COURSE:

Introduction to General Pharmaceutical Microbiology and Biotechnology (PMB 271)

TOPIC:

Protozoal Parasites of Public Importance

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INTRODUCTION

1.0 Parasites

A parasite is an organism that lives on/in another organism (host) and obtains its nourishment at the expense of the host. Three main classes of parasites that can cause disease in humans are protozoa, helminths, and ectoparasites.

2.0 Protozoans

Protozoan (singular), protozoa or protozoans (plural).

The word 'protozoa' meaning "first animals" are unicellular eukaryotes that are either free-living or parasitic. All protozoal species are assigned to the kingdom **Protista** in the Whittaker classification, and placed into various groups primarily on the basis of how they move. The groups are called phyla (singular, phylum) by some microbiologists and classes by others. They feed on organic matter such as other microorganisms or organic tissues and debris. The protozoa have the ability during their entire life cycle or part of it to move by locomotor organelles or by a gliding mechanism.

2.1 Classification

Protozoa of public importance (infectious to humans) are classified into groups/classes based on their mode of locomotion or based on the body system affected as tabulated in Tables 1 and 2 respectively. The various modes of locomotion are flagella, cilia, pseudopodia, or none motile.

Table 1: Grouping of protozoa parasites based on locomotary organelles

Group	Locomotary structure	Examples
Sarcodina	Pseudopodia (False feet)	• Amoeba in the large intestine: *Entamoeba histolytica*
Mastigophora	Flagella	• Hemoflagellates: *Trypanosoma*, *Leishmania* • Gastrointestinal: *Giardia lamblia* • Urogenital: *Trichomonas vaginalis*
Ciliophora	Cilia	• Gastrointestinal: *Balantidium coli*
Apicomplexa (Sporozoa)	adult stage are not motile	• Blood: *Plasmodium* • Tissue: *Toxoplasma gondii* • Gastrointestinal: *Cryptosporidium*

Table 2: Classification of Protozoal parasites according to sites of infection

S/N	System affected	Parasite	Disease	Vector/Habitat	Description/Clinical features
1	Nervous system	*Trypanosoma brucei*	African Sleeping sickness (trypanosomiasis)	Tsetse fly	Affects the blood, lymph nodes and CNS
		Trypanosoma cruzi	Chagas' disease (South American trypanosomiasis)	Triatomid bugs	Affects the heart and colon

2	Intestinal system	*Entamoeba histolytica*	Amoebic dysentery, Amoebic liver abscess (ALA)	Large intestine	Dysentery. Infected individuals pass the cysts in stools and remain carriers for long periods.
		Giardia lamblia	Giardiasis	Small intestine	Malabsorption and diarrhoea. Foul-smelling, watery discharge accompanies the infection, followed by abdominal pain.
		Balantidium coli	Balantidiasis	Large intestine	Tissue invasion may occur, and diarrhea is accompanied by blood and pus in the stools.
		Cryptosporidium parvum and *C. coccidi.*	Cryptosporidiosis	Small intestine	Mild gastroenteritis with abdominal pain and watery diarrhea. Symptoms tend to be very severe in AIDS patients, and the massive diarrhea can be lethal.
3	Genitourinary	*Trichomonas vaginalis*	Trichomoniasis (Vaginitis, Urethritis)	Vagina, Urethra	It grows along the mucosa of the reproductive tract, causing internal discomfort and a profuse, green-yellowish discharge with a foul odor.
4	Blood and Tissue	1. *Plasmodium vivax* 2. *Plasmodium falciparum* 3. *Plasmodium malariae* 4. *Plasmodium ovale* 5. *Plasmodium knowlesi*	Malaria	Erythrocytes	Fever, headache, Severe anemia, etc
		Leishmania donovani	Leishmaniasis	phlebotomine sand flies	Visceral leishmaniasis (affects several internal organs such as spleen, liver, and bone marrow). An important opportunistic infection associated with HIV.
		Leishmania tropica	Leishmaniasis		Cutaneous leishmanias (skin/oriental sores)
5	Respiratory	*Pneumocystis carinii*	*Pneumocystis* pneumonia		It is present in the lungs of many individuals, but does not invade the tissues unless the immune system is compromised. They are responsible for about half of the deaths associated with AIDS.
6	Cardiovascular and Lymphatic Systems	*Toxoplasma gondii.*	Toxoplasmosis	Urine or faeces of domestic cats	Symptoms are generally mild but, in pregnant women, the protozoa may pass to the unborn fetus and cause tissue destruction. It could also result in seizures, brain inflammation and eventually lead to death in AIDS patients.

3.0 Modes of Transmission

Transmission of:

- intestinal protozoa is majorly through the faecal-oral route (example, contaminated food or water, and contaminated hands), while
- protozoa that live in the blood or tissue of humans are transmitted by arthropod vectors (example, through the bite of a mosquito or sand fly).

4.0 Life cycle

During its life cycle, a protozoan generally passes through several stages that differ in structure and activity. Many protozoa alternate between:

- a free-living vegetative form known as **trophozoite** (Greek for "animal that feeds") and
- a resting stage known as **cyst.**

Trophozoite is a general term for the active, feeding, multiplying stage of most protozoa. In parasitic species this is the stage usually associated with pathogenesis. The protozoal cyst is somewhat analogous to the bacterial spore, since it resists harsh conditions in the environment. Many protozoal parasites are taken into the body in the cyst form.

A. *Entamoeba histolytica*

Distribution

Entamoeba histolytica has a worldwide spread, especially in environments having poor sanitation such as developing countries of the tropics. Most of cases are asymptomatic.

Habitat

Entamoeba histolytica thrives in the human colon.

Life Cycle

(1) The cysts (usually found in formed stools) and trophozoites (in loose stools) are passed out with faeces of infected human host. *(2)* Cysts are ingested through contaminated food or water. *(3)* the cysts undergoes excystation in the intestine and form trophozoites. *(4)* As the trophozoite passes down the intestine, it undergoes encystation (formation of cyst) and is excreted in the faeces (Fig. 1). The parasite completes its life cycle in human host. In most cases, *E. histolytica* remains as a commensal in the large intestine of host humans. Such individuals are carriers or asymptomatic cyst passers and are responsible for maintenance and transmission of infection in the community.

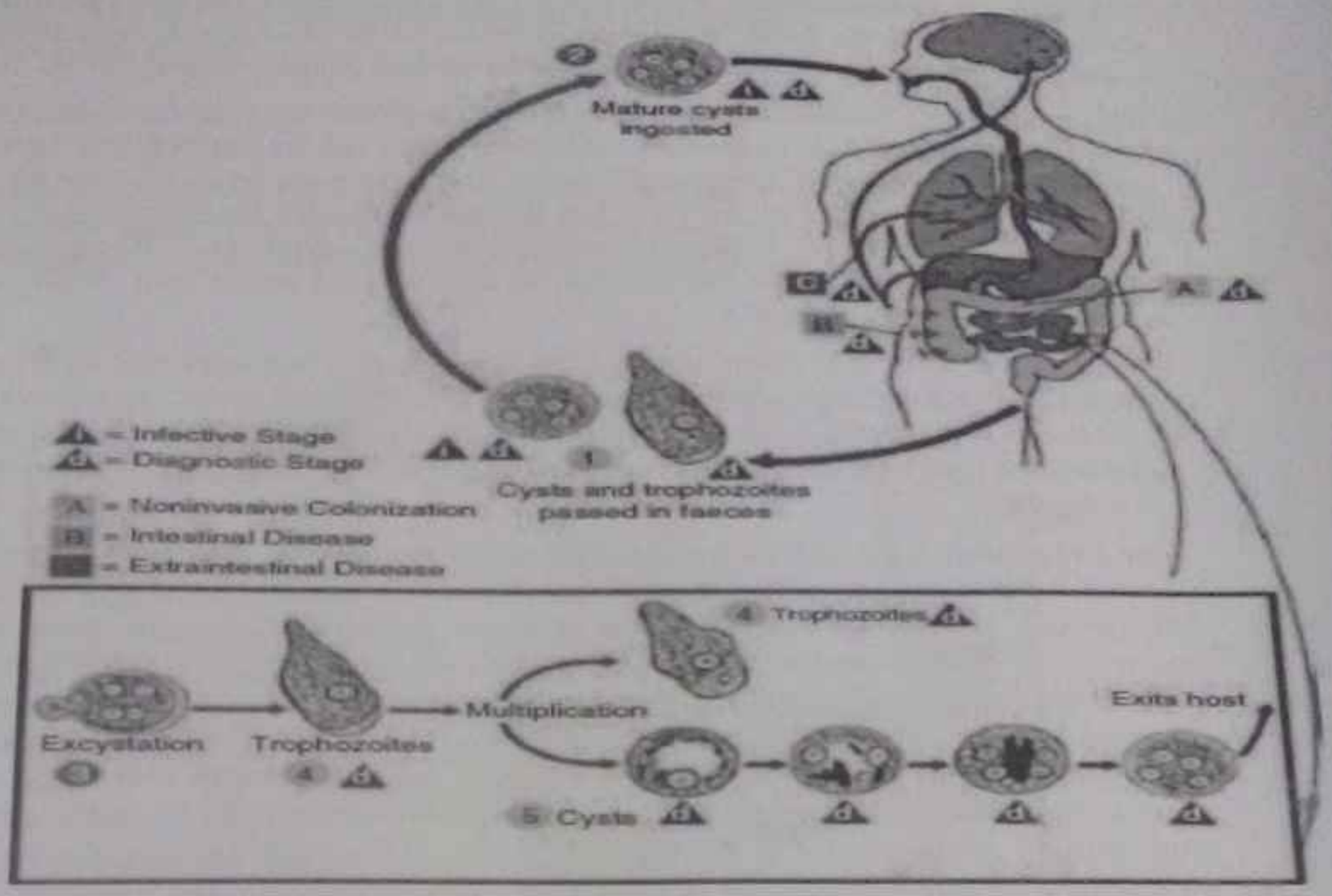

Fig 1: Life cycle of *Entamoeba histolytica* (Reproduced from https://www.cde.gov/dpdx/amebiasis/index.html)

Pathogenesis and Clinical Features

Entamoeba histolytica causes intestinal and extraintestinal amoebiasis.

In the lumen, the parasitedo not cause any illness. However, they cause disease only when the trophozoites invade the intestinal tissues. The trophozoite penetrates the epithelial cells in the colon, aided by its movement and histolysin, a tissue lytic enzyme, which damages the mucosal epithelium. Amoebic lectin mediates adherence.

Other complications of intestinal amoebiasis:

- Amoebic cerebral abscess
- Amoebic peritonitis
- Genitourinary amoebiasis
- Perianal ulceration
- Pulmonary amoebiasis
- Splenic abscess
- Toxic megacolon

Mucosal penetration produces discrete ulcers with pinhead centre and raised edges.

Sometimes, the invasion remains superficial and heals spontaneously. The ulcers are multiple and are confined to the colon, being most numerous in the caecum and recto-sigmoidal region. The intervening mucous membrane between the ulcers remains healthy.

The amoebic ulcer is flask shaped in cross-section. Multiple ulcers may coalesce to form large necrotic lesions with ragged and undermined edges and are covered with brownish slough. The ulcers generally do not extend deeper than submucosal layer. Amoebae are seen at the periphery of the lesions and extending into the surrounding healthy tissues. Clinical manifestations are diarrhoea, vague abdominal symptoms and dysentery. This may resemble bacillary dysentery. The ulcers may involve the muscular and serous coats of the colon, causing perforation and peritonitis.

Blood vessel erosion may cause haemorrhage. Deep ulcers form scars and may lead to strictures and partial obstruction. A granulomatous pseudotumoral growth may develop on the intestinal wall from a chronic ulcer. This amoebic granuloma or amoeboma may be mistaken for a malignant tumour. The incubation period for intestinal amoebiasis varies from 1 to 4 months.

Liver involvement is the most common extraintestinal complication of intestinal amoebiasis. About 5–10% of patients with intestinal amoebiasis will develop amoebic liver abscess (ALA). ALA arises from haematogenous spread of amoebic trophozoites from colonic mucosa or by direct extension. Often, ALA patients do not present with bowel symptoms. Liver damage may not be directly caused by the amoebae, but by lysosomal enzymes and cytokines from the inflammatory cells surrounding the trophozoites. The centre of the abscess contains thick brown pus (anchovy sauce), which is liquefied necrotic liver tissue free of amoeba. The trophozoite is in the wall of the abscess. Liver abscess may be multiple or more often solitary, usually located in the upper right lobe of the liver. Jaundice develops only when lesions are multiple or when they press on the biliary tract. Large, untreated abscess may rupture into the lungs and pericardium. The incidence of liver abscess is more common in adult males.

Other complications of intestinal amoebiasis are as shown listed above.

Prevention and Control

1. Boil drinking water
2. Wash fruits and vegetables in clean water before eating
3. Detection and treatment of carriers and prohibit them from food handling
4. Health education

B. *Giardia lamblia*

Distribution

It has a global distribution. It is endemic in the tropics and subtropics where sanitation is poor. Visitors to such areas develop traveller's diarrhoea.

Habitat

Giardia lamblia lives in the duodenum and upper jejunum.

Life Cycle

(1) Cysts are passed out in stool of an infected human.

(2) Infective cysts are ingested.

(*3*) The cyst excysts to release trophozoite in the small intestine.

(*4*) The trophozoites multiply by binary fission.

(*5*) The trophozoite encysts to become cyst which is passed out in the stool. Trophozoites are passed in loose stools.

Giardia completes its life cycle in 1 host. Infective stage is the mature cyst. Human acquires infection by ingestion of cysts in contaminated water and food. Direct person to person transmission may also occur in children, male homosexuals, and institutional occupants.

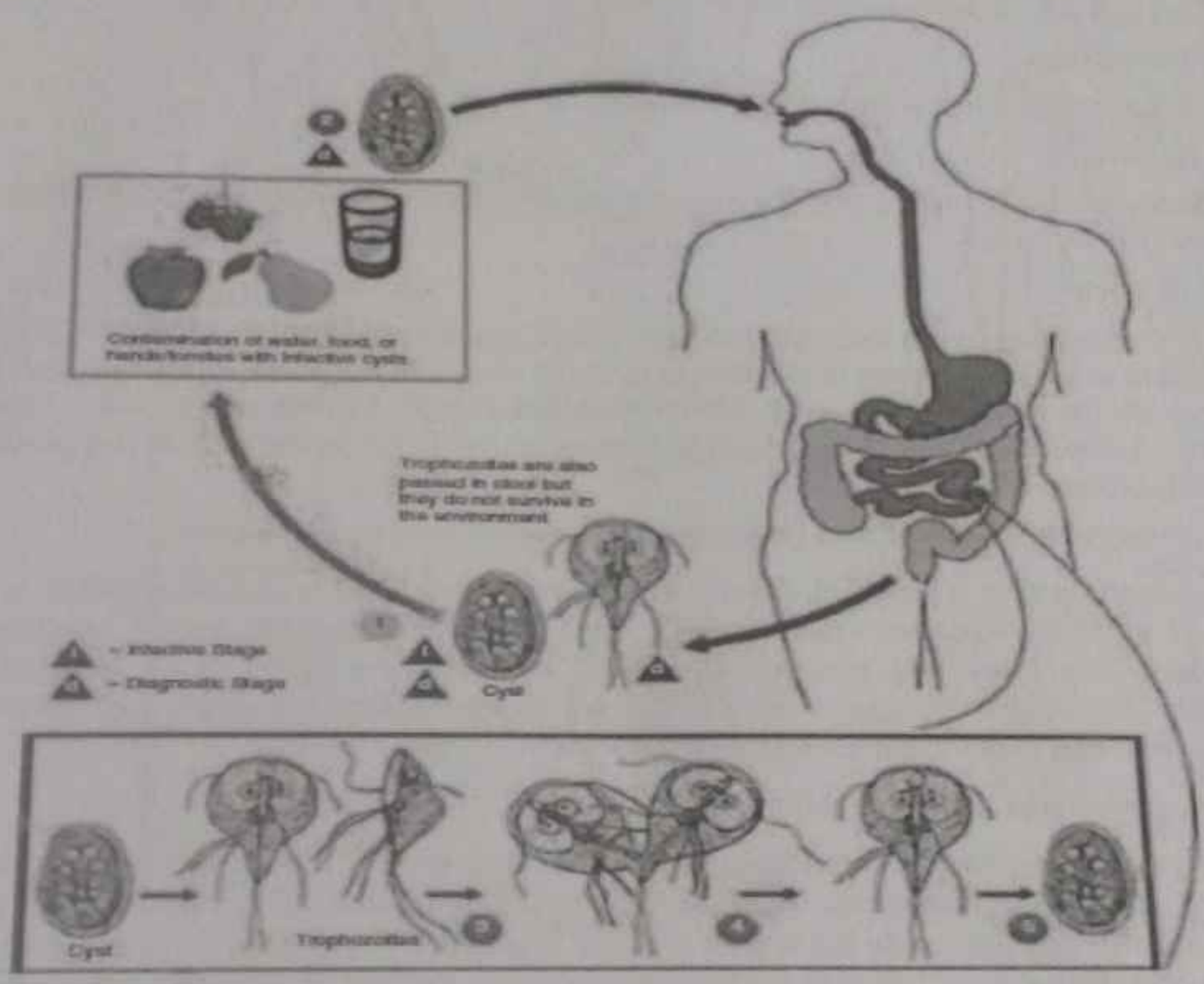

Fig. 2: Life cycle of *Giardia lamblia* (Reproduced from https://www.cdc.gov/dpdx/giardiasis/index.html)

Pathogenesis and Clinical Features

Trophozoite does not invade the tissue, but remains adhered to intestinal epithelium by means of the sucking disc causing stunting and shortening of the villi. Patients are usually asymptomatic, but in some cases, giardiasis may cause diarrhoea, fat malabsorption (steatorrhea), dull epigastric pain and flatulence. The stool contains excess mucus and fat. Children may develop chronic diarrhoea, malabsorption of fat and vitamin A and weight loss. Incubation period is about 2 weeks.

Prevention and Control

1. Proper faecal disposal

2. Personal hygiene
3. Boiling of drinking water
4. Filtration of drinking water
5. Wash fruits and vegetables with clean water before eating
6. Health education

C. Trichomonas vaginalis

It exists only in the trophozoite stage.

Distribution

It is distributed worldwide.

Habitat

In human, it lives mainly in the vagina and cervix of females. In males, it occurs mainly in the anterior urethra.

Life Cycle

(*1*) Trophozoites live in the vagina and cervix and may also be found in Bartholin's glands, urethra and urinary bladder in females. In males, it occurs mainly in the anterior urethra, but may also be found in the prostate. (*2*) Trophozoites multiply by longitudinal binary fission. (*3*) Trophozoites in vagina or orifice of urethra can be found in the vaginal and prostatic secretions and urine

Life cycle of *T. vaginalis* is completed in a human host. There is no cystic stage.

The trophozoite is transmitted directly from person to person. Sexual transmission is the usual mode of infection. Trichomoniasis often coexists with other sexually transmitted diseases; like candidiasis, gonorrhoea, syphillis, or human immunodeficiency virus (HIV). Babies may acquire infection during birth from infected mothers. Fomites such as towels have been implicated in transmission.

Pathogenesis and Clinical Features

Trichomonas vaginalis infects the vagina and secretes cysteine, proteases, lactic acid and acetic acid, which disrupt the glycogen levels and lower the pH of the vaginal fluid. Trophozoite does not invade the vaginal mucosa. The infection can range from mild irritation to severe inflammation. Infection is often asymptomatic, particularly in males, although some may develop urethritis, epididymitis and prostatitis.

In females, it may produce severe itching in the genital area with foul smelling yellowish green frothy discharge, dysuria, burning sensation with urination and dyspareunia.

Cervical erosion is common. The incubation period is 4 days to 4 weeks.

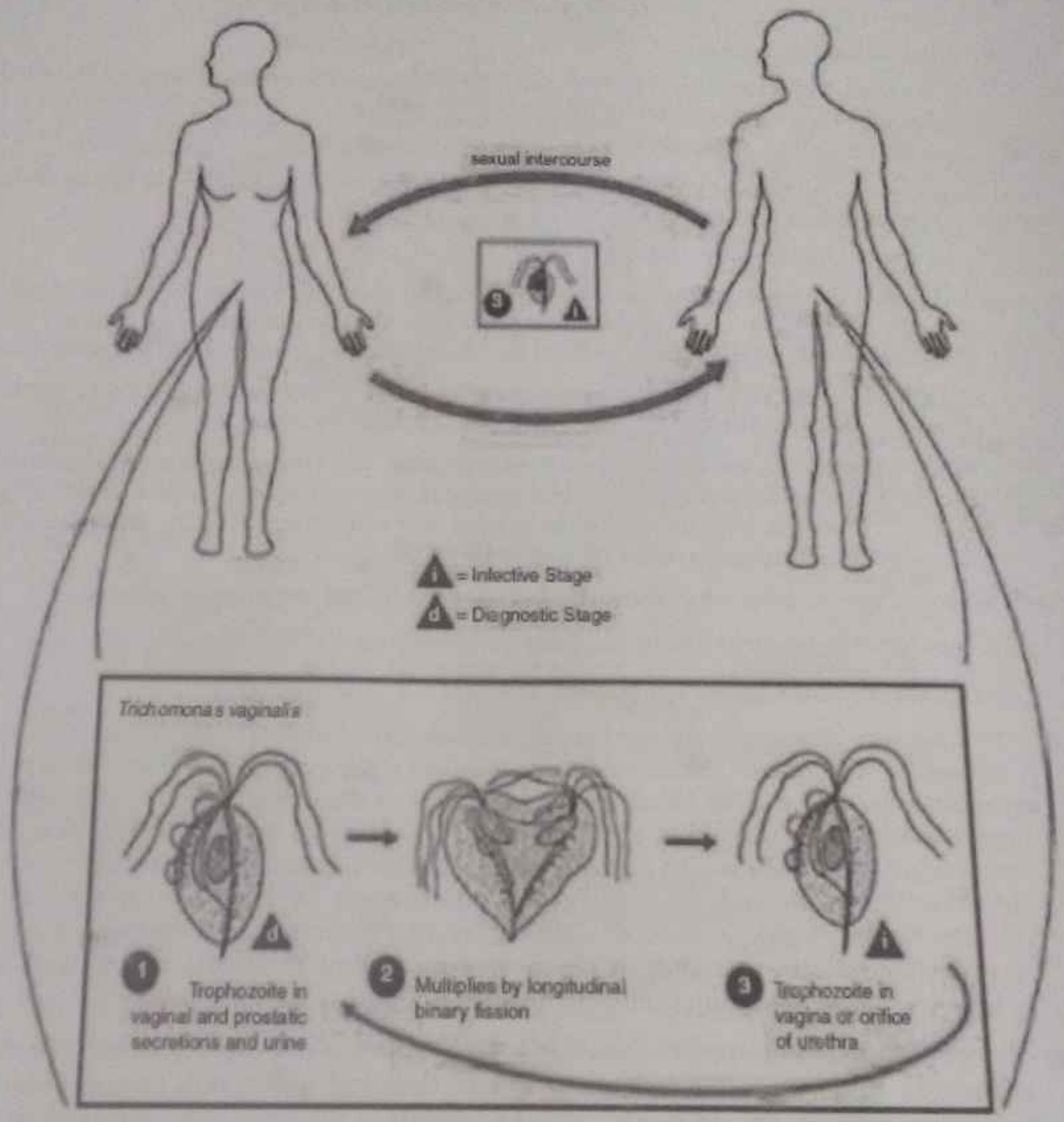

Fig. 3: Life cycle of *Trichomonas vaginalis* (Reproduced from https://www.cdc.gov/dpdx/trichomoniasis/index.html)

Prevention and Control

1. Treatment of sexual partner

2. Patients should be advised to abstain from sexual intercourse until they and their partners have completed treatment and follow-up

D. *Trypanosoma brucei gambiense*

Distribution

It is endemic in scattered foci in West and Central Africa. The principal vectors are *Glossina palpalis* and *Glossina tachynoides* (riverine tsetse flies).

Habitat

Trypanosomes live in human and other vertebrate hosts. From the blood, they invade regional lymph nodes and finally CNS.

Life Cycle (Fig. 4)

Trypanosoma brucei gambiense completes its life cycle in 2 hosts. Vertebrate hosts are humans. Game and other domestic animals can also be infected. (*1*) Tsetse fly (the invertebrate host) takes a blood meal and injects the infective metacyclic trypomastigotes.

(*2*) Injected metacyclic trypomastigotes transform into trypomastigotes and are carried to other sites via blood stream. (*3*) Trypomastigotes multiply by binary fission.

(*4*) Trypomastigotes are found in blood extracellular. (*5*) Trypomastigotes in the blood are ingested by tsetse fly and transform into procyclic trypomastigotes in the midgut of the fly (*6*). (*7–8*) Procyclic trypomastigotes transform into epimastigotes before transforming into metacyclic trypomastigotes in the fly's salivary gland.

Modes of transmission are via bite of infected tsetse fly and congenital transmission.

It is endemic in scattered foci in West and Central Africa.

Pathogenesis and Clinical Features

Trypanosoma brucei gambiense causes African trypanosomiasis (West African sleeping sickness). The illness is chronic and can persist for many years. There is an initial period of parasitaemia, followed by localization of parasites in the lymph nodes. A painless chancre appears on the skin at the site of bite by tsetse fly, followed by fever, chills, rash, anaemia and weight loss. There is high levels of immunoglobulins mainly IgM. Patient presents with hepatosplenomegaly and lymphadenopathy, particularly in the posterior cervical region (Winterbottom's sign). Invasion of CNS occurs after several months later and is marked by increasing headache, mental dullness, apathy and daytime sleepiness. The patient may fall into coma followed by death from other infections and physical weakness.

Histopathology examination of the brain shows chronic meningoencephalitis. The meninges are heavily infiltrated with lymphocytes, plasma cells and morula cells (atypical plasma cells containing mulberry-shaped masses of IgA). Vessels in the brain show perivascular cuffing. There is cellular infiltration of the brain and spinal cord, neuronal degeneration and microglial proliferation. Intracranial pressure is raised and CSF shows pleocytosis with increased protein.

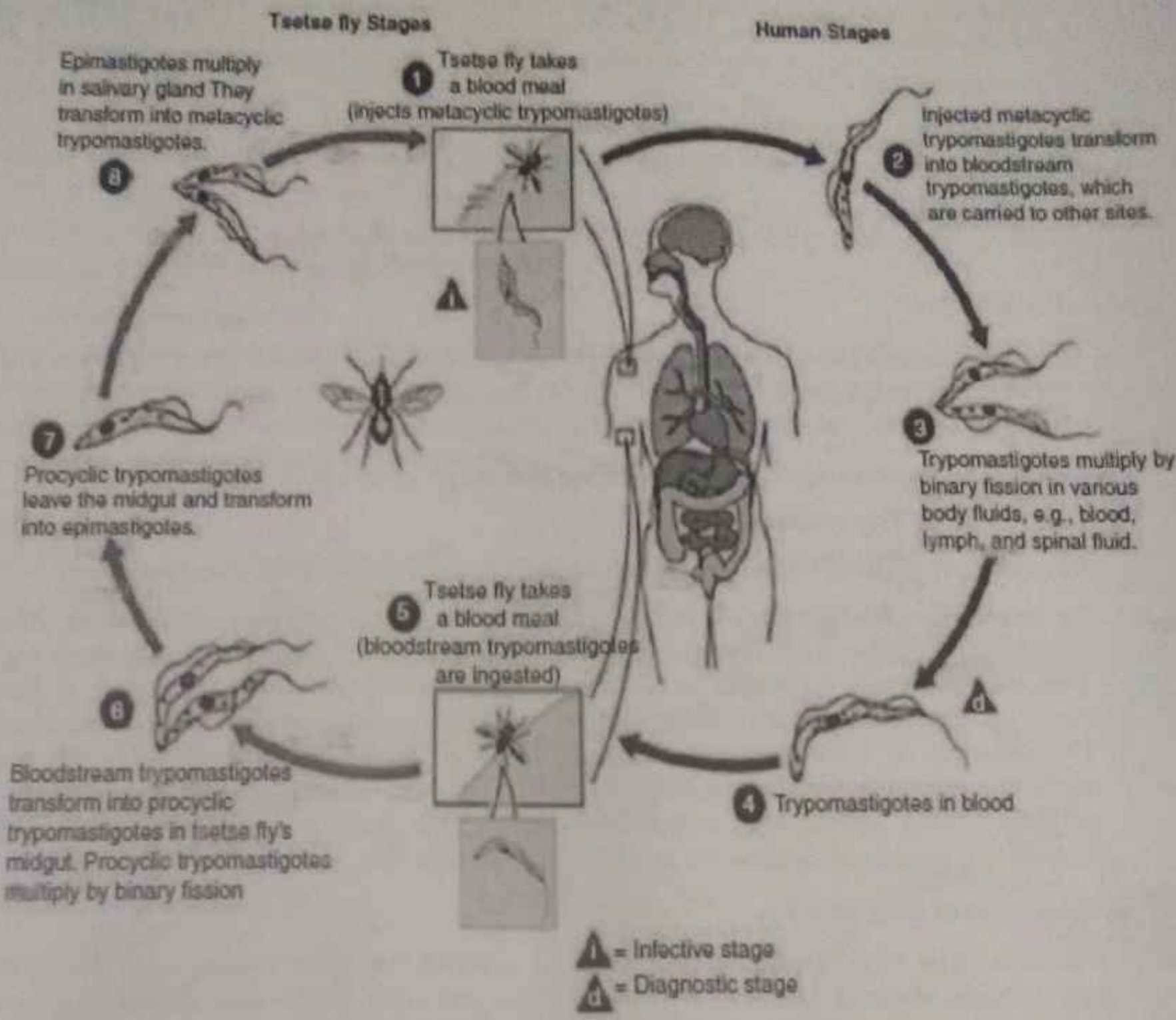

Fig. 4: Life cycle of *Trypanosoma brucei gambiense* (Reproduced from https://www.cdc.gov/dpdx/trypanosomiasisafrican/index.html)

E. *Trypanosoma brucei rhodesiense*

Distribution

It is found in Eastern and Central Africa. The principal vectors are *Glossina morsitans*, *Glossina palpalis* and *Glossina swynnertoni*. It is a zoonotic disease, with the reservoir hosts being game and domestic animals. It is usually transmitted by the vector from human to human. Its morphology, habitat and life cycle are similar to that of *T. brucei gambiense*.

Pathogenesis and Clinical Features

Trypanosoma brucei rhodesiense causes East African sleeping sickness. It is more acute than the Gambian form and appears after an incubation period of 4 weeks. It may end fatally within a year of onset, before the CNS symptoms develop.

Pathological features are similar in both diseases with some variations. Lymphadenitis is less prominent and typical sleeping sickness picture is seldom seen in East African trypanosomiasis.

Prevention and Control

1. Early diagnosis and early treatment of cases
2. Control of tsetse fly population using insecticides
3. Minimize contact with tsetse flies

F. *Trypanosoma cruzi*

Distribution

It is limited to South and Central America and it causes Chagas' disease, which is a zoonotic disease.

Habitat

In human, trypomastigotes are in the blood and amastigotes are in tissue.

Life Cycle of *Trypanosoma cruzi*

Trypanosoma cruzi completes its life cycle in 2 hosts. Human is the vertebrate host.

Its invertebrate host (vector) is reduviid bug or triatomid bug (*Triatoma infestans, Rhodnius prolixus* and *Panstrongylus megistus*). Its reservoir hosts are armadillos, cats, dogs and pigs. The infective stage to human is metacyclic trypomastigotes which are found in faeces of reduviid bugs. The bug defecates while feeding. The parasite enters human at the biting site. Transmission of infection to human and other reservoir hosts takes place when mucus membranes, conjunctiva, or wound on the surface of the skin is contaminated by faeces of the bug containing metacyclic trypomastigotes. Other modes of transmission are blood transfusion, organ transplantation and vertical transmission.

Development in Human

The metacyclic trypomastigotes in faeces of reduviid bug enter human body and invade the myocardium, skeletal muscles, neuroglial cells and cells of the reticuloendothelial system. Inside these cells, they transform into amastigotes form which divide by binary fission. The amastigotes will pass through promastigotes and epimastigotes forms, before becoming trypomastigotes again, which are released into the blood stream and are the infective stage for reduviid bug. No multiplication occurs in this stage.

Development in Reduviid Bugs

Bugs acquire infection by feeding on an infected mammalian host. The trypomastigotes are transformed into epimastigotes in the midgut, from where they migrate to the hindgut and multiply. These, in turn, develop into non-dividing metacyclic trypomastigotes, which are excreted in faeces. The development of *T. cruzi* in the vector takes 8–10 days.

Pathogenesis and Clinical Features

The incubation period of *T. cruzi* in human is 1–2 weeks. The disease manifests in acute and chronic forms.

1. Acute Chagas' disease

Acute phase occurs soon after infection and may last for 1–4 months. It is seen often in children less than 2 years of age. First sign appears within a week after invasion of parasite. 'Chagoma' is the subcutaneous lesion occurring at the site of inoculation.

Inoculation of the parasite in conjunctiva causes unilateral, painless oedema of periorbital tissues known as Romana's sign. This is a classical finding in acute Chagas' disease. There may be generalized infection with fever, lymphadenopathy and hepatosplenomegaly. The patient may die of acute myocarditis and meningoencephalitis.

Usually within 4–8 weeks, acute signs and symptoms resolve. Then, patient progresses into asymptomatic or chronic phase of *T. cruzi* infection.

2. Chronic Chagas' disease

The chronic form is found in adults and older children and becomes apparent years or even decades after the initial infection. In chronic phase, *T. cruzi* produces inflammatory response, cellular destruction and fibrosis of muscles and nerves which can present with cardiac myopathy, megaoesophagus and megacolon.

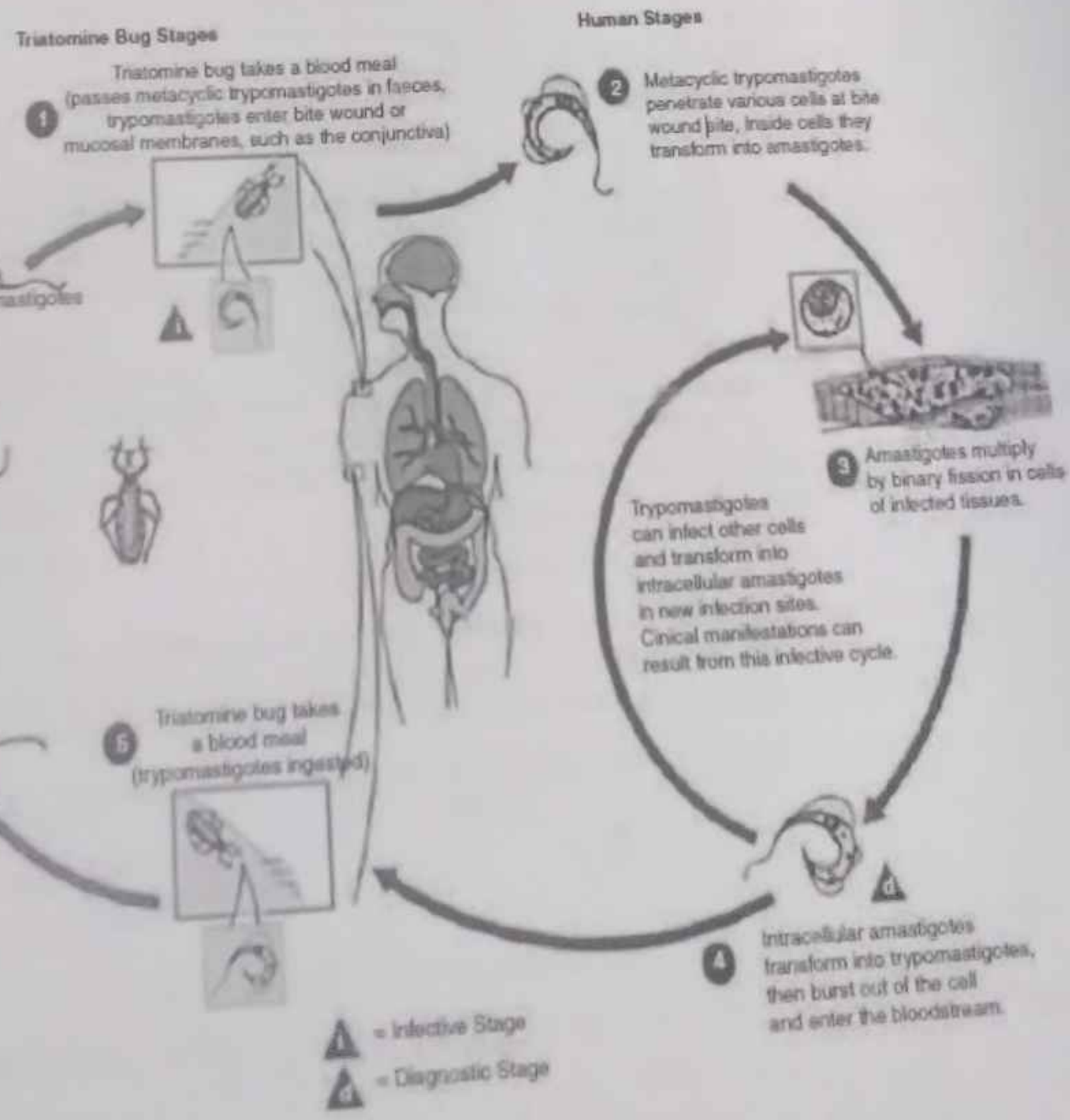

Fig. 5: Life cycle of *Trypanosoma cruzi* (Reproduced from https://www.cdc.gov/dpdx/trypanosomiasisamerican/index.html)

Prevention and Control

1. Insecticide to control the vector bug
2. Insect repellant and use of insect netting
3. Improvement in housing to eliminate breeding places of bugs

G. *Leishmania donovani*

Distribution

It causes visceral leishmaniasis or kala azar which is a major public health problem in many parts of the world.

Habitat

In human, the amastigotes are found in the reticuloendothelial system.

Life Cycle

Leishmania donovani completes its life cycle in 2 hosts. The vertebrate hosts are human, dog and other mammals. Its vector is the female sandfly (*Phlebotomus* species). Promastigote is the infective stage to humans. Humans acquire infection by bite of an infected female sandfly. Incubation period is 2–6 months. Other modes of transmission are congenital transmission, blood transfusion and accidental inoculation in the laboratory.

Pathogenesis and Clinical Features

Leishmania donovani causes visceral leishmaniasis or kala azar. The parasitized macrophages disseminate the infection to all parts of the body. In the reticuloendothelial system, the amastigotes multiply in the fixed macrophages. This causes a marked proliferation and destruction of reticuloendothelial tissue in these organs.

It causes hepatosplenomegaly and lymphadenopathy. The bone marrow is heavily infiltrated with parasitized macrophages causing pancytopenia. Severe anaemia may occur in kala azar, as a result of infiltration of the bone marrow as well as by the increased destruction of erythrocytes due to hypersplenism. Autoantibodies to red blood cells, white blood cells, and platelets may contribute to pancytopenia.

Patients usually present with fever and weight loss.

Some patients with visceral leishmaniasis in endemic areas may develop post kala azar dermal leishmaniasis (PKDL), about a year or 2 after recovery from the systemic illness. PKDL is seen mainly in India and East Africa and is a nonulcerative skin lesion.

Visceral leishmaniasis has emerged as an important opportunistic infection associated with HIV.

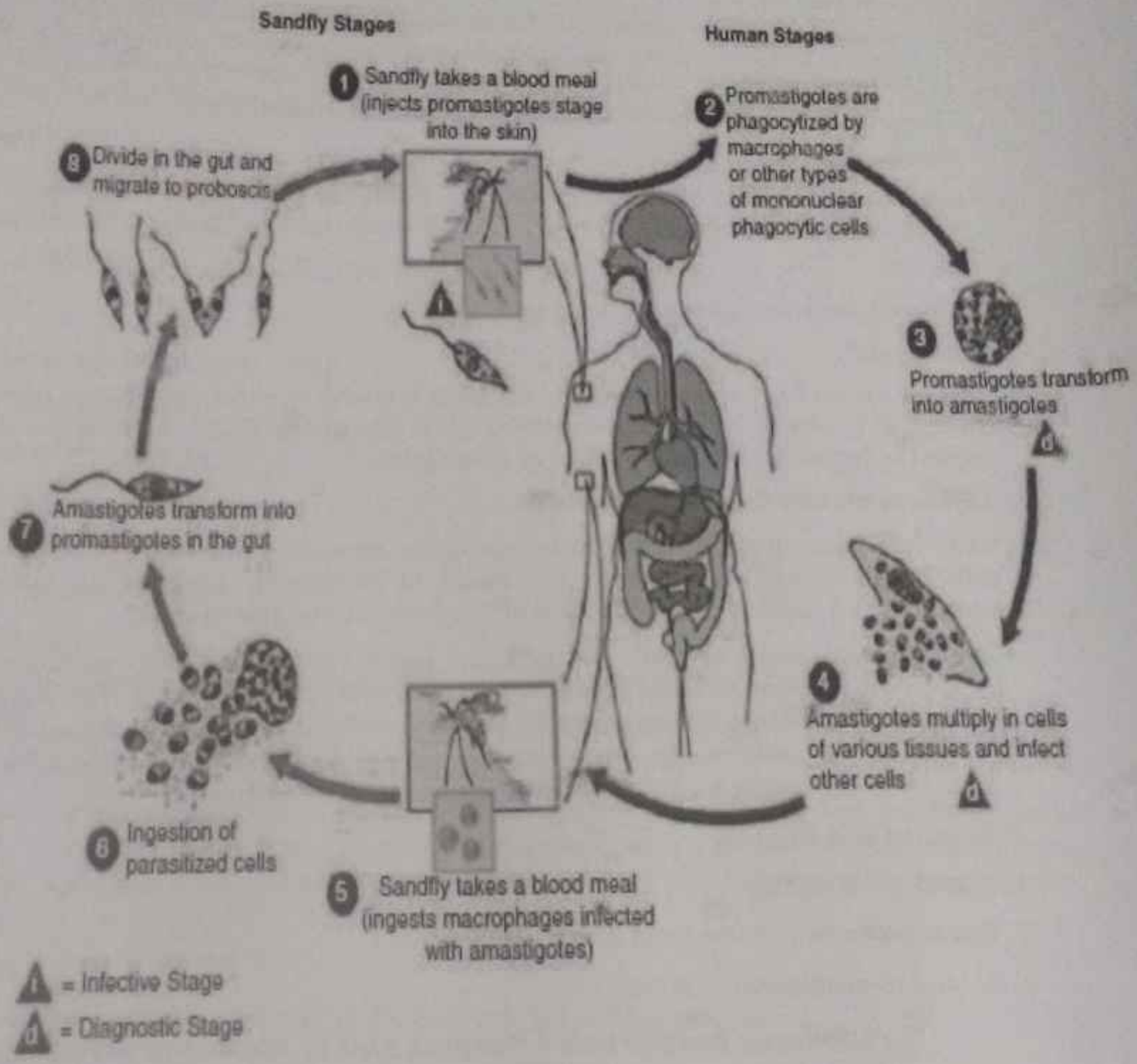

Fig. 6: Life cycle of *Leishmania donovani* (Reproduced from https://www.cdc.gov/dpdx/leishmaniasis/index.html)

Prevention and Control

1. Early detection and treatment of cases
2. Insecticide spraying
3. Control of animal reservoir hosts in cases of zoonotic kala azar
4. Use of protective clothing, bed nets, window mesh or insect repellants

H. *Leishmania tropica* Complex

It includes 3 species:

1. *Leishmania tropica*
2. *Leishmania major*
3. *Leishmania aethiopica*

These species cause old world cutaneous leishmaniasis (oriental sore).

Distribution

Leishmania tropica and *L. major* are found in Middle East, India, Afghanistan, eastern Mediterranean countries and North Africa. *L. aethiopica* occurs in Ethiopia and Kenya.

Habitat

In human, the amastigotes are found in the skin.

Life Cycle

The life cycle of *L. tropica* complex is similar to that of *L. donovani*. Incubation period varies from 2 to 8 months. Mode of transmission is via bite of sandflies from human to human or animal to human by direct inoculation of amastigotes.

Pathogenesis and Clinical Features

Early lesions are papular, followed by ulceration necrosis. Papule and ulcer are the main pathological lesions. Amastigotes are found in histiocytes. There is an inflammatory granulomatous reaction with infiltration of lymphocytes and plasma cells.

They heal over months to years, leaving scars. The anthroponotic urban type causes painless dry ulcerating lesions (oriental sore or Delhi boil) caused by *L. tropica*. The zoonotic rural type causes moist ulcers which are inflamed, often multiple, caused by *L. major*. Lesions due to *L. major* heal more rapidly than *L. tropica*. The non-ulcerative and often diffuse lesions caused by *L. aethiopica* are known as diffuse cutaneous leishmaniasis.

Prevention and Control

1. Insecticide spraying
2. Use of protective clothing and insect repellants
3. Control of mammalian reservoir

Leishmania braziliensis Complex and *L. mexicana* Complex

Distribution

Leishmania braziliensis complex and *L. mexicana* complex cause new world leishmaniasis in Central and South America.

Habitat

In human, amastigotes are found in the naso-oral mucosa.

Life Cycle

The life cycle of *Leishmania* species causing the new world cutaneous and mucocutaneous leishmaniasis is similar to that of *L. donovani*. The infection is transmitted to human from animals by bite of sandfly vectors of genus *Lutzomyia*. Sylvatic rodents and domestic animals are the common sources and reservoir of infection. Direct transmission also occurs from human to human.

Pathogenesis and Clinical Features

Leishmania mexicana complex causes cutaneous leishmaniasis which closely resembles the old world cutaneous leishmaniasis. However, a specific lesion caused by *L. mexicana* is chiclero ulcer which is characterized by ulcerations in pinna. *L. braziliensis* complex causes both cutaneous and mucocutaneous leishmaniasis.

Prevention and Control

1. Insect repellants, insecticide spraying
2. Use protective clothing

Due to sylvatic and rural nature of the disease, control is often difficult.

I. Malaria Parasites

Causative agents of human malaria:

1. *Plasmodium vivax*
2. *Plasmodium falciparum*
3. *Plasmodium malariae*
4. *Plasmodium ovale*
5. *Plasmodium knowlesi*

Distribution

Plasmodium vivax is the predominant malaria parasite in most parts of the world.

P. falciparum is mostly confined to the tropics and subtropics. It is well known to be the fatal form of human malaria and is also known as malignant tertian.

Plasmodium malariae occurs in subtropical and temperate areas. It is less frequently seen than *P. vivax* or *P. falciparum*. *Plasmodium ovale* is confined to West Africa. *Plasmodium knowlesi*, a monkey malaria is distributed in Southeast Asia where the reservoir macaques are prevalent.

Habitat

In human, the parasites are found in the erythrocytes and hepatocytes.

Vectors

Human malaria is transmitted by over 60 species of female *Anopheles* mosquito.

Life Cycle

Malaria parasite completes its life cycle in 2 hosts. Its definitive host is the female *Anopheles* mosquito. Humans are the intermediate host. Modes of transmission are via bite of infected *Anopheles* mosquito, blood transfusion, congenital transmission and shared syringes.

1. Asexual phase (in intermediate host)

The asexual multiplication is known as schizogony. It takes place in the red blood cells (erythrocytic schizogony) and in the liver cells (exoerythrocytic or pre-erythrocytic schizogony).

2. Sexual phase (in definitive host)

Maturation and fertilization of the gametocytes take place in the mosquito, giving rise to a large number of sporozoites (sporogony).

3. Human cycle (schizogony)

Humans acquire infection from the bites of infective female *Anopheles* mosquito.

The sporozoites, which are the infective forms of the parasite, are present in the salivary gland of the mosquito. They are injected into blood capillaries when the mosquito takes a blood meal. The sporozoites circulate in the blood stream and enter the liver parenchymal cells (hepatocytes).

4. Exoerythrocytic cycle

Within 30 min, the sporozoites reach the liver and enter the hepatocytes to initiate the stage of pre-erythrocytic schizogony. In *P. vivax* and *P. ovale*, they form schizonts which persist and remain dormant (hypnozoite). From time to time, the dormant schizonts are reactivated and release merozoites, which go on to infect RBCs causing clinical relapse.

5. Erythrocytic cycle

The merozoites released by pre-erythrocytic schizonts in the liver invade the RBCs and form rings or young trophozoites. The parasite feeds on the haemoglobin.

It does not metabolize haemoglobin completely and leaves behind haemozoin or malaria pigment.

6. Sporogonic cycle

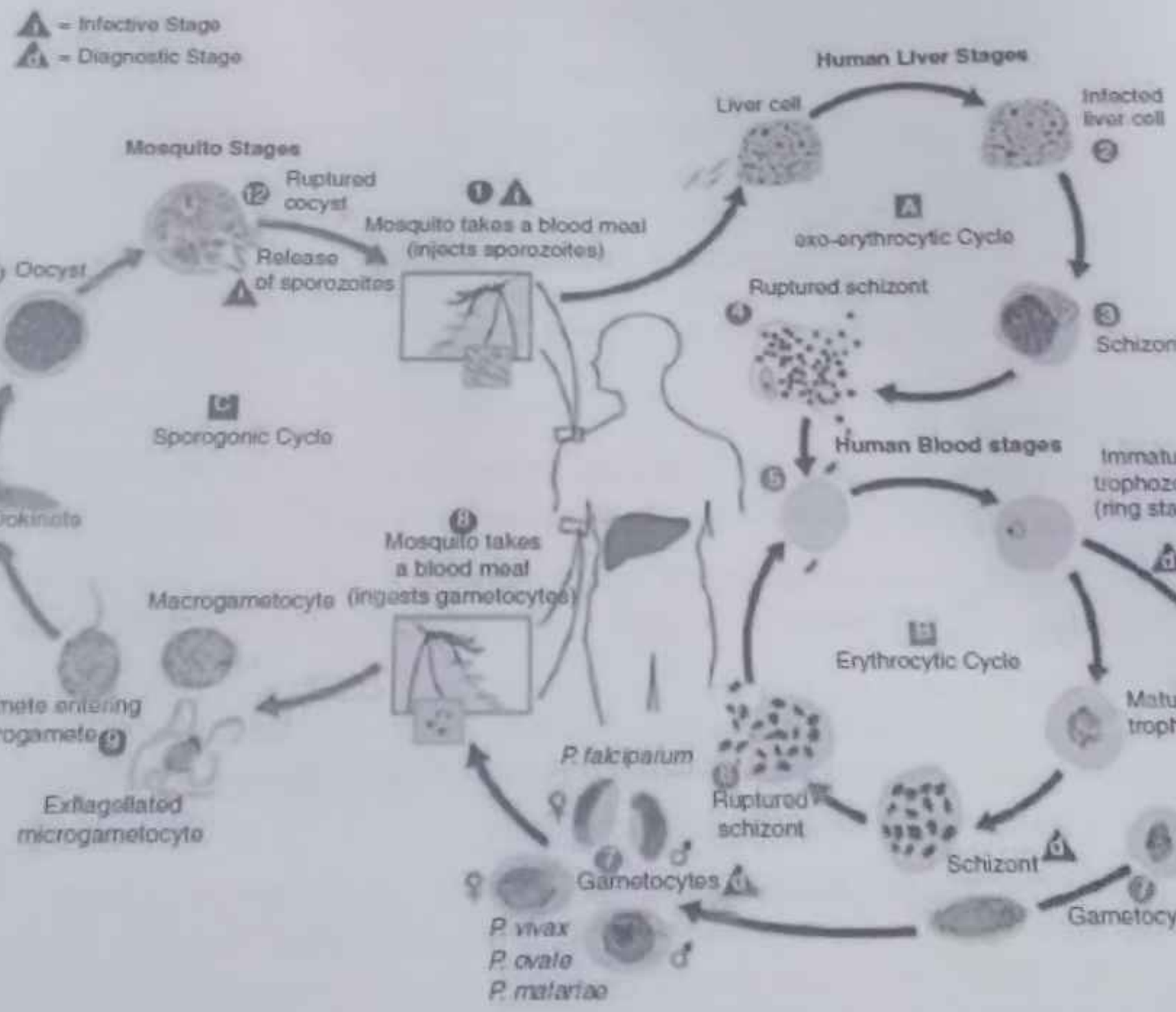

Fig. 7: Life cycle of malaria (Reproduced from https://www.cdc.gov/dpdx/malaria/index.html)

When a female *Anopheles* mosquito ingests parasitized erythrocytes along with its blood meal, the asexual forms of malaria parasite are digested. The gametocytes undergo further development in the midgut (stomach) of mosquito.

The nuclear material and cytoplasm of the male gametocytes divide to produce 8 microgametes (exflagellation). The female gametocyte (macrogamete) is fertilized by the microgamete to form zygote. The zygote develops into a motile form called ookinete. It penetrates the epithelial lining of the mosquito stomach wall and comes to lie beneath the basement membrane. It forms an oocyst within which numerous sporozoites are formed. The mature oocyst ruptures releasing sporozoites into the body cavity, from where some find their way to the salivary glands. The mosquito is now infective and when it feeds on humans, the sporozoites are injected into skin capillaries to initiate infection. The time taken for completion of sporogony in the mosquito is about 1–4 weeks, depending on the species and environmental temperature.

Pathogenesis and Clinical Features

The disease process in malaria occurs due to local or systemic response of the host to parasite antigens. The typical presentation of malaria is periodic bouts of fever with chills and rigors. The febrile paroxysm follows the completion of erythrocytic schizogony when the mature schizont ruptures, releasing red cell fragments, merozoites, malaria pigments and other parasitic debris. It is commonly associated with severe headache, nausea, and vomiting.

Liver is enlarged and congested. Haemozoin pigments are found in the parenchymal cells. Spleen is soft, moderately enlarged, and congested in acute infection. In chronic infection, the spleen undergoes fibrosis and the sinusoids are dilated. Anaemia is caused by rupture of infected red blood cells and other causes of anaemia are by complement-mediated, autoimmune haemolysis and hypersplenism. A decreased erythropoiesis in the bone marrow may also contribute to anaemia.

Complications

Cerebral malaria is the most serious complication of *P. falciparum* infection.

The brain in *P. falciparum* infection is congested. Late stage schizonts of *P. falciparum* secrete a protein on the surface of RBCs to form knobs. This knob produces specific adhesive proteins, which promote adhesion of infected RBCs to other non-infected RBCs and adhere to the receptors on capillary endothelial cells. These sequestrated RBCs cause obstruction of cerebral microvasculature, which results in anoxia, ischaemia and haemorrhage causing cerebral malaria. It is the most common cause of death in malignant malaria. Cerebral malaria is manifested by headache, hyperpyrexia, confusion and finally coma. The pathogenesis of cerebral malaria is likely a multi-factorial process with sequestration, inflammation and endothelial dysfunction in the microvascular of the brain leading to coma.

Pulmonary oedema may develop secondary to parenteral fluid administration or as a result of anoxia affecting the pulmonary microcirculation. Acute respiratory distress syndrome (ARDS) is a complication of severe, complicated falciparum malaria and has also been described in vivax and knowlesi malaria. Non-immune individuals are more prone to develop this condition. There is increased alveolar-capillary permeability resulting in intravascular fluid loss into the lungs. Blackwater fever is sometimes seen in falciparum malaria, in patients who have experienced repeated infections and inadequate treatment with quinine. Clinical manifestations include bilious vomiting and prostration, with passage of dark red or blackish urine (blackwater).The pathogenesis is due to massive intravascular haemolysis caused by anti-erythrocyte antibodies, giving rise to haemoglobinuria.

Complications of blackwater fever include renal failure, acute liver failure, and circulatory collapse.

Acute renal failure may occur in severe falciparum malaria most likely due to tubular necrosis. Acute renal failure has also been described in severe malaria caused by other species. Nephrotic syndrome has been reported in malariae malaria.

Immune complexes may cause structural glomerular damage and the associated nephrotic syndrome.

Tropical splenomegaly syndrome (TSS) or hyper-reactive malarial splenomegaly is a chronic benign condition seen in some adults in endemic areas. This results from abnormal immunological response to malaria and is characterized by splenomegaly, high titres of anti-malaria antibodies and absence of malaria parasites in peripheral blood smears. Hypergammaglobulinemia (IgM) is its other feature. Liver is also enlarged, congested, with marked lymphocytic infiltration. TSS responds to anti-malarial treatment.

Other complications of malaria are hypoglycemia and hyperparasitaemia.

Recrudescence

Recrudescence occurs when parasites persist although the level of parasitaemia is below the fever or microscopic threshold. Erythrocytic schizogony continues in the body at low levels and parasitaemia gradually increase to cross the fever threshold.

New malarial attacks then occur. These malaria attacks appear within 8 weeks after the primary attack. Recrudescence may be due to waning immunity of the host or to antigenic variation and is seen in all human malaria.

Relapse

It is seen in *P. vivax* and *P. ovale* infections, caused by the reactivation of hypnozoite stage in the liver. This leads to initiation of erythrocytic cycles and new attacks of malarial fever. Reactivation of hypnozoite stage usually occurs from 24 weeks to 5 years after the primary attack.

Prevention and Control

1. Chemoprophylaxis

For travellers visiting endemic areas, chemoprophylaxis provides effective protection. The drugs recommended are proguanil, chloroquine or mefloquine weekly or doxycycline daily. Prophylaxis should begin 1 week before travelling and be continued while in the endemic area and for 4–6 weeks after departure from endemic area.

2. Vector Control Strategies

(a) Insecticide residual spraying (IRS): The spraying of the indoor surfaces of house with residual insecticides

(b) Insecticide treated bed nets (ITN)

(c) Use of repellants, protective clothing, mosquito coils and screening of house

3. Anti-larval Measures

J. *Toxoplasma gondii*

Distribution

Toxoplasma gondii is cosmopolitan in distribution, with the widest range of hosts ranging from birds and warm-blooded animals including humans.

Habitat

In human, the parasites are found in the tissue, commonly in the musculoskeletal, brain and eye.

Life Cycle

(1) Oocysts are passed out in faeces of cat. (*2*) The oocysts are ingested by rodents and follow the life cycle to (*3*) form tissue cysts. (*4*) The definitive host (cat) ingests tissue cyst present in intermediate host. (*5*) The oocysts ingested by other intermediate hosts (e.g. sheep and pig) will follow the life cycle and become tissue cysts. (*6*) Humans acquire infection when they ingest uncooked meat containing tissue cysts or ingestion of oocysts via (*7*) drinking contaminated water or eating unwashed fruits and vegetables. (*8*) Humans can also acquire infection via blood transfusion, (*9-10*) organ transplant or (*11*) congenital infection.

Toxoplasma gondii completes its life cycle in 2 hosts. Definitive host is where both sexual and asexual cycles take place. In the intermediate hosts, only asexual cycle occurs. Modes of transmission to human are by eating uncooked or undercooked infected meat containing tissue cysts, ingestion of infective oocysts (through food, water or fingers contaminated with oocysts), intrauterine infection from mother to foetus (congenital toxoplasmosis) and blood transfusion or organ transplantation from infected donors.

Both sexual reproduction (gametogony) and asexual reproduction (schizogony) occur within the epithelial cells of the small intestine of the cat. Cat acquires infection by ingestion of tissue cysts in rats and other animals or by ingestion of oocysts passed in its faeces. The zoites released in the small intestine undergo asexual multiplication (schizogony) leading to formation of merozoites. Some merozoites are carried to extraintestinal tissues or organs and form tissue cysts. Some merozoites transform into male and female gametocytes and initiate sexual cycle (gametogony) with the formation of microgamete and macrogamete. A macrogamete is fertilized by motile microgamete and develops into oocyst which sporulates in the soil after being excreted in faeces of cat. An oocyst with 8 sporozoites is the infective form.

In humans, after ingestion of oocysts or tissue cyst, sporozoites from oocyst and bradyzoites from tissue cysts enter the intestinal mucosa and multiply asexually by endodyogeny to form tachyzoites. Tachyzoites are carried to other extraintestinal organs via circulation to form tissue cysts. Cysts are formed in many organs particularly in muscles and brain as a response to developing host immunity. The dormant bradyzoites inside the cyst may be reactivated in immunosuppressed patients causing clinical illness.

Pathogenesis and Clinical Features

Toxoplasma gondii is an opportunistic parasite. Most human infections are asymptomatic.

Clinical toxoplasmosis may be congenital or acquired and the manifestations depend on the immune status of the infected person. Toxoplasmosis may cause fatal complications in AIDS patients.

Congenital toxoplasmosis occurs when *T. gondii* is transmitted transplacentally from mother with primary *Toxoplasma* infection to foetus. The risk of foetal infection increases with the progress of pregnancy and severity of foetal damage is highest when infection is transmitted in the first trimester of pregnancy. Most infected newborns are asymptomatic at birth and may remain so throughout. Some develop clinical manifestations of toxoplasmosis weeks, months and even years after birth.

The manifestations of congenital toxoplasmosis include chorioretinitis, intracerebral calcifications, psychomotor disturbances and hydrocephalus.

Acquired toxoplasmosis is mostly asymptomatic. The most common manifestations of acute acquired toxoplasmosis are cervical lymphadenopathy, fever, headache, myalgia and splenomegaly. The illness may resemble viral infection and is self-limiting. Rarely but some may present with pneumonitis, myocarditis and meningoencephalitis which can be fatal.

Toxoplasmosis in immuno-compromised patients may be due to reactivation of chronic or latent infection. Involvement of the brain is most common, causing toxoplasmic encephalitis. Symptoms may include headache, confusion, ataxia, hemiparesis and seizures.

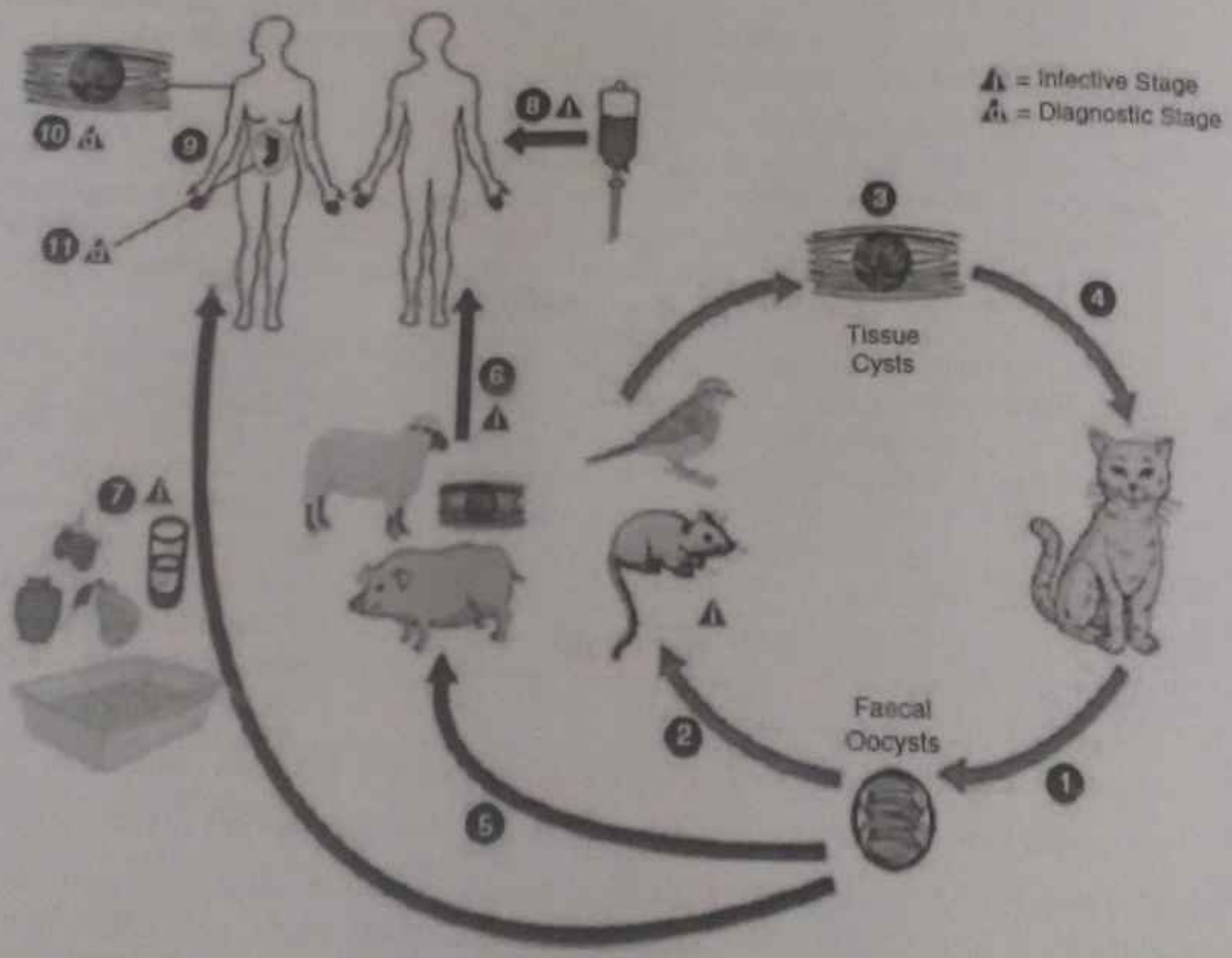

Fig. 8: Life cycle of *Toxoplasma gondii* (Reproduced from https://www.cdc.gov/dpdx/toxoplasmosis/index.html)

Prevention and Control

1. Individuals at risk, particularly pregnant women, children and immuno-compromised persons should avoid contact with cat and its faeces

2. Proper cooking of meat
3. Proper washing of hands, washing of vegetables and fruits before eating
4. Screening for *T. gondii* antibody on all blood donors
5. Pet cats should be fed with canned or cooked food
6. Cats' faeces should be discarded daily

Currently, there is no effective vaccine available for humans.

K. Cryptosporidium parvum (Crypto)

Distribution

It has a ubiquitous distribution. Two species, *Cryptosporidium hominis* (humans are the only natural host) and *C. parvum* (infects various species of mammals) can cause human infections. *Cryptosporidium* causes intractable diarrhoea in AIDS patients and immuno-compromised persons.

Habitat

Cryptosporidium parvum inhabits the small intestine. It may also be found in stomach, large intestine and lungs.

Life Cycle

(*1*) Thick-walled sporulated oocysts are passed out in faeces of infected host. (*2–3*) Humans acquire infection via ingestion of contaminated water and food.

The parasite completes its life cycle, sexual and asexual phases in a single host.

Besides humans, the parasite can infect other animals. Reservoir hosts include mammals, birds and reptiles. Sporulated oocyst is the infective stage to humans.

Mode of transmission is through ingestion of food and water contaminated with oocysts or by direct contact with infected animals.

Pathogenesis and Clinical Features

Clinical manifestations of cryptosporidiosis (Crypto) depend on the immune status of the host. Infection in immuno-competent persons may be asymptomatic or cause self-limiting watery diarrhoea, nausea, abdominal cramping and weight loss. It can also cause traveller's diarrhoea, as well as waterborne outbreaks. In immuno-compromised hosts and AIDS patients, diarrhoea can be profuse, chronic and persistent causing severe fluid and electrolyte depletion and weight loss. The small intestine may show villous atrophy, crypt hyperplasia and lymphocyte infiltration. Incubation period is 2–14 days.

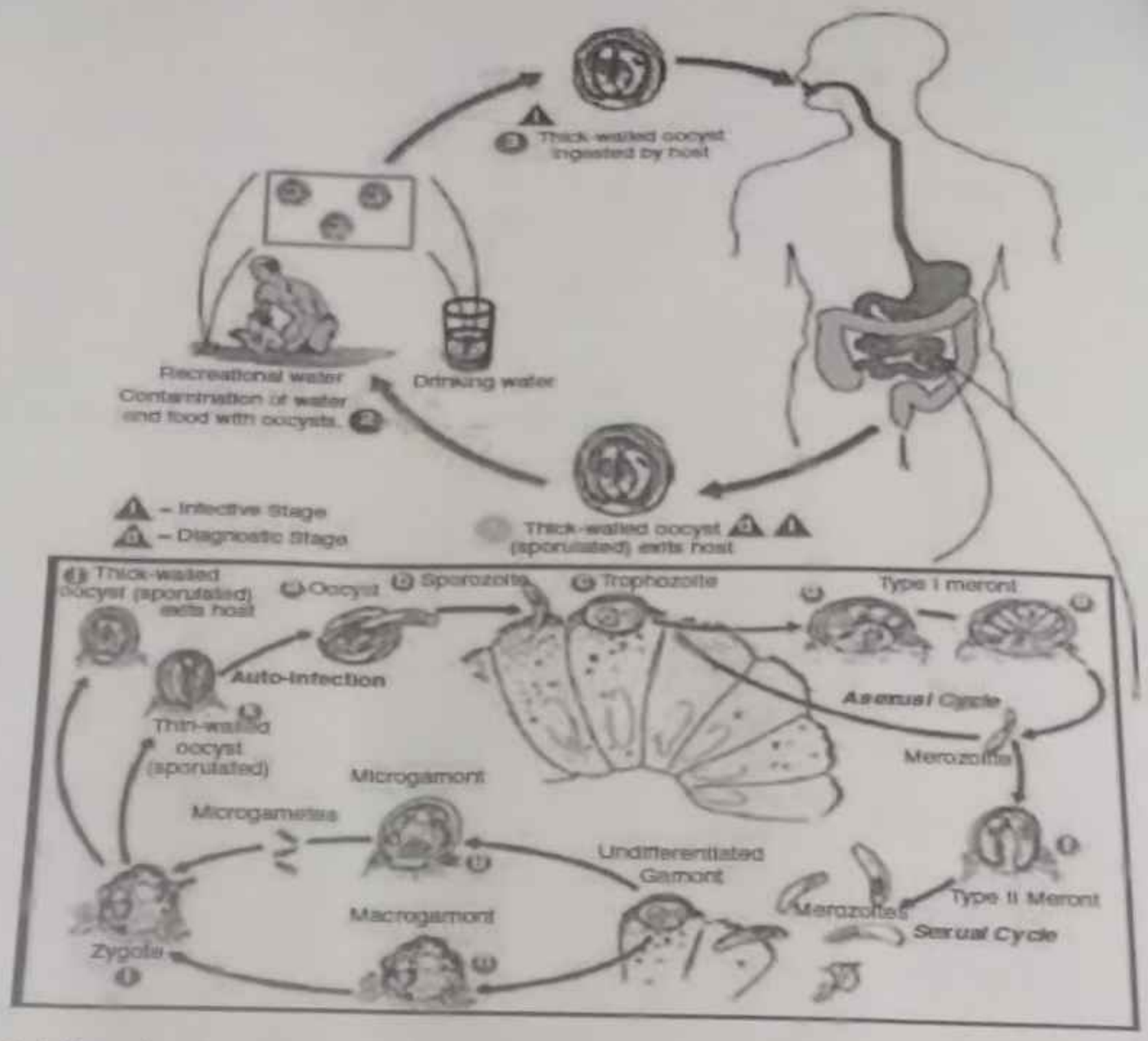

Fig. 9: Life cycle of Cryptosporidium parvum (Reproduced from https://www.cdc.gov/dpdx/cryptosporidiosis/index.html)

Prevention and Control

1. Proper faecal disposal
2. Personal hygiene
3. Boiling of drinking water
4. Filtration of drinking water
5. Wash fruits and vegetables with clean water before eating
6. Health education

L. *Balantidium coli*

Balantidium coli is the largest intestinal protozoa of human and it exists in 2 stages (trophozoite and cyst).

Distribution

It is distributed worldwide.

Habitat

Balantidium coli resides in the large intestine of humans, pigs and non-human primates.

Life Cycle

(*1*) Cyst is passed out in the stool of infected human. (*2*) Humans acquire infection by ingesting cyst through contaminated food or water. (*3*) In the intestine, the cyst undergoes excystation to release trophozoite. (*4*) The trophozoites divide by binary fission. (*5*) It encysts as it passes down the colon and is excreted in faeces.

Trophozoites can be found in loose stools.

Balantidium coli completes its life cycle in 1 host only. Infection is acquired from pigs and other animal reservoirs or from human carriers. Pig is its reservoir host; hence, Balantidiasis is a zoonotic infection (zoonosis).

Pathogenesis and Clinical Features

Clinical disease results when the trophozoites burrow into the intestinal mucosa and initiate inflammatory reaction. This leads to mucosal ulcers, resembling lesions in amoebiasis. Unlike *E. histolytica, B. coli* infection does not involve extra intestinal sites.

Most infections are asymptomatic. Symptomatic disease resembles intestinal amoebiasis causing diarrhoea or dysentery with abdominal colic, nausea and vomiting.

Occasionally, intestinal perforation and peritonitis may occur.

Prevention and Control

1. Boil drinking water and eat cooked food
2. Personal hygiene
3. Proper sanitation
4. Treat infected pigs
5. Treat positive cases

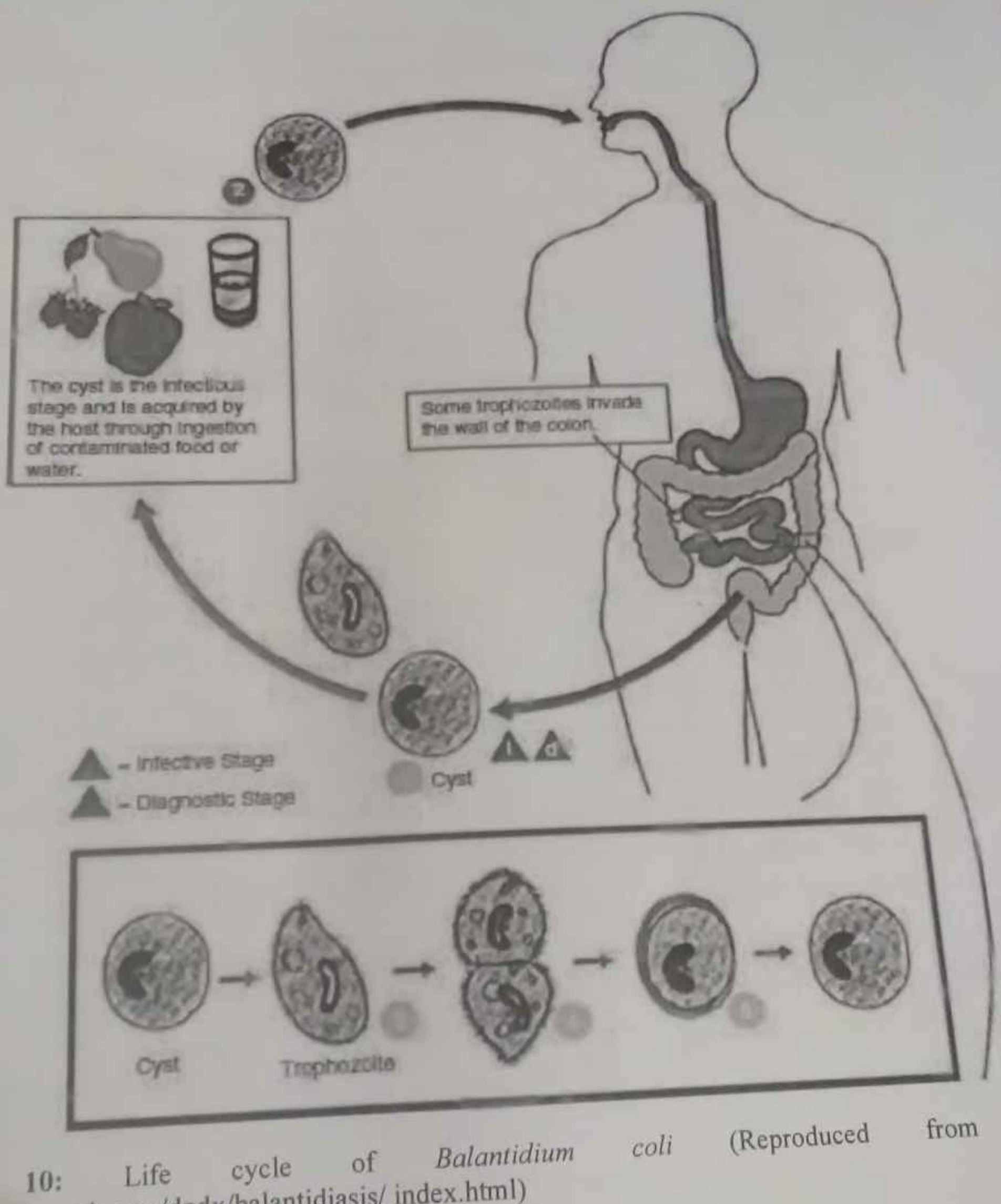

Fig. 10: Life cycle of *Balantidium coli* (Reproduced from https://www.cdc.gov/dpdx/balantidiasis/ index.html)