

Leishmaniasis

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Leishmaniasis, also spelled **leishmaniosis**, is a disease caused by protozoan parasites of the genus *Leishmania* and spread by the bite of certain types of sandflies.^[2] The disease can present in three main ways: cutaneous, mucocutaneous, or visceral leishmaniasis.^[2] The cutaneous form presents with skin ulcers, while the mucocutaneous form presents with ulcers of the skin, mouth, and nose, and the visceral form starts with skin ulcers and then later presents with fever, low red blood cells, and enlarged spleen and liver.^{[2][3]}

Infections in humans are caused by more than 20 species of *Leishmania*.^[2] Risk factors include poverty, malnutrition, deforestation, and urbanization.^[2] All three types can be diagnosed by seeing the parasites under the microscope.^[2] Additionally, visceral disease can be diagnosed by blood tests.^[3]

Leishmaniasis can be partly prevented by sleeping under nets treated with insecticide.^[2] Other measures include spraying insecticides to kill sandflies and treating people with the disease early to prevent further spread.^[2] The treatment needed is determined by where the disease is acquired, the species of *Leishmania*, and the type of infection.^[2] Some possible medications used for visceral disease include liposomal amphotericin B,^[4] a combination of pentavalent antimonials and paromomycin,^[4] and miltefosine.^[5] For cutaneous disease, paromomycin, fluconazole, or pentamidine may be effective.^[6]

Leishmaniasis



Cutaneous leishmaniasis in the hand of a Central American adult

Pronunciation Leishmaniasis / ˌliːfməˈnaɪəsɪs/

leishmaniosis / ˌliːʃˈmeɪniˈoʊsɪs/ or / ˌliːʃˈmæniˈoʊsɪs/^[1]

Classification and external resources

Specialty Infectious disease

ICD-10 B55
(<http://apps.who.int/classifications/icd10/browse/2016/en#/B55>)

ICD-9-CM 085 (<http://www.icd9data.com/getICD9Code.aspx?icd9=085>)

DiseasesDB 3266 (<http://www.diseasesdatabase.com/ddb3266.htm>) 29171 (<http://www.diseasesdatabase.com/ddb29171.htm>)

MedlinePlus 001386 (<https://medlineplus.gov/ency/article/001386.htm>)

eMedicine emerg/296 (<http://www.emedicine.com/emerg/topic296.htm>)

Patient UK Leishmaniasis (<http://patient.info/doctor/leishmaniasis>)

MeSH D007896 (https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi?field=uid&term=D007896)

About 12 million people are currently infected^[7] in some 98 countries.^[3] About 2 million new cases^[3] and between 20 and 50 thousand deaths occur each year.^{[2][8]} About 200 million people in Asia, Africa, South and Central America, and southern Europe live in areas where the disease is common.^{[3][9]} The World Health Organization has obtained discounts on some medications to treat the disease.^[3] The disease may occur in a number of other animals, including dogs and rodents.^[2]

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Signs and symptoms

The symptoms of leishmaniasis are skin sores which erupt weeks to months after the person is bitten by infected sand flies.

Leishmaniasis may be divided into the following types:^[10]

- Cutaneous leishmaniasis is the most common form, which causes an open sore at the bite sites, which heals in a few months to a year and half, leaving an unpleasant-looking scar.^{[2][3]} Diffuse cutaneous leishmaniasis produces widespread skin lesions which resemble leprosy, and may not heal on its own.^[3]
- Mucocutaneous leishmaniasis causes both skin and mucosal ulcers with damage primarily of the nose and mouth.^{[2][3]}
- Visceral leishmaniasis or *kala-azar* ('black fever') is the most serious form, and is potentially fatal if untreated.^[2] Other consequences, which can occur a few months to years after infection, include fever, damage to the spleen and liver, and anemia.^[2]



Cutaneous leishmaniasis ulcer

Leishmaniasis is considered one of the classic causes of a markedly enlarged (and therefore palpable) spleen; the organ, which is not normally felt during examination of the abdomen, may even become larger than the liver in severe cases.

Cause

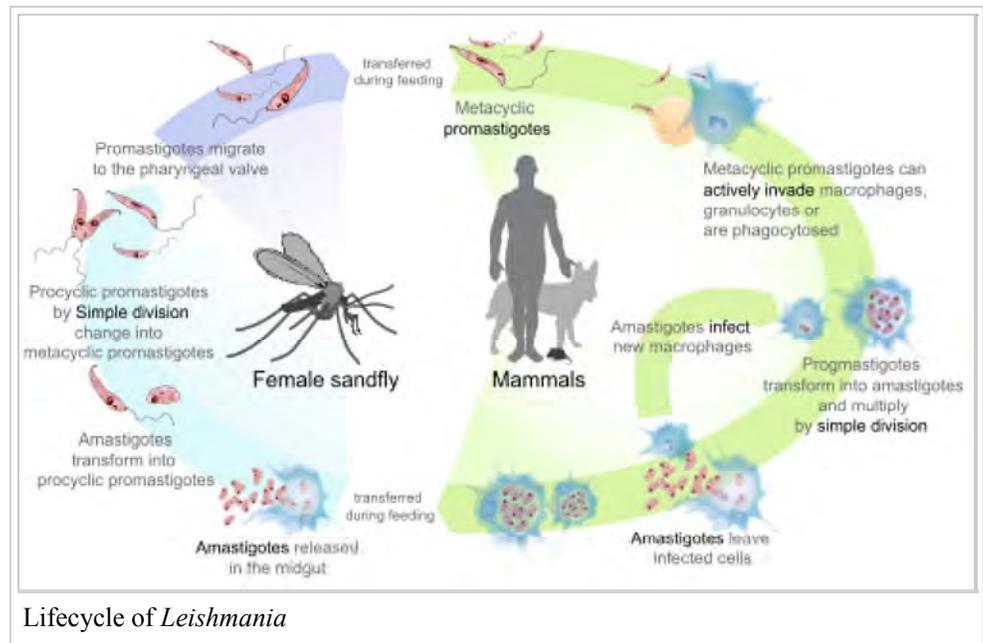
Leishmaniasis is transmitted by the bite of infected female phlebotomine sandflies^[2] which can transmit the protozoa *Leishmania*.^[2] The sandflies inject the infective stage, metacyclic promastigotes, during blood meals (1). Metacyclic promastigotes that reach the puncture wound are phagocytized by macrophages (2) and transform into amastigotes (3).

Amastigotes multiply in infected cells and affect different tissues, depending in part on which *Leishmania* species is involved (4). These differing tissue specificities cause the differing clinical manifestations of the various forms of leishmaniasis. Sandflies become infected during blood meals on infected hosts when they ingest macrophages infected with amastigotes (5,6). In the sandfly's midgut, the parasites differentiate into promastigotes (7), which multiply, differentiate into metacyclic promastigotes, and migrate to the proboscis (8).

The genomes of three *Leishmania* species (*L. major*, *L. infantum*, and *L. braziliensis*) have been sequenced, and this has provided much information about the biology of the parasite. For example, in *Leishmania*, protein-coding genes are understood to be organized as large polycistronic units in a head-to-head or tail-to-tail manner; RNA polymerase II transcribes long polycistronic messages in the absence of defined RNA pol II promoters, and *Leishmania* has unique features with respect to the regulation of gene expression in response to changes in the environment. The new knowledge from these studies may help identify new targets for urgently needed drugs and aid the development of vaccines.^[11]

Vector

Although most of the literature mentions only one genus transmitting *Leishmania* to humans (*Lutzomyia*) in the New World, a 2003 study by Galati suggested a new classification for New World sand flies, elevating several subgenera to the genus level. Elsewhere in the world, the genus *Phlebotomus* is considered the vector of leishmaniasis.^[11]



Organisms

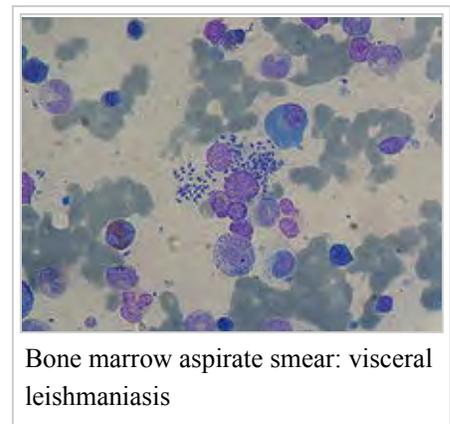
Visceral disease is usually caused by *Leishmania donovani*, *L. infantum*, or *L. chagasi*,^[3] but occasionally these species may cause other forms of disease.^[3] The cutaneous form of the disease is caused by more than 15 species of *Leishmania*.^[3]

Risk factors

Risk factors include poverty, malnutrition, deforestation, lack of sanitation and urbanization.^[2]

Diagnosis

Leishmaniasis is diagnosed in the hematology laboratory by direct visualization of the amastigotes (Leishman-Donovan bodies). Buffy-coat preparations of peripheral blood or aspirates from marrow, spleen, lymph nodes, or skin lesions should be spread on a slide to make a thin smear and stained with Leishman stain or Giemsa stain (pH 7.2) for 20 minutes. Amastigotes are seen within blood and spleen monocytes or, less commonly, in circulating neutrophils and in aspirated tissue macrophages. They are small, round bodies 2–4 μm in diameter with indistinct cytoplasm, a nucleus, and a small, rod-shaped kinetoplast. Occasionally, amastigotes may be seen lying free between cells.^[12] However, the retrieval of tissue samples is often painful for the patient and identification of the infected cells can be difficult. So, other indirect immunological methods of diagnosis are developed, including enzyme-linked immunosorbent assay, antigen-coated dipsticks, and direct agglutination test. Although these tests are readily available, they are not the standard diagnostic tests due to their insufficient sensitivity and specificity.



Several different polymerase chain reaction tests are available for the detection of *Leishmania* DNA.^[3] With this assay, a specific and sensitive diagnostic procedure is finally possible.

Most forms of the disease are transmitted only from nonhuman animals, but some can be spread between humans. Infections in humans are caused by about 21 of 30 species that infect mammals; the different species look the same, but they can be differentiated by isoenzyme analysis, DNA sequence analysis, or monoclonal antibodies.

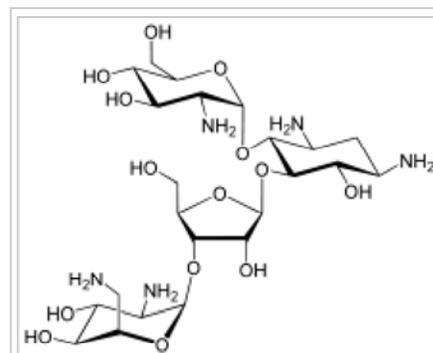
Prevention

- Leishmaniasis can be partly prevented by using nets treated with insecticide while sleeping.^[2] To provide good protection against sandflies fine mesh sizes of 0.6mm or less are required, but a mosquito net with 1.2mm mesh will provide a limited reduction in the number of sandfly bites.^[13] Finer mesh sizes have the downside of higher cost and reduced air circulation which can cause overheating. Many Phlebotomine sandfly attacks occur at sunset rather than at night, so it may also be useful to put nets over doors and windows or to use insect repellents.
- Use of insecticide-impregnated dog collars and treatment/culling of infected dogs.

- Spraying houses and animal shelters with insecticides.^[13]

Treatment

The treatment is determined by where the disease is acquired, the species of *Leishmania*, and the type of infection.^[2] For visceral leishmaniasis in India, South America, and the Mediterranean, liposomal amphotericin B is the recommended treatment and is often used as a single dose.^{[3][4]} Rates of cure with a single dose of amphotericin have been reported as 95%.^[3] In India, almost all infections are resistant to pentavalent antimonials.^[3] In Africa, a combination of pentavalent antimonials and paromomycin is recommended.^[4] These, however, can have significant side effects.^[3] Miltefosine, an oral medication, is effective against both visceral and cutaneous leishmaniasis.^[5] Side effects are generally mild, though it can cause birth defects if taken within 3 months of getting pregnant.^{[3][5]} It does not appear to work for *L. major* or *L. braziliensis*.^[6]



Paromomycin is an inexpensive (US\$10) and effective treatment for leishmaniasis.

The evidence around the treatment of cutaneous leishmaniasis is poor.^[3] A number of topical treatments may be used for cutaneous leishmaniasis. Which treatments are effective depends on the strain, with topical paromomycin effective for *L. major*, *L. tropica*, *L. mexicana*, *L. panamensis*, and *L. braziliensis*.^[6] Pentamidine is effective for *L. guyanensis*.^[6] Oral fluconazole or itraconazole appears effective in *L. major* and *L. tropica*.^{[3][6]}

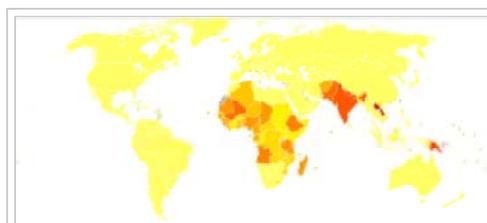
Epidemiology



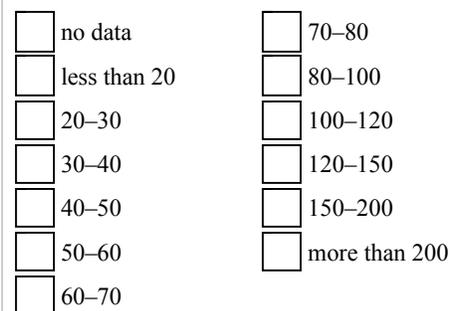
Cutaneous leishmaniasis in North Africa; *Leishmania infantum* = green, *Leishmania major* = blue, *Leishmania tropica* = red^[14]

Leishmaniasis occurs in 88 tropical and subtropical countries. About 350 million people live in these areas. The settings in which leishmaniasis is found range from rainforests in Central and South America to deserts in western Asia and the

Middle East. It affects as many as 12 million people worldwide, with 1.5–2.0 million new cases each year.^[15] The visceral form of leishmaniasis has an estimated incidence of 500,000 new cases.^[16] More than 90% of the world's cases of visceral leishmaniasis are in India, Bangladesh, Nepal, Sudan, and Brazil.^[17] As of 2010, it caused about 52,000 deaths, down from 87,000 in 1990.^[8] Different types of the disease occur in



Disability-adjusted life year for leishmaniasis per 100,000 inhabitants.



different regions of the world.^[2] Cutaneous disease is most common in Afghanistan, Algeria, Brazil, Colombia, and Iran, while mucocutaneous disease is most common in Bolivia, Brazil, and Peru, and visceral disease is most common in Bangladesh, Brazil, Ethiopia, India, and Sudan.^[2]

Leishmaniasis is found through much of the Americas from northern Argentina to South Texas, though not in Uruguay or Chile, and has recently been shown to be spreading to North Texas.^[18] Leishmaniasis is also known as *papalomoyo*, *papa lo moyo*, *úlceras de los chicleros*, and *chiclera* in Latin America.^[19] During 2004, an estimated 3,400 troops from the Colombian army, operating in the jungles near the south of the country (in particular around the Meta and Guaviare departments), were infected with leishmaniasis. Allegedly, a contributing factor was that many of the affected soldiers did not use the officially provided insect repellent because of its disturbing odor. Nearly 13,000 cases of the disease were recorded in all of Colombia throughout 2004, and about 360 new instances of the disease among soldiers had been reported in February 2005.^[20]

The disease is found across much of Asia, and in the Middle East. Within Afghanistan, leishmaniasis occurs commonly in Kabul, partly due to bad sanitation and waste left uncollected in streets, allowing parasite-spreading sand flies an environment they find favorable.^{[21][22]} In Kabul, the number of people infected was estimated to be at least 200,000, and in three other towns (Herat, Kandahar, and Mazar-i-Sharif) about 70,000 more occurred, according to WHO figures from 2002.^[23] Kabul is estimated as the largest center of cutaneous leishmaniasis in the world, with around 67,500 cases as of 2004.^[24] Africa, in particular the East and North,^[14] is also home to cases of leishmaniasis.

Leishmaniasis is mostly a disease of the developing world, and is rarely known in the developed world outside a small number of cases, mostly in instances where troops are stationed away from their home countries. Leishmaniasis has been reported by U.S. troops stationed in Saudi Arabia and Iraq since the Gulf War of 1990, including visceral leishmaniasis.^{[25][26][27]} In September 2005, the disease was contracted by at least four Dutch marines who were stationed in Mazari Sharif, Afghanistan, and subsequently repatriated for treatment.

History

Descriptions of conspicuous lesions similar to cutaneous leishmaniasis appear on tablets from King Ashurbanipal from the seventh century BCE, some of which may have derived from even earlier texts from 1500 to 2500 BCE. Persian physicians, including Avicenna in the 10th century CE, gave detailed descriptions of what was called *balkh* sore.^[28] In 1756, Alexander Russell, after examining a Turkish patient, gave one of the most detailed clinical descriptions of the disease. Physicians in the Indian subcontinent would describe it as *kala-azar* (pronounced *kālā āzār*, the Urdu, Hindi, and Hindustani phrase for "black fever", *kālā* meaning black and *āzār* meaning fever or disease). In the Americas, evidence of the cutaneous form of the disease in Ecuador and Peru appears in pre-Inca pottery depicting skin lesions and deformed faces dating back to the first century CE. Some 15th- and 16th-century texts from the Inca period and from Spanish colonials mention "valley sickness", "Andean sickness", or "white leprosy", which are likely to be the cutaneous form.^[29]

It remains unclear who first discovered the organism. David Douglas Cunningham, Surgeon Major of the British Indian army, may have seen it in 1885 without being able to relate it to the disease.^{[30][31]} Peter Borovsky, a Russian military surgeon working in Tashkent, conducted research into the etiology of "oriental sore", locally known as *sart* sore, and in 1898 published the first accurate description of the causative agent, correctly described the parasite's relation to host tissues and correctly referred it to the protozoa. However, because his results were published in Russian in a journal with low circulation, his results were not internationally acknowledged during his lifetime.^[32] In 1901, Leishman identified certain organisms in smears taken from the spleen of a patient who had died from "dum-dum fever" (Dum Dum is an area close to Calcutta) and proposed them to be trypanosomes, found for the first time in India.^[33] A few months later, Captain Charles Donovan (1863–1951) confirmed the finding of what became known as Leishman-Donovan bodies in smears taken from people in Madras in southern India.^[34] But it was Ronald Ross who proposed that Leishman-Donovan bodies were the intracellular stages of a new parasite, which he named *Leishmania donovani*.^[35] The link with the disease *kala-azar* was first suggested by Charles Donovan, and was conclusively demonstrated by Charles Bentley's discovery of *L. donovani* in patients with *kala-azar*.^[36] The disease became a major problem for Allied troops fighting in Sicily during the Second World War; research by Leonard Goodwin then showed pentostam was an effective treatment.^[37]



A 1917 case of cutaneous leishmaniasis in the Middle East, known then locally as "Jericho buttons" for the frequency of cases near the ancient city of Jericho

Society and culture

The Institute for OneWorld Health has reintroduced the drug paromomycin for treatment of leishmaniasis, results with which led to its approval as an orphan drug. The Drugs for Neglected Diseases Initiative is also actively facilitating the search for novel therapeutics. A treatment with paromomycin will cost about \$10. The drug had originally been identified in the 1960s, but had been abandoned because it would not be profitable, as the disease mostly affects poor people.^[38] The Indian government approved paromomycin for sale in August 2006.^[39]

The World Health Organization has gotten a reduced cost for liposomal amphotericin B at \$18 a vial, but many vials may be needed for treatment and it must be kept cool.^[3]

Research

Several potential vaccines are being developed, under pressure from the World Health Organization, but as of 2013 none are available.^[40] The team at the Laboratory for Organic Chemistry at the Swiss Federal Institute of Technology (ETH) in Zürich are trying to design a carbohydrate-based vaccine.^[16] The genome of the parasite *L. major* has been sequenced,^[41] possibly allowing for identification of proteins that are used by the pathogen but not by humans; these proteins are potential targets for drug treatments.

In February 2012, the nonprofit Infectious Disease Research Institute launched the world's first human clinical trial of the visceral leishmaniasis vaccine, a recombinant form of two fused *Leishmania* parasite proteins with an adjuvant. Two phase-1 clinical trials with healthy volunteers are to be conducted. The first one takes place in Washington and is followed by a trial in India.^[42]

In 2009, the Hebrew University of Jerusalem Kuvin Center for the Study of Infectious and Tropical Diseases, in a collaborative effort with Addis Ababa University, was awarded a grant by the Bill & Melinda Gates Foundation for research into visceral leishmaniasis in Ethiopia. The project will gather data to be analyzed to identify the weak links in the transmission cycle, and devise methods for control of the disease.^[43]

HIV protease inhibitors have been found to be active against *Leishmania* species in two *in vitro* studies in Canada and India. The studies reported the intracellular growth of parasites was controlled by nelfinavir and ritonavir in a human monocyte cell line and also in human primary monocyte-derived macrophages.^[44]

Since September 2011, a World Community Grid project called Drug Search for Leishmaniasis has the goal to find new drugs against this disease.^[45]

Notable cases

Marguerite Higgins, Pulitzer Prize-winning journalist, died in early 1967 from leishmaniasis contracted while on an assignment the previous year.

Magazine photographer Joel Sartore was diagnosed with the disease after a skin lesion failed to heal following a photo shoot in the Bolivian wilderness. Following intensive IV treatment similar to chemotherapy, his infection has resolved.^[46]

While filming the latest series of *Extreme Dreams* in Peru, UK television presenter Ben Fogle caught the disease. He was left bedridden for three weeks on his return home. Fogle was treated at London's Hospital for Tropical Diseases.^[47]

During his two-and-a-half-year walk through the Amazon, Ed Stafford tested positive for cutaneous leishmaniasis in Oriximiná, Para, Brazil. He convinced the local doctor that he could not stay in one place for treatment due to his undertaking, and was prescribed with 20 days of intravenous injections that he self-administered in the jungle.

See also

- CVBD Canine vector-borne diseases
- Tropical disease

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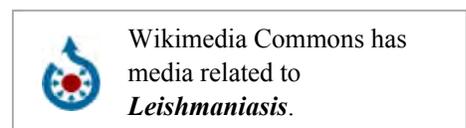


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External links

- Leishmaniasis



(https://www.dmoz.org/Health/Conditions_and_Diseases/Infectious_Diseases/Parasitic/Leishmaniasis) at DMOZ

- Doctors Without Borders' Leishmaniasis Information Page (<http://www.doctorswithoutborders.org/our-work/medical-issues/kala-azar-leishmaniasis>)
- CDC Leishmaniasis Page (<http://www.cdc.gov/parasites/leishmaniasis/>)

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Categories: Leishmaniasis | Parasitic infestations, stings, and bites of the skin

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