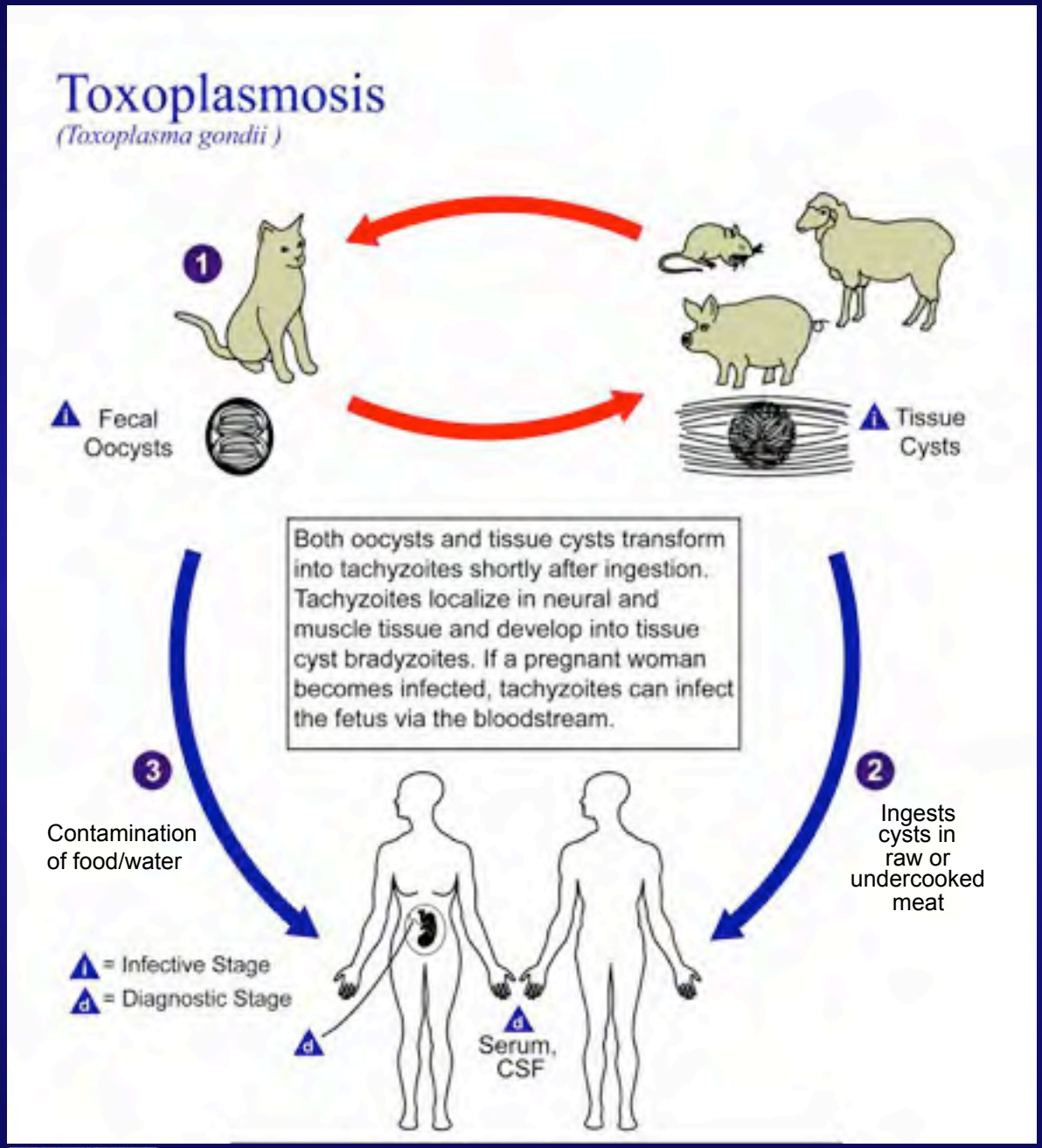
Entry of Apicomplexa into cells



- Cats infected by predation
- 10^7 oocysts passed in feces
- Stable in soil/water for months
- Either indirect thru intermediate

host or direct via food/water

- Vertical transmission during pregnancy



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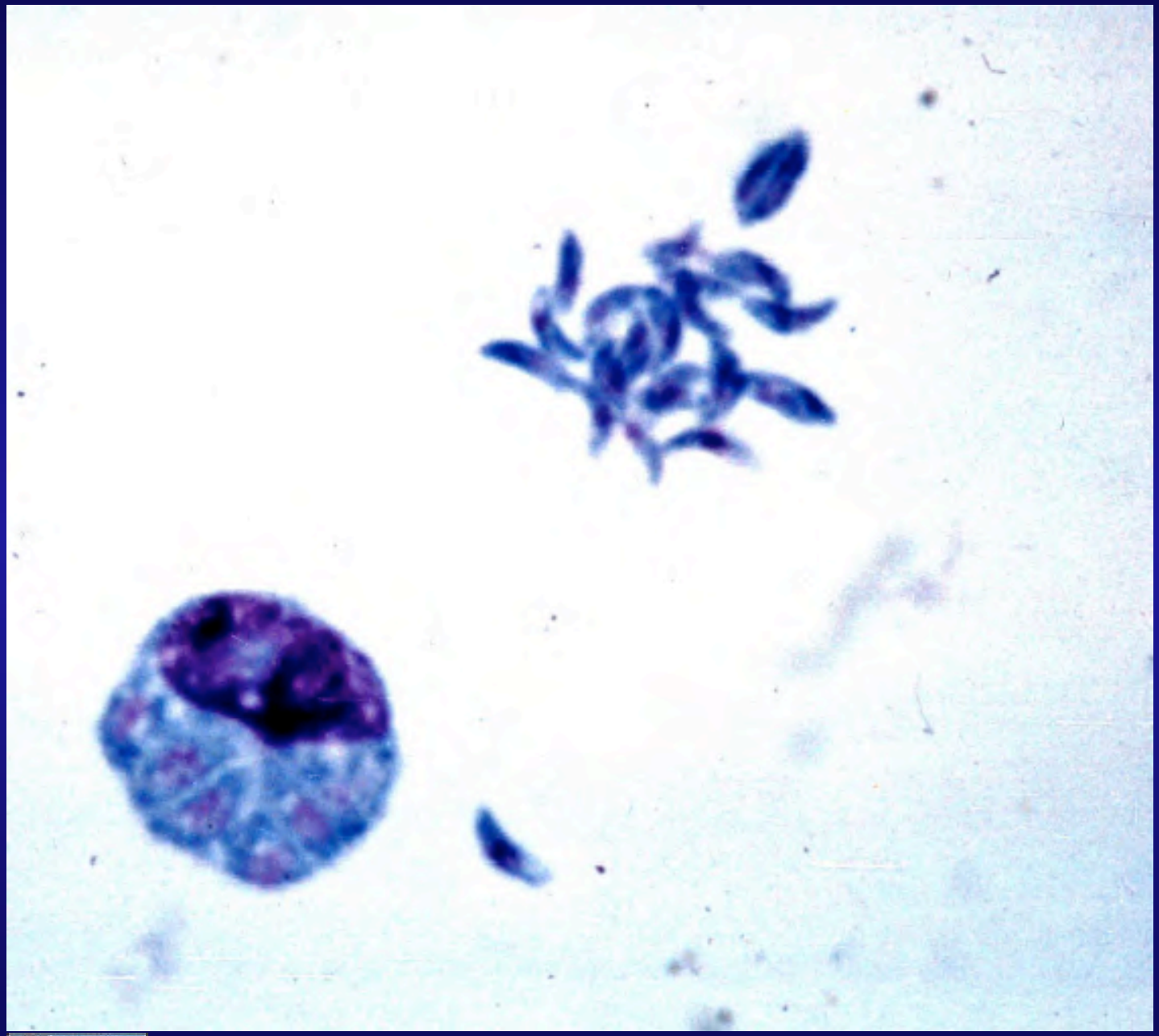
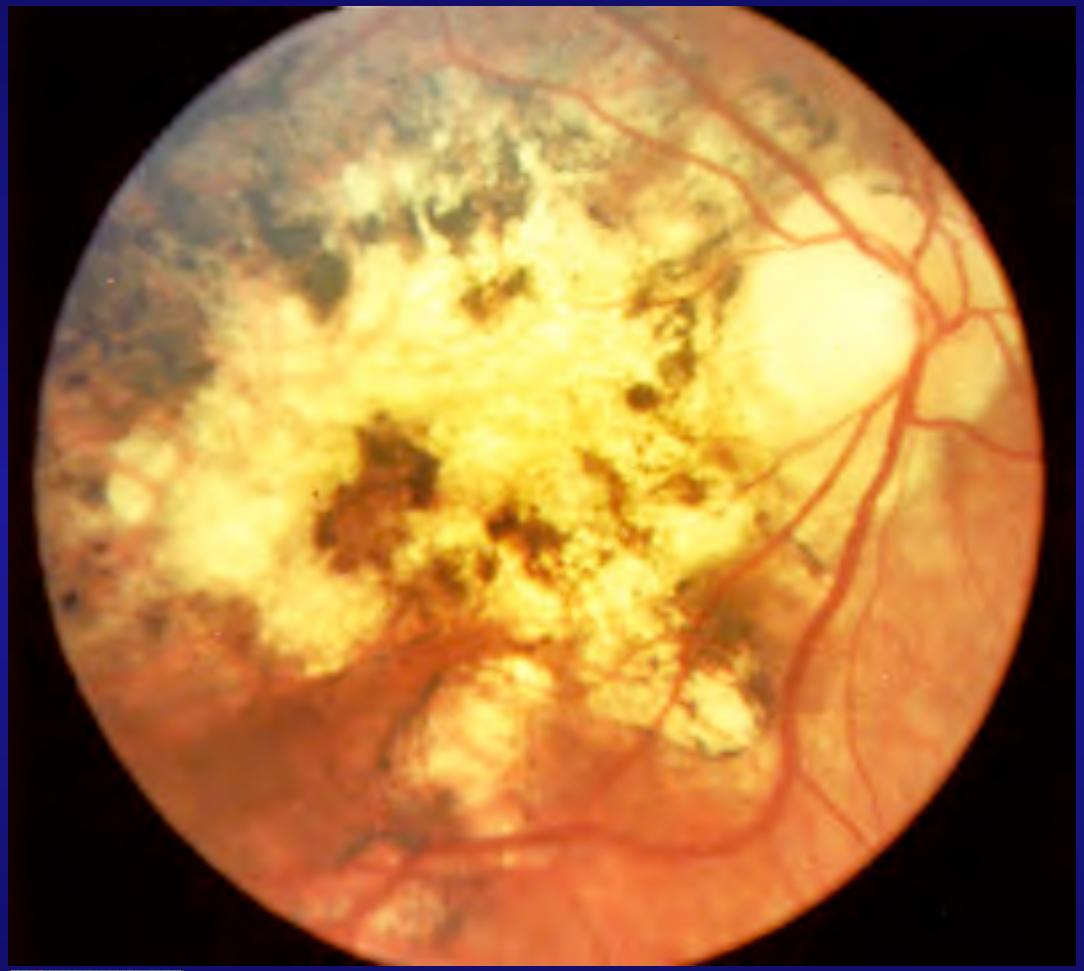


Toxoplasmosis - clinical syndromes

- acute acquired toxoplasmosis
- congenital toxoplasmosis
- ocular toxoplasmosis
- cerebral toxoplasmosis (AIDS)

congenital toxoplasmosis

- 30-40% transplacental if mother is infected during pregnancy
- 60% of infected newborns are asymptomatic (but later show chorioretinitis)
- affected infants may have hydrocephalus, hepatosplenomegaly, jaundice, fever, anemia, pneumonia



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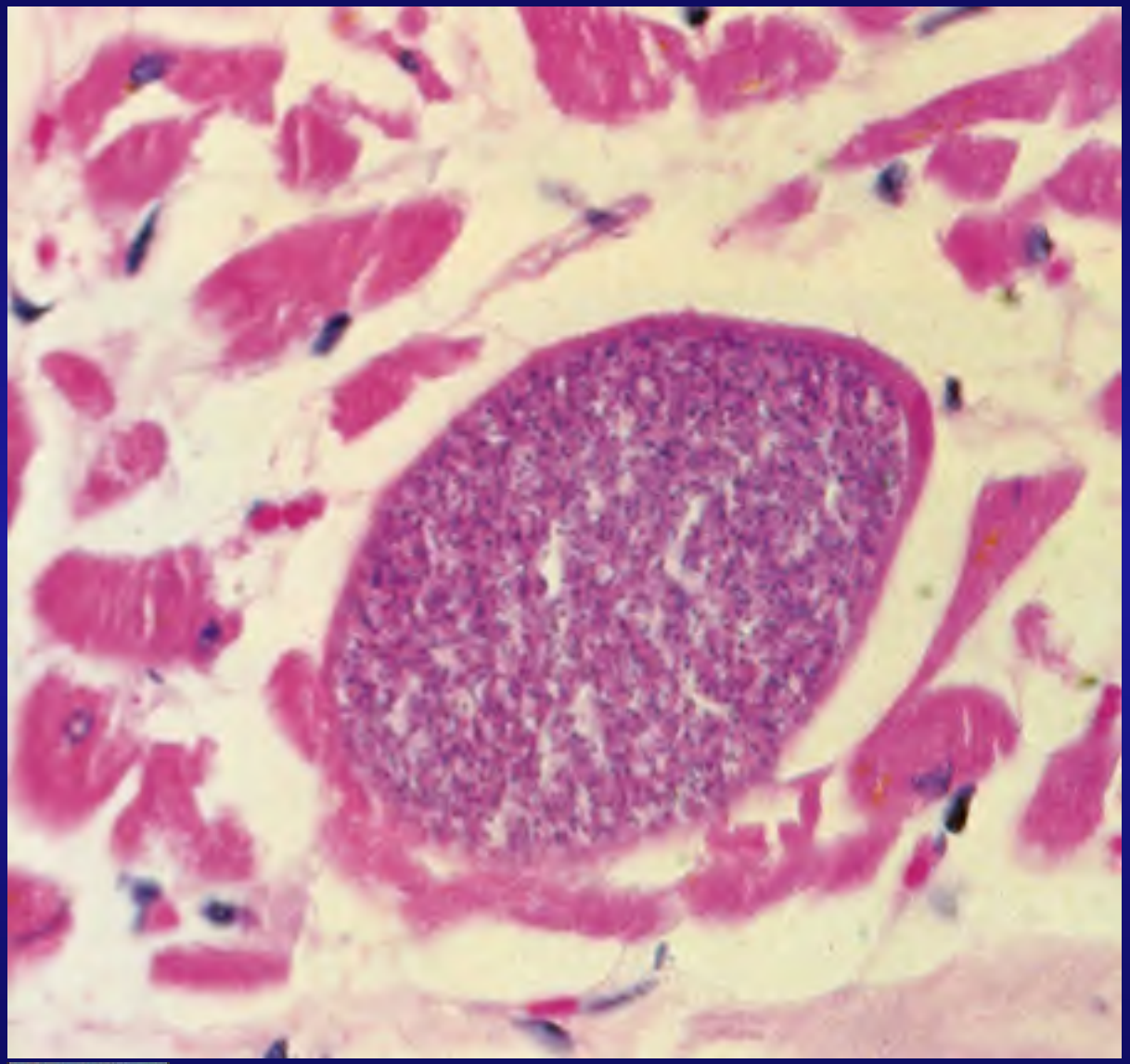

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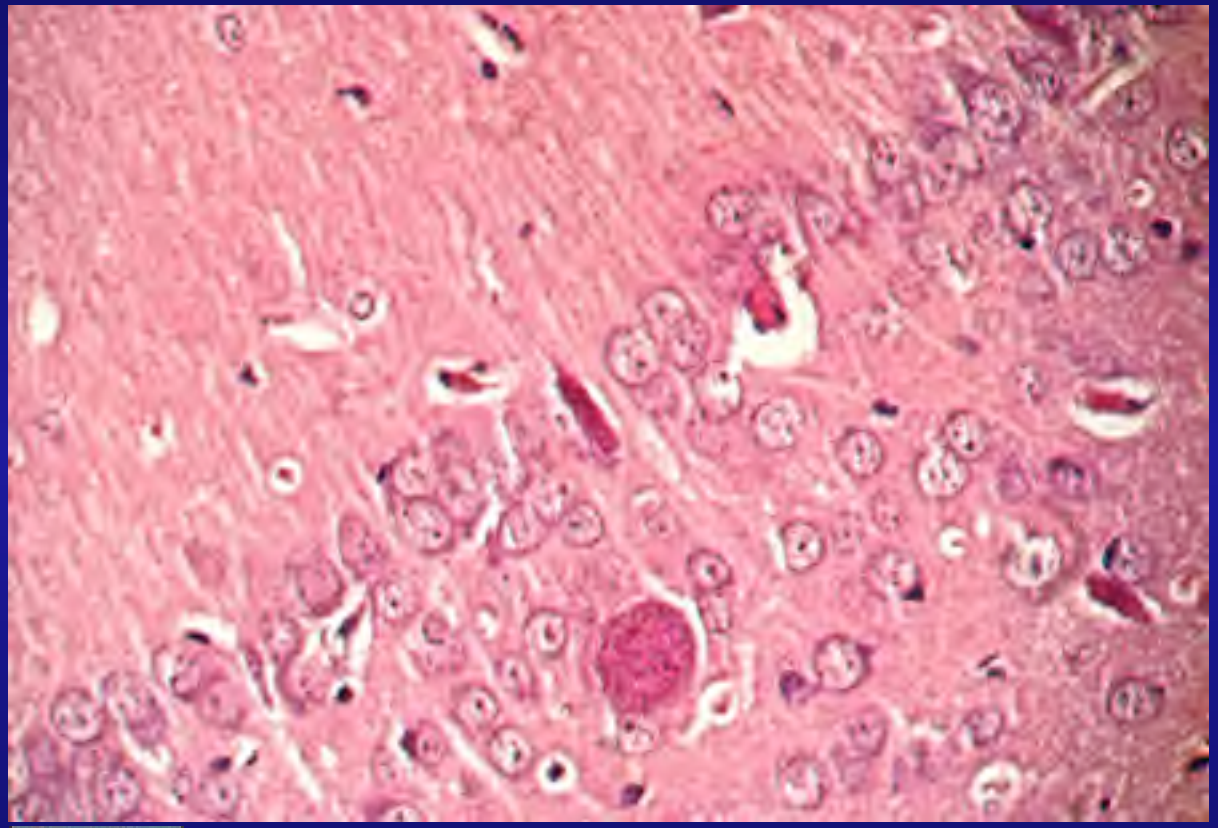

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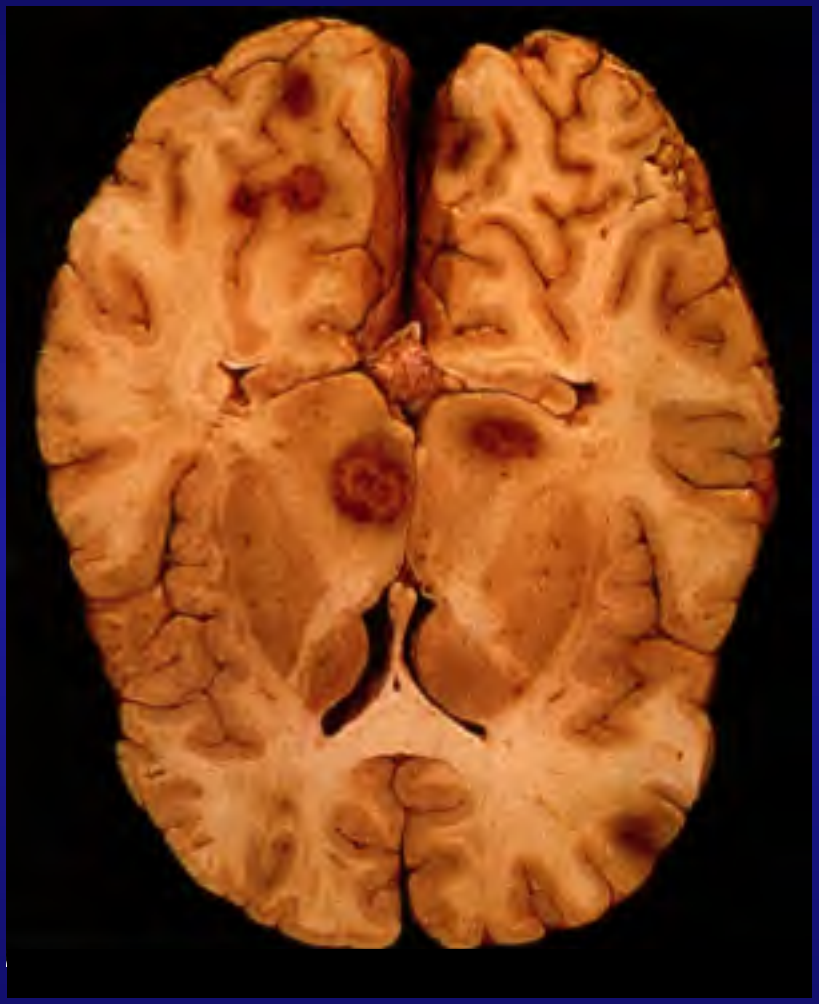

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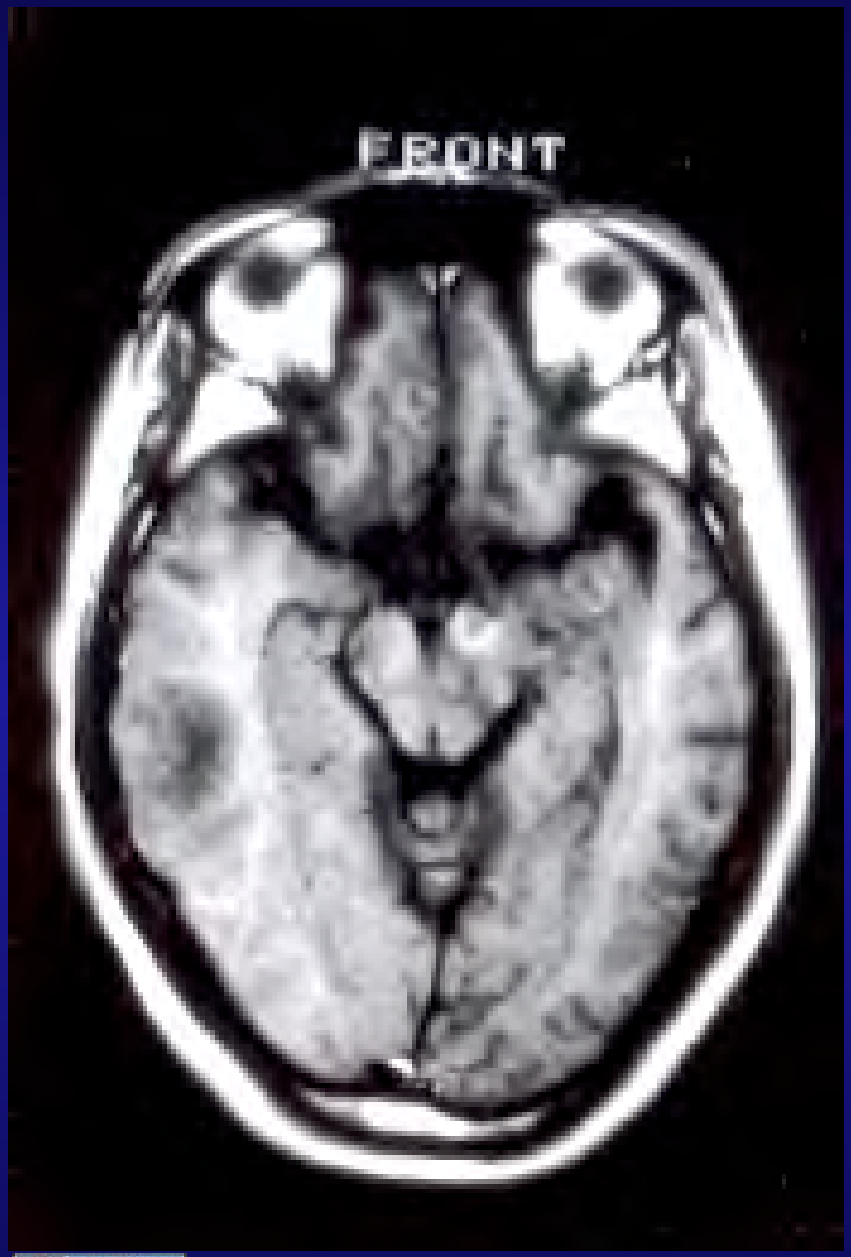

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Diagnosis of toxoplasmosis

- direct identification is difficult
- culture is not routinely done
- serology
  - IFA or ELISA
  - single high IgM or very high IgG level
  - seroconversion not reliable in AIDS
- clinical features and response to rx

Treatment of toxoplasmosis

When RX is indicated . . .

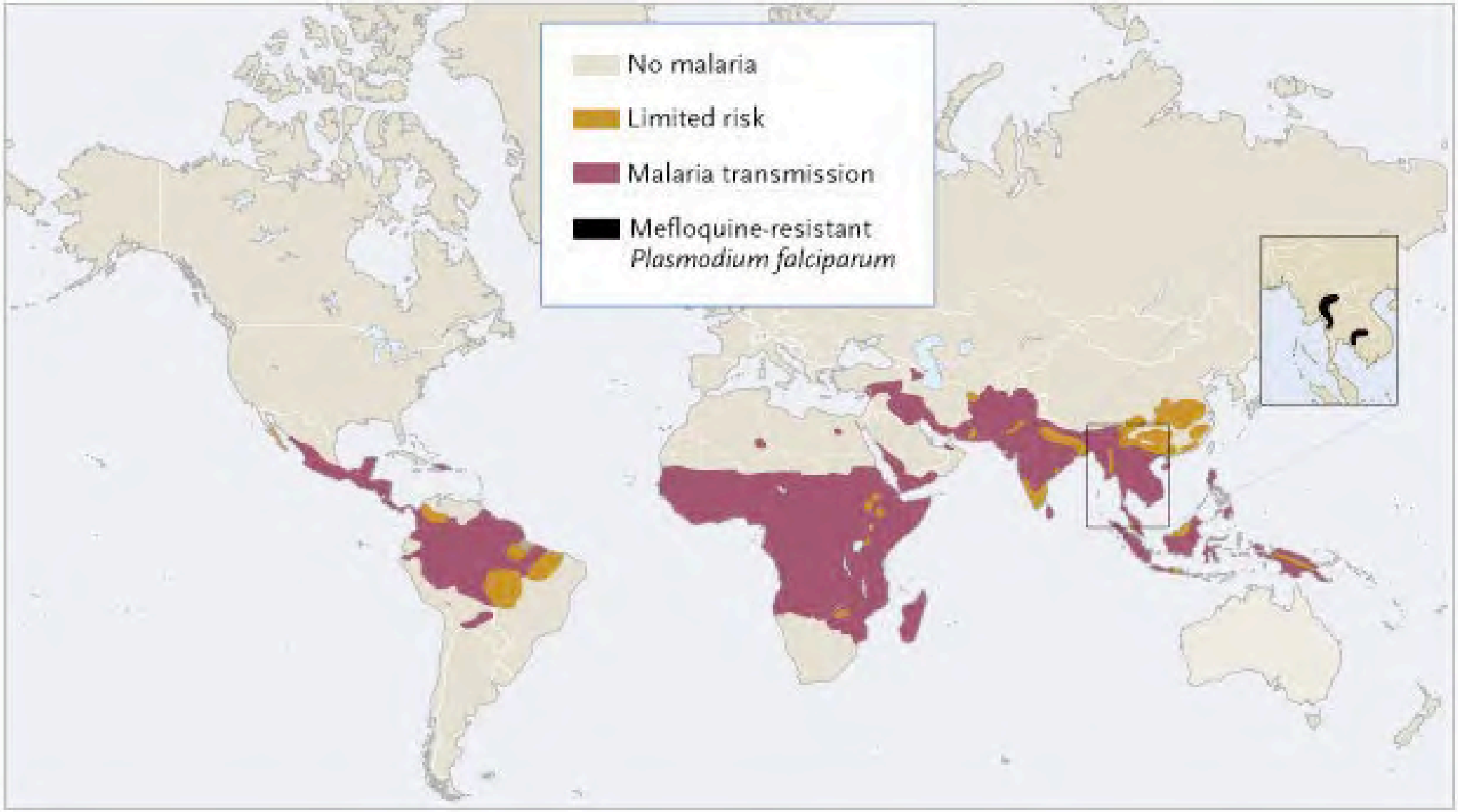
sulfadiazine + pyrimethamine*

OR

clindamycin + pyrimethamine*

*** plus folinic acid**

Malaria



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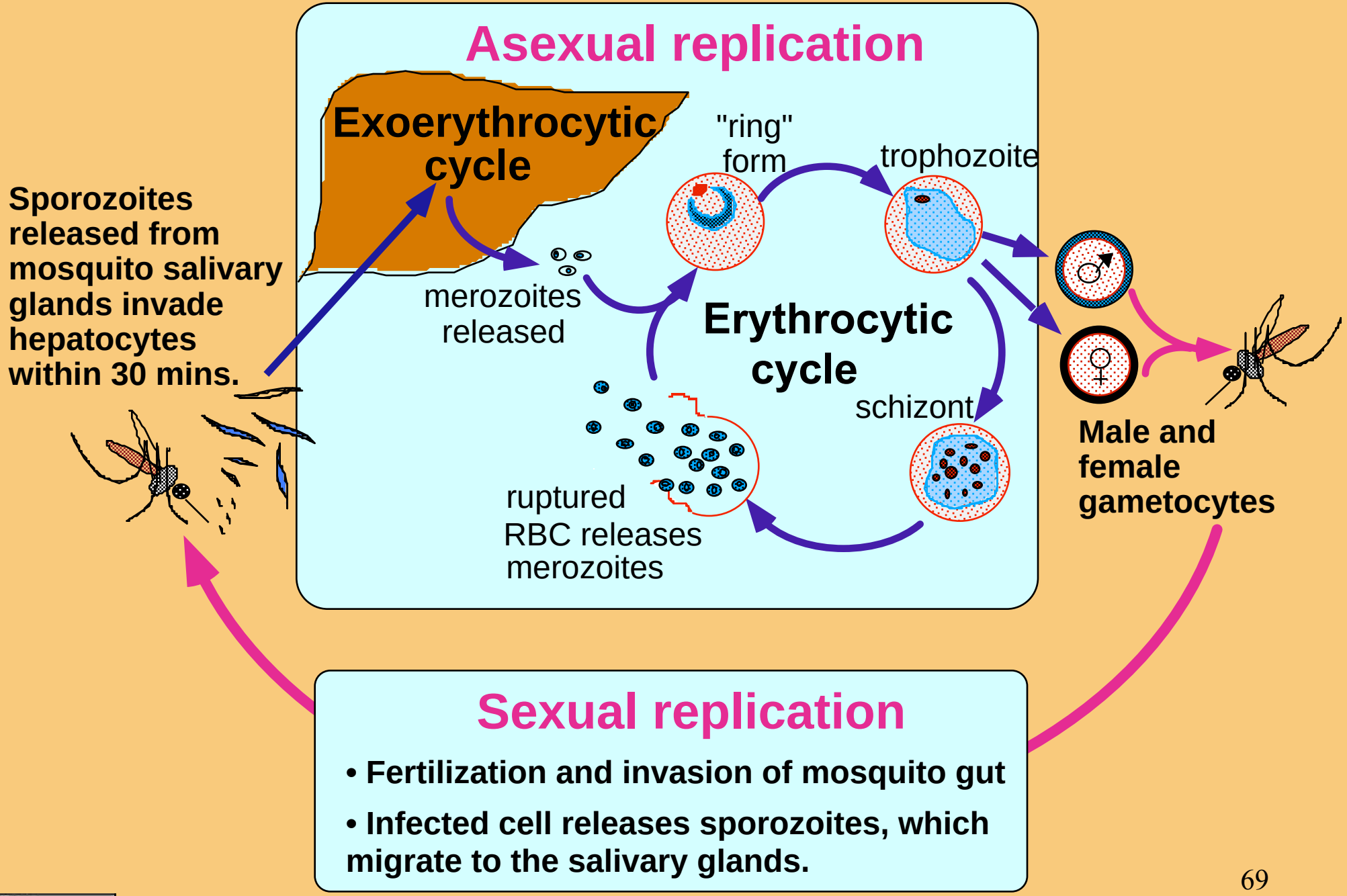
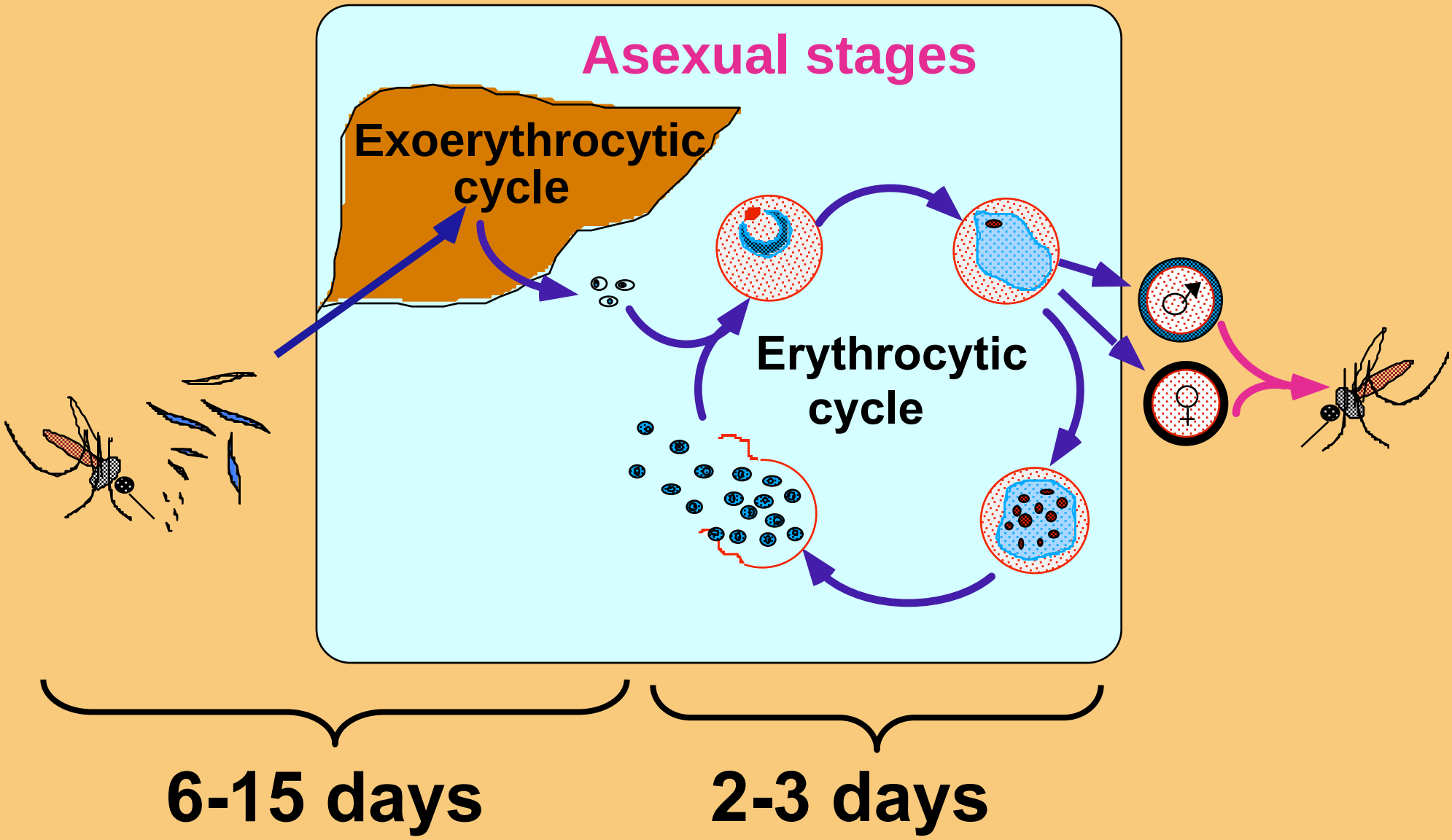
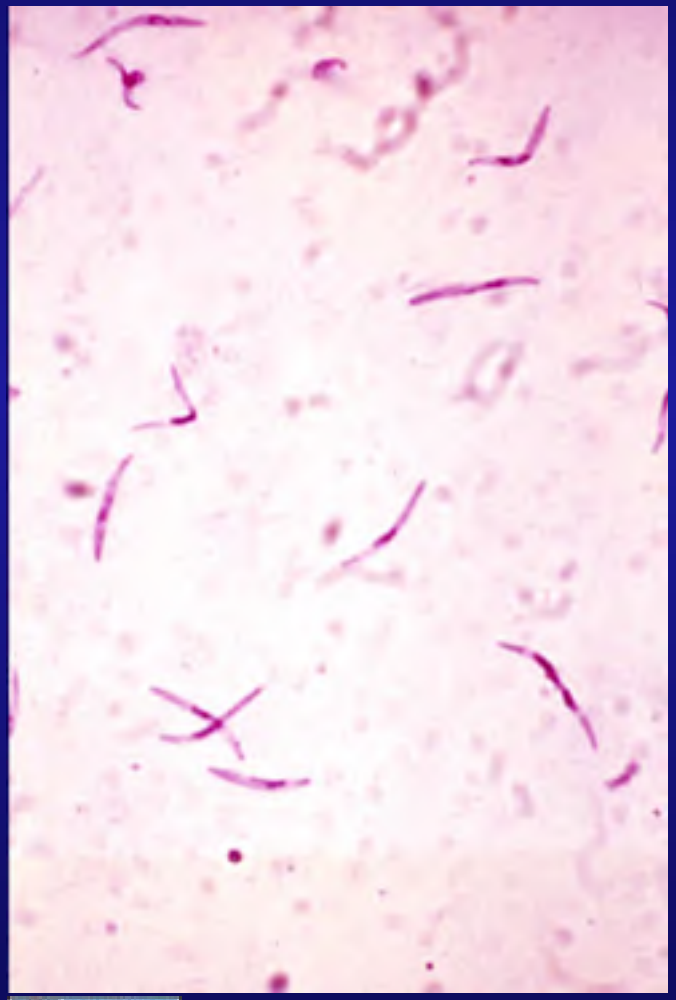
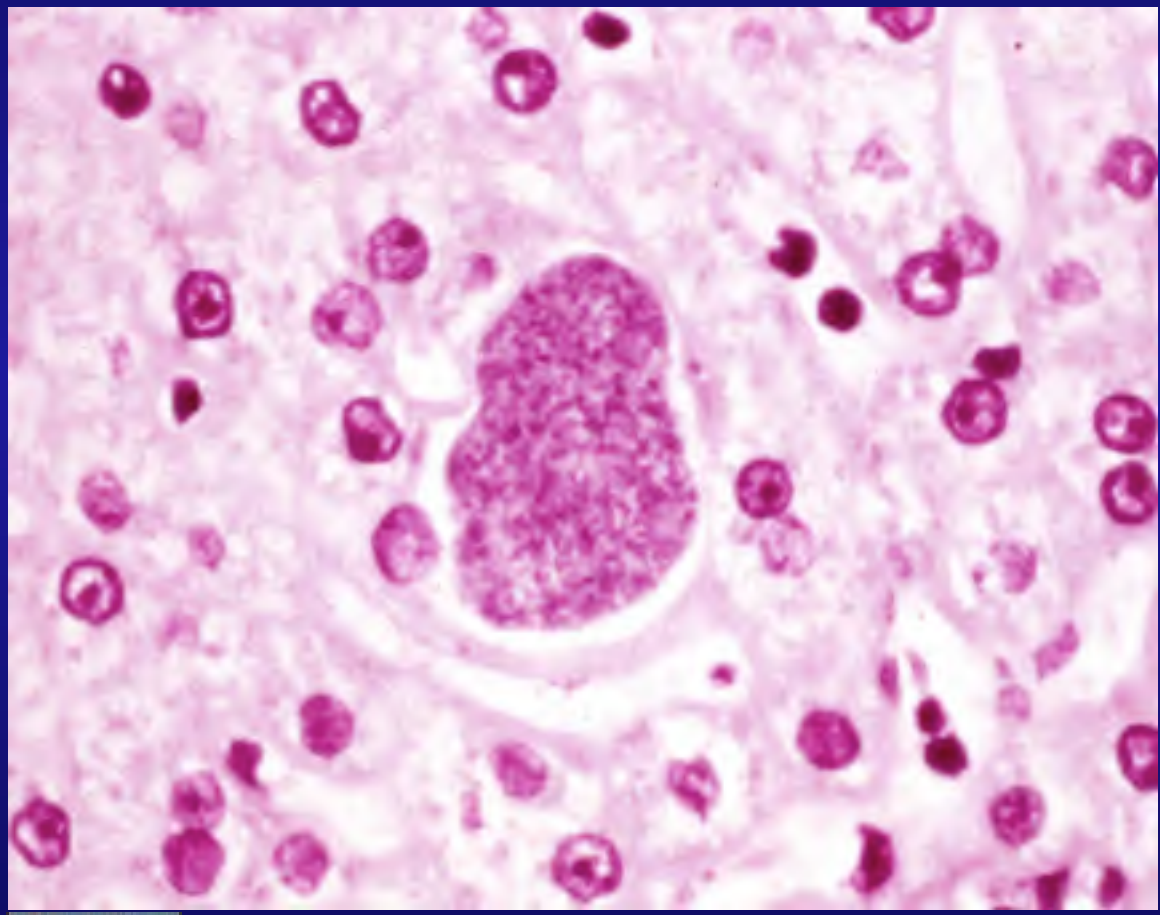




Sporozoites and hepatic schizont



PD-INEL McGill University Department of Medicine



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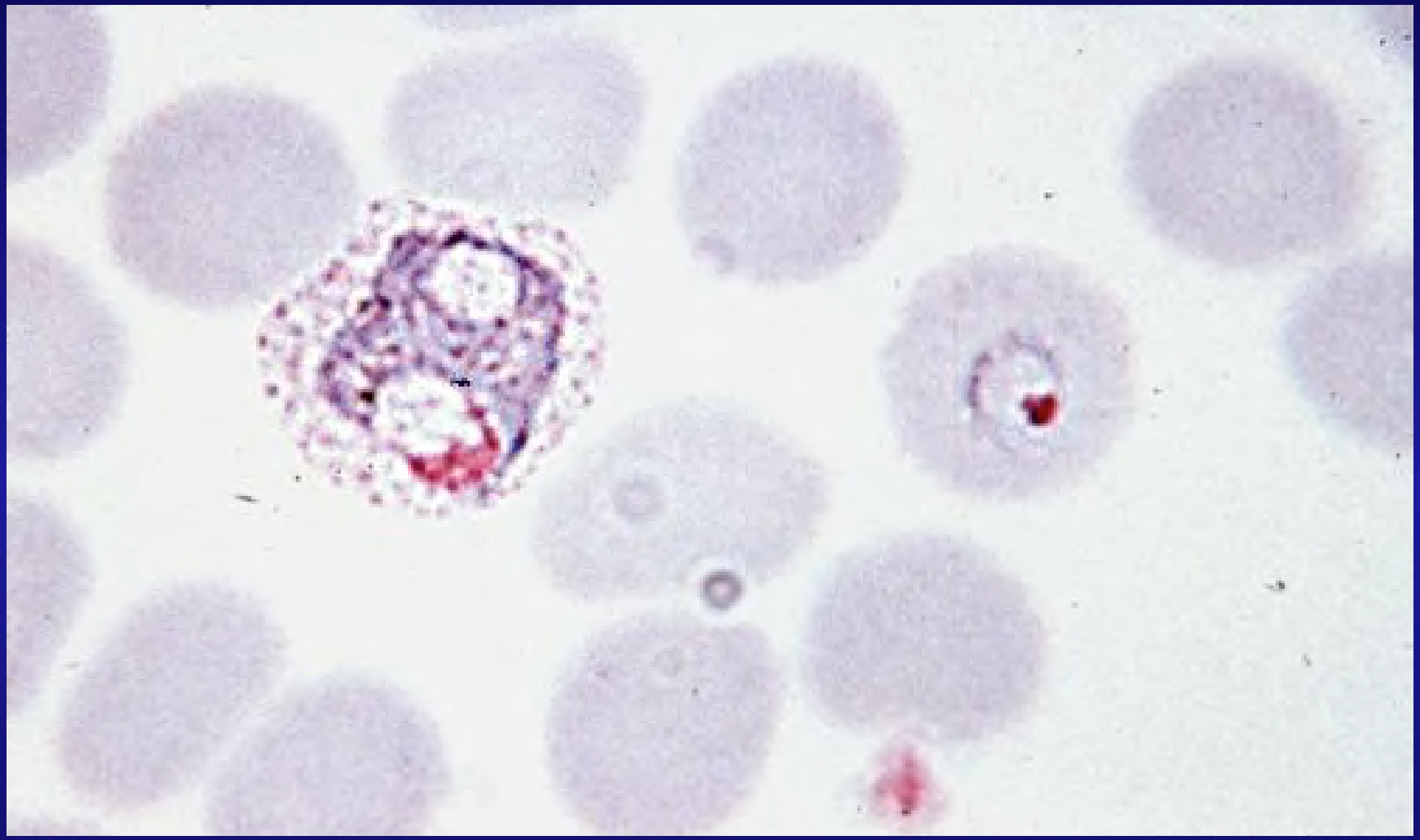

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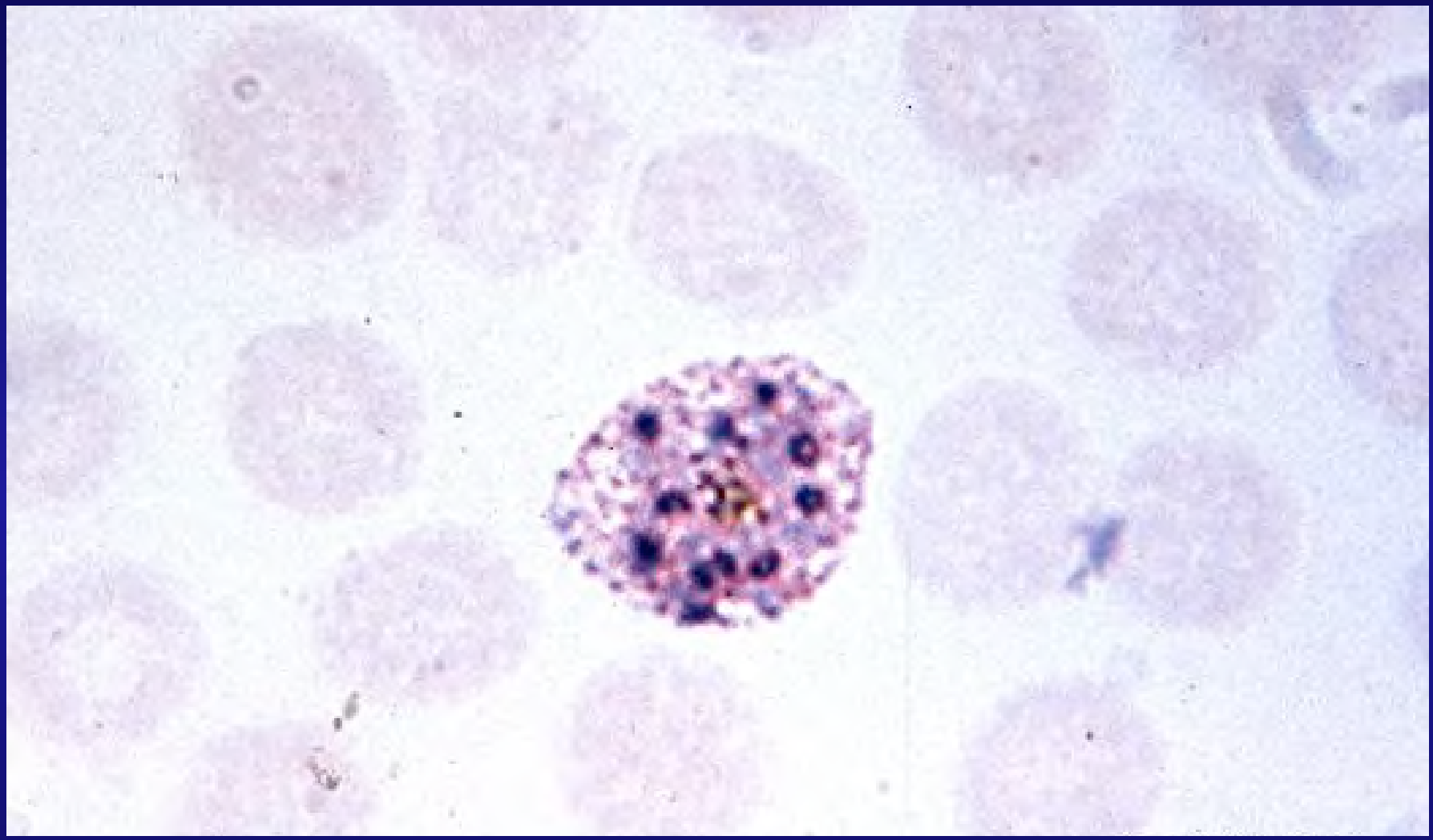
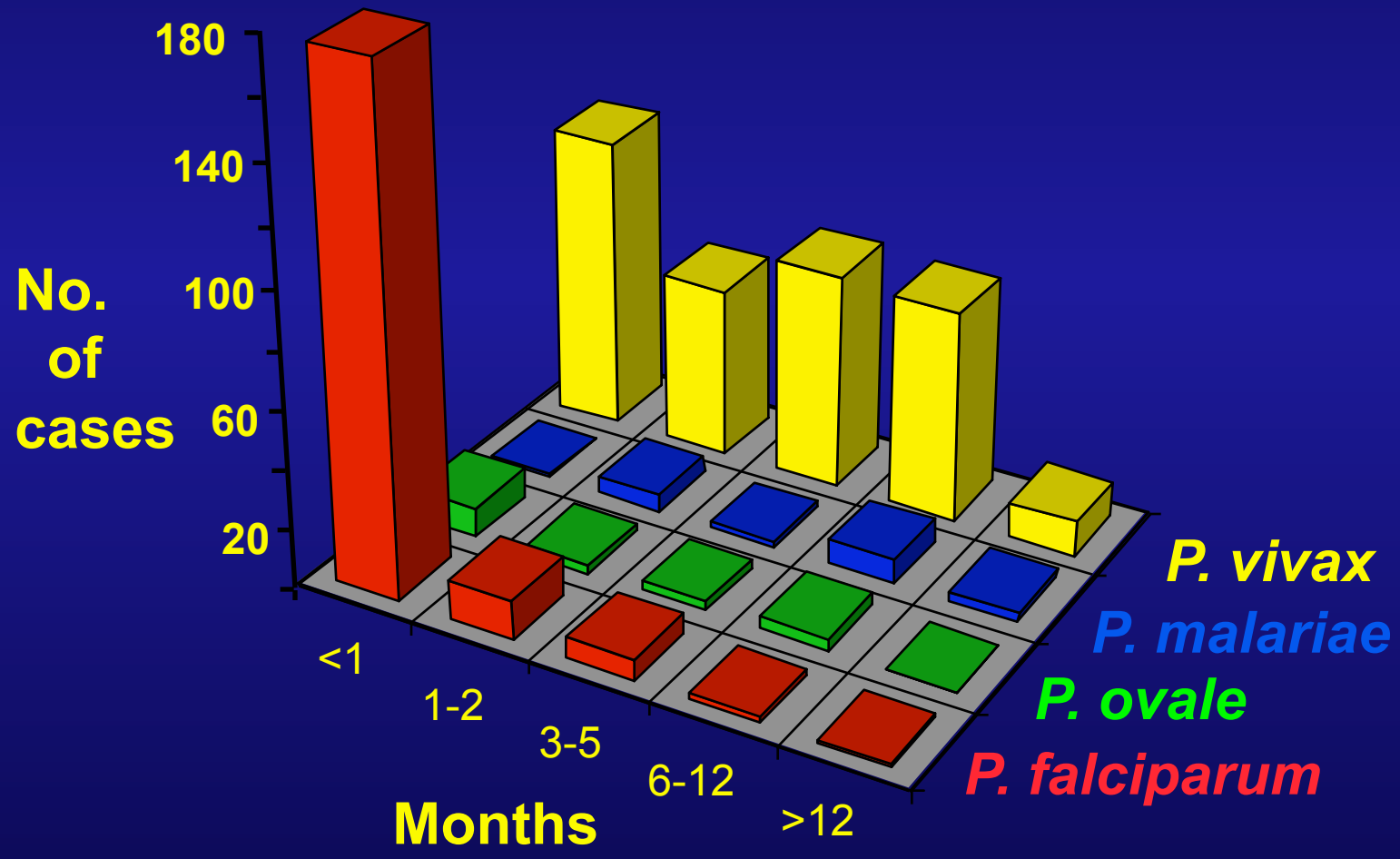


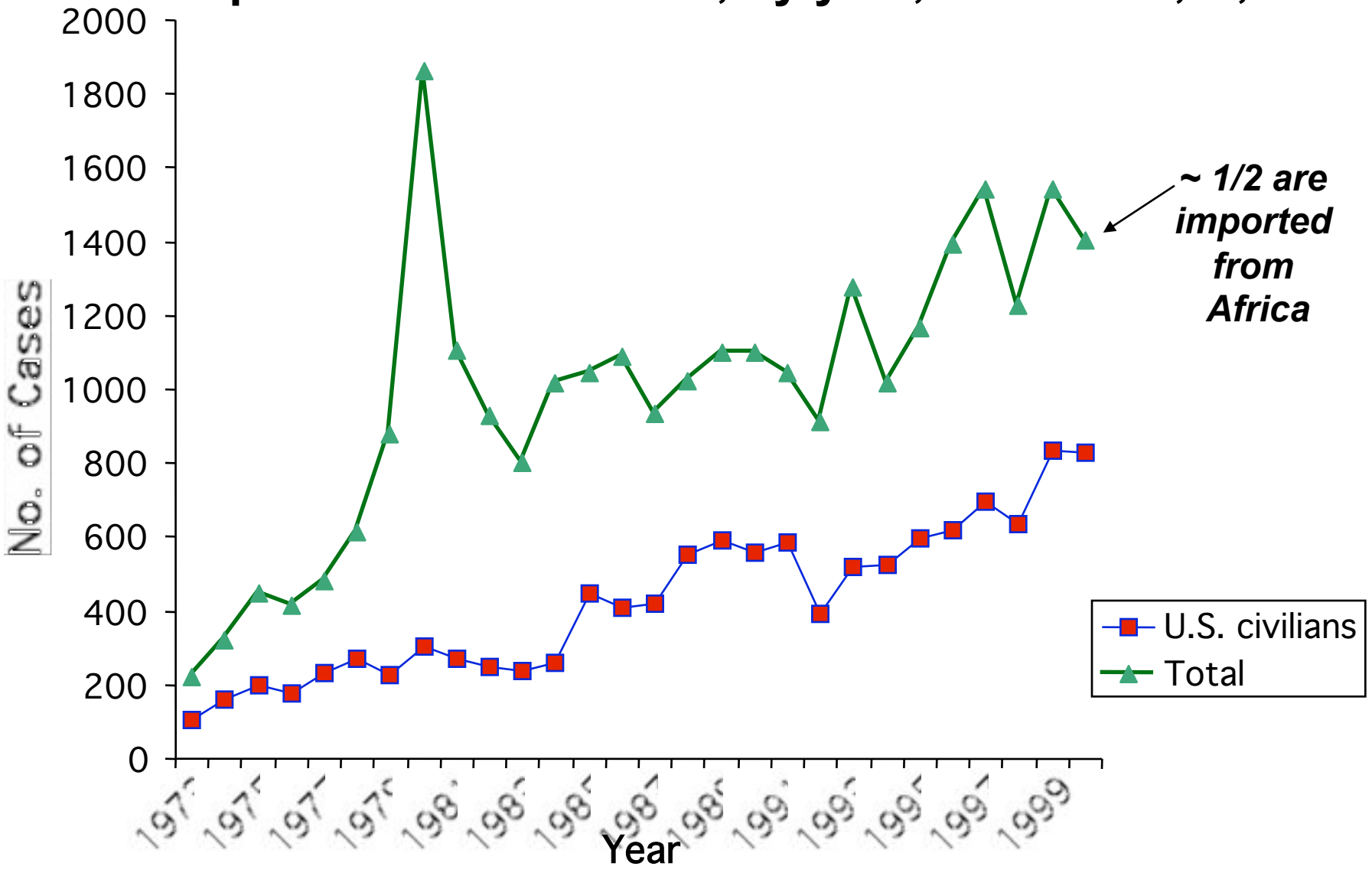
Plasmodium species

SPECIES	ERYTHROCYTIC CYCLE	HEPATIC LATENCY	RECURRENCES
P. falciparum	48 hrs	no	no
P. vivax	48 hrs	yes	yes
P. ovale	48 hrs	yes	yes
P. malariae	72 hrs	no	yes

Imported malaria cases, by species and interval between date of arrival and onset of illness — U.S., 1992



Imported malaria cases, by year, 1973-2000, U,S.



Stable and unstable malaria transmission

	"stable" continuous transmission	"unstable" epidemic malaria
Clinical disease	children	all ages
Mortality	children	all ages
Enl. Spleen rate (2-9 yrs)	>10%	<10%
Immunity among adults	high	low
Parasitism rate	high	low

Malaria - clinical features

- **paroxysms associated with synchronous release of merozoites from RBCs**
  - **Infected RBCs release substances that stimulate the release of TNFα and IL-1 from host cells**
  - **rigorous chills, fever, myalgia, severe headache ± GI symptoms (5-6 hours)**
  - **profuse sweating and exhaustion (2-3 hours)**

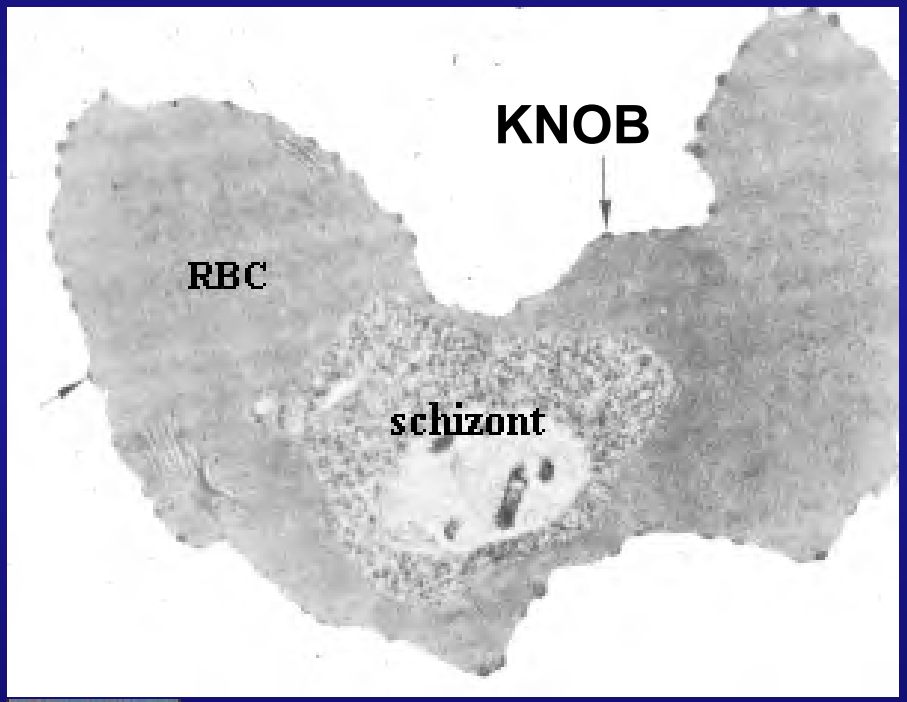
Malaria - clinical features

- immunologically-mediated hematologic changes
  - anemia
  - thrombocytopenia
  - leukopenia

Enhanced virulence of *P. falciparum*

- merozoites can enter RBCs of any age
- parasitemias reach very high levels
- adhesin proteins deployed on infected RBCs (trophozoites and schizonts)
  - attachment to venular endothelial cells (e.g., via ICAM-1)
  - reduced blood flow in small vessels --> microinfarction, hemorrhage

Adherent *P. falciparum* schizonts



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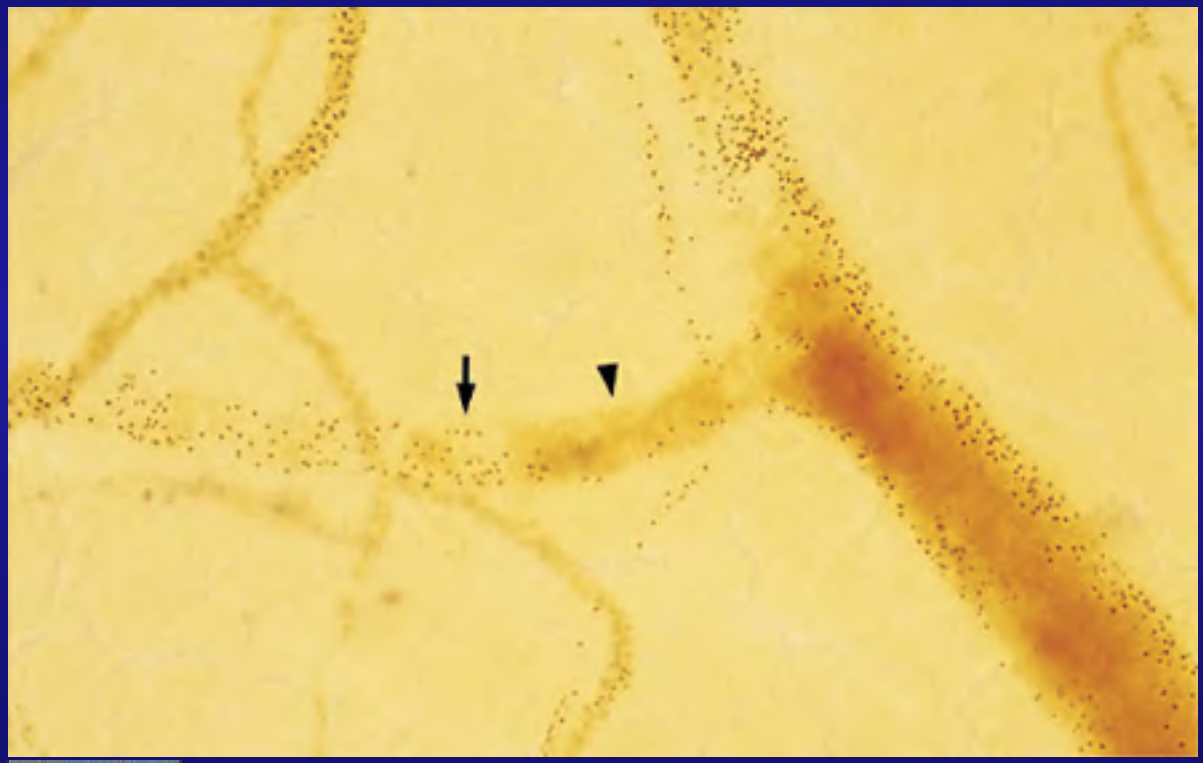

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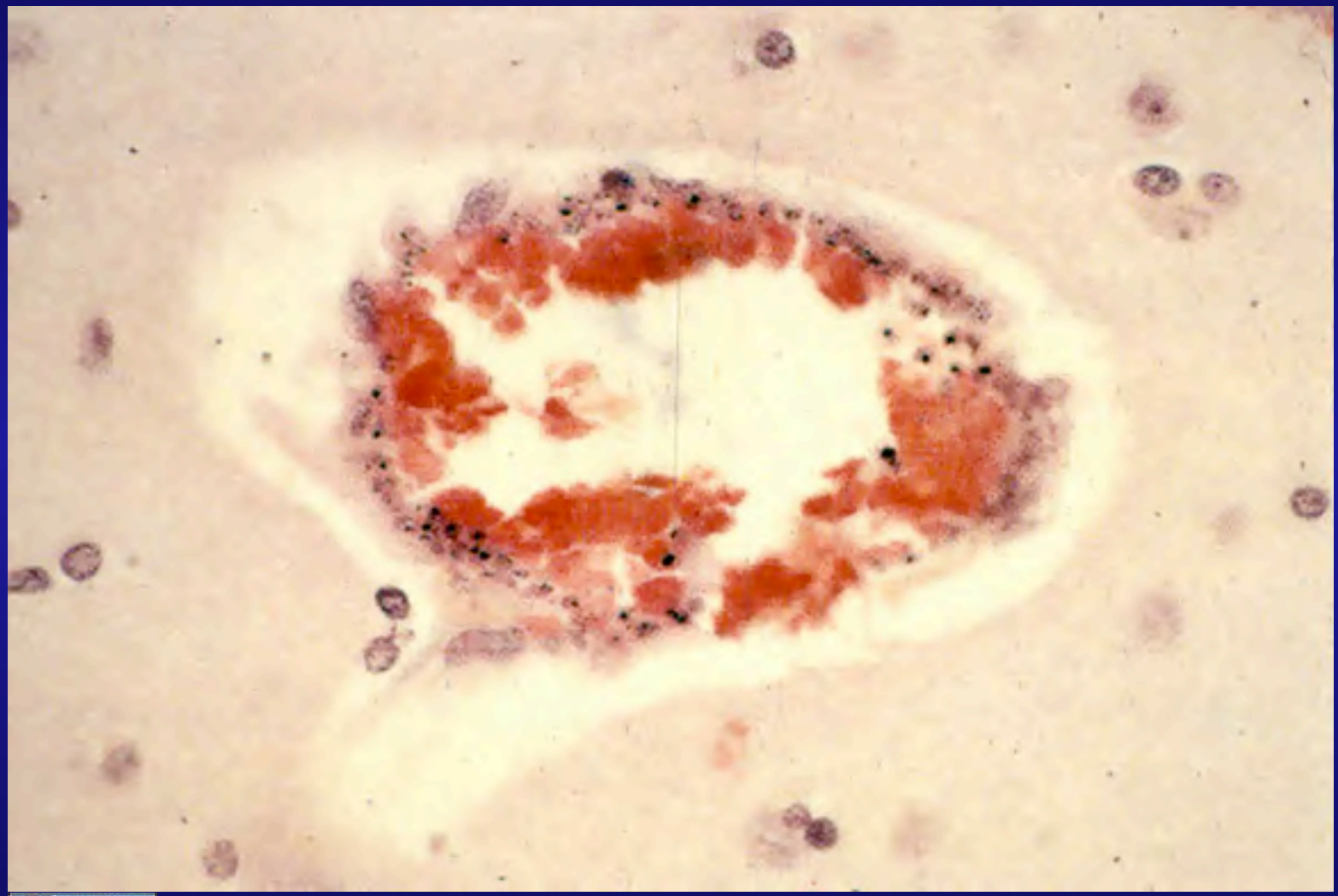
Schizonts adhering to retinal blood vessels



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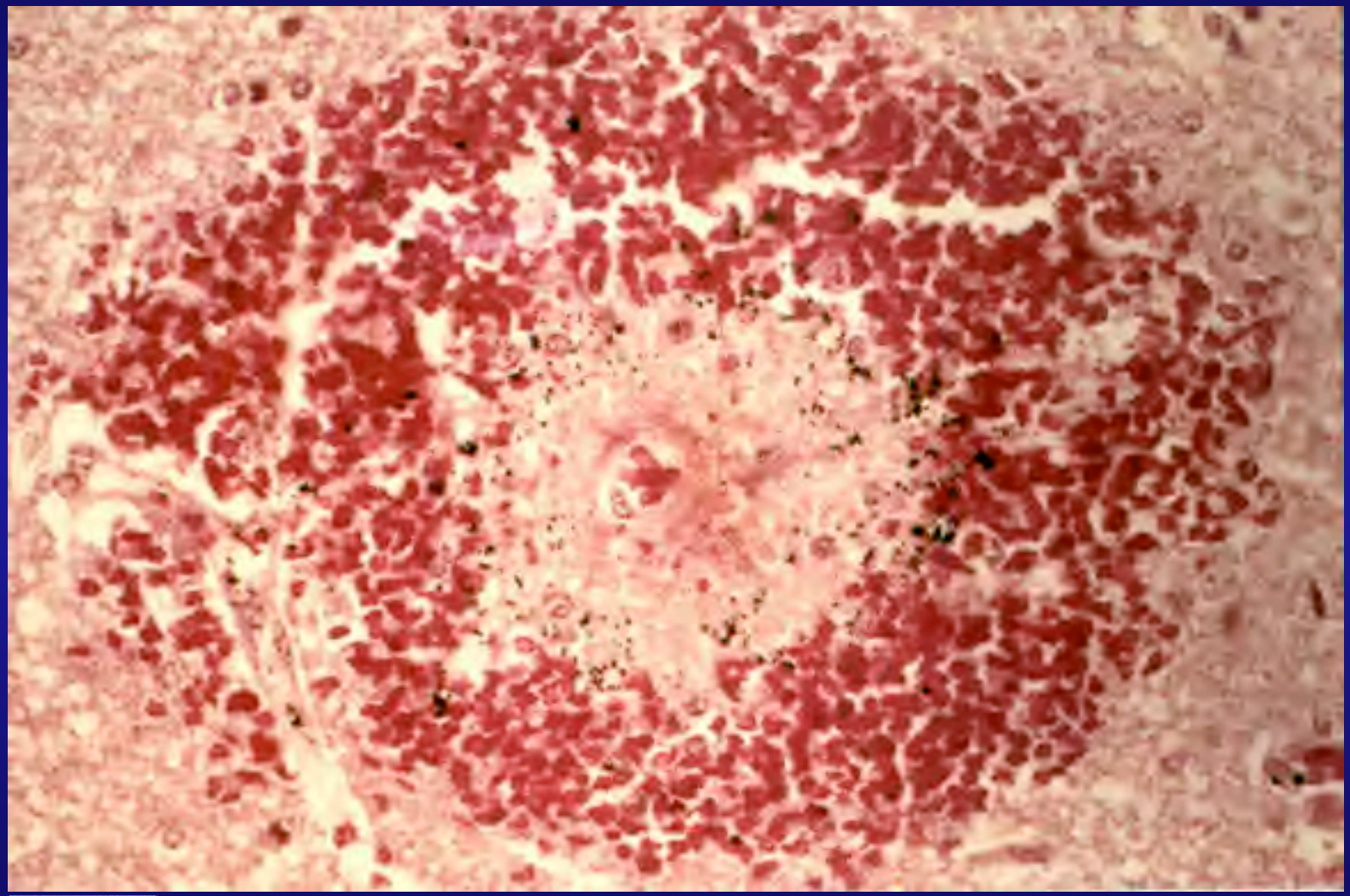

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Antimalarial treatment

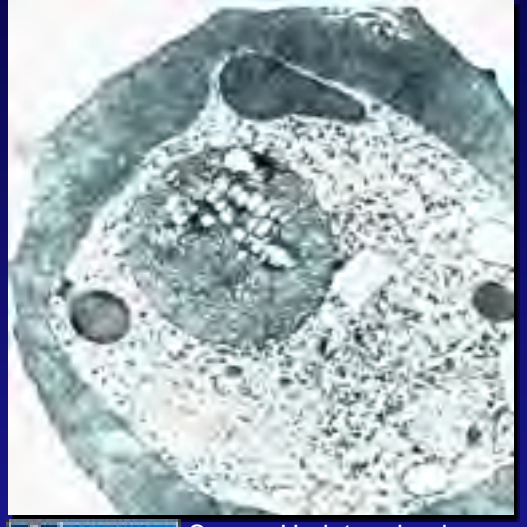
- **based on species and location acquired**
  - **chloroquine-sensitive species**

    rx: chloroquine (blocks heme iron detoxification)
  - **Chloroquine ® *P. falciparum***

    Rx (quinine + doxycycline) or Malarone®
- **Add primaquine for *P. vivax* and *P. ovale***

Hemezoin Formation: Eating the Host From the Inside Out

- Hemeglobin 300 mg/ml inside RBC!
- Parasite digests hemeglobin for nutrients and to create room for growth
- Problem: Free heme is extremely toxic because generates oxygen radicals
- Solution: sequester in hemezoin crystals!
- Most malaria drugs interfere with hemezoin formation



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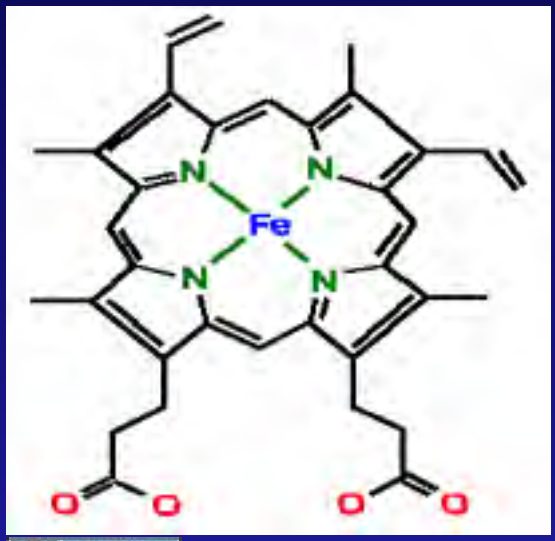

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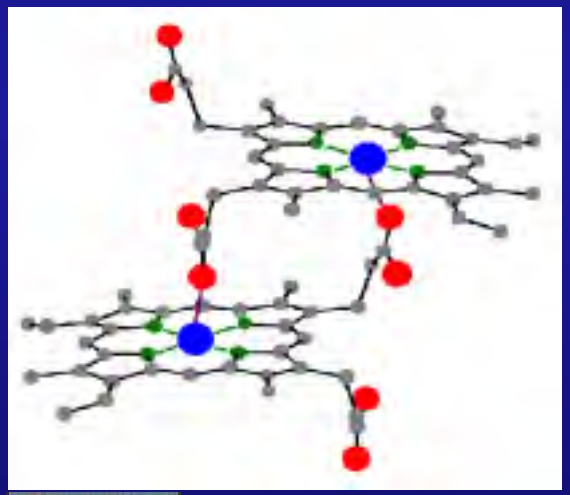

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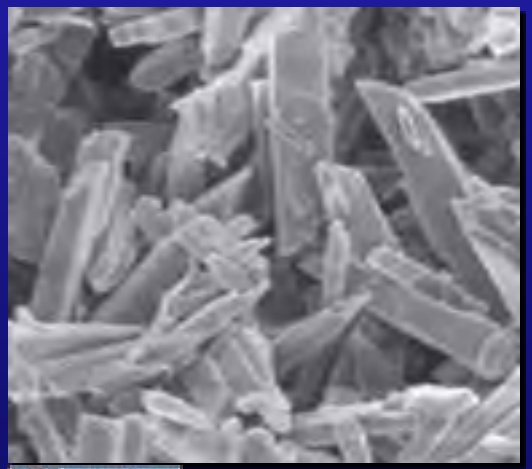

PD-INEL Madame Curie Bioscience Database

Sequence of the creation of hemozoin in red cell removed

Based on what you have just learned, suggest three simple strategies to prevent the propagation of malaria.

1) _____

2) _____

3) _____

Strategies to prevent malaria

1) **mosquito control** (insecticides, remove habitats)
2) **mosquito protection** (nets, screens, repellants)
3) **mass treatment**

- **vaccines** (immunity is species and stage-specific)
- **release of genetically altered mosquitoes**

Leishmaniasis

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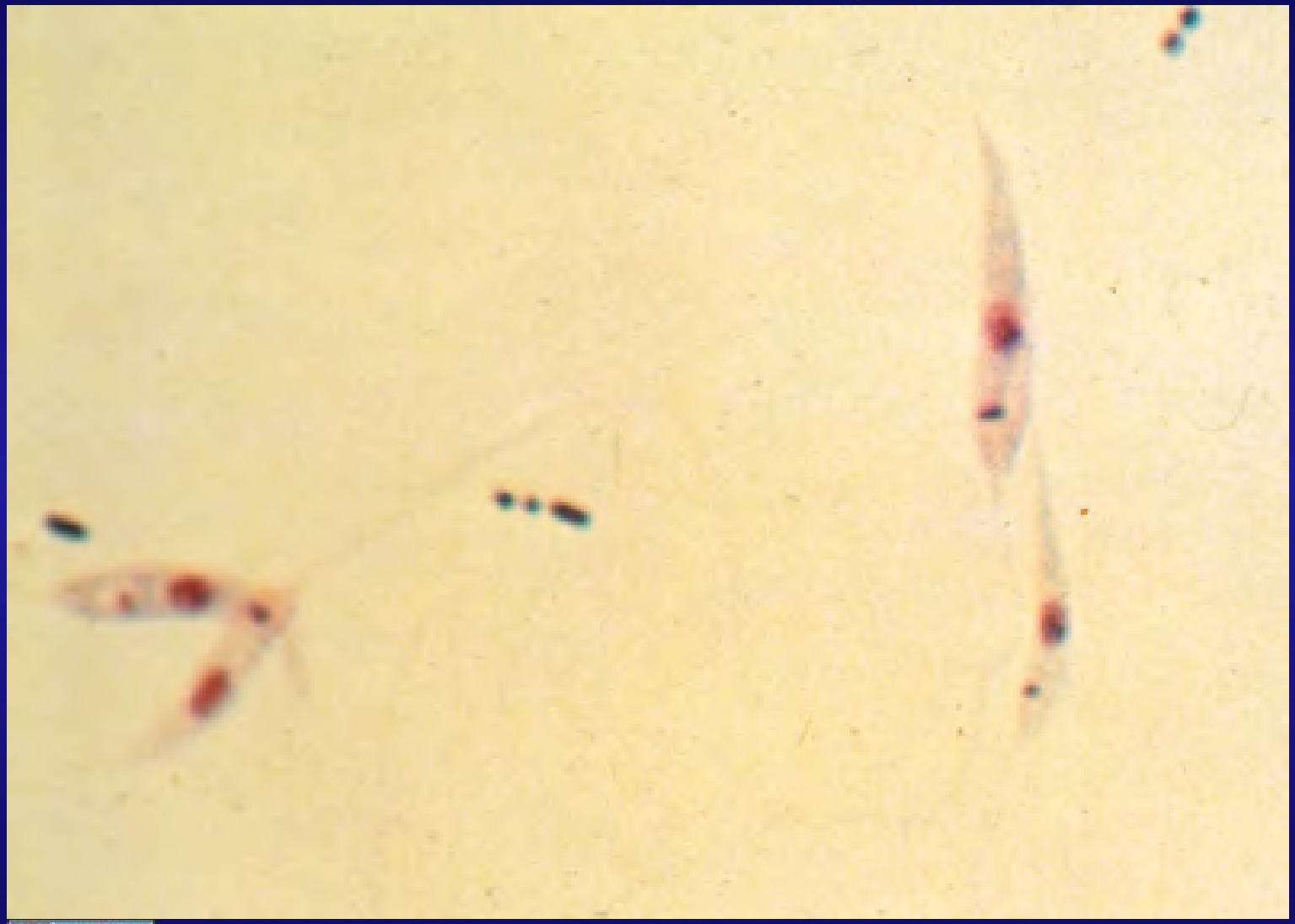

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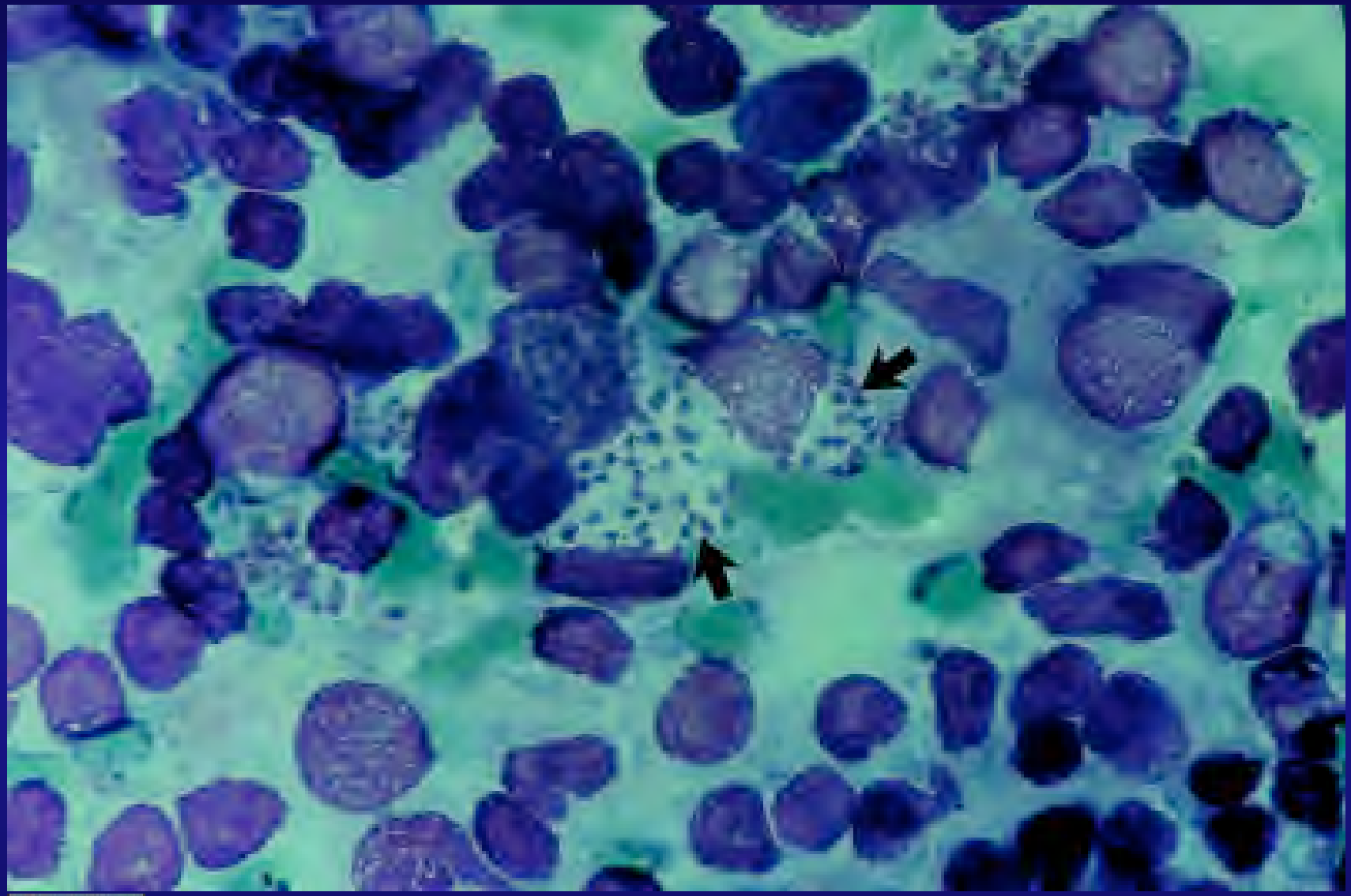

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Leishmania **are intracellular parasites that reside in macrophage phagolysosomes**

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Chronic skin ulcerations with raised edges at site of sand fly bite.

(organisms do not survive well at 37°C, therefore, they don't tend to disseminate)

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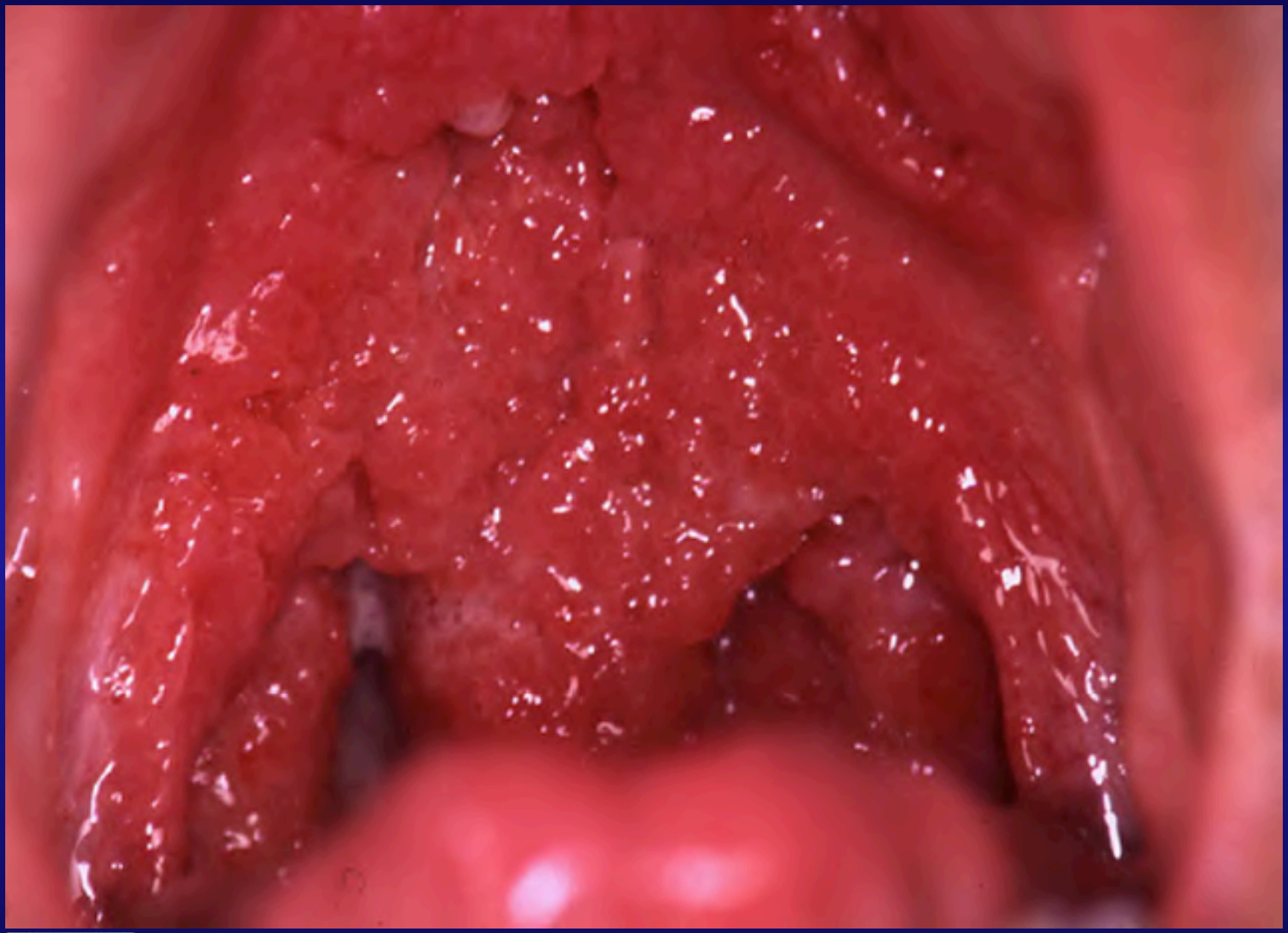
***L. braziliensis* lasts longer and may recur later with destructive lesions in the nose and throat**



McGill University Department of Medicine

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Visceral leishmaniasis - "Kala-azar"

- Infection of macrophages in the liver, spleen and lymph nodes
- Fever, malaise, weight loss, abdominal pain
- Dx: aspirate of bone marrow, spleen or liver; serology
- Outcome: 75-90% fatal if untreated (death 2° to bacterial pneumonia)

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