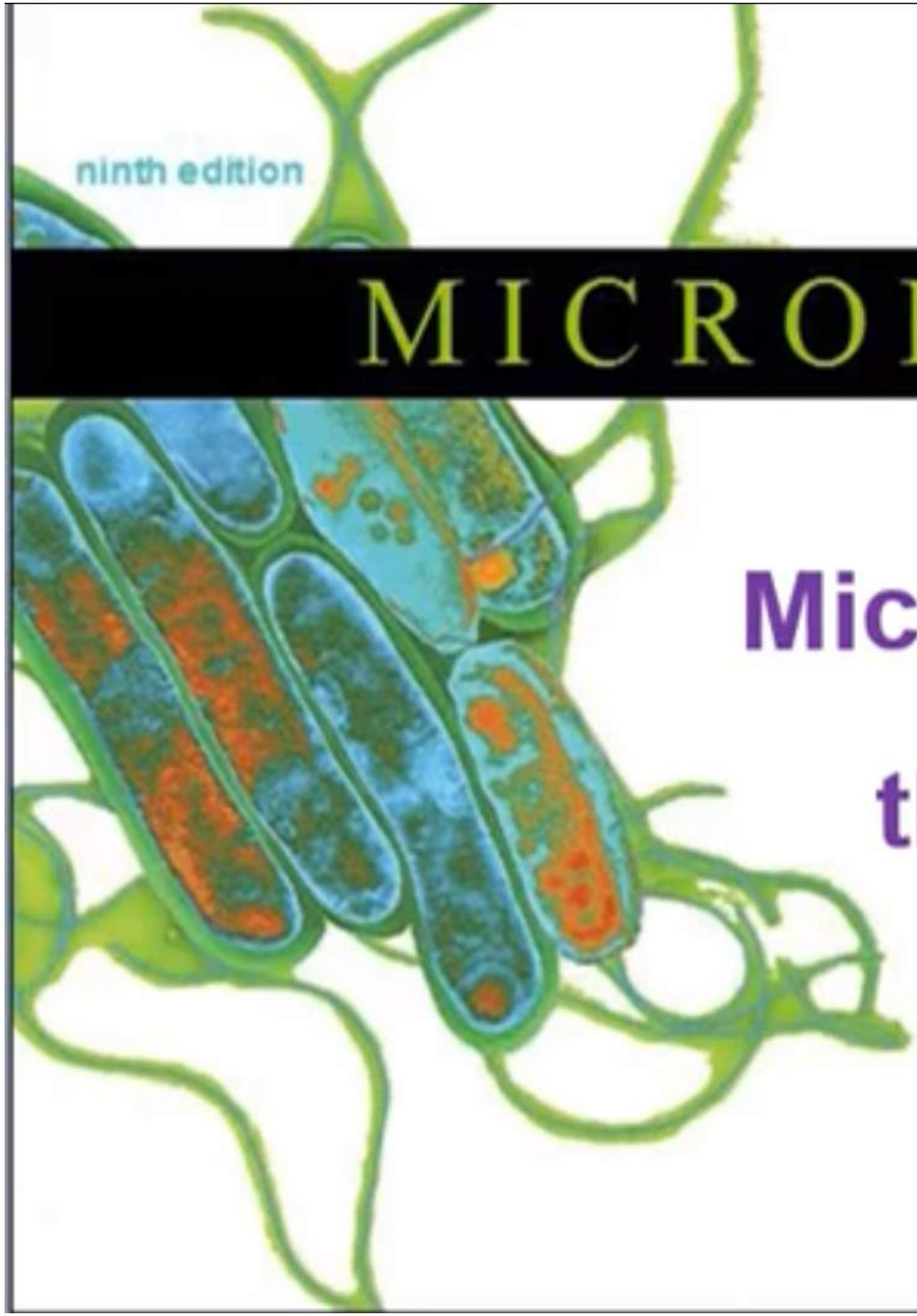


ninth edition

TORTORA | FUNKE | CASE

MICROBIOLOGY

an introduction

Microbial Diseases of the Cardiovascular and Lymphatic Systems (II)

LEARNING OBJECTIVES

- List the signs and symptoms of septicemia
- Differentiate gram-negative sepsis, gram-positive sepsis, and puerperal sepsis.
- Describe bacterial endocarditis and rheumatic fever.
- Discuss the epidemiology of tularemia, brucellosis, anthrax, gas gangrene.
- Describe pathogens that are transmitted by animal bites and scratches.
- Compare and contrast the causative agents, vectors, reservoirs, symptoms, treatments, and preventive measures for plague, Lyme disease, and Rocky Mountain Spotted Fever.
- Describe infectious mononucleosis.
- Compare and contrast the causative agents, vectors, reservoirs, and symptoms for yellow fever.
- Compare and contrast the causative agents, modes of transmission, reservoirs, and symptoms for Ebola hemorrhagic fever and *Hantavirus* pulmonary syndrome. Also, for Chagas' disease, toxoplasmosis, malaria, and babesiosis.
- Describe Swimmer's Itch.

VIRAL DISEASES OF THE CARDIOVASCULAR AND LYMPHATIC SYSTEMS

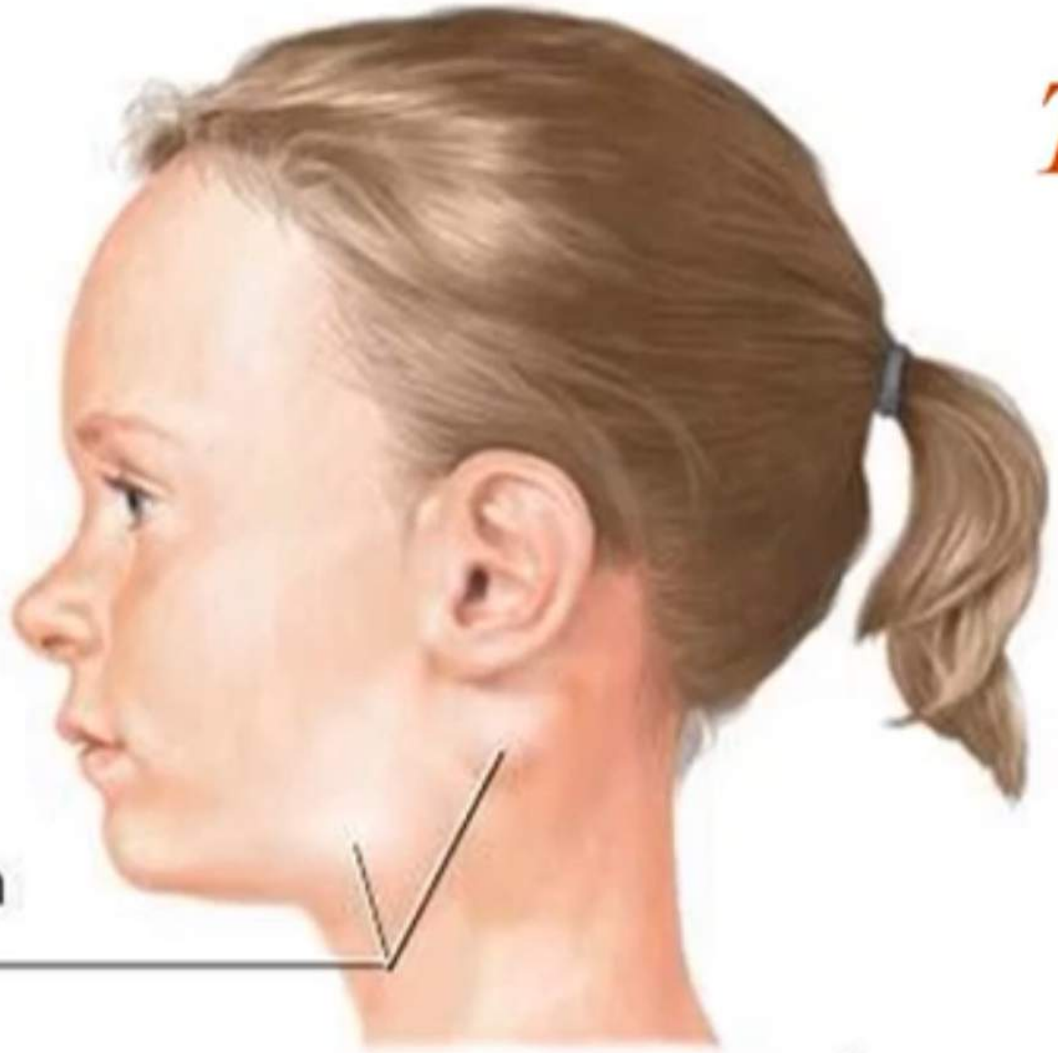
- Infectious Mononucleosis
- Viral Hemorrhagic Fevers

Infectious Mononucleosis

- "Kissing disease" – caused by **Epstein-Barr virus** (EBV) of *Herpesviridae*, also known as HHV-4
- Well-established relationship between ***HHV-4*** and oncogenesis (Burkitt's Lymphoma etc.)
- Virus multiplies in parotid glands and is present in saliva. It causes the proliferation of atypical lymphocytes (life-long infection) – Transmission via saliva
- Most people (~95%) infected. Childhood infection usually asymptomatic. Adolescent infection → Mononucleosis.
- Characteristic triad: fever, pharyngitis, and lymphadenopathy (+spleno- and hepatomegaly) lasting for 1 to 4 weeks.

Mononucleosis causes:

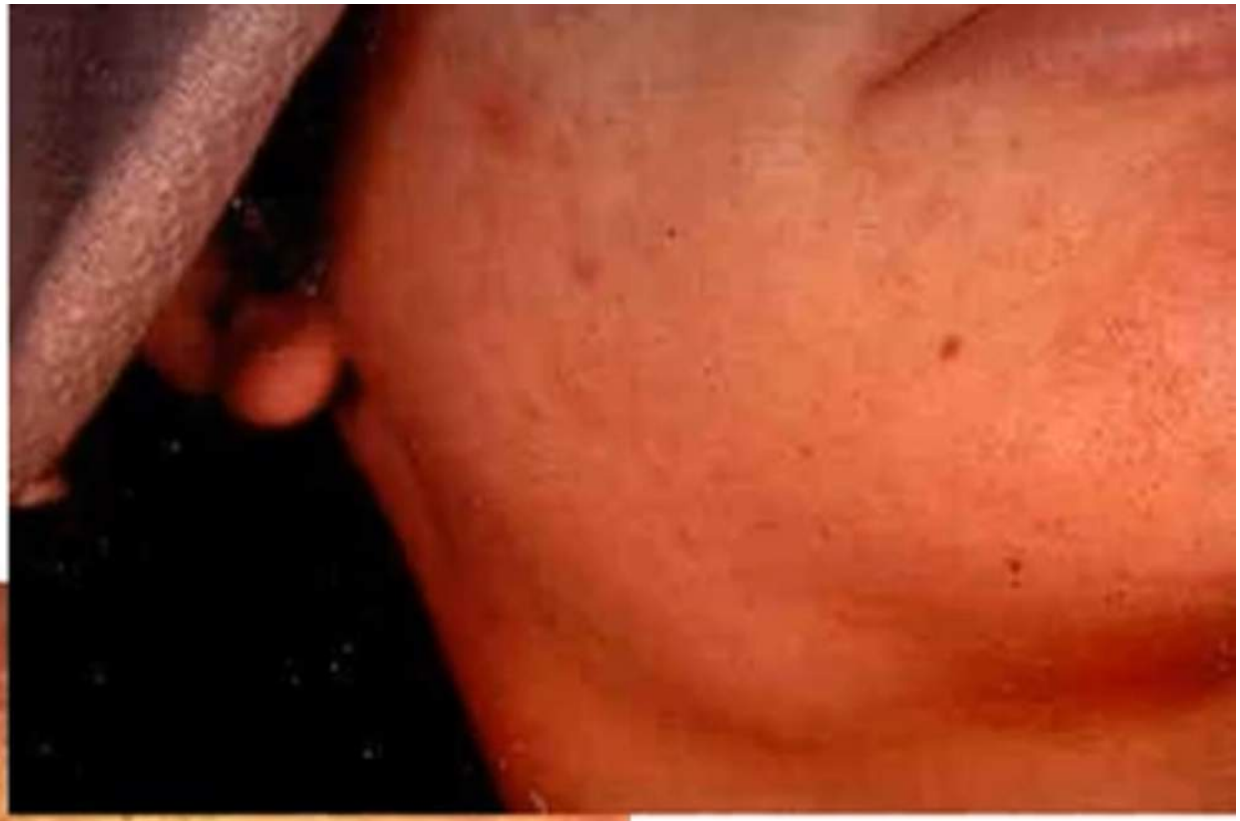
- Fever
- Fatigue
- Sore throat
- Swollen lymph glands

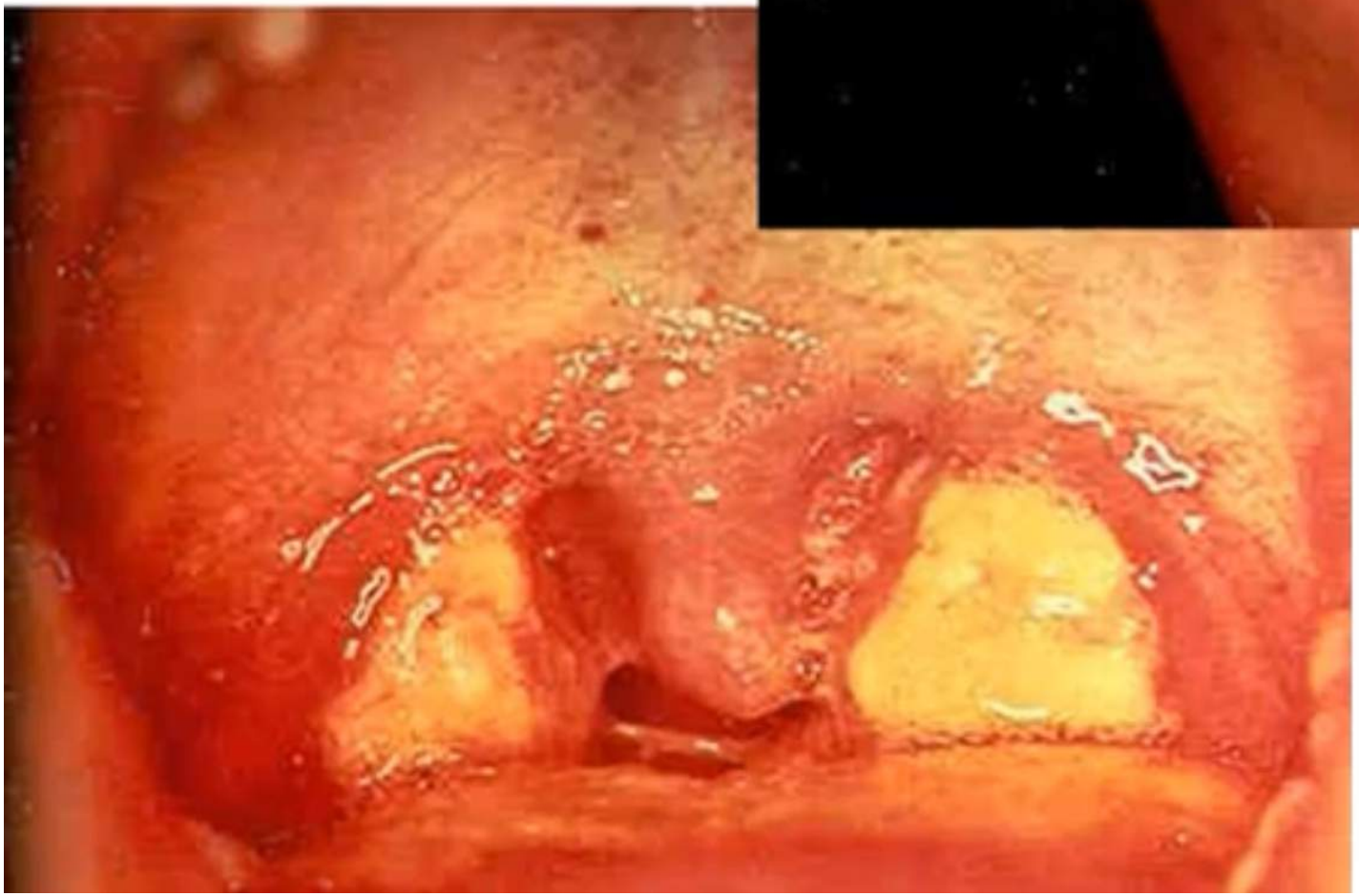


Triad

Swollen lymph nodes, sore throat, fatigue and headache are some of the symptoms of mononucleosis. It is generally self-limiting and most patients can recover in 4 to 6 weeks without medications.

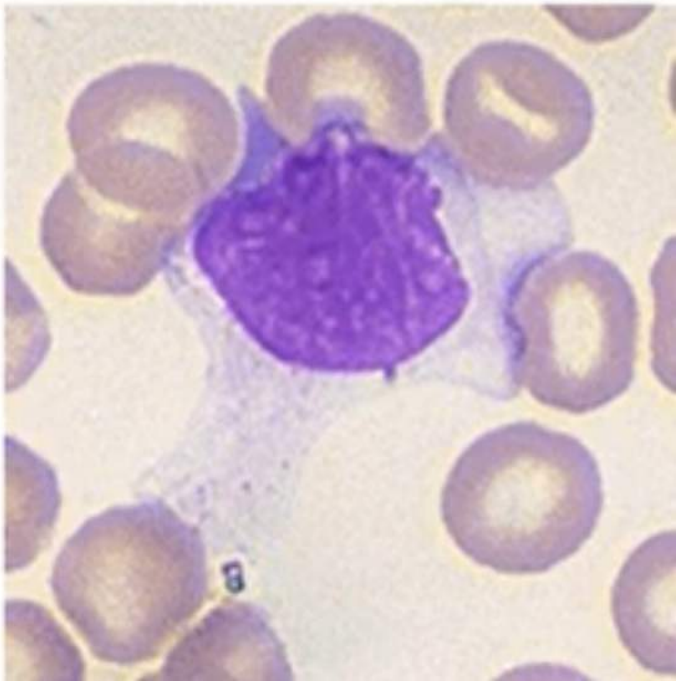
Young adults present with fever, pharyngitis, lymphadenopathy, and tonsillitis.



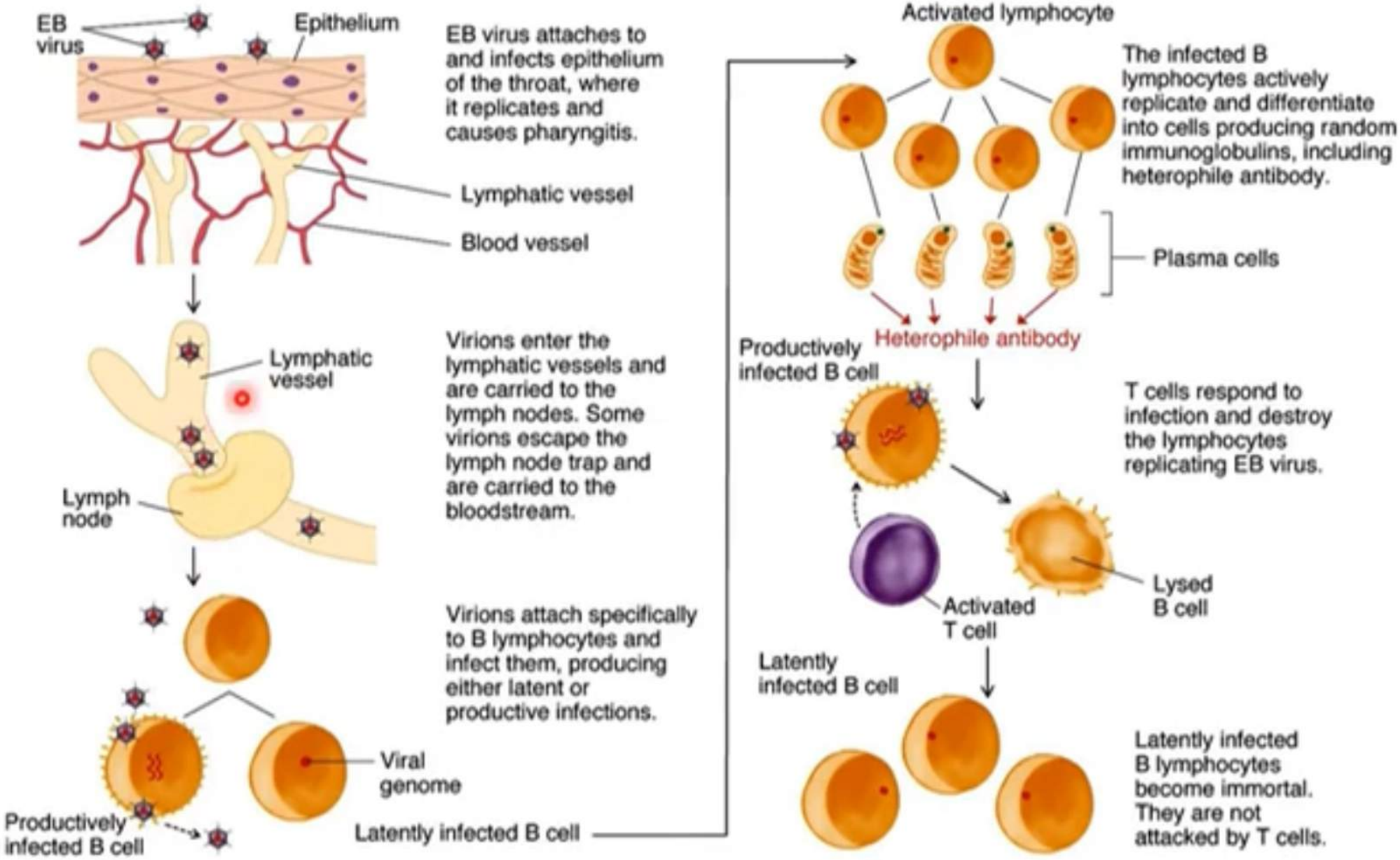


- Proliferation of infected B cells results in massive activation and proliferation of T_c cells (CD8 cells) → characteristic lymphoid hyperplasia.
- Transformation of B cells to immortal plasmacytoid cells → secrete a wide variety of IgMs = heterophile antibodies (Monospot test)
- Commercially-available test kits are 70-92% sensitive and 96-100% specific

"Downy cell": lymphocytes infected by EBV or CMV in infectious mononucleosis. Cytoplasmic rim is intensely blue and has tendency to "stream" around adjacent red cells.

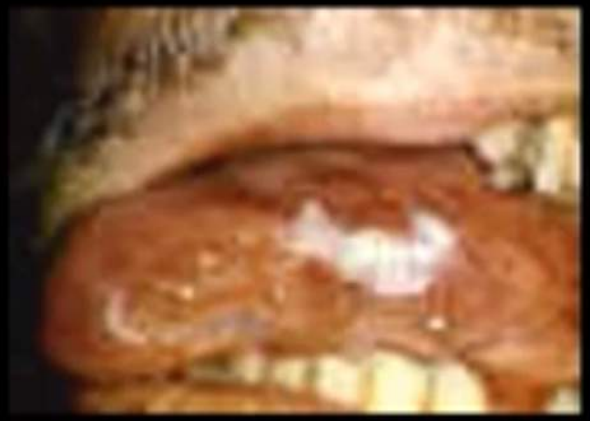


Pathogenesis of infectious mononucleosis

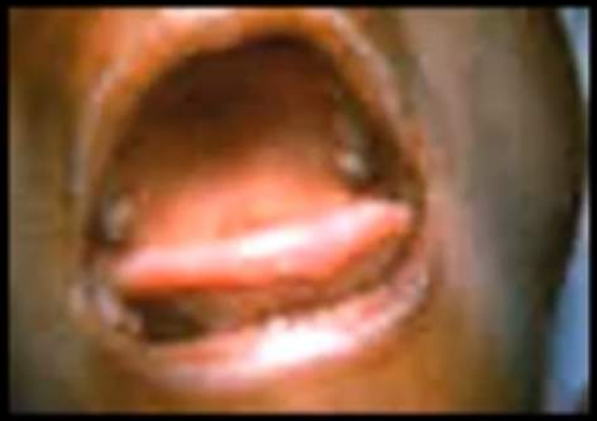


Epstein- Barr Virus

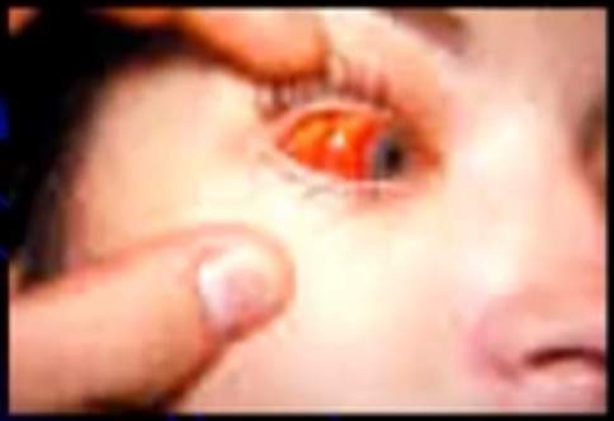
- Infectious mononucleosis
- Burkitt's lymphoma
- Nasal pharyngeal carcinoma
- B-cell lymphomas
- Hairy leukoplakia



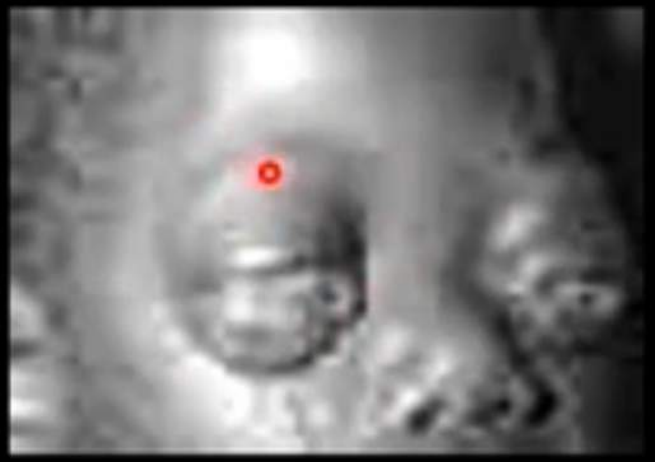
Oral hairy leukoplakia of tongue in AIDS



Tongue and palate of patient with infectious mononucleosis



Conjunctival hemorrhage due to infectious mononucleosis



Burkitt's Lymphoma

Laboratory diagnosis

- **Hematologic approach:** absolute lymphocytosis (atypical lymphs)

- **Immunologic approach:**

  a) Heterophil antibody test (**Monospot test**)

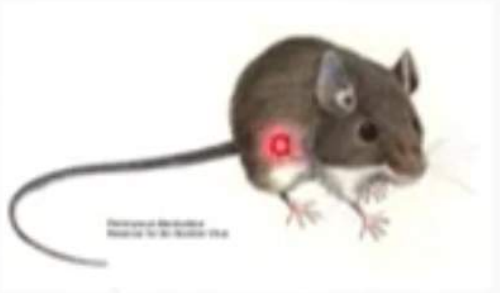
  b) EBV-specific Abs tests:

  - **IgM VCA**
  - **IgG VCA**

Viral Hemorrhagic Fevers

Classic			
Yellow fever	Flavivirus	*Aedes aegypti*	Monkeys
Dengue & DHF	Flavivirus	• *A. aegypti* • *A. albopictus*	No known reservoir
Emerging			
Marbug	Filovirus	• Monkeys (?)	
Ebola	Filovirus	• Monkeys (?)	
Lassa fever	Arenavirus	• Rodents	
Argentine hemorrhagic fever	Arenavirus	• Rodents	
Bolivian hemorrhagic fever	Arenavirus	• Rodents	
Hantavirus pulmonary syndrome	Hantavirus	• Rodents	

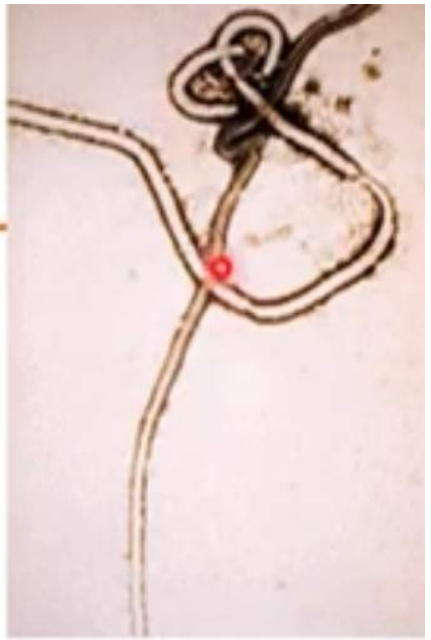
ARBOVIRUSES

FAMILY	ENVELOPE	SYMMETRY	GENOME	
Togaviridae Flaviviridae	Yes	icosahedral	single strand RNA (+ve)	
Bunyaviridae	yes	helical	single strand RNA (-ve) segmented	
Reoviridae	no	icosahedral	double strand RNA segmented	

ARBOVIRUSES
FEVER AND HEMORRHAGIC FEVER

NAME	DISEASE	OCCURRENCE	VECTOR
Flaviviridae Family			
Dengue Fever	fever, hemorrhagic fever	Worldwide - tropic regions	
Yellow Fever	hemorrhagic fever	South and Central America and Africa	Mosquito
Reoviridae Family			
Colorado tick fever	fever	North America	Tick

Viral Hemorrhagic Fevers

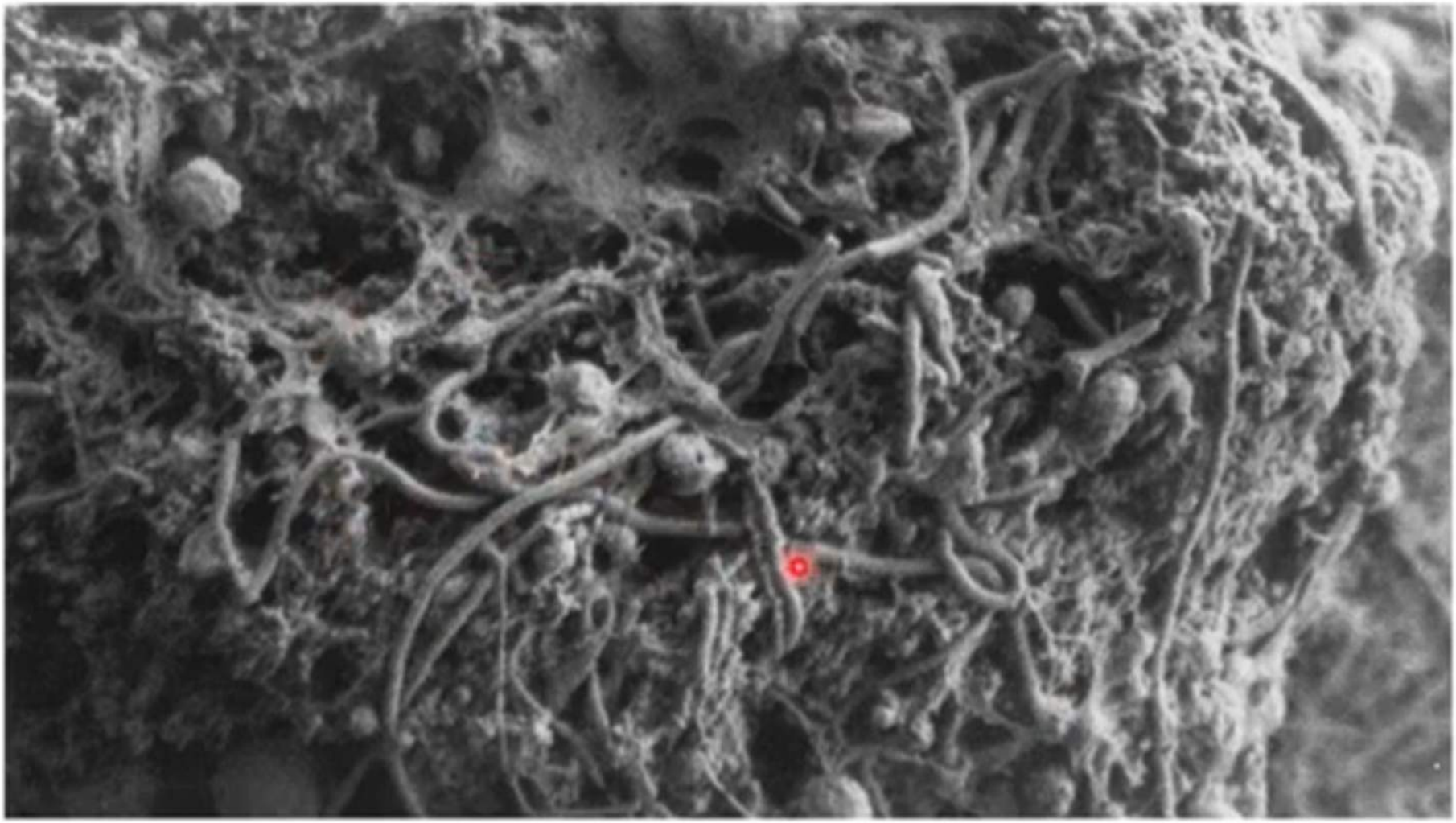


- Enveloped RNA viruses: Arenaviruses, filoviruses, bunyaviruses, and flaviviruses
- Viruses geographically restricted to where their host species live
- For some viruses, after accidental transmission from host, humans to human transmission
- Human cases or outbreaks sporadic and irregular. Not easily predictable

➢ **Marburg VHF**: 1967 outbreak in Marburg (D) – imported from Africa; Mortality rate 25%

➢ **Ebola HF**: 1995 major outbreaks in Zaire and Sudan; Mortality rate 50 – 90%

Ebola Virus



Classic Viral Hemorrhagic Fevers: Yellow Fever

Caused by arbovirus (flaviviridae)
transmitted by mosquitoes

Direct damage to liver and heart → jaundice, hemorrhaging, weak heart → circulatory and kidney failure

African and American tropical jungles

Diagnosis: test for presence of virus-neutralizing antibodies

No treatment

Highly effective attenuated vaccine

YELLOW FEVER VIRUS (Flavivirus family)

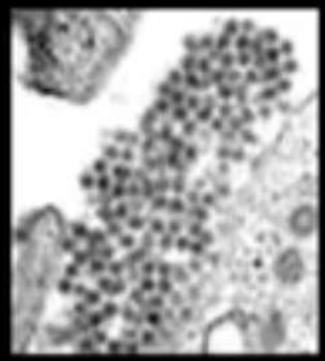
- only found in Africa and South America
- transmitted by mosquitoes
- Natural hosts of the virus include monkeys and man
- It has an urban and a jungle cycle

- Infection results in severe systemic disease, hemorrhages, degeneration of the liver, kidney and heart

- The case-fatality rate can be 50%

- There is an effective vaccine (live, attenuated strain called 17D)

DENGUE VIRUS (Flavivirus family)



- **Dengue fever:**

  - natural hosts are monkeys and man

  - mosquitoes are the vector (*A. aegypti*)

  - occurs worldwide (50-100 million cases per year)

  - (breakbone fever): severe pains in muscle & joints (associated with influenzalike symptoms)

- **Dengue Hemorrhagic Fever:**

  - It is a much more disease with fatality rate ~ 10%

  - Dengue hemorrhagic fever (DHF) may resemble classical dengue

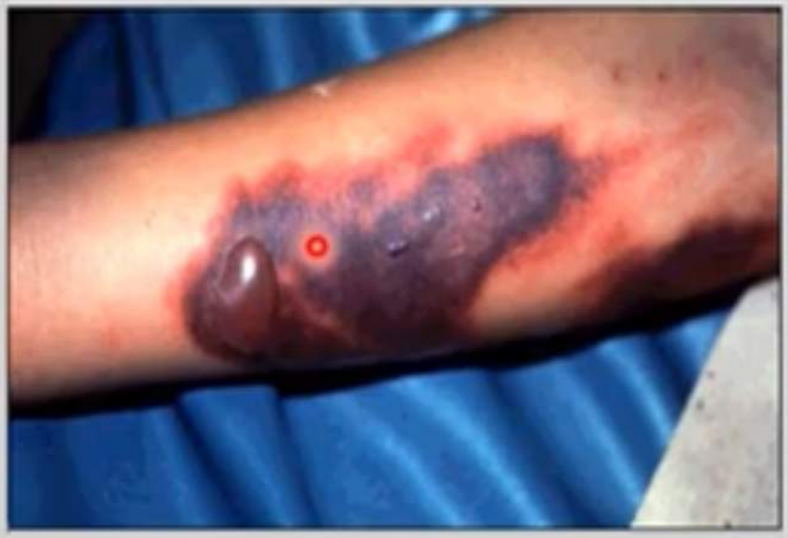
  - But shock & hemorrhage (GI & skin) develop

  - dengue shock syndrome (DSS) is due to the large amounts of cross-reacting Abs

  - No antiviral therapy or vaccine is available

DENGUE HEMORRHAGIC FEVER/DENGUE SHOCK SYNDROME

- hemorrhages
- plasma leakage
- hemoconcentration
- hypotension
- circulatory failure
- shock



Caption: A large subcutaneous haemorrhage on the upper arm of a patient with dengue haemorrhagic fever. (Image courtesy of the Wellcome Trust)

flavivirus

Hemorrhagic

Manifestation

Fig:WHO/TDR/Welcome Trust

Hantavirus Pulmonary Syndrome (HPS)

Korean hemorrhagic fever caused by
Hantaan virus of ***Bunyaviridae***

HPS first reported in US in spring of 1993.

Transmission through urine, droppings, or saliva of infected rodents → humans breathe in aerosolized virus.

No person to person transmission.

Sudden respiratory failure

Mortality rate > 35%

PARASITIC DISEASES OF THE CARDIOVASCULAR AND LYMPHATIC SYSTEMS

- American Trypanosomiasis (Chagas' Disease)
- Toxoplasmosis
- Malaria
- Babesiosis
- Schistosomiasis

❖ American Trypanosomiasis or Chagas Disease

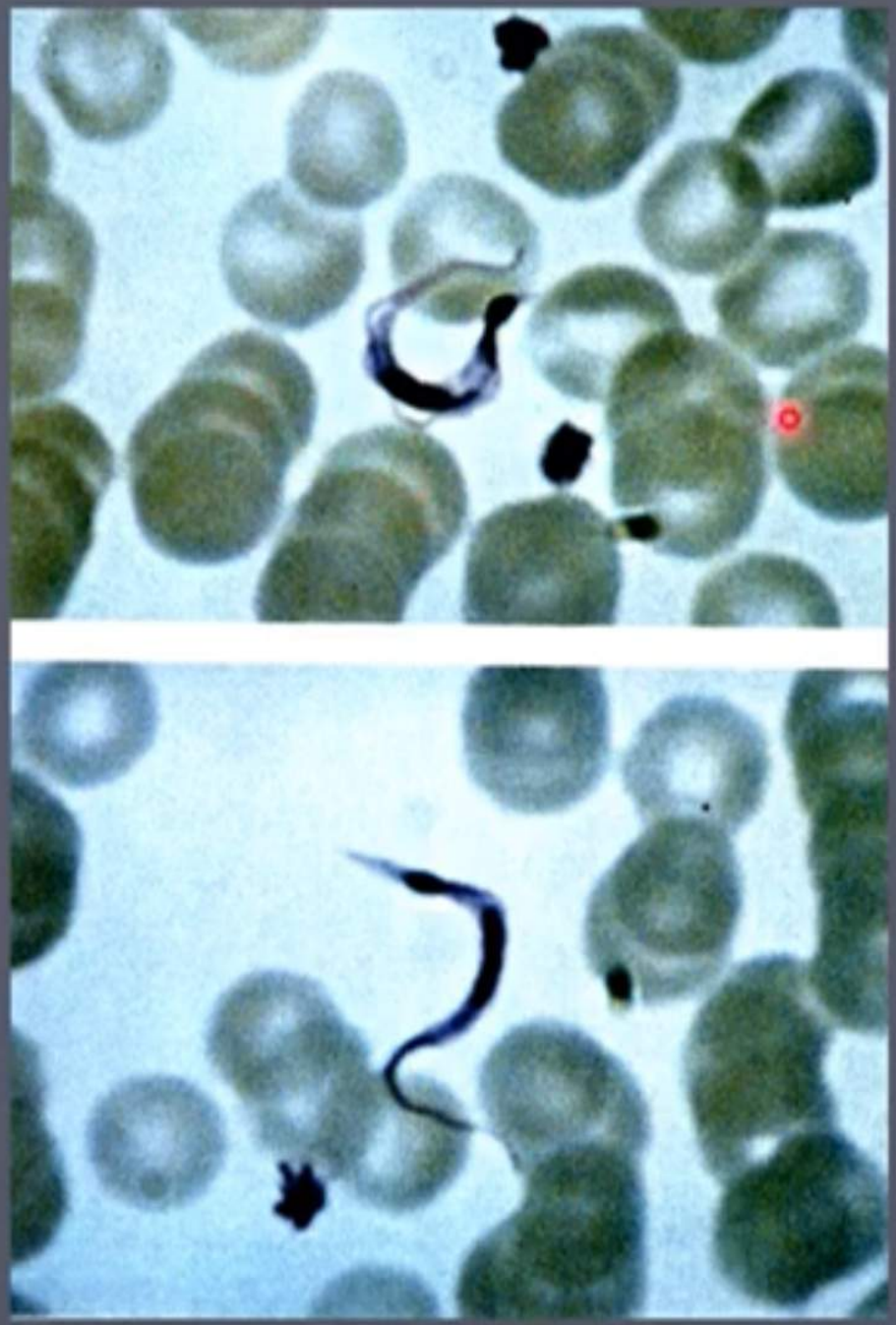
Trypanosoma cruzi

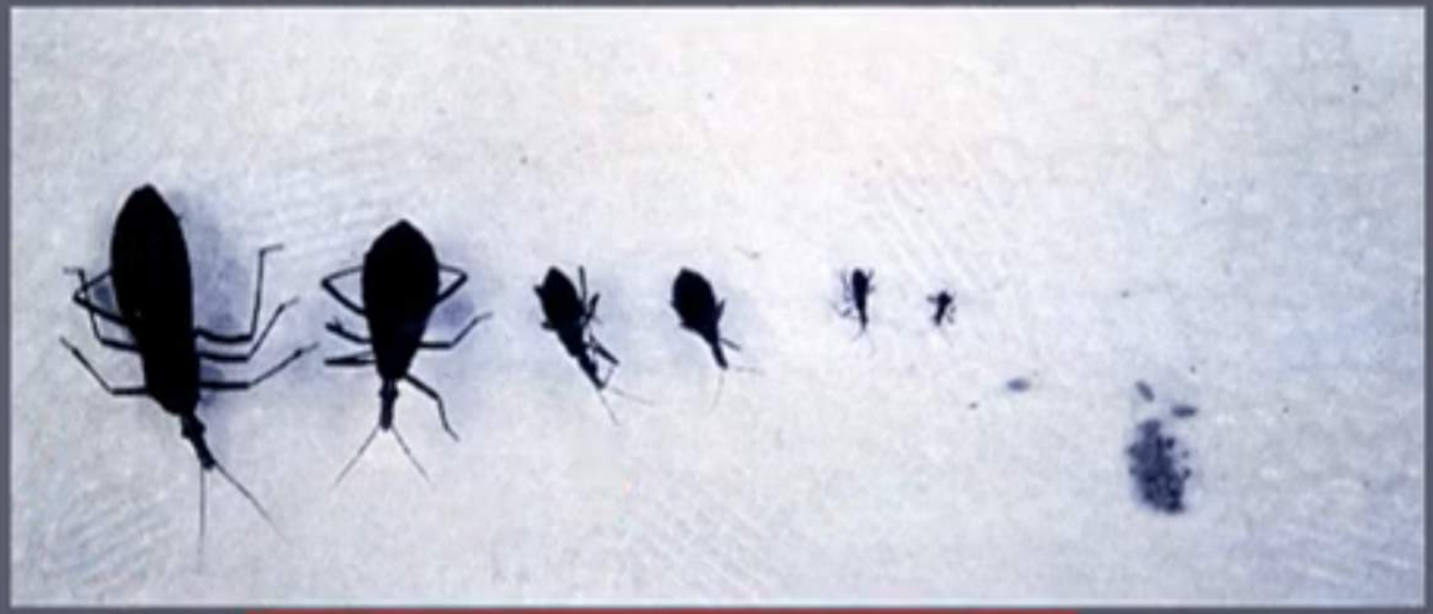
Reservoir: Rodents, opossums, armadillos

Vector: night feeding reduviid bugs (kissing bugs)

Symptoms in 1% of infected. Acute phase (fever etc.) to chronic phase (heart damage)

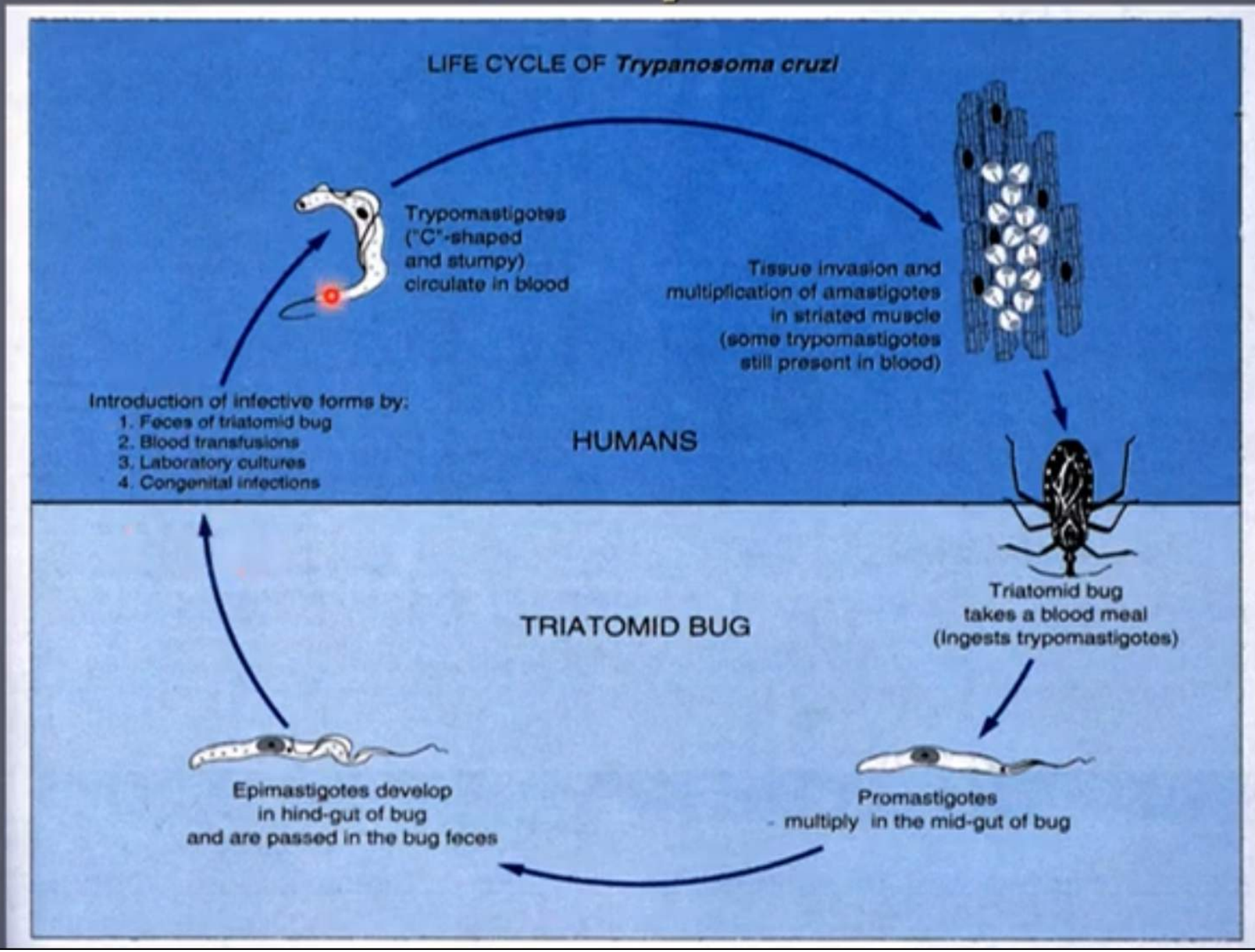
Antigenic variation ⇒ persistent evasion of immune system
⇒ Cyclic parasitemia (7-10 days)





Triatoma (Reduviid bug)

Life Cycle


LIFE CYCLE OF *Trypanosoma cruzi*
Trypomastigotes ("C"-shaped and stumpy) circulate in blood
Tissue invasion and multiplication of amastigotes in striated muscle (some trypomastigotes still present in blood)
Introduction of infective forms by:
1. Feces of triatomid bug
2. Blood transfusions
3. Laboratory cultures
4. Congenital infections
HUMANS
Triatomid bug takes a blood meal (Ingests trypomastigotes)
TRIATOMID BUG
Epimastigotes develop in hind-gut of bug and are passed in the bug feces
Promastigotes multiply in the mid-gut of bug

Symptoms

- Acute pahse: facial edema (related to site of bug bite) & "chagoma" Fever lymphadenopathy & hepatospleno-megaly. Resolution in ~2 months.

- Chronic form may lead to death from cardiac arrhythmias & heart failure. May include autoimmune aspects.

Pathology & Immunology

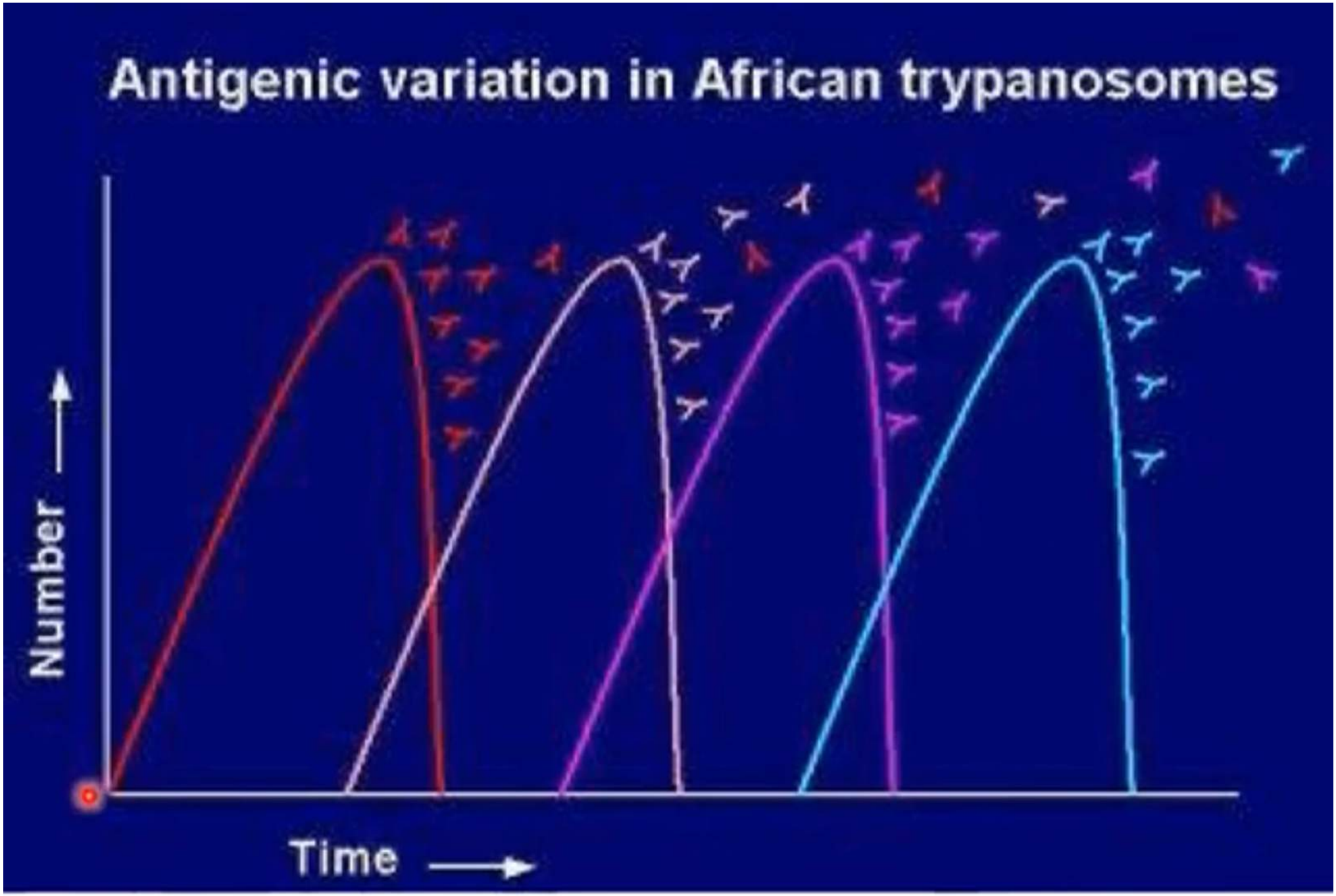
- Myocardial, glial and RES cells are most common intracellular growth sites.
- Cardiac muscle is most severely affected. Neuronal damage gives rise to arrhythmias & loss of muscle tone in the colon & esophagus (megacolon & megaesophagus).
- Acute phase: both tryps and amastigotes in the blood; chronic phase: amastigotes in the tissues

Diagnosis

- Clinical Diagnosis:Cardiac dilation, megacolon & megaesophagus
- Presence of tryps in thick or thin films
- Stained biopsy specimens may reveal amastigotes
- Serology may be used (CF)

Treatment & Control

- Nifurtimox kills tryps, but not amastigotes in tissues
- No cure for chronic infection
- Control measures: reduce contact between the vectors and man

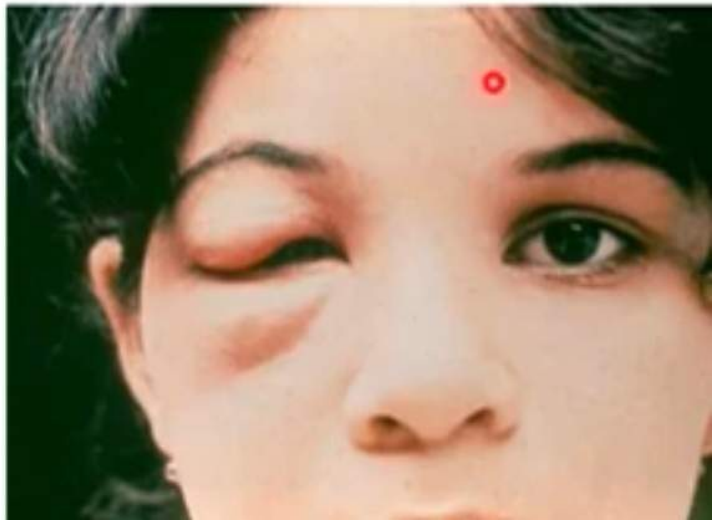


*Course of trypanosome infection: emergence of variant surface glycoproteins (**VSG**) - Host antibodies indicated with Y's.*

Millions in Latin America affected. No cure and little effective treatment

Romaña's sign: pathogonomic, early sign of Chagas disease.

→ Unilateral severe conjunctivitis, swelling of eyelid, inflammation of tear gland, swelling of regional lymph nodes.



❖ Toxoplasmosis

Toxoplasma gondii

> 60 mio people infected in US (mostly asymptomatic)

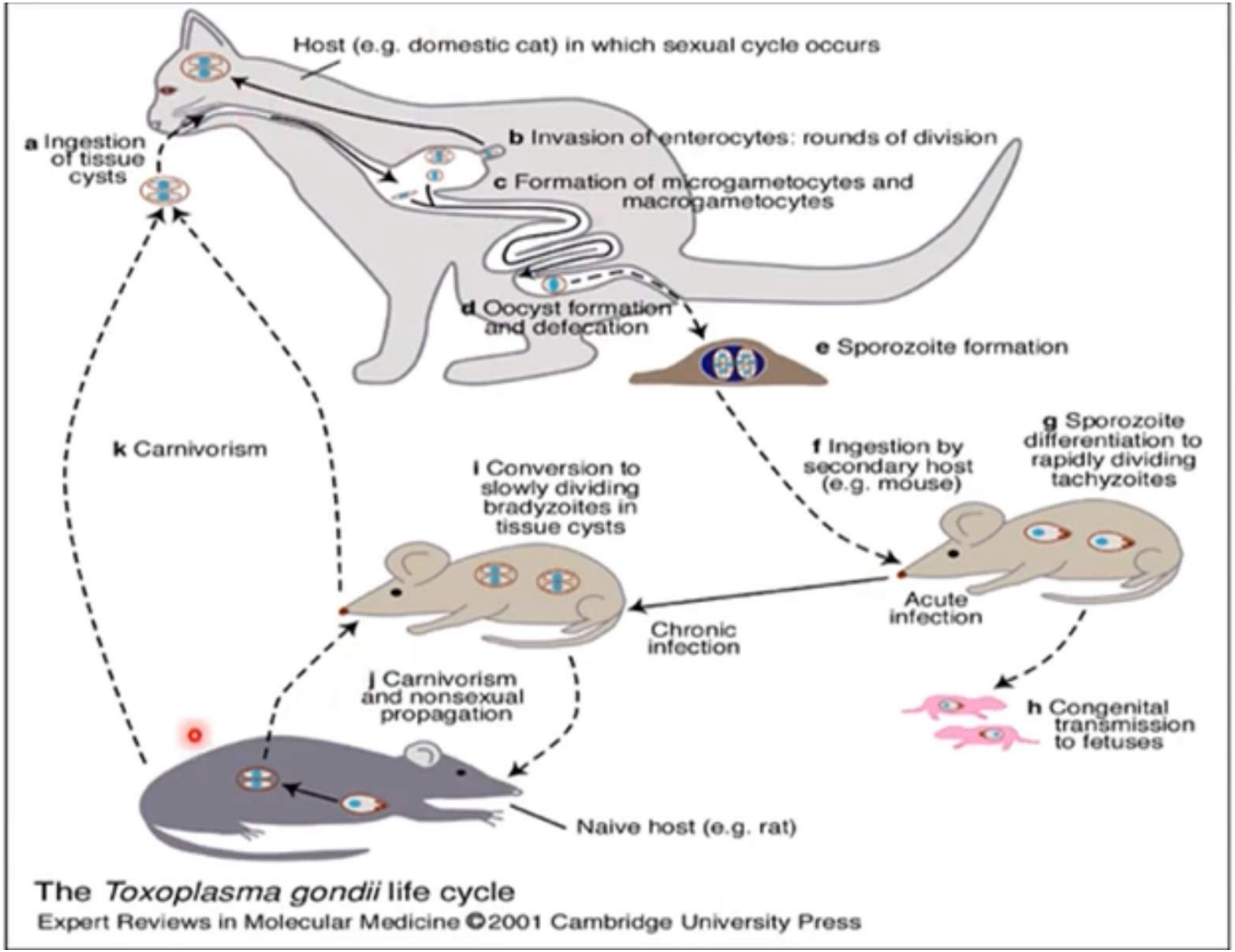
Zoonosis – Transmission via undercooked meat, cat feces, drinking water. Flu-like symptoms

Can cross placenta ⇒ Congenital risk (TORCH) → brain damage or vision problems

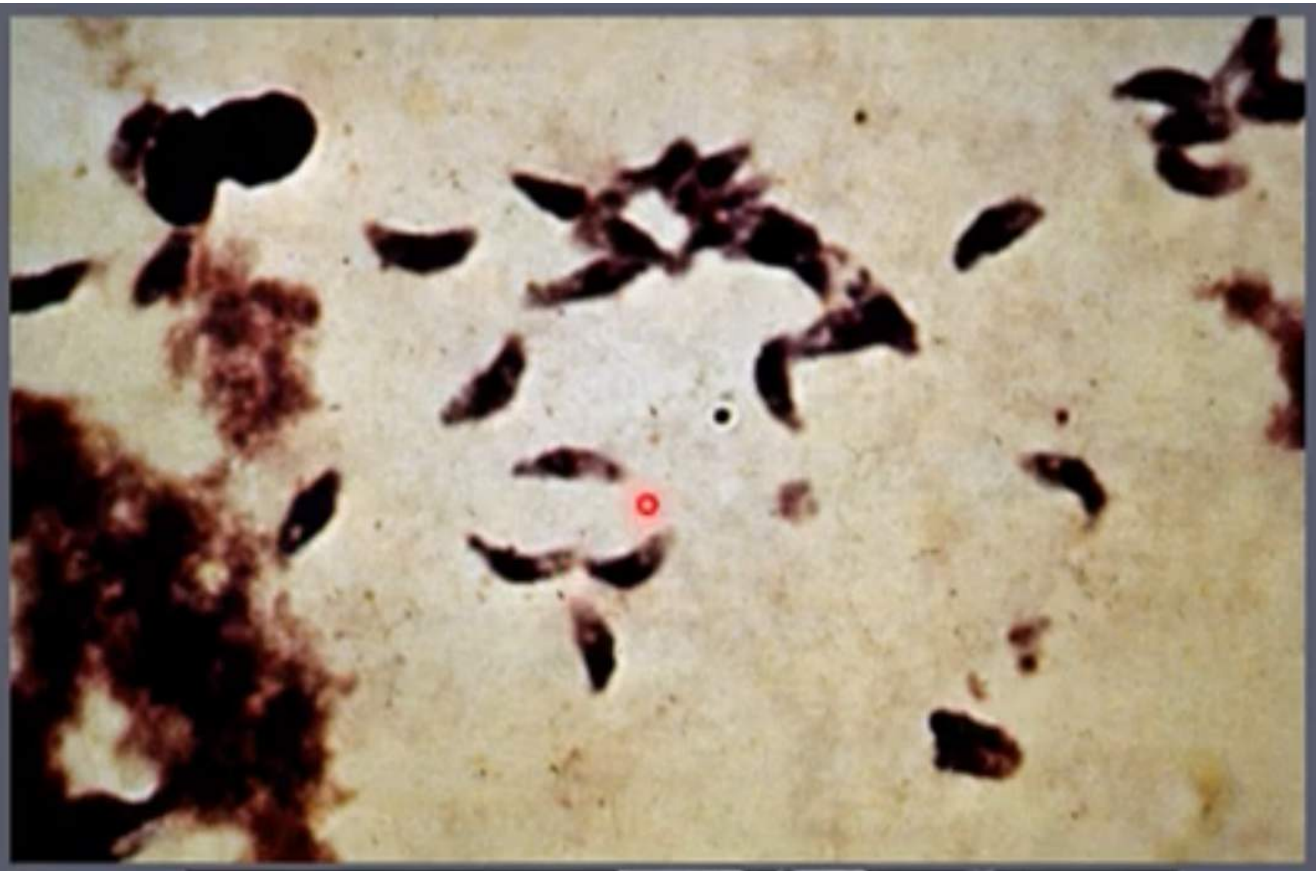
Risk of new infection or reactivation in the immunosuppressed

T. gondii undergoes sexual reproduction in the intestinal tract of domestic cats, and oocysts are eliminated in cat feces.

Toxoplasmosis can be identified by serological tests, but interpretation of the results is uncertain.



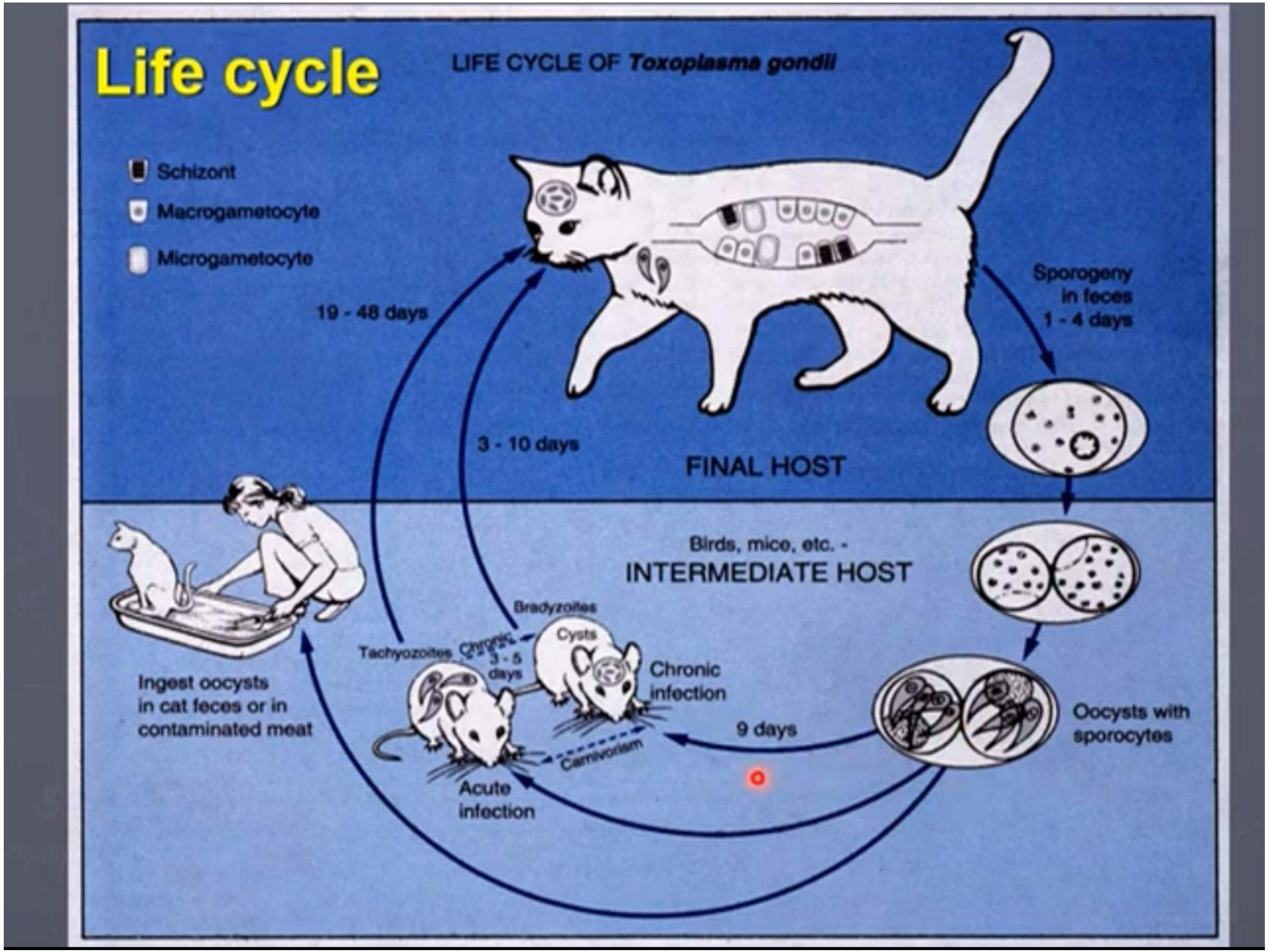
The *Toxoplasma gondii* life cycle



Clinical manifestations

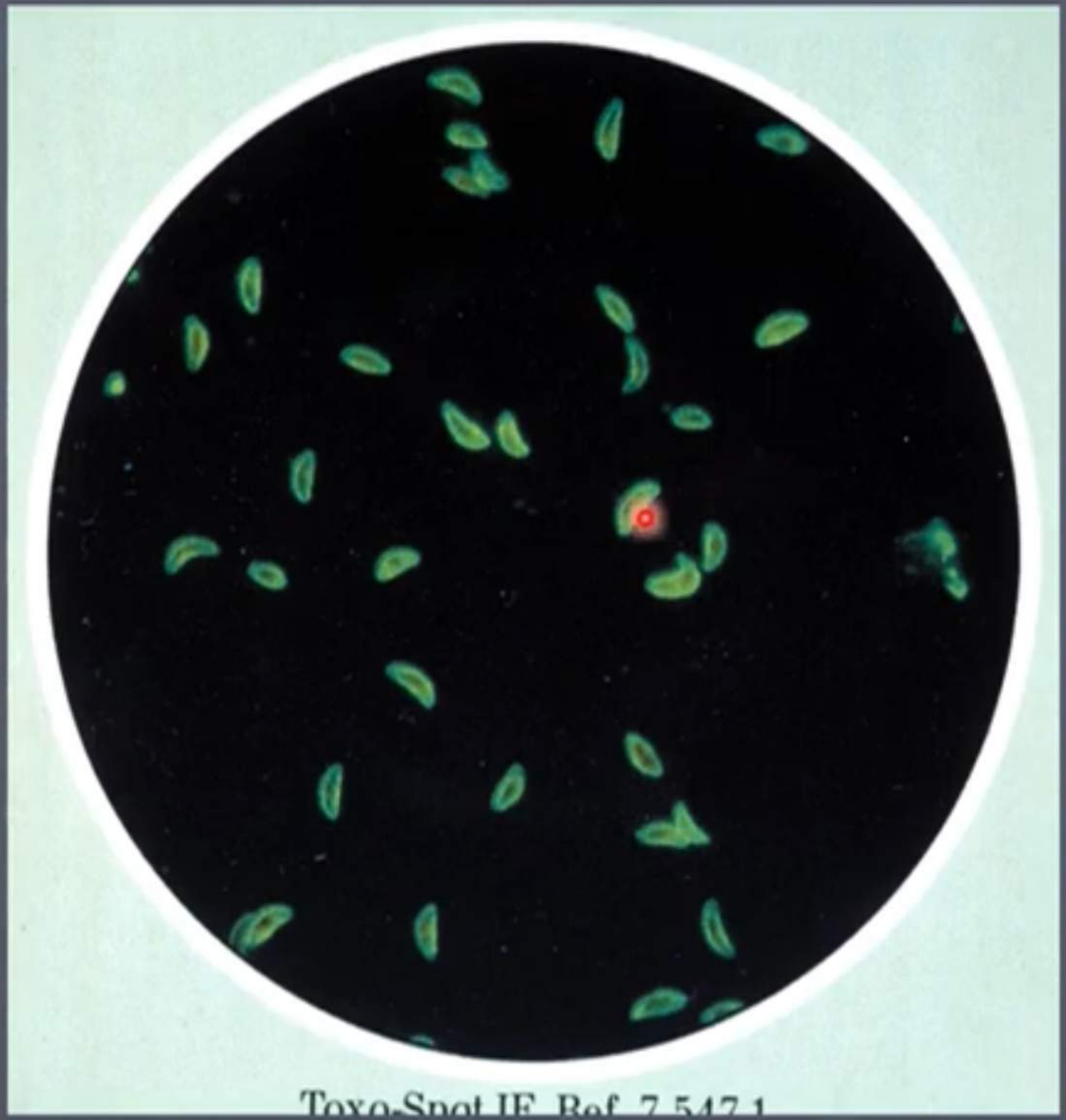
- Immunocompetent host: Asymptomatic
- Immunocompromised host: Reactivation disease
- Congenital infection: Consequences depend upon the gestational age of the fetus. Spontaneous abortion, CNS damage, eye involvement

Life cycle


LIFE CYCLE OF *Toxoplasma gondii*
Schizont
Macrogametocyte
Microgametocyte
19 - 48 days
3 - 10 days
Sporogeny in feces 1 - 4 days
FINAL HOST
Birds, mice, etc. -
INTERMEDIATE HOST
Bradyzoites
Cysts
Tachyzoites
Chronic 3 - 5 days
Chronic infection
Ingest oocysts in cat feces or in contaminated meat
9 days
Carnivorism
Acute infection
Oocysts with sporocytes

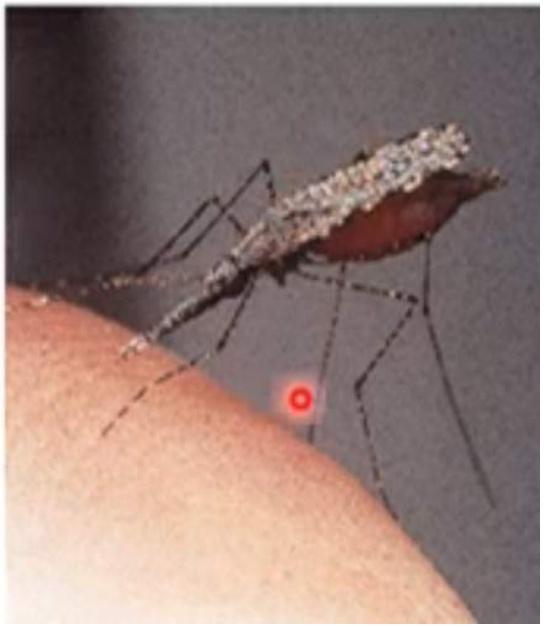
Laboratory diagnosis

- Diagnosed by enzyme immunoassay for IgM antibody (acute) or IgG antibody (chronic)
- Banana-shaped trophs can be seen in Giemsa-stained blood smears during acute-phase infection from mice inoculated with patient samples


Toxo-Spot IF Ref. 7.547.1

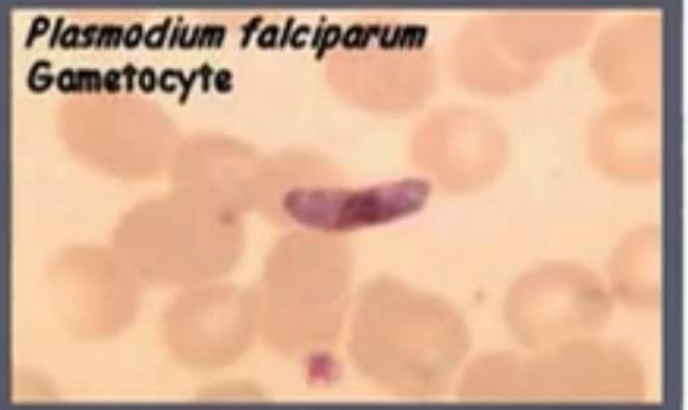
❖ Malaria

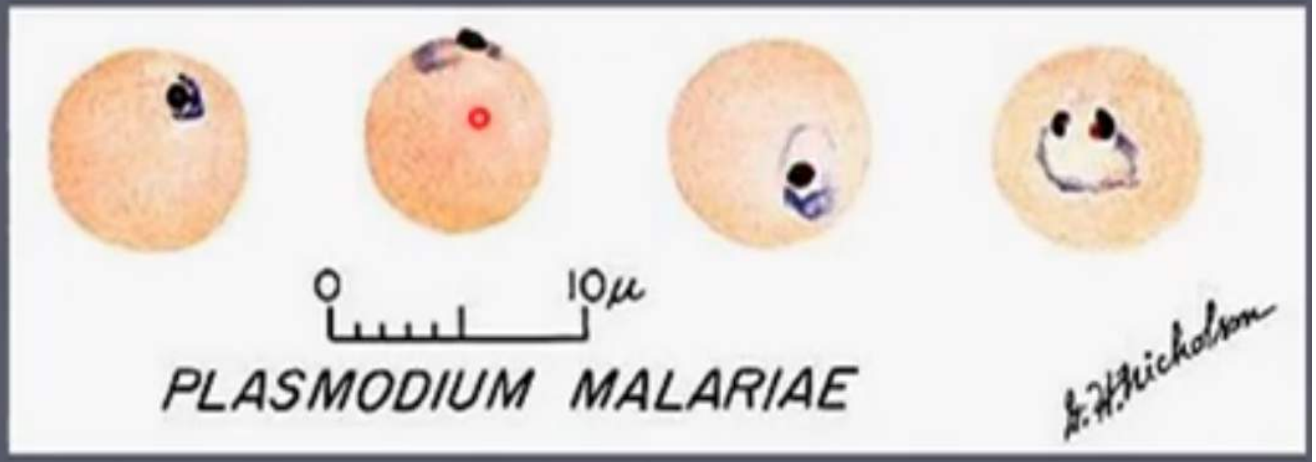
- Four species of Plasmodium: ***P. falciparum*** (malignant)
- Vector: *Anopheles* mosquito
- Worldwide 300-500 million cases; ~ 1.5 – 3 million people die; ~ 1,200 cases in US
- *Plasmodium* infects red blood cells ⇒ microscopic diagnosis
- Symptoms: chills, fever, vomiting, headache; at intervals of 2 to 3 days
- New drugs are being developed as the protozoa develop resistance to drugs such as chloroquine.

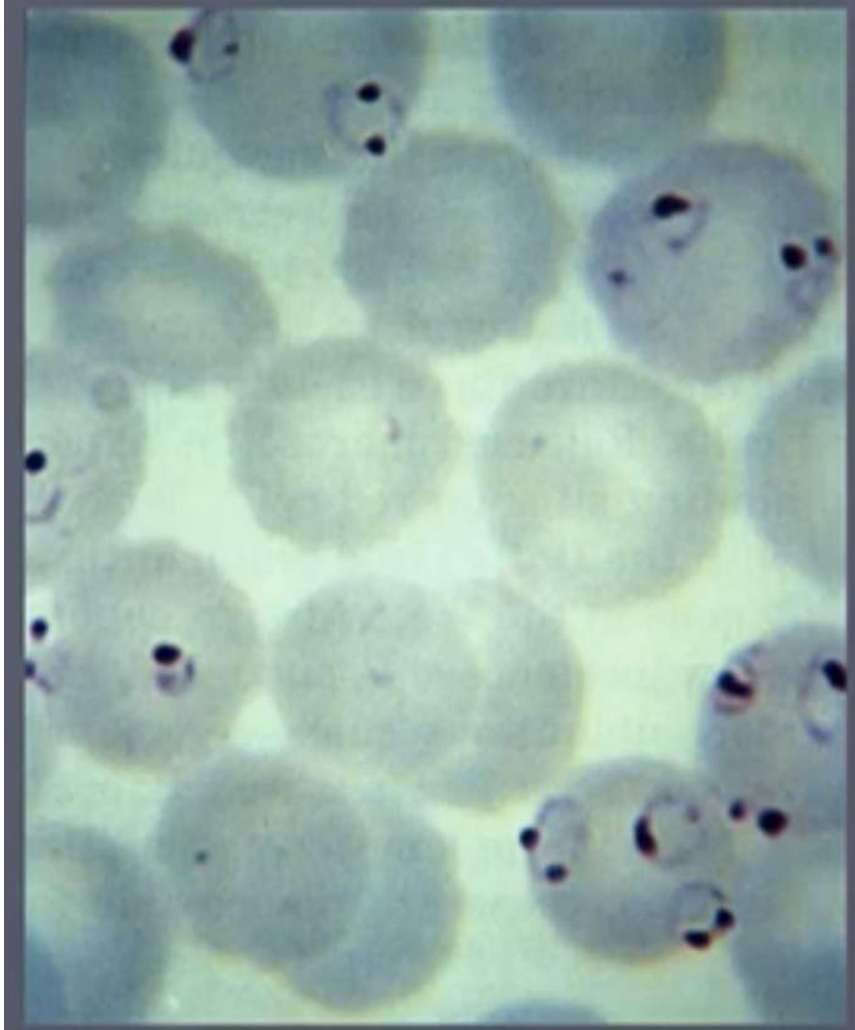


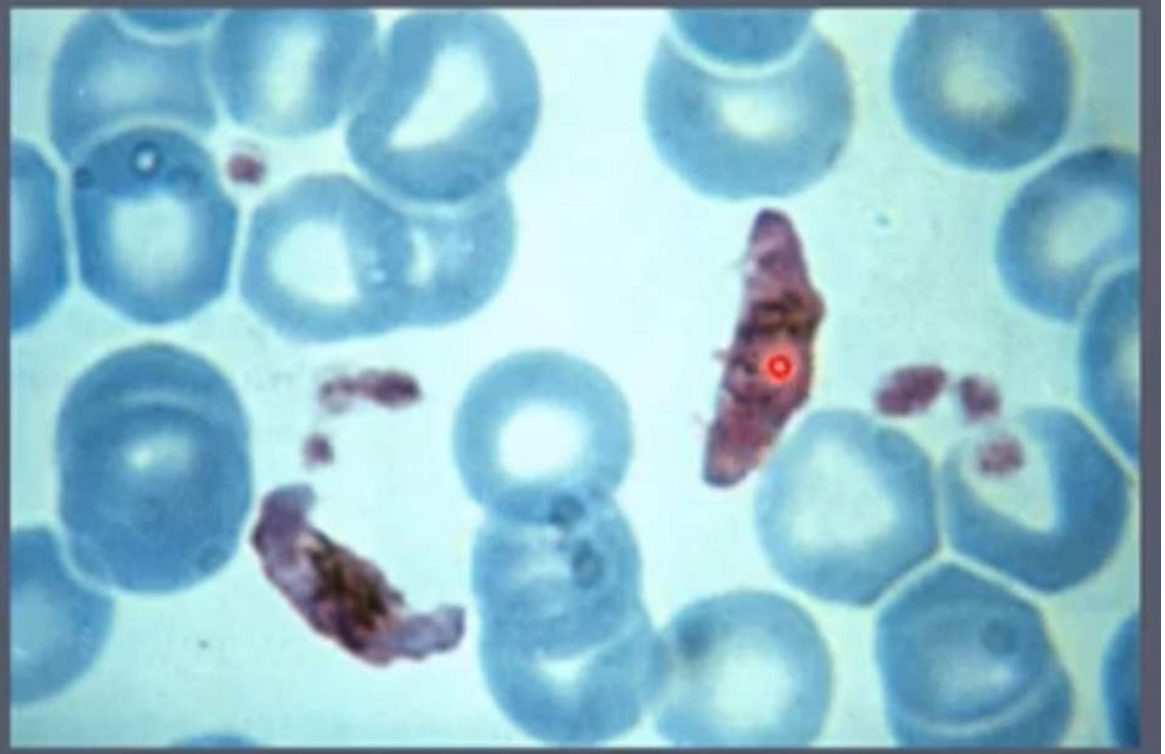
Morphology

- Trophozoite (1-2 µm)
- Sexual forms (gametocytes)

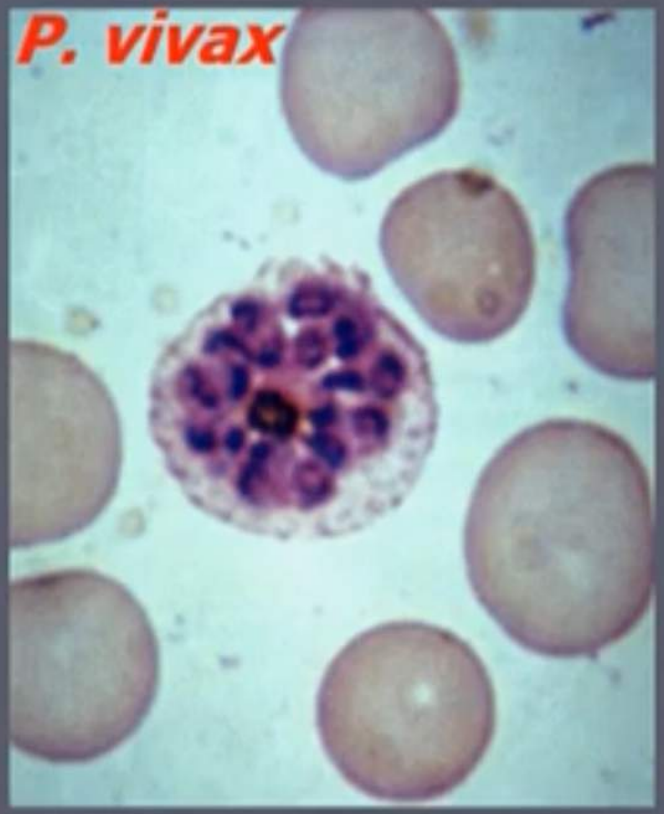


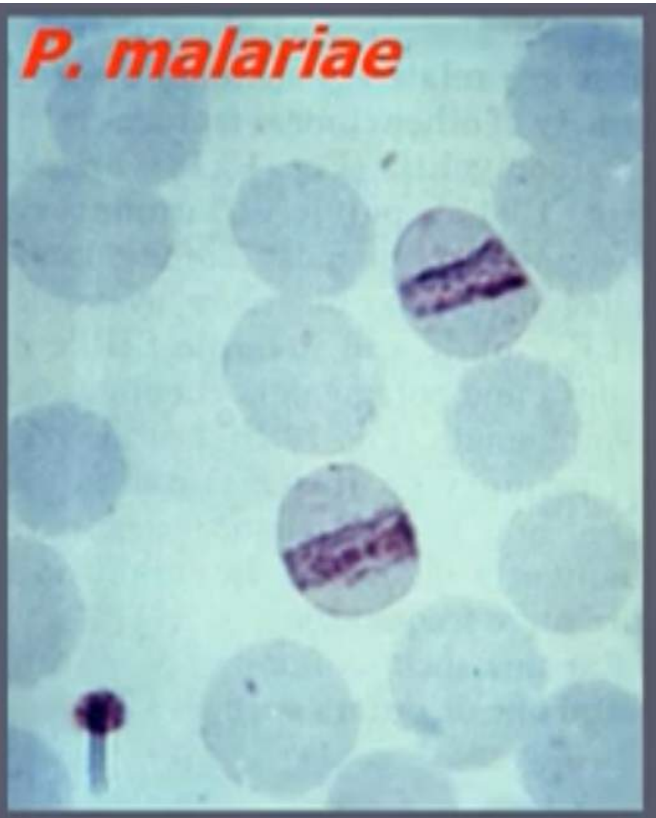


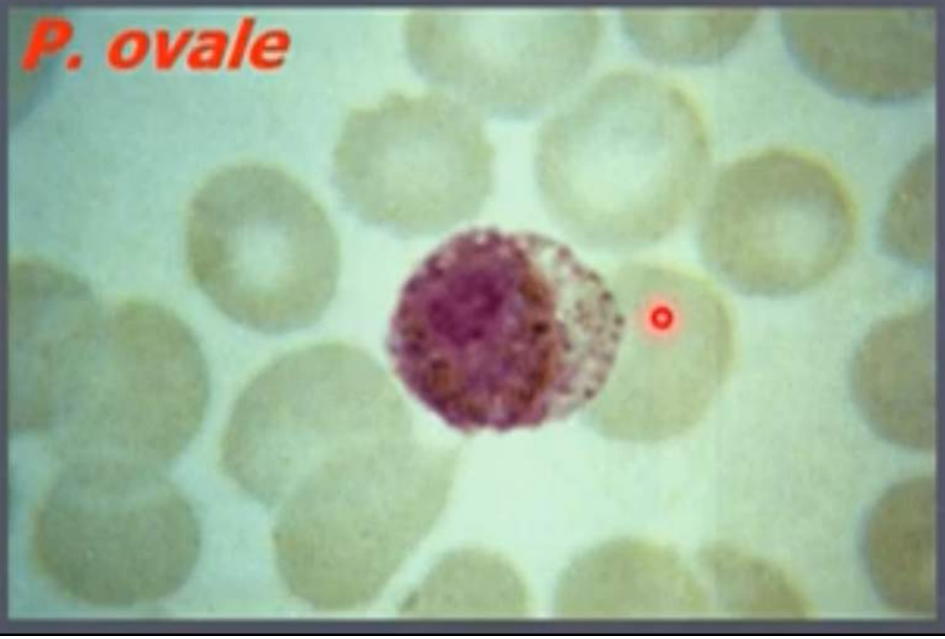




P. falciparum


P. vivax


P. malariae


P. ovale

Mode of transmission

- Zoonotic transmission via female *Anopheles* mosquito, or (rarely) by inoculation of infected blood

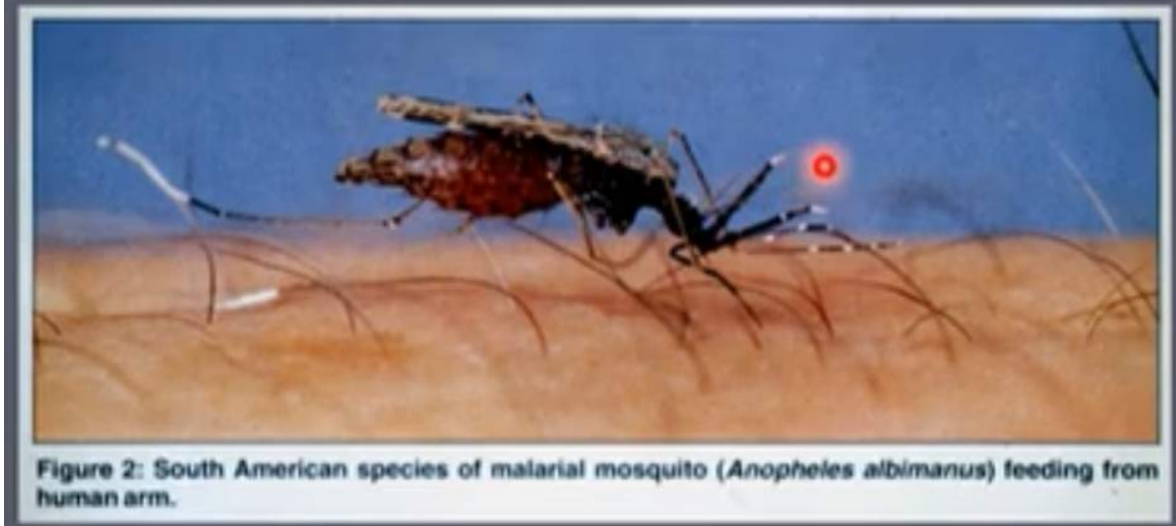
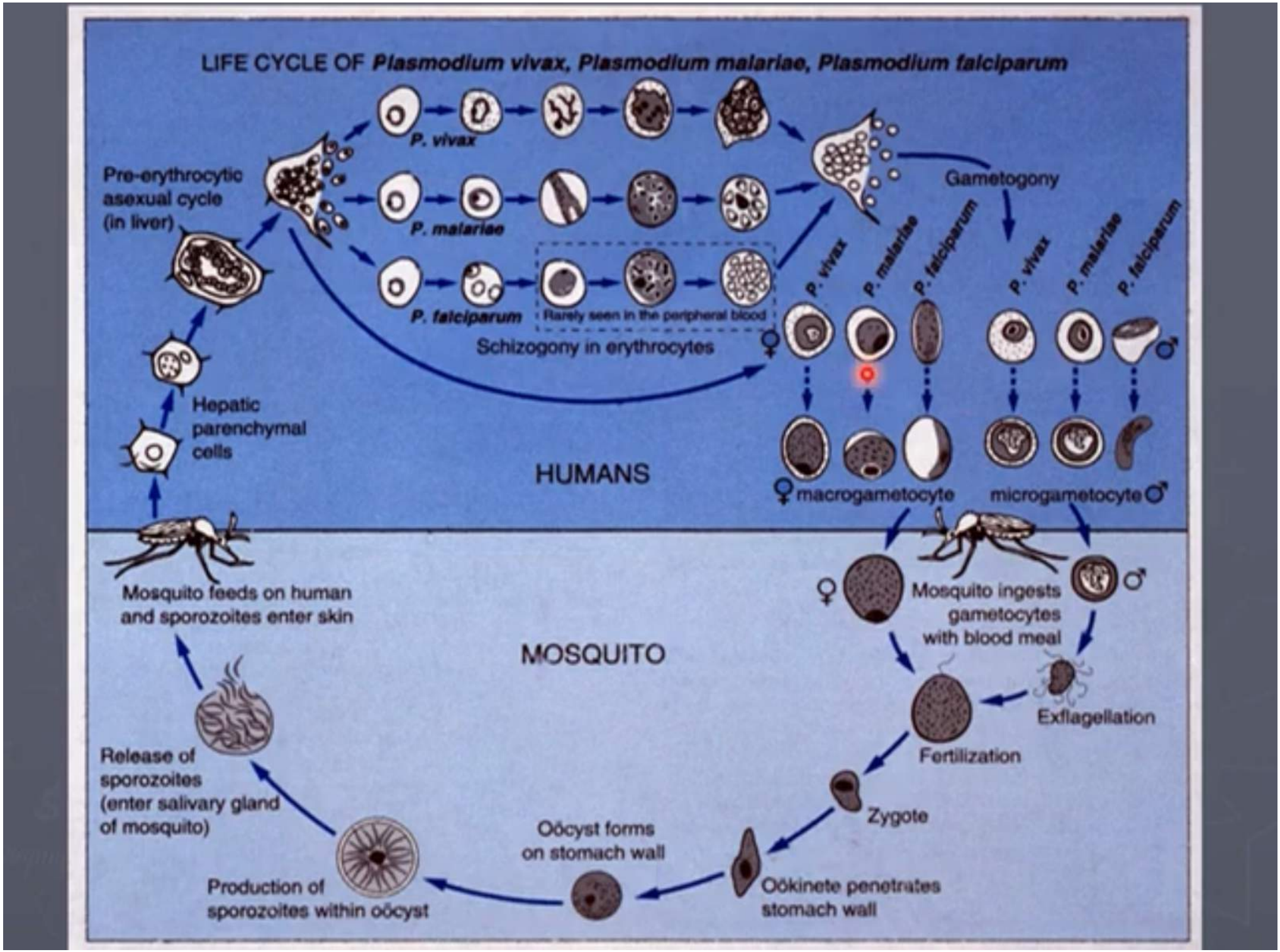
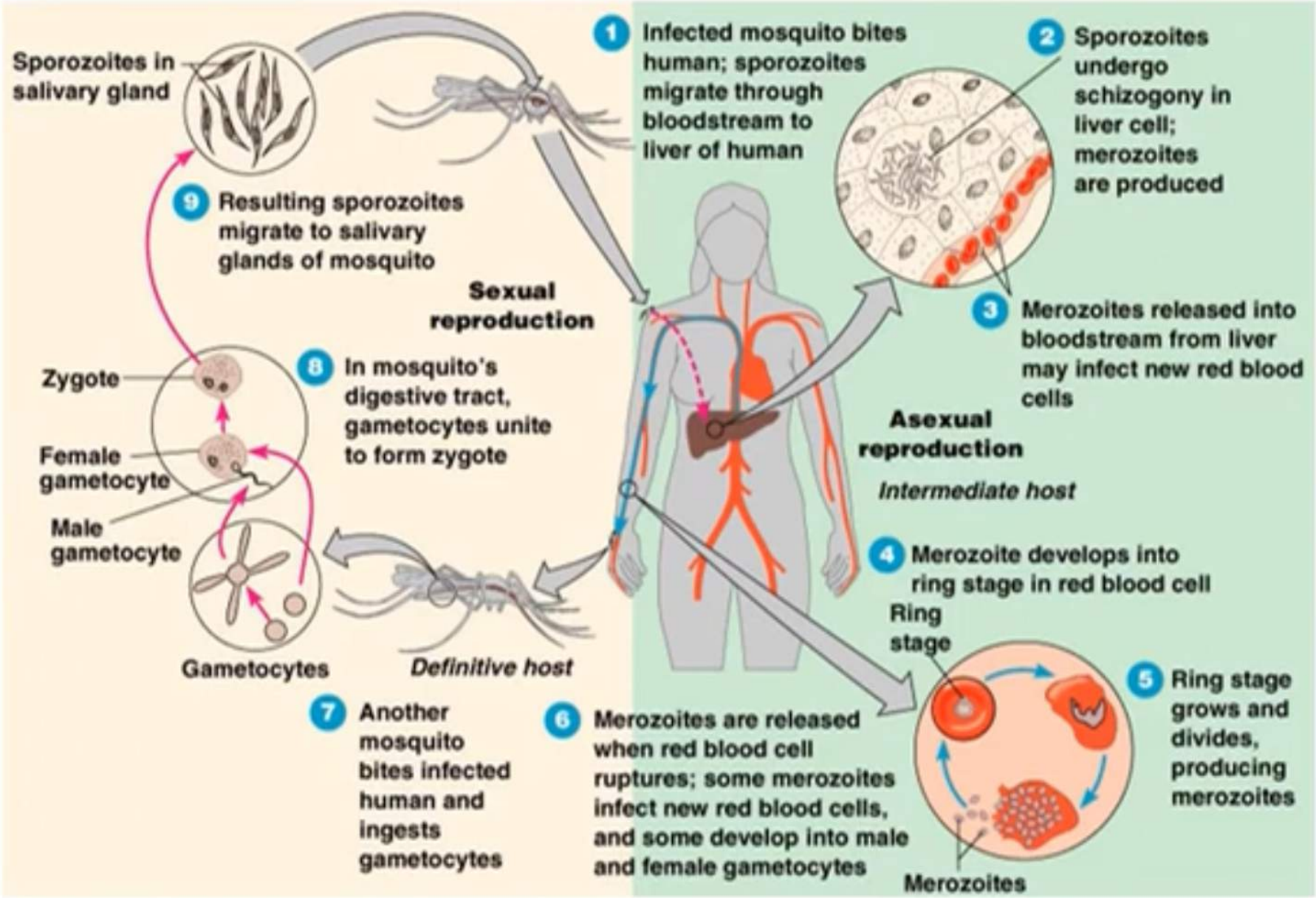


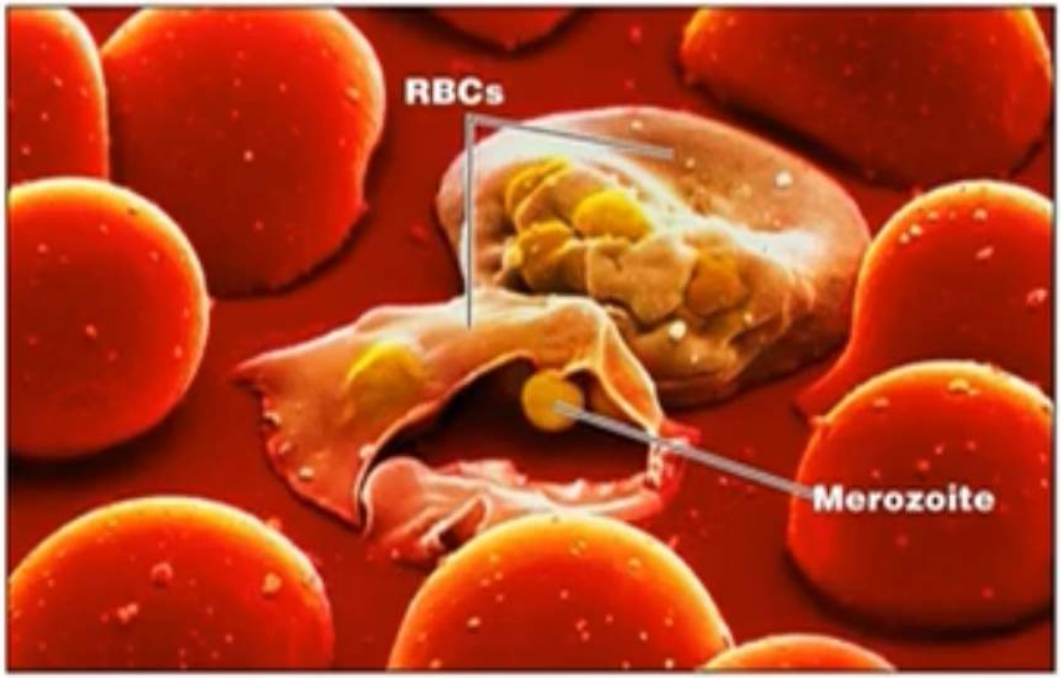
Figure 2: South American species of malarial mosquito (*Anopheles albimanus*) feeding from human arm.


LIFE CYCLE OF Plasmodium vivax, Plasmodium malariae, Plasmodium falciparum
P. vivax
P. malariae
P. falciparum
Rarely seen in the peripheral blood
Pre-erythrocytic asexual cycle (in liver)
Hepatic parenchymal cells
Schizogony in erythrocytes
Gametogony
HUMANS
macrogametocyte
microgametocyte
Mosquito feeds on human and sporozoites enter skin
Mosquito ingests gametocytes with blood meal
MOSQUITO
Exflagellation
Fertilization
Zygote
Oökinete penetrates stomach wall
Oöcyst forms on stomach wall
Production of sporozoites within oöcyst
Release of sporozoites (enter salivary gland of mosquito)

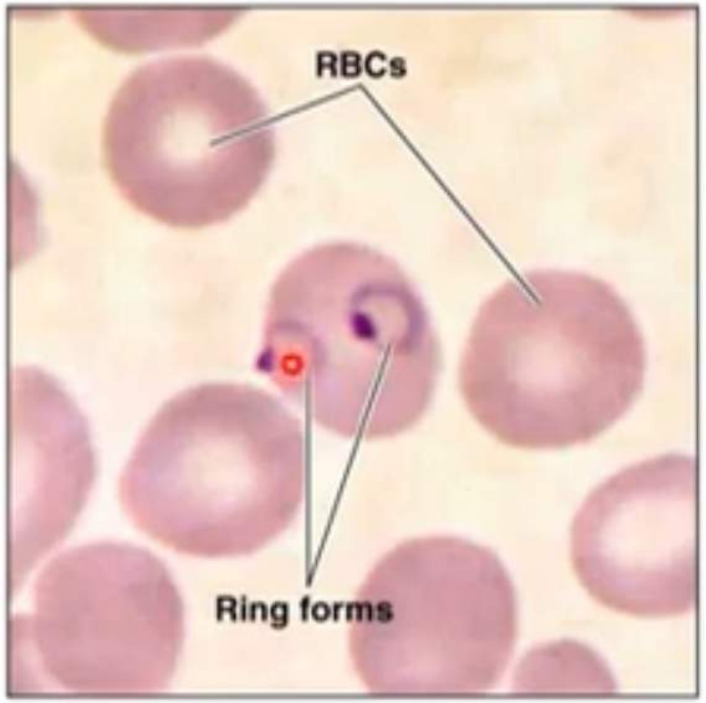
Malaria



Microscopic Diagnosis

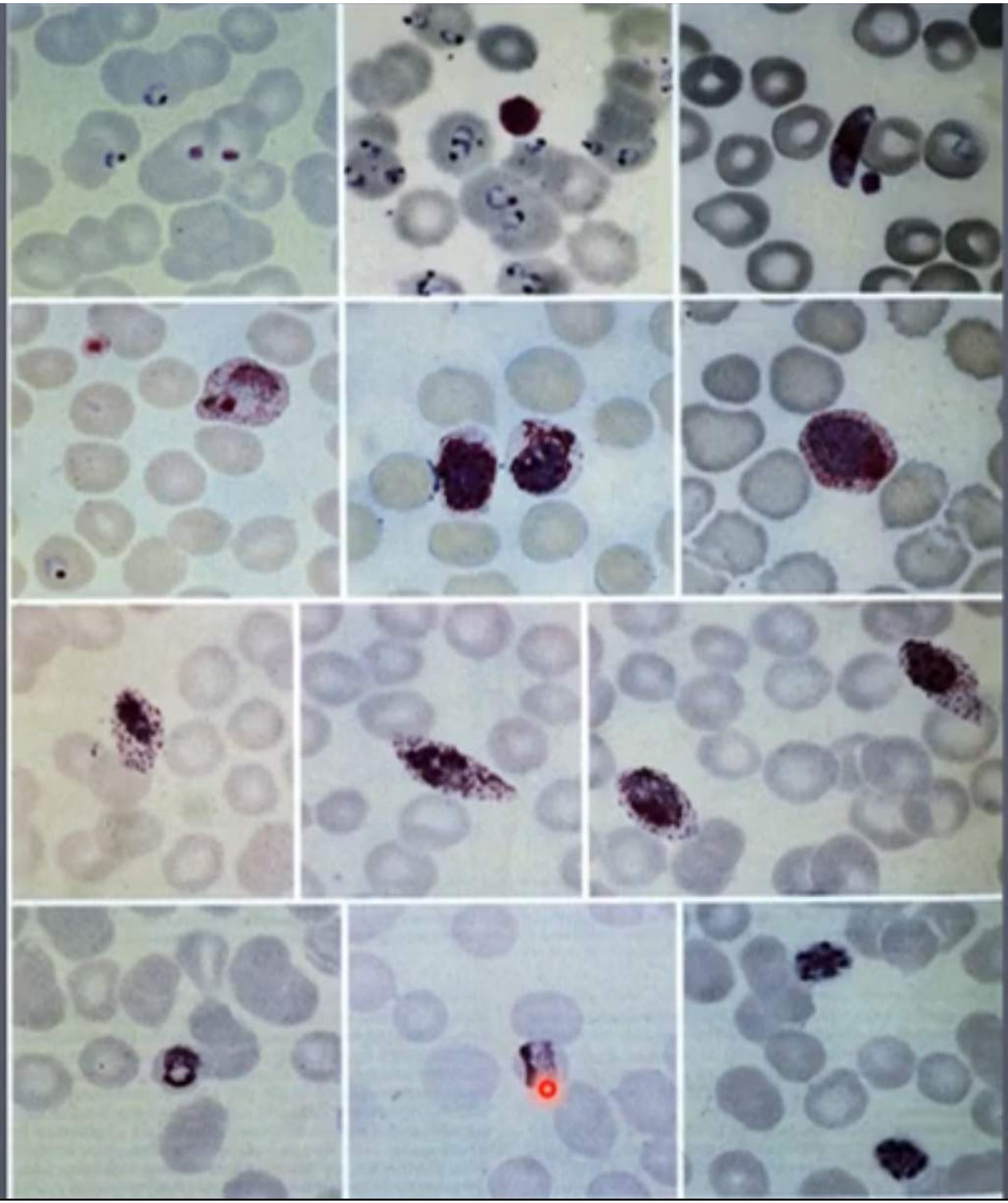


(a) Merozoites being released from lysed RBC. SEM 1 μm

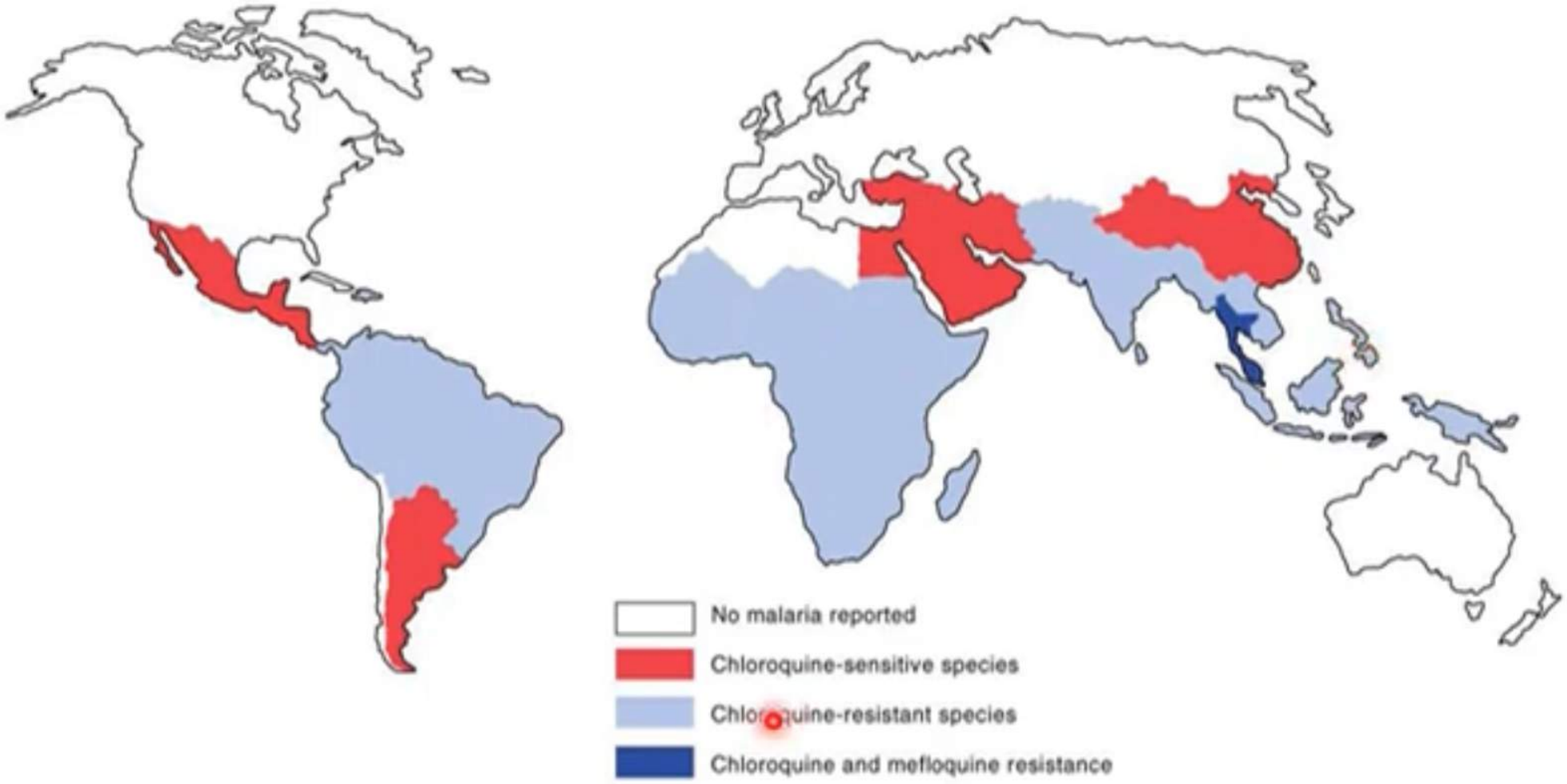


(b) Malarial blood smear; note the ring forms. LM 5 μm

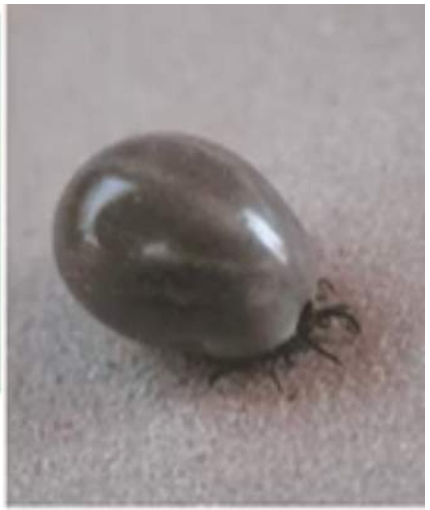
Diagnosis



Distribution of Malaria



❖ Babesiosis



Babesia microti

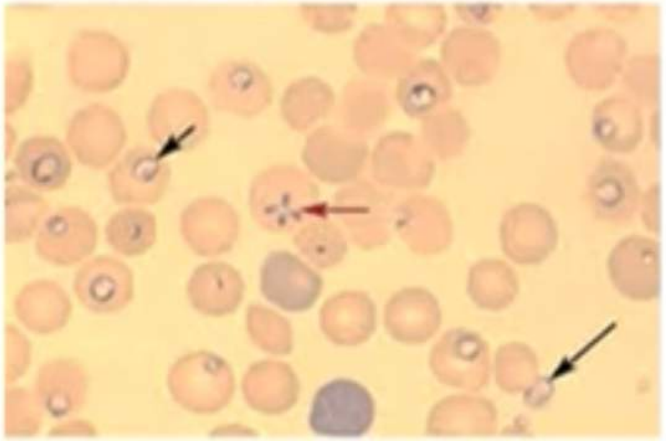
Vector *Ixodes* tick - Zoonosis

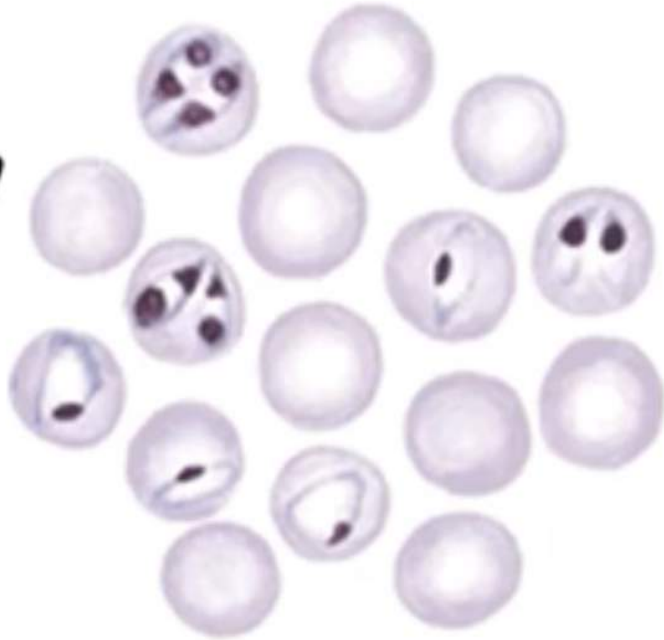
Hemoprotozoan → rupture of RBCs →

hemolytic anemia, fever, Jaundice

In malaria-endemic areas

misdiagnosis as *Plasmodium*





❖ Schistosomiasis / Bilharzia(sis)

- *Schistosoma mansoni,*
- *S. haematobium*, and
- *S. japonicum*
- 250 million people infected worldwide
- Cercaria penetrates skin when exposed to contaminated water → worms grow inside blood vessels and produce eggs → eggs travel to liver (liver damage), intestine or bladder.
- Treatment available *(praziquantel)*

Schistosomiasis (Bilharziasis)

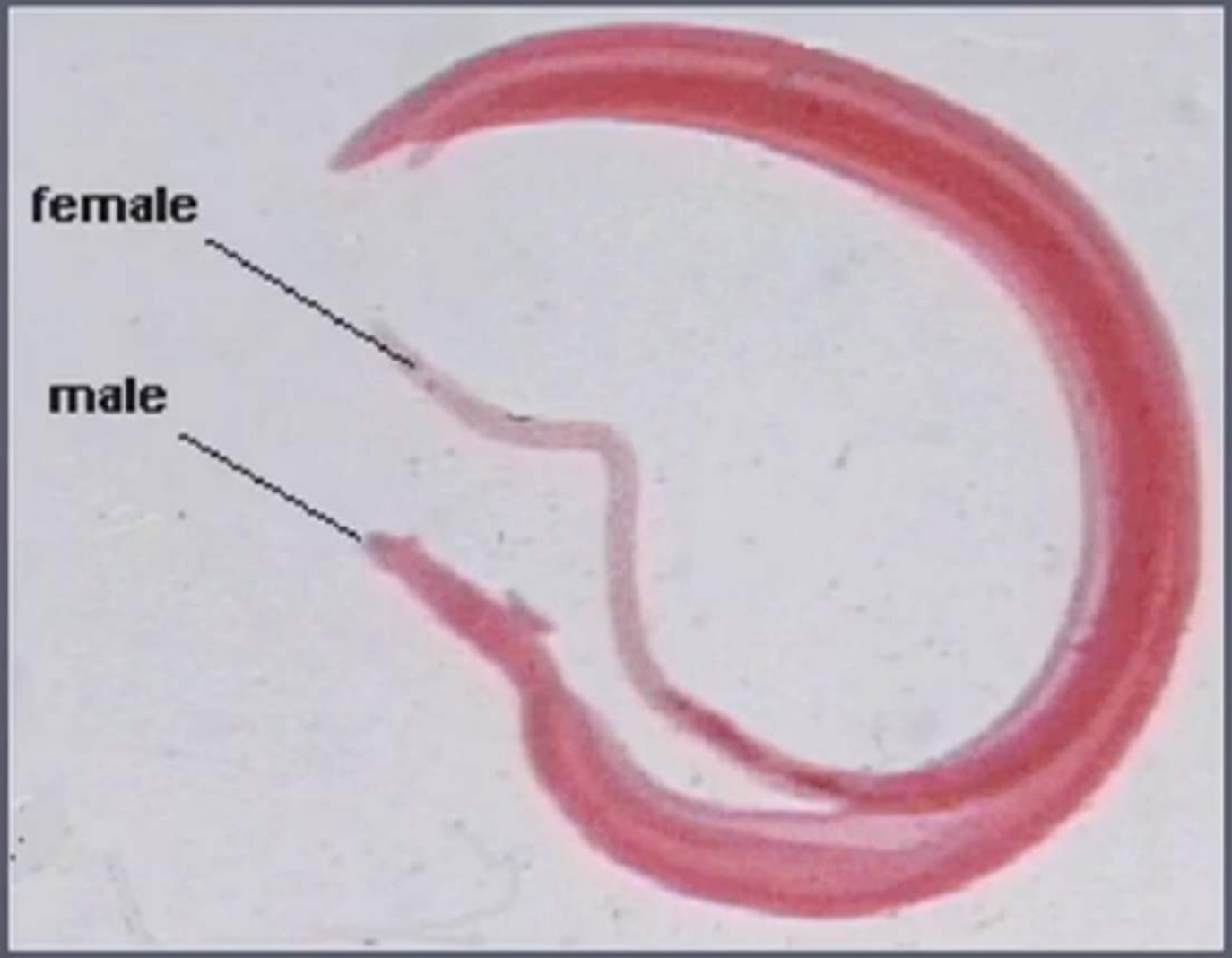
- *S. hematobium* is prevalent in Africa
- *S. mansoni* is found in Africa and America
- *S. japonicum* is common in the far east
- ~ 250 million people are infected
- ~ 600 million are at risk

Schistosomiasis

- **Tissue damage (granulomas) in response to eggs lodging in tissues**

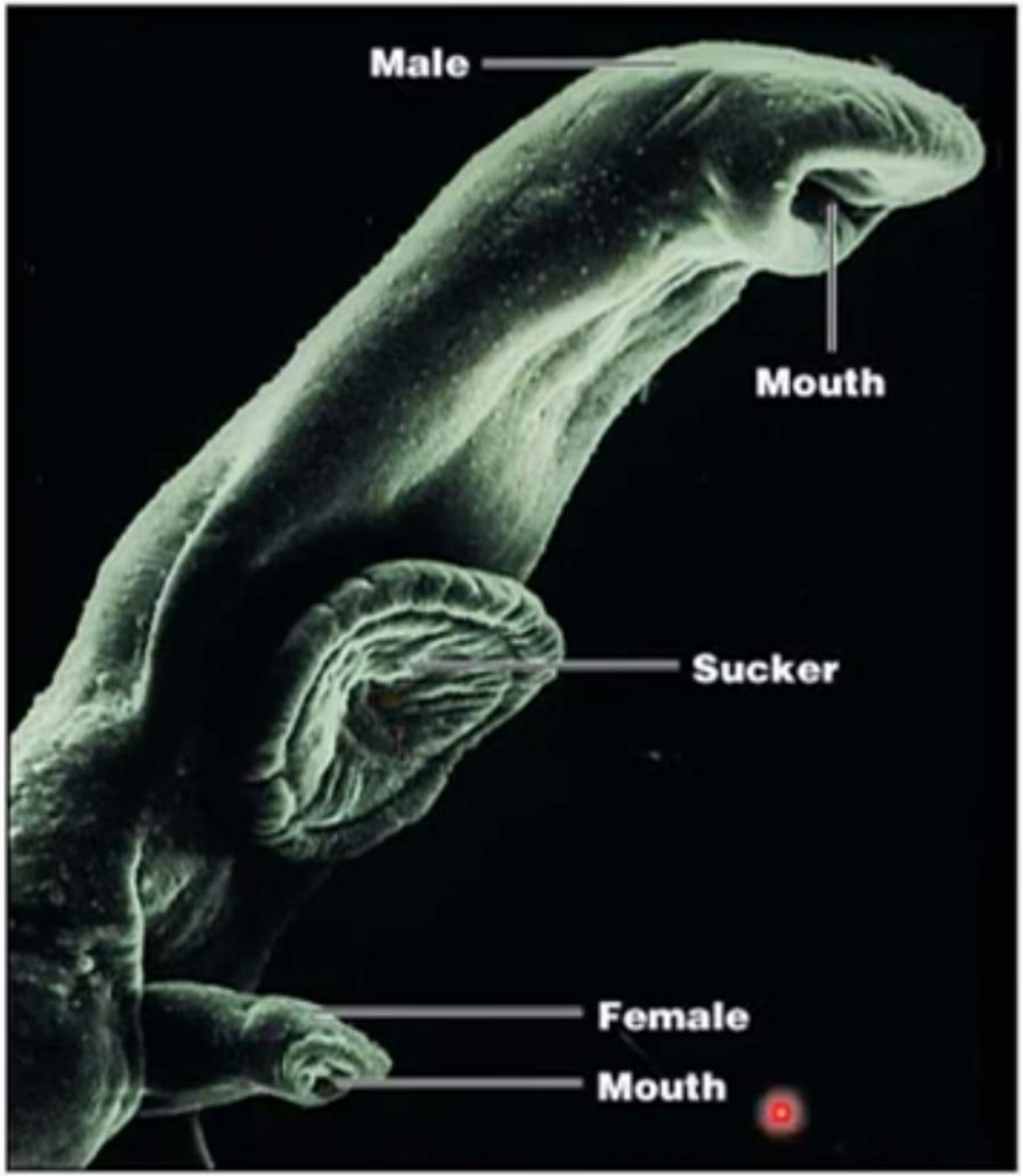
• *S. haemotobium*	Granulomas in urinary bladder wall	Africa, Middle East
• *S. japonicum*	Granulomas in intestinal wall	East Asia
• *S. mansoni*	Granulomas in intestinal wall	African, Middle East, South American, Caribbean
• Swimmer's itch	Cutaneous allergic reaction to cercariae	U.S. parasite of wildfowl


S. mansoni
S. intercalatum



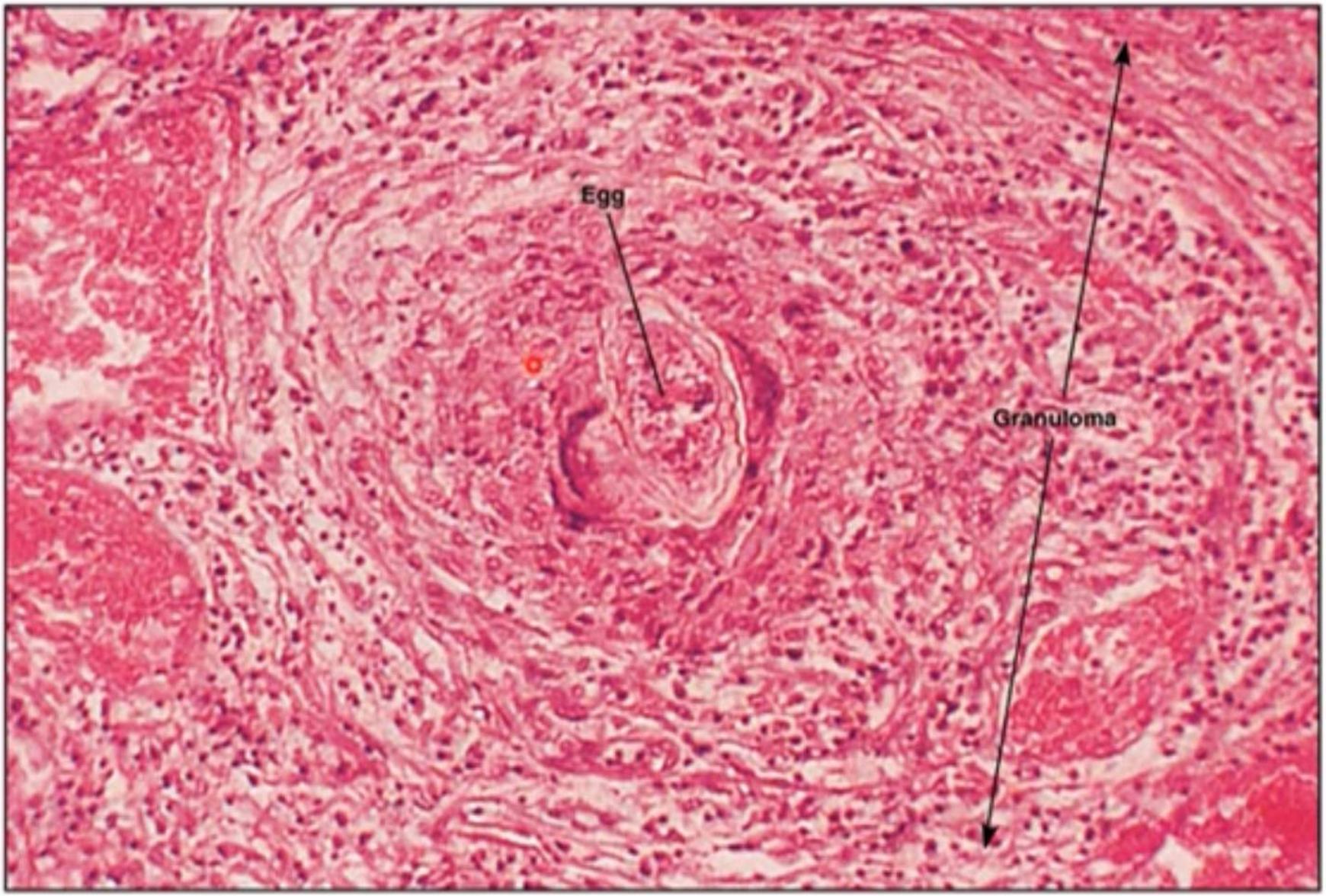
Gynaecophoric canal „deep ventral groove"

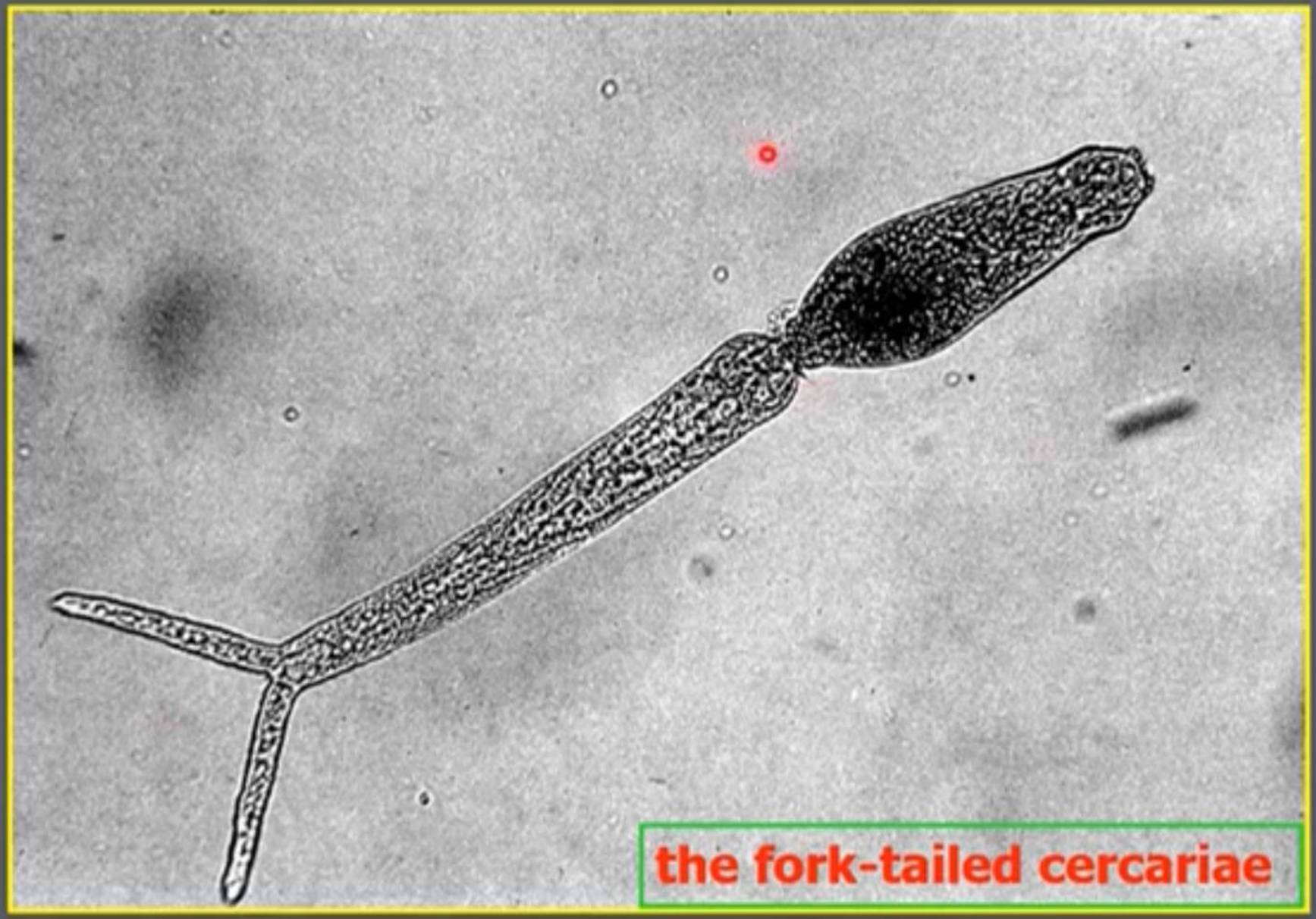
Schistosomiasis

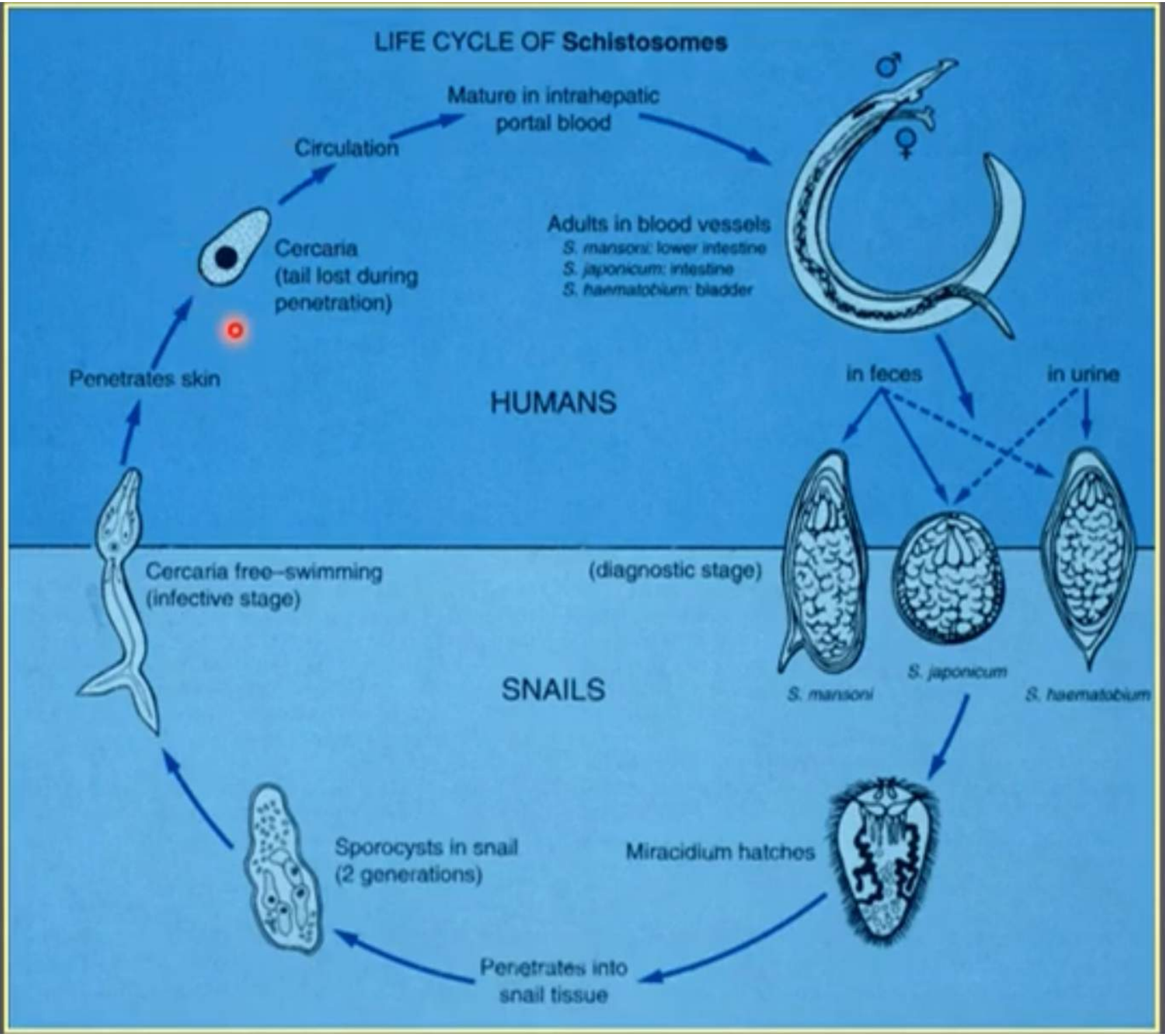


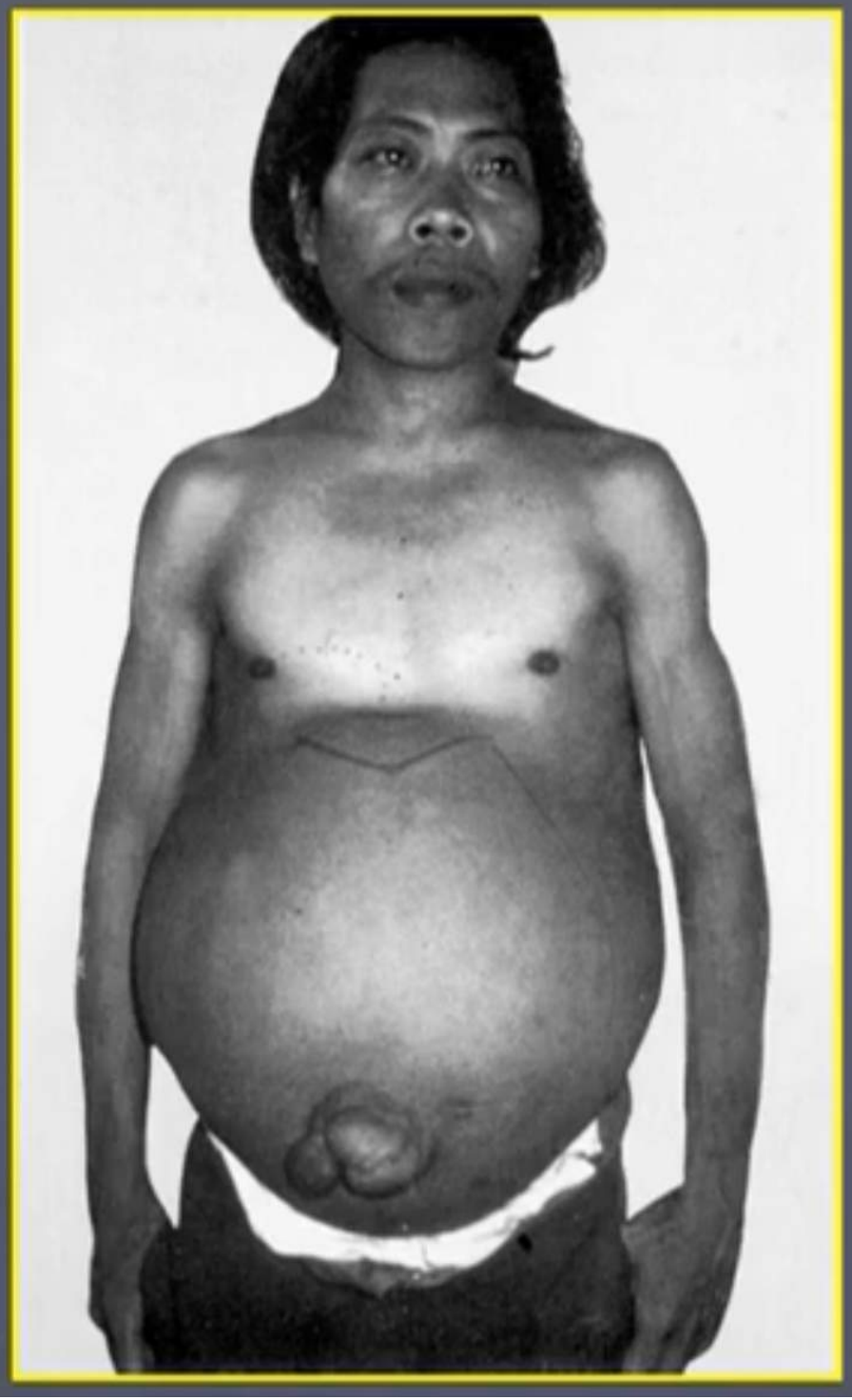
Male and female schistosomes

Schistosomiasis

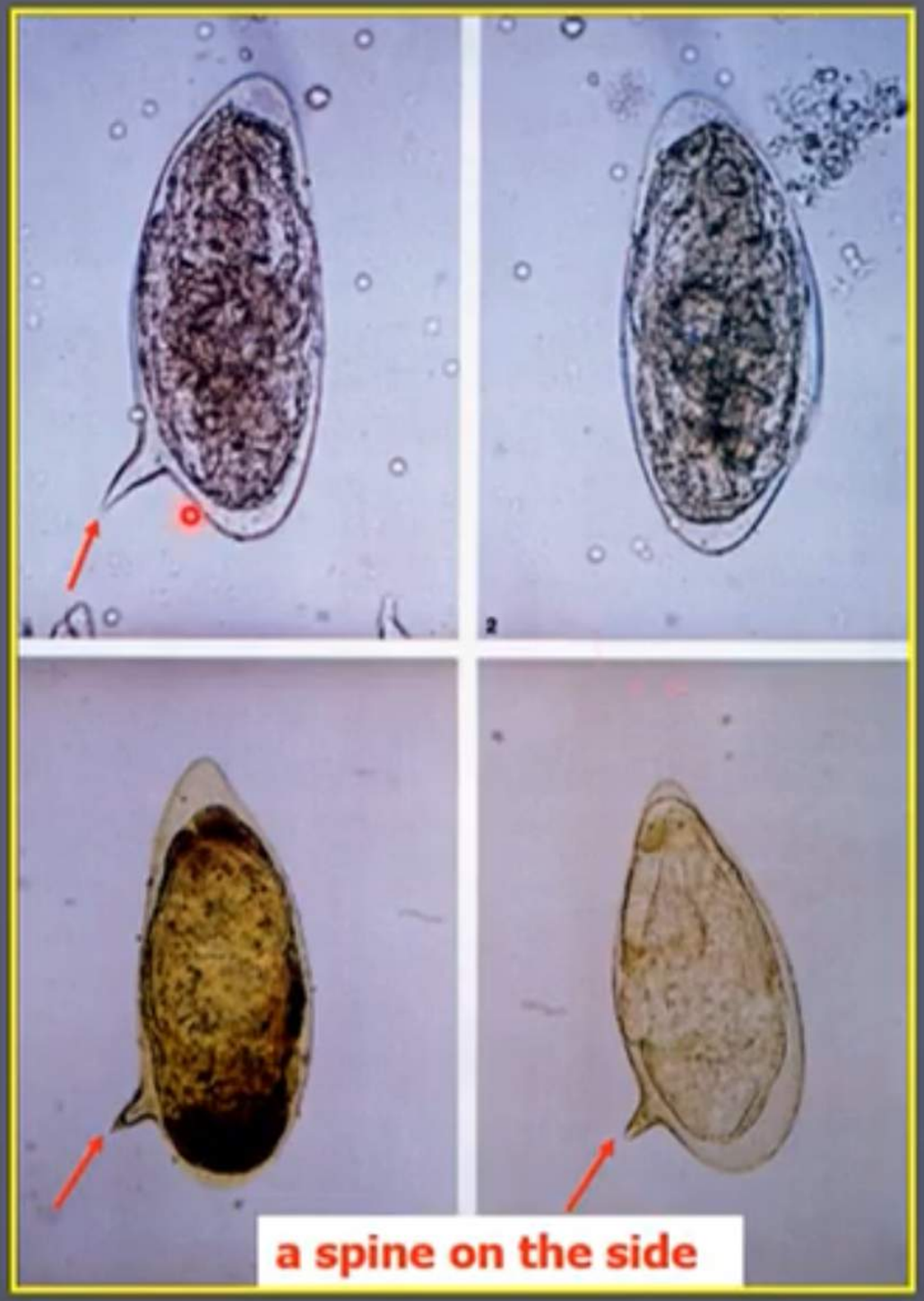



the fork-tailed cercariae

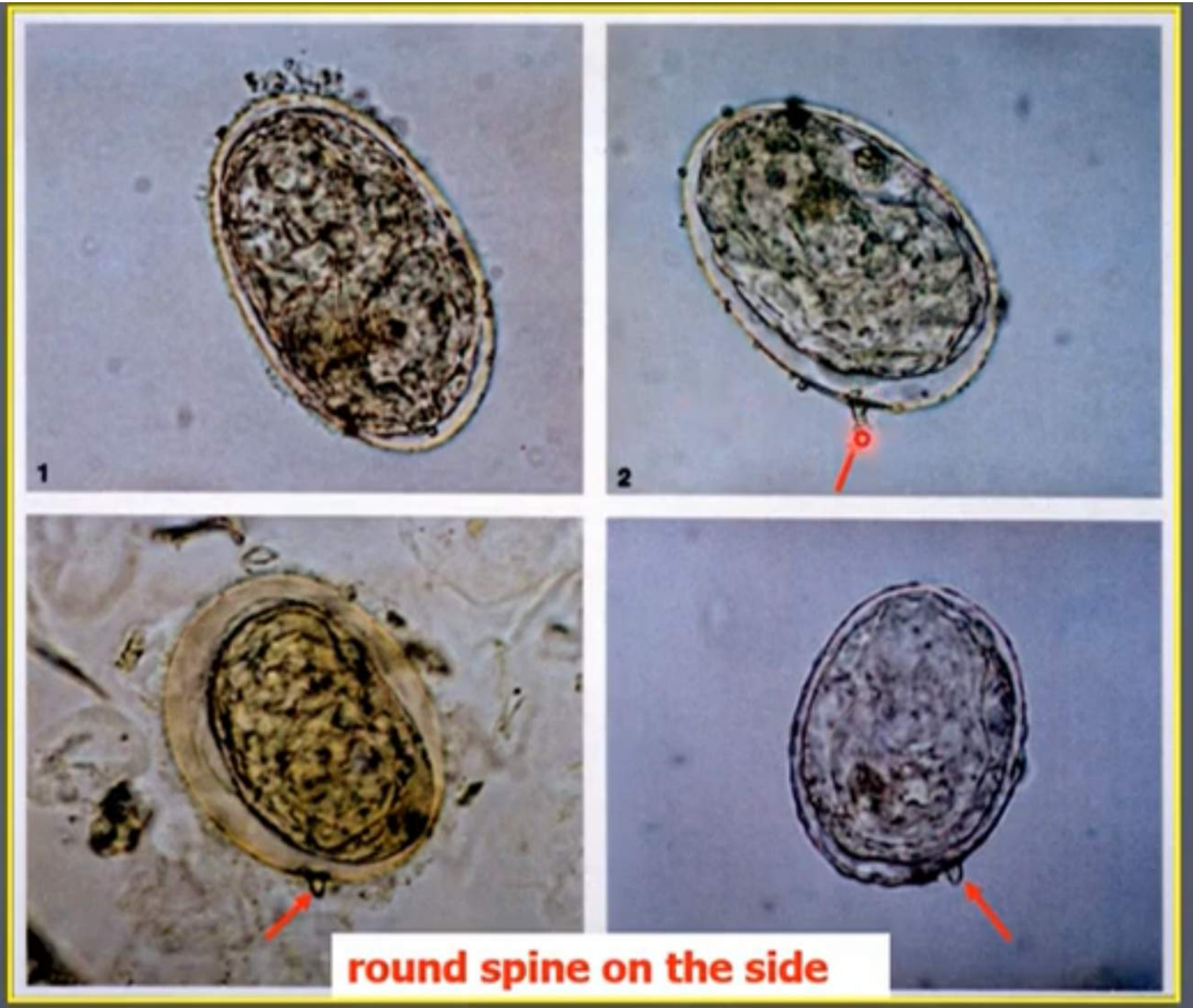

LIFE CYCLE OF Schistosomes
Mature in intrahepatic portal blood
Circulation
Cercaria (tail lost during penetration)
Adults in blood vessels
S. mansoni: lower intestine
S. japonicum: intestine
S. haematobium: bladder
Penetrates skin
HUMANS
in feces
in urine
Cercaria free–swimming (infective stage)
(diagnostic stage)
SNAILS
S. mansoni
S. japonicum
S. haematobium
Sporocysts in snail (2 generations)
Miracidium hatches
Penetrates into snail tissue



S. hematobium eggs in urine



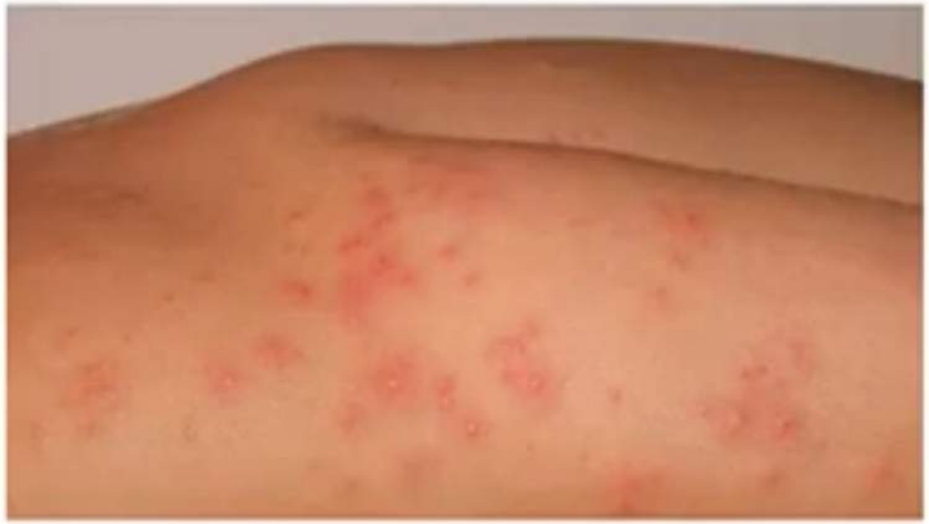
***S. mansoni* eggs in feces**



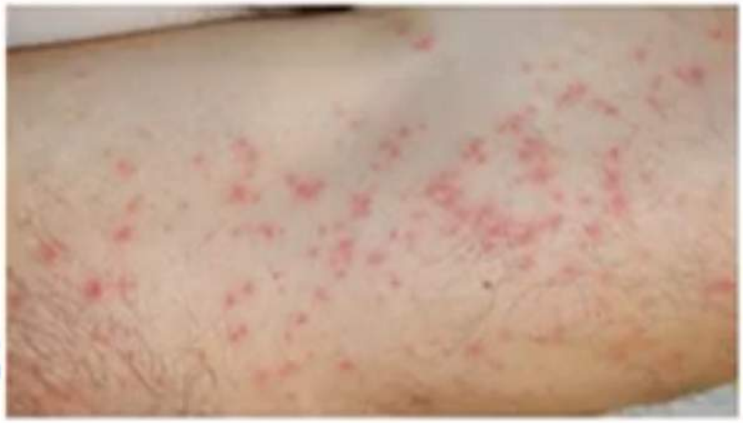
S. japonicum eggs in feces

Other Schistosomes: Swimmer's Itch or Cercarial Dermatitis

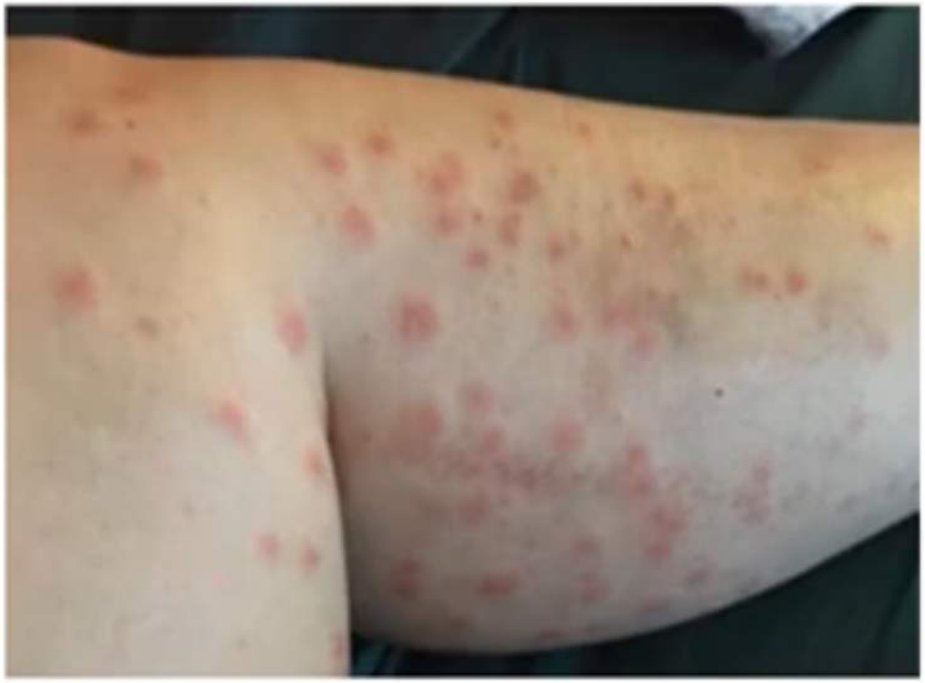
Schistosome cercaria accidentally enters human skin (bird is definitive host for adult parasite)

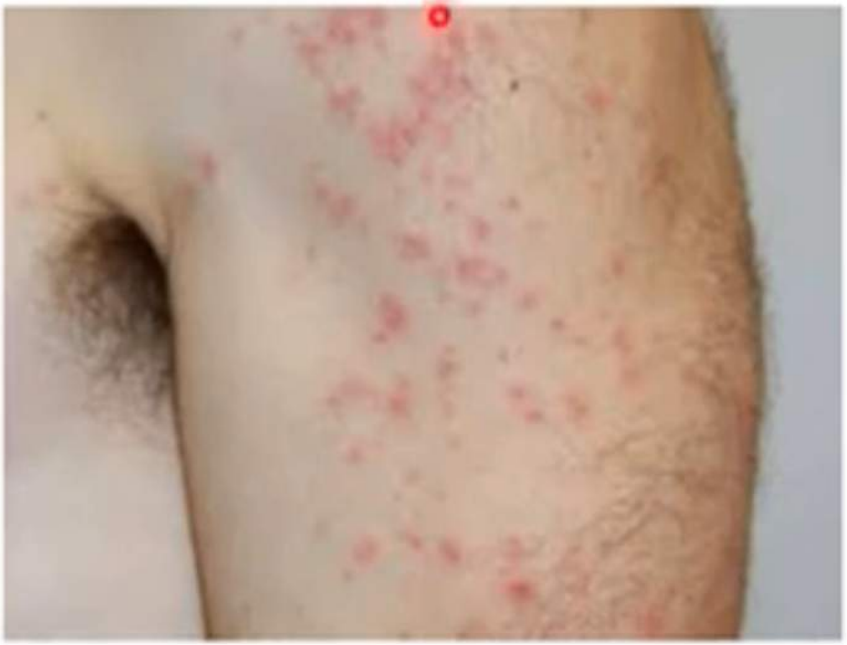


Almost every state in US (Most predominant in the north). Also in more than 30 countries.



Disappears without treatment (~ 7 days) – no internal organs involved





Parasites after entering → dermatitis in previously sensitized individuals. Sensitivity rarely disappears; usually gets worse in subsequent exposures.

Widely scattered from Michigan lakes to Alaska.