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CHAPTER TWO
BLOOD AND TISSUE PROTOZOA

SECTIONS

- Part 1: Trypanosomiasis and Leishmaniasis
- Part 2: Malaria
- Part 3: Other blood and tissue protozoa

TEACHING OBJECTIVES

Epidemiology, morbidity and mortality
Morphology of the organism
Life cycle, hosts and vectors
Disease, symptoms, pathogenesis and site
Diagnosis
Prevention and control


Incidence of *T. brucei gambiense* sleeping

PARASITOLOGY - CHAPTER TWO

BLOOD AND TISSUE PROTOZOA

PART 1

TRYPANOSOMIASIS AND LEISHMANIASIS

Dr Abdul Ghaffar
Professor Emeritus
University of South Carolina

Blood protozoa of major clinical significance include members of genera:

- Trypanosoma (*T. brucei* and *T. cruzi*)
- Leishmania (*L. donovani*, *L. tropica* and *L. braziliensis*)
- Plasmodium (*P. falciparum*, *P. ovale*, *P. malariae* and *P. vivax*)
- Toxoplasma *(T. gondii)*
- Babesia (*B. microti*)

TRYPANOSOMIASIS

African trypanosomiasis (Sleeping sickness)

Etiology

There are two clinical forms of African trypanosomiasis:

- A slowly developing (chronic) disease, West African Sleeping Sickness, caused by *Trypanosoma brucei gambiense*
- A rapidly progressing (acute) disease, East African Sleeping Sickness, caused by *T. brucei rhodesiense*.

Epidemiology

T. b. gambiense is found in the western and central regions of Africa, whereas *T. b. rhodesiense* is restricted to the eastern third of the continent (figure 2E). Most cases of sleeping sickness (98%) are the chronic West African form but the number of new cases have fallen in recent years from 27,862 in 1999 to 6,228 in 2013 (78% reduction). At the same time, the number of new cases of the acute East African form has fallen from 619 to 86 over the same time period (86% fall).

Most East African Sleeping Sickness occurs in 13 countries with the highest incidence in Zambia, Malawi, Uganda and Tanzania. Cases of West African Sleeping Sickness are documented annually in 24 countries with most in The Central African Republic, The Democratic Republic of the Congo, northern Uganda, Chad, Angola and Sudan. Thirty five million people and 25 million cattle are at risk. Regional epidemics of the disease have been the cause of major health and economic disasters.

Occasionally, a traveler to endemic counties contracts Sleeping Sickness. About one case of East

sickness 2013
WHO

Incidence of *T. brucei rhodesiense* sleeping sickness 2013
WHO

African Sleeping Sickness is imported into the United States each year, usually in someone who has recently travelled to the region. In the case, of West African Sleeping Sickness, most infections diagnosed in the United States are in people who have immigrated from an endemic region. These are very rare.

Vector and Reservoir

In both West African and East African Sleeping Sickness, the vector is the Tsetse Fly (*Glossina* sp) and both sexes of the fly can transmit the parasite in their saliva. In endemic areas, however, only a few flies are carrieers. The animal reservoir for *T. b. gambiense* is other humans but domestic animals can also carry the parasite. The reservoirs for *T. b. rhodesiense* are wild animals and cattle.

Very occasionally, an unborn baby may be infected from an infected mother. It is also possible that people have been very rarely infected as a result of blood transfusions.

Morphology

T. b. gambiense and *T. b. rhodesiense* are similar in appearance: The organism measures 10 - 30 micrometers x 1-3 micrometers. It has a single central nucleus and a single flagellum originating at the kinetoplast and joined to the body by an undulating membrane (Figure 2A-D). The outer surface of the organism is densely coated with a layer of glycoprotein, the variable surface glycoprotein (VSG).

Figure 1A

During a blood meal on the mammalian host, an infected tsetse fly (genus *Glossina*) injects metacyclic trypomastigotes into skin tissue. The parasites enter the lymphatic system and pass into the bloodstream ❶. Inside the host, they transform into bloodstream trypomastigotes ❷, are carried to other sites throughout the body, reach other blood fluids (e.g., lymph, spinal fluid), and continue the replication by binary fission ❸. The entire life cycle of African Trypanosomes is represented by extracellular stages. The tsetse fly becomes infected with bloodstream trypomastigotes when taking a blood meal on an infected mammalian host (❹, ❺). In the fly's midgut, the parasites transform into procyclic trypomastigotes, multiply by binary fission ❻, leave the midgut, and transform into epimastigotes ❼. The epimastigotes reach the fly's salivary glands and continue multiplication by binary fission ❽. The cycle in the fly takes approximately 3 weeks. Humans are the main reservoir for *Trypanosoma brucei gambiense*, but this species can also be found in animals. Wild game animals are the main reservoir of *T. b. rhodesiense*.
CDC DPDx Parasite Image Library

Figure 1B

Forms of *Trypansoma brucei* observed in the tsetse fly and in the human blood stream
T. brucei is transmitted by tsetse flies of the genus Glossina. Parasites are ingested by the fly when it takes a blood meal on an infected mammal. The parasites multiply in the fly, going through several developmental stages in the insect gut and salivary glands (procyclic trypanosomes, epimastigotes, metacyclic trypanosomes). The cycle in the fly takes approximately 3 weeks. When the fly bites another mammal, metacyclic trypanosomes are inoculated, and multiply in the host's blood and extracellular fluids such as spinal fluid. Humans are the main reservoir for *T. b. gambiense*, but this species can also be found in animals. Wild game animals are the main reservoir of *T. b. rhodesiense*.

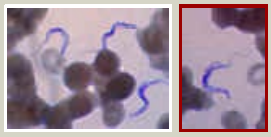


Figure 2A

Two areas from a blood smear from a patient with African trypanosomiasis. Thin blood smear stained with Giemsa. Typical trypomastigote stages (the only stages found in patients), with a posterior kinetoplast, a centrally located nucleus, an undulating membrane, and an anterior flagellum. The two Trypanosoma brucei species that cause human trypanosomiasis, *T. b. gambiense* and *T. b. rhodesiense*, are undistinguishable morphologically. The trypanosomes length range is 14-33 µm
CDC DPDx Parasite Image Library

Figure 2B

Blood smear from a patient (a U.S. traveler) with *Trypanosoma brucei rhodesiense*. A dividing parasite is seen at the right. Dividing forms are seen in African trypanosomiasis, but not in American trypanosomiasis (Chagas' disease)
CDC DPDx Parasite Image Library

Figure 2D

Structure of *Trypanosoma brucei*

Figure 2E
Distribution of West African or Gambian Sleeping Sickness and East African or Rhodesian Sleeping Sickness

Figure 2C
Blood smear from a patient with *Trypanosoma brucei gambiense*.
CDC - Image contributed by Pr. J. Le Bras, Hôpital Bichat - Claude Bernard, Paris, France.

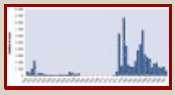


Figure 2F Reported number of cases of African trypanosomiasis in Uganda, 1939-1998 WHO

Between 1962 and 1975, no cases were reported. Increased reporting during 1977 to 1983 reflected an epidemic of rhodesiense sleeping sickness in Busuga (south-eastern Uganda). However the increases shown between 1986 and 1992 corresponded to both the resumption of systematic population screening for gambiense sleeping sickness in the western part of the country and to a resurgence of rhodesiense sleeping sickness in Busuga.

Figure 3 Tsetse fly. The vector of African trypanosomiasis © OhioState University, College of Biology

Life cycle
The infective, metacyclic form of the trypanosome is injected into the primary host during a bite by the vector, the tsetse fly (figure 3). The organism transforms into a dividing trypanosomal (trypomastigote) blood form (figure 1B) as it enters the draining lymphatic and blood stream. The trypanosomal form enters the vector during the blood meal and travels through the alimentary canal to the salivary gland where it proliferates as the crithidial form (epimastigote) and matures to infectious metacyclic forms (Figure 1B). Trypomastigotes can traverse the walls of blood and lymph capillaries into the connective tissues and, at a later stage, cross the choroid plexus into the brain and cerebrospinal fluid. The organism can be transmitted through blood transfusion.

Symptoms
The clinical features of Gambian and Rhodesian disease are the same, however they vary in severity and duration. Rhodesian disease progresses more rapidly and the symptoms are often more pronounced. The symptoms of the two diseases are also more pronounced in Caucasians than in the local African population. Classically, the progression of African trypanosomiasis can be divided into three stages: the bite reaction (chancre), parasitemia (blood and lymphoid tissues), and CNS stage.

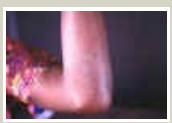
Bite reaction
A non-pustular, painful, itchy chancre (Figure 4 A and B) forms 1-3 weeks after the bite and lasts 1-2 weeks. It leaves no scar.

Parasitemia
Parasitemia and lymph node invasion is marked by attacks of fever which starts 2-3 weeks after the bite and is accompanied by malaise, lassitude, insomnia headache and lymphadenopathy and edema (figure 4E). Painful sensitivity of palms and ulnar region to pressure (Kerandel's sign) may develop in some Caucasians. Very characteristic of Gambian disease is visible enlargement of the glands of the posterior cervical region (Winterbottom's sign) (Figure 4C). Febrile episodes may last few months as in Rhodesian disease or several years as in Gambian disease. Parasitemia is more prominent during the acute stage than during the recurrence episodes.

CNS Stage
The late or CNS stage is marked by changes in character and personality. They include lack of interest and disinclination to work, avoidance of acquaintances, morose and melancholic attitude alternating with exaltation, mental retardation and lethargy, low and tremulous speech, tremors of tongue and limbs, slow and shuffling gait, altered reflexes, etc. Males become impotent. There is a slow progressive involvement of cardiac tissue. The later stages are characterized by drowsiness and uncontrollable urge to sleep. The terminal stage is marked by wasting and emaciation. Death results from coma, intercurrent infection or cardiac failure (figure 5).

In the case of *T. b. rhodesiense* disease, death occurs within months of CNS involvement whereas *T. b. gambiense*-caused disease is slower and, without treatment, death occurs within 3 to 7 years.

Figure 4A



The partially healed chancre on the arm of a female patient in a ward of a rural clinic.
WHO/TDR/Crump

Figure 4B
The leg of a teenage girl who has sleeping sickness, showing the chancre at the site of the tsetse fly bite
WHO/TDR/Kuzoe

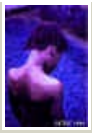
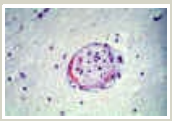
 Figure 4C
Winterbottoms sign CDC
DPDx Parasite Image Library

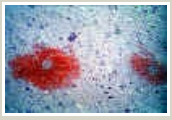
 Figure 4D
Neurological complications can occur as a result of infection and, as seen here, patients may be immobilised for their own safety.
WHO/TDR/Kuzoe

 Figure 4E
A male sleeping sickness patient with myxoedema.
WHO/TDR/Kuzoe

 Figure 5A
The damaged brain of a patient who had died from African trypanosomiasis (or sleeping sickness).
WHO/TDR/Kuzoe

 Figure 5B
A young boy with advanced African trypanosomiasis (or sleeping sickness) exhibiting marked wasting and skin damage caused as a result of the intense itching which can accompany late-stage disease.
WHO/TDR/Kuzoe

 Figure 5C
Neuropathology of Human African Trypanosomiasis: Acute haemorrhagic leucoencephalopathy (AHL): This slide shows very delicate fibrinoid necrosis in the wall of a small artery in the thalamus.
Produced by the Dept. of Neuropathology, Southern General Hospital, Glasgow).

 Figure 5D
Neuropathology of Human African Trypanosomiasis: Acute haemorrhagic leucoencephalopathy: This slide shows the foci of haemorrhage around small blood vessels. Produced by the Dept. of Neuropathology, Southern General Hospital, Glasgow).

The clinical features of Rhodesian disease are similar but briefer and more acute. The acuteness and severity of disease do not allow typical sleeping sickness. Death is due to cardiac failure within 6-9 months.

Pathology and Immunology
An exact pathogenesis of sleeping sickness is not known, although immune complexes and inflammation have been suspected to be the mechanism of damage to tissues. The immune response against the organism does help to eliminate the parasite but it is not protective, since the parasite has a unique ability of altering its surface antigens, the Variable Surface Glycoproteins (VSGs) - see the chapter on Molecular Biology of Trypanosomes. Consequently, there is a cyclic fluctuation in the number of parasites in blood and lymphatic fluids and each wave of parasite represents a different antigenic variant. The parasite causes polyclonal expansion of B lymphocytes and plasma cells and an increase in total IgM concentration. It stimulates the reticuloendothelial function. It also causes severe depression of cell mediated and humoral immunity to other antigens.

Diagnosis
Detection of parasite by microscopy in the bloodstream, lymph secretions and enlarged lymph node aspirate provides a definitive diagnosis in early (acute) stages. Classically, a lymph node (posterior cervical node) aspirate is used as it may be difficult to detect a low parasitemia in the blood. The parasite in blood can be concentrated by centrifugation or by the use of anionic support media. Cerebrospinal fluid must always be examined for organisms. Immuno-serology (enzyme-linked immune assay, immunofluorescence) may be indicative but does not provide definite diagnosis.

Treatment and Control

The blood stage of African trypanosomiasis can be treated with reasonable success according to the stage that the disease has reached. Pentamidine isethionate is used for first stage *T. b. gambiense* infection. Other drugs available for use are suramin, melarsoprol, eflornithine or nifurtimox. Suramin has been reported also to be effective in prophylaxis although they may mask early infection and thus increase the risk of CNS disease. Cases with CNS involvement should be treated with melarsoprol, an organic arsenic compound; however this drug has been linked to fatal encephalopathy.

The most effective means of prevention is to avoid contact with tsetse flies. Vector eradication is usually impractical due to the vast area involved. Immunization has not been effective due to antigenic variation.

Treatment of African trypanasomiasis (CDC)

American trypanosomiasis (Chagas' disease)

Etiology

Chagas' disease is caused by the protozoan hemoflagellate, *Trypanosoma cruzi*.

Epidemiology

American trypanosomiasis, also known as Chagas' disease, is scattered irregularly in Central and South America, stretching from parts of Mexico to Argentina (figure 6). It is estimated that over 8 million people are infected by the parasite and 50 million are at risk. About 50,000 people die each year from the disease.

Figure 6 Chaga's disease: Countries in which American trypanosomiasis is endemic. WHO

CDC estimates that there are as many as 300,000 infected people in the United States and cases cases have been reported in Texas, California and Maryland. Most of these infections were acquired in countries of Central and South America where the disease is endemic and vector-borne cases are very rare..

Morphology

Depending on its host environment, the organism occurs in three different forms (Figure 7 and 9B).

- The trypanosomal (trypomastigote) form (figure 7A), found in mammalian blood, is 15 to 20 microns long and morphologically similar to African trypanosomes.
- The crithidial (epimastigote) form (figure 7B) is found in the insect intestine.
- The leishmanial (amastigote) form (figure 7C), found intracellularly or in pseudocysts in mammalian viscera (particularly in myocardium and brain), is round or oval in shape, measures 2-4 microns and lacks a prominent flagellum.

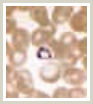


Figure 7A *Trypanosoma cruzi*, trypomastigote form, in a blood smear (Giemsa stain) CDC DPDx Parasite Image Library

Life cycle

The organism is transmitted to mammalian host by many species of kissing or triatomine (riduvid) bug (figure 8), most prominently by *Triatoma infestans*, *Triatoma sordida*, *Panstrongylus megistus* and *Rhodnius prolixus*.

Transmission takes place during the feeding of the bug which normally bites in the facial area (hence the name, kissing bug) and has the habit of defecating during feeding. The metacyclic trypamastigotes, contained in the fecal material, gain access to the mammalian tissue through the wound which is often rubbed by the individual that is bitten. Subsequently, they enter various cells, including macrophages, where they differentiate into amastigotes and multiply by binary fission. The amastigotes differentiate into non-replicating trypomastigotes and the cells rupture to release them into the bloodstream. Additional host cells, of a variety of types, can become infected and the trypomastigotes once again form amastigotes inside these cells. Uninfected insect vectors acquire the organism when they feed on infected animals or people containing trypomastigotes circulating in their blood. Inside the alimentary tract of the insect vector, the trypomastigotes differentiate to form epimastigotes and divide longitudinally in the mid and hindgut of the insect where they develop into infective metacyclic trypomastigotes (figure 9C).

Figure 7B *Trypanosoma cruzi,* crithidia. CDC DPDx Parasite Image Library

Transmission may also occur between humans by

- Blood transfusion
- Mother to baby via a transplacental route
- Organ transplantation
- Very rarely via contaminated food or drink

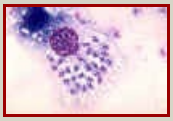


Figure 7C. *Trypanosoma cruzi*. Leishmanial form CDC DPDx Parasite Image Library

More than one hundred mammalian species of wild and domestic animals including cattle, pigs, cats, dogs, rats, armadillo, raccoon and opossum are naturally infected by *T. cruzi* and serve as a reservoir.

Symptoms

Chagas' disease can be divided into three stages: the primary lesion, the acute stage, and the chronic stage. The primary lesion, chagoma, appearing at the site of infection, within a few hours of a bite, consists of a slightly raised, flat non-purulent erythematous plaque surrounded by a variable area of hard edema. It is usually found on the face, eyelids, cheek, lips or the conjunctiva, but may occur on the abdomen or limbs. When the primary chagoma is on the face, there is an enlargement of the pre-

Figure 8
Riduvid bug, the vector of American trypanosomiasis


Figure 9A
Ramana's sign: unilateral conjunctivitis and orbital edema


Figure 9B
Megacolon in Chaga's disease

and post- auricular and the submaxillary glands on the side of the bite. Infection in the eyelid, resulting in a unilateral conjunctivitis and orbital edema (Ramana's sign) (figure 9A), is the commonest finding.

Acute Stage: The acute stage appears 7-14 days after infection. It is characterized by restlessness, sleeplessness, malaise, increasing exhaustion, chills, fever and bone and muscle pains. Other manifestations of the acute phase are cervical, axillary and iliac adenitis, hepatomegaly, erythematous rash and acute myocarditis. There is a general edematous reaction associated with lymphadenopathy. Diffuse myocarditis, sometimes accompanied by serious pericarditis and endocarditis, is very frequent during the initial stage of the disease. In children, Chagas' disease may cause meningo-encephalitis and coma. Death occurs in 5-10 percent of infants. Hematologic examination reveals lymphocytosis and parasitemia.

Chronic Stage: The acute stage is usually not recognized and often resolves with little or no immediate damage and the infected host remains an asymptomatic carrier. An unknown proportion (guessed at 10-20%) of victims develop a chronic disease. They alternate between asymptomatic remission periods and relapses characterized by symptoms seen in the acute phase. Cardiac arrhythmia is common. The chronic disease results in an abnormal function of the hollow organs, particularly the heart, esophagus and colon.

The cardiac changes include myocardial insufficiency, cardiomegaly, disturbances of atrio-ventricular conduction and the Adams-Stoke syndrome. Disturbances of peristalsis lead to megaesophagus and megacolon (figure 9B).

Pathology and Immunology

The pathological effects of acute phase Chagas' disease largely result from direct damage to infected cells. In later stages, the destruction of the autonomic nerve ganglions may be of significance. Immune mechanisms, both cell mediated and humoral, involving reaction to the organism and to autologous tissues have been implicated in pathogenesis.

T. cruzi stimulates both humoral and cell mediated immune responses. Antibody has been shown to lyze the organism, but rarely causes eradication of the organism, perhaps due to its intracellular localization. Cell mediated immunity may be of significant value. While normal macrophages are targeted by the organism for growth, activated macrophages can kill the organism. Unlike *T. brucei*, *T. cruzi* does not alter its antigenic coat. Antibodies directed against heart and muscle cells have also been detected in infected patients leading to the supposition that there is an element of autoimmune reaction in the pathogenesis of Chagas' disease. The infection causes severe depression of both cell mediated and humoral immune responses. Immunosuppression may be due to induction of suppressor T-cells and/or overstimulation of macrophages.

Diagnosis

Clinical diagnosis is usually easy among children in endemic areas. Cardiac dilation, megacolon and megaesophagus in individuals from endemic areas indicate present or former infection. Definitive diagnosis requires the demonstration of trypanosomes by microscopy or biological tests (in the insect or mice). Antibodies are often detectable by complement fixation or immunofluorescence and provide presumptive diagnosis.

Treatment and Control

There is no curative therapy available. Most drugs are either ineffective or highly toxic. Recently two experimental drugs, Benznidazol and Nifurtimox have been used with promising results in the acute stage of the disease, however their side effects limit their prolonged use in chronic cases.

Control measures are limited to those that reduce contact between the vectors and man. Attempts to develop a vaccine have not been very successful, although they may be feasible.

Treatment of American trypanasomiasis (Chagas disease) (CDC)


Figure 9C
An infected triatomine insect vector (or “kissing” bug) takes a blood meal and releases trypomastigotes in its feces near the site of the bite wound. Trypomastigotes enter the host through the wound or through intact mucosal membranes, such as the conjunctiva ❶. Common triatomine vector species for trypanosomiasis belong to the genera *Triatoma*, *Rhodinius*, and *Panstrongylus*. Inside the host, the trypomastigotes invade cells, where they differentiate into intracellular amastigotes ❷. The amastigotes multiply by binary fission ❸ and differentiate into trypomastigotes, and then are released into the circulation as bloodstream trypomastigotes ❹. Trypomastigotes infect cells from a variety of tissues and transform into intracellular amastigotes in new infection sites. Clinical manifestations can result from this infective cycle. The bloodstream trypomastigotes do not replicate (different from the African trypanosomes). Replication resumes only when the parasites enter another cell or are ingested by another vector. The “kissing” bug becomes infected by feeding on human or animal blood that contains circulating parasites ❺. The ingested trypomastigotes transform into epimastigotes in the vector’s midgut ❻. The parasites multiply and differentiate in the midgut ❼ and differentiate into infective metacyclic trypomastigotes in the hindgut ❽.

Trypanosoma cruzi can also be transmitted through blood transfusions, organ transplantation, transplacentally, and in laboratory accidents.
CDC DPDx Parasite Image Library

Guest article

New approaches for vaccines against a neglected disease – leishmaniasis

LEISHMANIASIS

Etiology

More than 20 species of Leishmania are pathogenic for man:

- *L. donovani* causes visceral leishmaniasis (Kala-azar, black disease, dumdum fever)
- *L. tropica* (*L. t. major, L. t. minor* and *L. ethiopica*) causes cutaneous leishmaniasis (oriental sore, Delhi ulcer, Aleppo, Delhi or Baghdad boil)
- *L. braziliensis* (also, *L. mexicana* and *L. peruviana*) are etiologic agents of mucocutaneous leishmaniasis (espundia, Uta, chiclero ulcer)

Epidemiology

Leishmaniasis is prevalent in more than 90 countries world wide: ranging from south east Asia, Indo-Pakistan, Mediterranean area of southern Europe, north and central Africa, and south and central America. A few cases of cutaneous leishmaniasis have been found in the United States (Texas and Oklahoma). These have been acquired during travel to endemic areas

The annual number of cases worldwide have been estimated to be:

- Cutaneous leishmaniasis: Between 700,000 and 1.2 million
- Visceral leishmaniasis: Between 200,000 and 400,000

Morphology

Amastigote (leishmanial form) is oval and measures 2-5 microns by 1 - 3 microns (figure 10A-D), whereas the leptomonad measures 14 - 20 microns by 1.5 - 4 microns, a similar size to trypanosomes (Figure 10E).


Incidence of cutaneous Leishmaniasis 2012
WHO


Incidence of visceral Leishmaniasis 2012
WHO

Figure 10 A B C


A


B


C

Leishmania tropica amastigotes from a skin touch preparation. In A, a still intact macrophage is practically filled with amastigotes, several of which have clearly visible a nucleus and a kinetoplast (arrows); in B, amastigotes are being freed from a rupturing macrophage. Patient with history of travel to Egypt, Africa, and the Middle East. Culture in NNN medium followed by isoenzyme analysis identified the species as L. tropica minor. CDC


Figure 10D

Leishmania mexicana mexicana in skin biopsy. Hematoxylin and eosin stain. The amastigotes are lining the wall of two vacuoles, a typical arrangement. The species identification was derived from culture followed by isoenzyme analysis. 26-year old man from Austin, Texas, with a lesion on his left arm. CDC DPDx Parasite Image Library


Figure 10E

*Leishmania donovan*i, leptomonad forms.
CDC DPDx Parasite Image Library

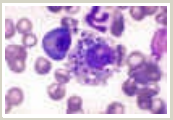


Figure 10G

Bone marrow smear showing *Leishmania donovani* parasites in a bone marrow histiocyte from a dog (Giemsa stain).
CDC/Dr. Francis W. Chandler


Figure 10I

Leishmania donovani in bone marrow cell. Smear.
CDC/Dr. L.L. Moore, Jr.


Figure 10 F

Giemsa stained leishmanial promastigotes from a culture in which the bar-shaped kinetoplast in the organism closest to the center of the group "rosette" may be
seen.

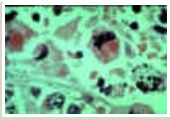


Figure 10H

Erythrophagocytosis in the liver (H&E X 400)
WHO/TDR/El-Hassan

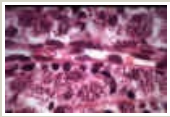


Figure 10J

Periarterial sheath of macrophages of the spleen showing heavy parasitisation with amastigotes (H&E X 400)
WHO/TDR/El-Hassan

Life cycle

The organism is transmitted by the bite of about 30 species of blood-feeding sand flies (*Phlebotomus*) which carry the promastigote in the anterior gut and pharynx. The parasites gain access to mononuclear phagocytes where they transform into amastigotes and divide until the infected cell ruptures. The released organisms infect other cells. The sandfly acquires the organisms during the blood meal; the amastigotes transform into flagellate promastigotes and multiply in the gut until the anterior gut and pharynx are packed. Dogs and rodents are common reservoirs (figure 11F).

Symptoms

Visceral leishmaniasis (kala-azar, dumdum fever)
L. donovani organisms in visceral leishmaniasis are rapidly eliminated from the site of infection, hence there is rarely a local lesion, although minute papules have been described in children. They are localized and multiply in the mononuclear phagocytic cells of spleen, liver, lymph nodes, bone marrow, intestinal mucosa and other organs. One to four months after infection, there is occurrence of fever, with a daily rise to 102-104 degrees F, accompanied by chills and sweating. The spleen and liver progressively become enlarged (figure 11B, C and E). With progression of the diseases, skin develops hyperpigmented granulomatous areas (kala-azar means black disease). Chronic disease renders patients susceptible to other infections. Untreated disease results in death.

Figure 11A
Many children suffering from visceral leishmaniasis develop a noticeable thickening, stiffening and darkening of the eyelashes and eyebrows.
WHO/TDR/Crump

Figure 11B

Profile view of a teenage boy suffering from visceral leishmaniasis. The boy exhibits splenomegaly, distended abdomen and severe muscle wasting. WHO/TDR/Kuzoe

Figure 11C

A 12-year-old boy suffering from visceral leishmaniasis. The boy exhibits splenomegaly and severe muscle wasting.
WHO/TDR/El-Hassan

Figure 11D

Jaundiced hands of a visceral leishmaniasis patient.
WHO/TDR/El-Hassan

Figure 11E

Enlarged spleen and liver in an autopsy of an infant dying of visceral leishmaniasis.
WHO/TDR/El-Hassan

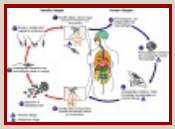


Figure 11F

Leishmaniasis is transmitted by the bite of female phlebotomine sandflies. The sandflies inject the infective stage, promastigotes, during blood meals ❶. Promastigotes that reach the puncture wound are phagocytized by macrophages ❷ and transform into amastigotes ❸. Amastigotes multiply in infected cells and affect different tissues, depending in part on the *Leishmania* species ❹. This originates the clinical manifestations of leishmaniasis. Sandflies become infected during blood meals on an infected host when they ingest macrophages infected with amastigotes (❺, ❻). In the sandfly's midgut, the parasites differentiate into promastigotes ❼,

which multiply and migrate to the proboscis 8.
CDC DPDx Parasite Image Library

Cutaneous leishmaniasis (Oriental sore, Delhi ulcer, Baghdad boil)
In cutaneous leishmaniasis, the organism (*L. tropica*) multiplies locally, producing of a papule, 1-2 weeks (or as long as 1-2 months) after the bite. The papule gradually grows to form a relatively painless ulcer. The center of the ulcer encrusts while satellite papules develop at the periphery. The ulcer heals in 2-10 months, even if untreated but leaves a disfiguring scar (figure 12). The disease may disseminate in the case of depressed immune function.

Mucocutaneous leishmaniasis (espundia, Uta, chiclero)
The initial symptoms of mucocutaneous leishmaniasis are the same as those of cutaneous leishmaniasis, except that in this disease the organism can metastasize and the lesions spread to mucoid (oral, pharyngeal and nasal) tissues and lead to their destruction and hence sever deformity (figure 12E). The organisms responsible are *L. braziliensis*, *L. mexicana* and *L. peruviana*.

Pathology
Pathogenesis of leishmaniasis is due to an immune reaction to the organism, particularly cell mediated immunity. Laboratory examination reveals a marked leukopenia with relative monocytosis and lymphocytosis, anemia and thrombocytopenia. IgM and IgG levels are extremely elevated due to both specific antibodies and polyclonal activation.

Diagnosis
Diagnosis is based on a history of exposure to sandfies, symptoms and isolation of the organisms from the lesion aspirate or biopsy, by direct examination or culture. A skin test (delayed hypersensitivity: Montenegro test) and detection of anti-leishmanial antibodies by immuno-fluorescence are indicative of exposure.

Treatment and Control
Sodium stibogluconate (Pentostam) is the drug of choice. Pentamidine isethionate is used as an alternative. Control measures involve vector control and avoidance. Immunization has not so far been effective but a new vaccine is under investigation.

Treatment of Leishmaniasis (CDC)


Figure 12A
Skin ulcer due to leishmaniasis, hand of Central American adult.
CDC/Dr. D.S. Martin

Figure 11F


Figure 12C
Scar on skin of upper leg representing healed lesion of leishmaniasis
CDC

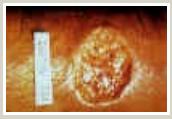


Figure 12B
Crater lesion of leishmaniasis, skin CDC


Figure 12D
Non-healing cutaneous leishmaniasis lesion on ear lobe
WHO/TDR/El-Hassan


Figure 12E
Girl with diffuse muco- cutaneous leishmaniasis of the face which is responding to treatment
WHO/TDR/El-Hassan


Figure 12F
Cutaneous leishmaniasis skin lesion. The lesion measured about 1 inch in diameter and was moist with raised borders. There was no drainage;
however, the lesion did appear to be infected.

Return to the Parasitology Section of Microbiology and Immunology On-line

<< Previous Next >>

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