Peruvian Moche, Dum Dum Fever, and Reservoir Dogs

BACKGROUND

The combination of variable pathophysiology, geographical distinctiveness, inconsistent clinical penetrance and severity, and complex host-parasite interactions make for a beguiling Neglected Tropical Disease that affects 12 million of the world's poorest. How to make head or tail of leishmaniasis? We can start by appreciating that the leishmania parasite infects phagocytic cells, playing a game of tip-and-run with host immunity. Caught early and trapped locally, the parasite replicates inside dendritic cells—the dermal macrophages—causing only **cutaneous disease**. But another species (there are 20 that are pathogenic to humans) in a different host in a different global region may show a propensity for spread, this time via circulating macrophages, to the nasopharynx/oropharynx and urogenital sites, causing **mucosal disease —** or wider still, infiltrating the deeper reticuloendothelial cells of the spleen, liver, and bone marrow, to present as **visceral leishmaniasis**. Visceral disease, presenting with hepatosplenomegaly, weight loss, anaemia, and undulating fever, is the most feared form of leishmaniasis. Untreated it is a uniformly fatal wasting disease, second only to malaria as the biggest parasitic killer worldwide. The more limited and rarely lethal mucosal leishmaniasis, and the mostly limited and never fatal cutaneous leishmaniasis, are both major causes of morbidity.

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Leishmaniasis - Key Points

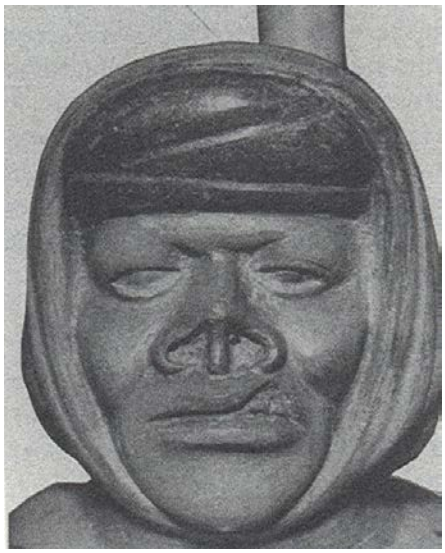
- Leishmania infect macrophages, implicating the reticuloendothelial system:
  - **Cutaneous** — stay at the site of inoculation
  - **Mucosal** — metastasise to naso-oropharyngeal and urogenital mucosae
  - **Visceral** — widespread involvement of spleen, liver, and bone marrow
- Geographic subtypes demonstrate some host-parasite specificity
  - Old World — Middle East, Europe, Africa, Asia
  - New World —Americas
- Variable degrees of clinical presentation possible
  - Acute Infection
  - Subacute Infection
  - Chronic Infection
  - Latent (opportunistic) Infection
- 90% of visceral cases are found in 6 countries:
  - Bangladesh
  - Brazil
  - Ethiopia
  - India
  - South Sudan
  - Sudan

The history of leishmania is a fascinating, tortuous yet inescapable tale.

HISTORY

Paleoparasitology suggests leishmania are many millions of years old. Rather than causing population decimation, true to parasite form leishmania likely follow human development ('Red Queen Theory'). Initially a reptilian zoonosis arising out of the Middle East (earliest fossilised sandflies from Lebanon), it spread to the New World across the Bering Strait following the break-up of Gondwana in the Jurassic era (during the Pangea single landmass of the Triassic period). The disease may also have been brought to Brazil by seafaring Phoenicians and Syrians. With its distinctive features, leishmaniasis is readily identifiable in the 7th century BC Assyrian records of King Ashurbanipal, while molecular amplification techniques have demonstrated leishmania DNA in Nubian mummies (Zink et al, 2006). The deformed faces of 1st century Incan pottery are thought to depict mucocutaneous leishmaniasis.

'Huaco mochica', a pre-Columbian ceramic showing mutilation of the upper lip suggestive of mucosal leishmaniasis (Tuon et al, 2008: 162)



Moche (northern Peru) 100-800 C.E. Possible case of leishmaniasis [Image: Pinterest]

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Mummified face from a Peruvian cemetery showing extensive lesions consistent with mucocutaneous leishmaniasis, likely L. braziliensis complex. Examination of the teeth and skull and X-Rays reflect that of a 6-year-old girl with "severe facial defect, which consisted of erosion and lesions of the nose, lips, mandible, cheeks, and gums." Giemsa tissue stains show macrophages with the Leishmania parasite. (Gerszten et al, 2012: 253).

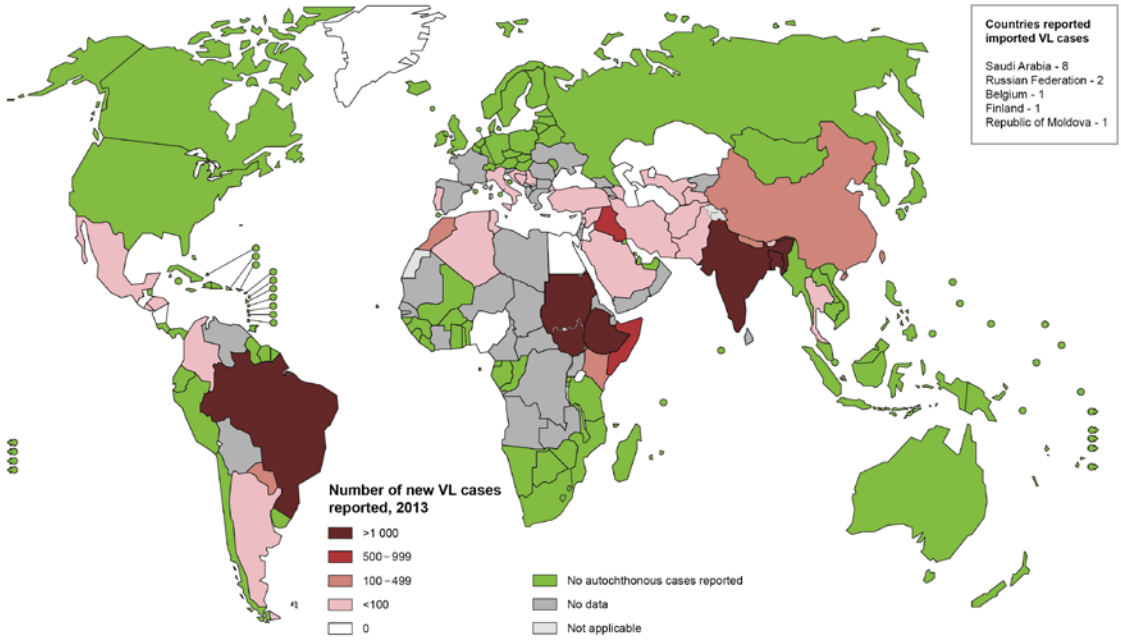
Recognised then far and wide throughout history, leishmaniasis has picked up various nicknames — *Baghdad Boil*, *Jericho Buttons*, *Aleppo Evil*, to name a few. To tenth century Muslim physicians, it was known as *Balkh sores***.** And from central Asian zoonotic reservoirs, the disease was transferred, around the 14th century, to the Indian subcontinent. By the mid-18th century, visceral leishmaniasis is also described in Africa. Kala-azar (Hindi: "Black-Fever") is first recognised in Jessore (India) in 1824, in febrile patients thought to have malaria but failing to respond to quinine. By 1862 the disease is spreading, reaching epidemic levels in Burdwan, and still being attributed by many to a virulent form of malaria. In 1756, Alexander Russell accurately describes cutaneous leishmaniasis *('Aleppo Boil')* in a Turk: "*After it is cicatrised, it leaves an ugly scar, which remains through life, and for many months has a livid colour. When they are not irritated, they seldom give much pain.*" David Cunningham (1885), and later James Homer Wright, discover the cutaneous parasite, while a Russian military surgeon, Peter Borovski, publishes his discovery of the visceral parasite, in a lesser-fancied journal, in 1898. Scotsman **William Boog Leishman**, a British army doctor in Dum Dum (near Calcutta), finds the leishmania parasite while examining tissue sections of the swollen spleen of a British soldier who had bouts of fever, anaemia, and wasting, in 1903. Leishman identifies—and implicates—ovoid bodies in "*Dum Dum fever*". Weeks later, **Charles Donovan**, Professor of physiology at Madras University, recognises these symptoms in patients with *kala-azar*. Receiving coincidental reports from both Leishman and Donovan, then BMJ senior-editor in London, Ross synthesises their discovery of "Leishman-Donovan bodies", later called ***Leishmania donovani***. Brothers Edouard and Etienne Sergent experimentally prove leishmania transmission to humans from a *Phlebotomus* (genus) sandfly in 1921, and the mode of transmission, through a bite, is confirmed in 1941. Cutaneous leishmaniasis was seen in American expats returning from the infant Saudi oil industry.

EPIDEMIOLOGY

Visceral leishmaniasis typically involves cells of the reticuloendothelial system—in the liver, spleen, and the bone marrow—of 200,000 to 400,000 new cases (20,000-30,000 deaths) worldwide each year. The disease is split geographically into Old and New World types, with multiple parasite species in each, suggesting a common ancestor vector before continental separation (see above). Global travel and military conflict has seen the disease spread more widely, including emergence of resistance strains with HIV co-infection.

A common feature is that disease occurs in rural or semi-urban areas associated with malnutrition, displacement, poor infrastructure, and weakened immunity, but is also linked to deforestation and urbanisation. More than 90% of the world's visceral

leishmaniasis occurs in the Indian subcontinent (India and Bangladesh, but also Nepal), East Africa (Sudan, South Sudan, Ethiopia), and Brazil. Most of the remainder is concentrated around the Mediterranean basin.



Status of endemicity of visceral leishmaniasis, worldwide, 2013. Predominant regions affected are the Mediterranean basin (visceral predominates), South-East Asia (visceral), East Africa (visceral), Middle East, North Africa and Eurasia (cutaneous), and the Americas (cutaneous and visceral). [Control of Neglected Tropical Diseases (NTD), World Health Organisation].

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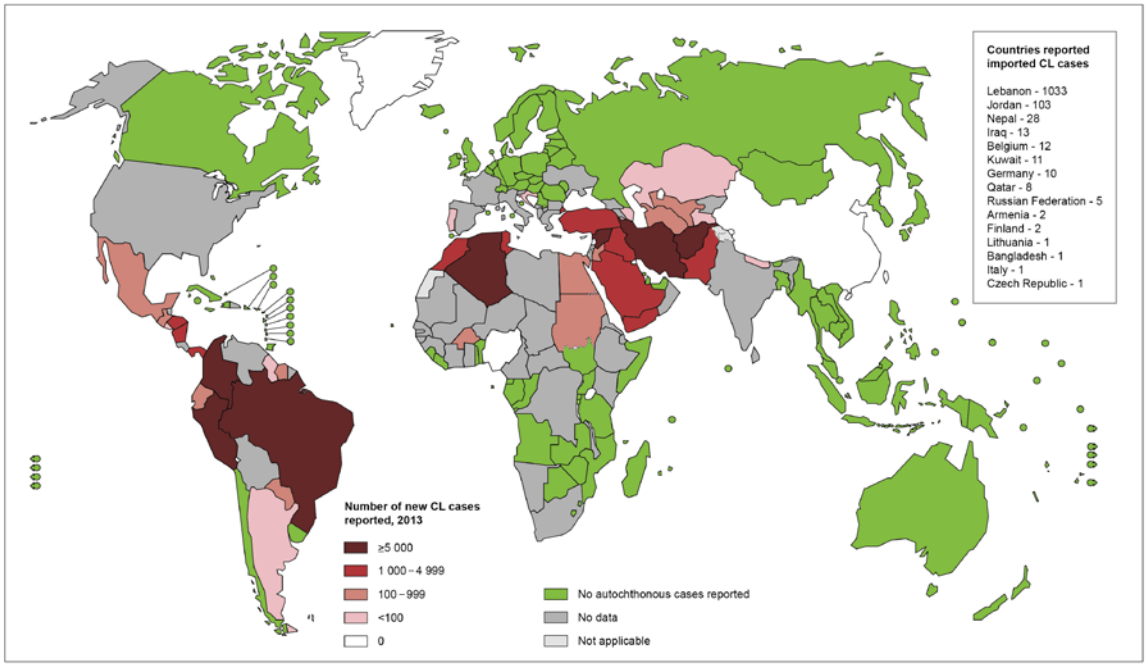
Status of endemicity of cutaneous leishmaniasis, worldwide, 2013



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2015. All rights reserved

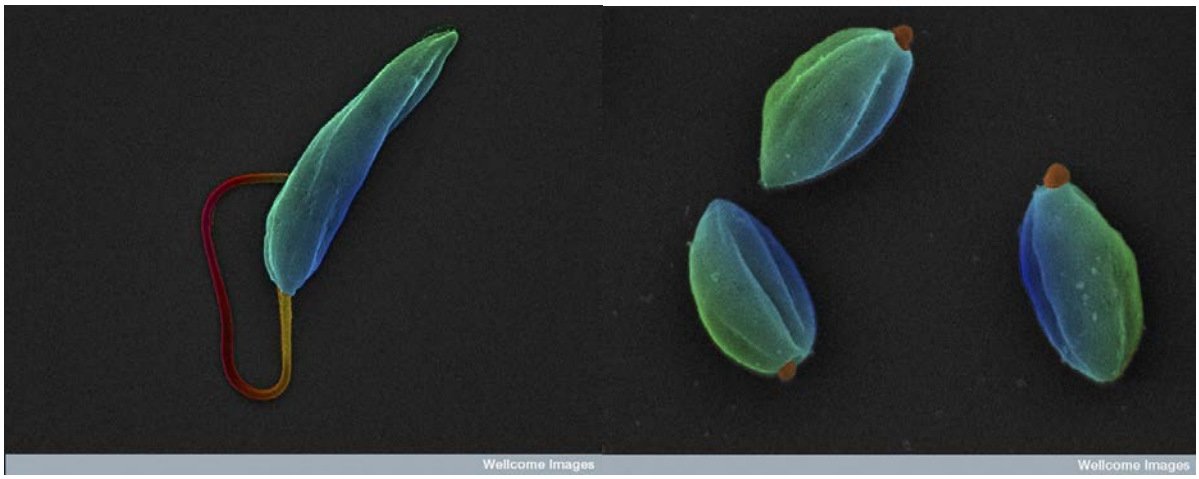
Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

South America, North Africa, and the Middle East into Eurasia see most of the world's cutaneous leishmaniasis. [Control of Neglected Tropical Diseases (NTD), World Health Organisation].

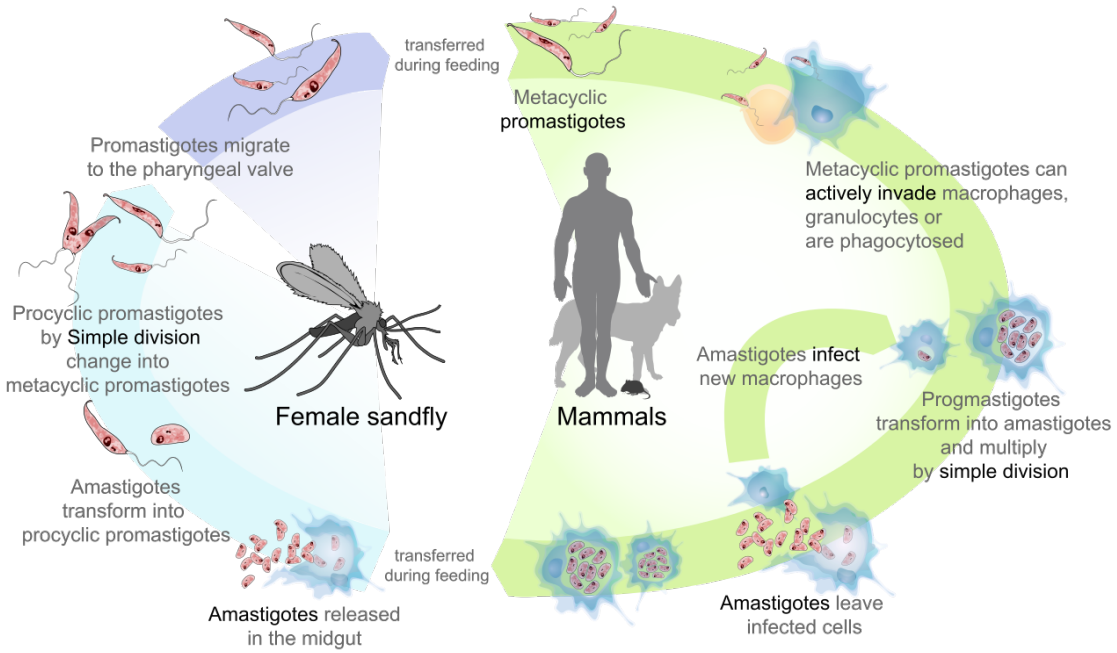
BIOLOGY

Leishmania are obligate intracellular protozoa, of which some 31 species are implicated for human disease. *L. donovani* and *L. infantum/L. chagasi* are the most common cause of visceral leishmaniasis.



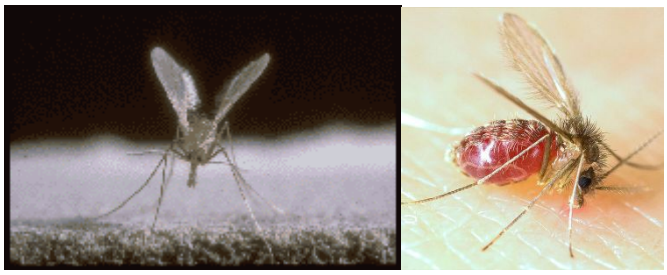
Scanning electron micrograph of Leishmania mexicana in mastigote (left) and amastigote (right) stages [Image credit: University of Oxford, Richard Wheeler. Wellcome Images - cc-by 4.0 licence]

Infection is transmitted from the bite of **phlebotomine sand fly**, arthropods whose habitat spans the world's inter-tropical and temperate regions (between latitudes 50°N and 40°S but sparing the Pacific Islands and New Zealand). The bite of the tiny and noiseless sandfly may go unnoticed but present as an itchy papule hours or days later.



Life cycle of Leishmania donovani [Wikimedia Commons]

The sand-fly's habitat is at the opening of the burrows of certain rodents (with different specie-host specificity), in the bark of old trees, ruined buildings, cracks in house walls, animal shelters, household rubbish — wherever there is humidity which allows for organic matter to enrich the larvae. From there the sand-fly will roam, dusk to dawn, across a span of several hundred metres in search of a blood meal. Occasionally the same sand fly species will bite both animal and human, transmitting the infection from that reservoir to people.



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*Intermediate Host: the female **Phlebotomus** sandfly; and a blood-fed **Lutzomyia** longipalpis sandfly are about a third the size of a mosquito. A single blood meal can support the production of 100 eggs. The Lutzomyia genus (New World) of sandfly may be found in and around caves, feeding off bats. [Wikimedia Commons]*

The first non-sandfly specie transmission of leishmaniasis was identified in the Northern Territory, Australia (Rose et al, 2004)—an as yet undescribed specie of day-feeding midge (subgenus Forcipomyia (Lasiohelea)) was likely infecting the red kangaroo with a parasite strain most closely related to *Leishmania enriettii* (Dougall et al, 2011).

Midge [Image: Dougall et al, 2011]

Congenital and parenteral transmission (blood transfusion, needle sharing) have also been reported.

Over 70 animal species have been identified as the natural **reservoir hosts** for the parasite: humans, which are the parasite's definitive host; and dogs a common reservoir host. Sporadic infection is now seen in returned travellers from Eastern Europe or soldiers from the Middle East, otherwise infection is not seen in Americans. There is, however, an endemic cycle in dogs (*L. tropica*, from middle Europe) in the Unites States, particularly along the eastern seaboard.

Reservoir Dog: Leishmaniasis is an endemic infection of dogs along the entire Mediterranean basin, where L. infantum is a "visceralising" form of cutaneous disease. Note also the lesion of the nose. [Wikimedia Commons]

CLINICAL PRESENTATION

There are three main presentations of leishmaniasis—visceral, cutaneous, and mucosal (or mucocutaneous) forms. Manifestations depend on host immune factors and pathogenic strain, with a distinct geographical split: disease in the Old World is principally caused by *L. donovani* and spread by the **Phlebotomus** sand fly, causing widespread infection of the reticuloendothelial system, including Kuepfer cells of liver and bone marrow; in the New World, *L braziliensis* is spread through the bite of **Lutzomyia** sand flies and causes disease of the naso-oropharynx and urogenital tract.

Cutaneous leishmaniasis

The result of local infection of dermal macrophages, this is the most common form of leishmaniasis. It infects 700,000 to 1.3 million people each year. Almost all cases occur in the Americas, the Mediterranean basin, Middle East, and Central Asia — mostly from the six countries of **Afghanistan**, **Algeria**, **Brazil**, **Colombia**, **Iran**, and **Syria**.

- *L. major* (Old World) — *L. major, L. tropica*, *L aethiopica*, *L. infantum*, *L. donovani*
- *L. mexicana* (New World) — *L. mexicana*, *L. amazonensis*, and *L. venezuelensis*

Unless superinfected or near a joint, lesions are generally painless and can persist months to years — evolving from papules to nodules to ulcers, to scabs or crusts, and leaving behind atrophic scars. Multiple (sometimes hundreds) of primary and satellite, and often disfiguring, skin lesions can be seen, and regional lymphadenopathy is common.

Left: ulcer of cutaneous leishmaniasis [CDC]; Right: forearm lesion [Wikimedia Commons]

Cutaneous disease—in both the Old and the New World—was thought to involve the skin only. That was until a cutaneous form of leishmania *(L. tropica)* 'visceralised' in American troops during Operation Desert Storm. It demonstrates that the introduction of a new host to an old disease can give unpredictable results, highlighting some interplay between immunogenetics and parasite. Because it is not life-threatening, cutaneous disease has been neglected by funding agencies and big pharma.

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Mucosal leishmaniasis (espundia)

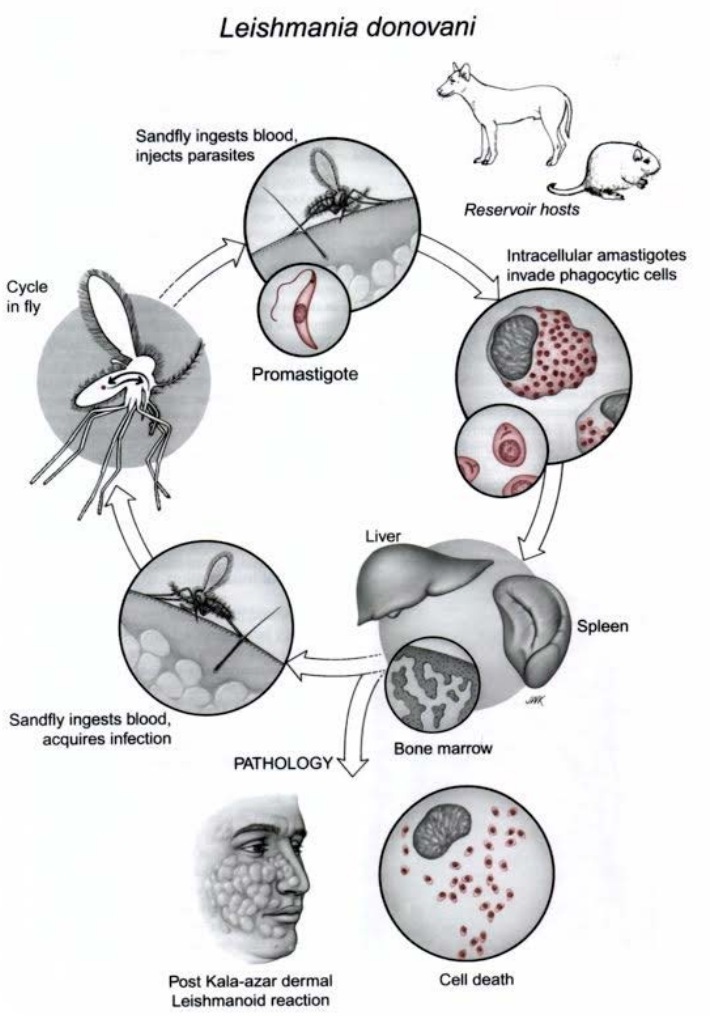
Mucosal disease is caused predominantly by *L. braziliensis*, which is thought to proliferate (and lesions slowly advance) early in the course of the disease in the nasal area because of its lower body temperature and the lack of cellular immune response in cartilage (Gerszten et al, 2012). It is thought to be the delayed metastatic sequelae of untreated (or poorly treated) cutaneous or visceral disease. Leishmania implicated in mucosal disease are mostly of the *braziliensis sp*., but also *panamensis*, and occasionally *guyanensis* or *amazonensis*. Disease causes a gradually disabling and personally degrading partial or total destruction of the mucosa. Almost 90% of mucosal leishmaniasis occurs in **Bolivia**, **Brazil**, and **Peru**.

Visceral leishmaniasis

Here again the permutations are many, including in clinical presentation and in spectrum of severity, resulting from widespread infection of macrophages throughout the reticuloendothelial system. Over 90% of new cases occur in 6 countries: **Bangladesh**, **Brazil**, **Ethiopia**, **India**, **South Sudan** and **Sudan**. The illness can present acutely, subacutely, or chronically. The incubation period can be weeks to months, or an asymptomatic infection that manifests opportunistically years to decades later. It is caused by *L. donovani* or *L. infantum (Old World) or L. chagasi (New World)*. It affects internal organs but can occasionally 'metastasise' to mucosae or even skin. Atypical manifestations, such as GIT involvement and drug-resistance, is seen in HIV-coinfected patients. Thankfully, amidst all this variability, there is a somewhat stereotypical presentation of visceral disease that can guide us:

- Fever, usually described as undulating (dromedary or 'camel-back' fever)
- Weight loss (cachexia, wasting)
- Hepatosplenomegaly (spleen usually more prominent than liver)
- Pancytopenia
- Hypergammaglobulinemia: high-protein, low-albumin state
- Lymphadenopathy (especially seen in Sudan)

A secondary cutaneous eruption, complicating visceral leishmaniasis in *L. donovani* endemic areas, seen particular after partial treatment, is **post kala-azar dermal leishmaniasis** (PKDL). Pale maculopapular or nodular, and not ulcerative, lesions that but for India, heal spontaneously. These lesions are thought to act as a reservoir of infection.



The life-cycle of L. donovani, the principal cause of visceral leishmaniasis in the Old World.

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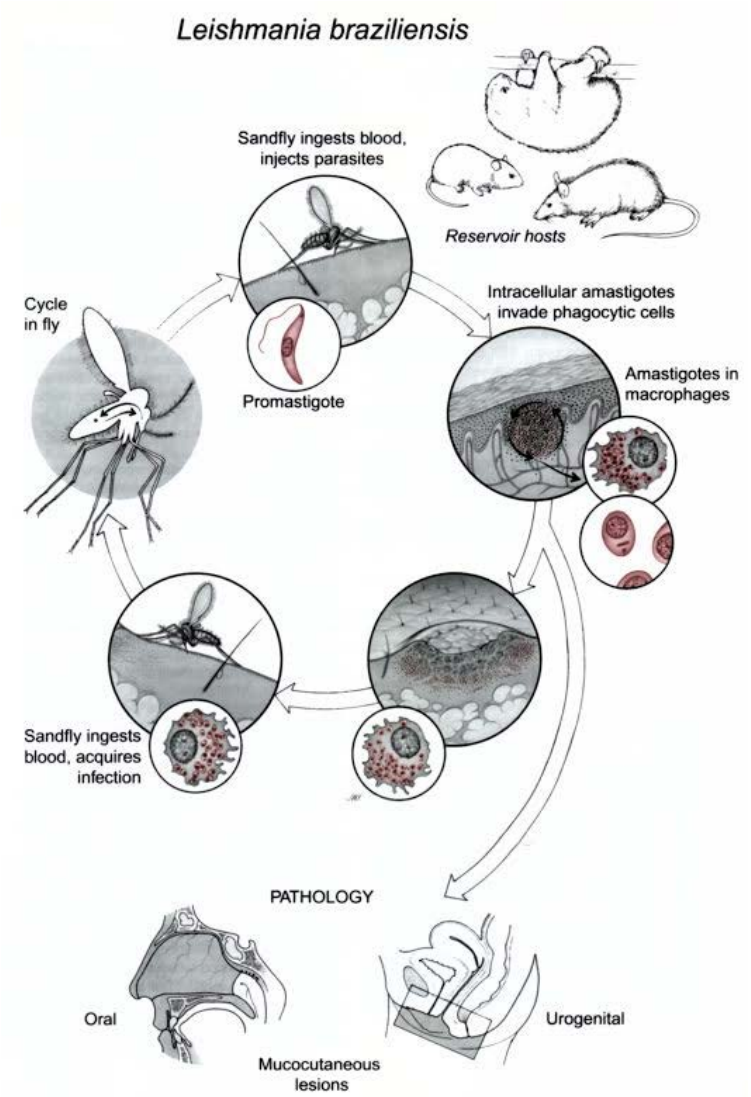

Life-cycle of L. braziliensis, the principal cause of visceral leishmaniasis in the New World.

Palpable splenomegaly (cf. malaria, schistosomiasis) in a person with visceral leishmaniasis [CDC]

PATHOPHYSIOLOGY

The sand fly, on taking a blood meal, injects the flagellated parasite **(promastigote)**. Unlike plasmodia (direct injection into blood stream), leishmania depend on phagocytosis for their life-cycle. The sand fly injects chemoattractants, and dendritic cells quickly engulf the parasite. Depending upon parasite-host response, then one of two things may happen: the dendritic cells migrate away from the site of infection to the reticuloendothelial organs; or the dendritic cells stay locally, the parasite entering a 'parasitophorous vacuole'—a phagosome that is protected, by way of parasitic connivance, from lysosomal degradation. [In the case of *T. gondii,* recall that the parasite prevented lysosomal fusion with the phagosome. Leishmania does this too but it has also developed a different evasion mechanism: producing stronger lytic enzymes that hydrolyse the phagocytic lysosomal hydrolases before they have a chance to enzymatically destroy the parasite. Rather than destroying the offender, the phagocytes end up harbouring the parasite, nurturing and transporting it instead.] The flagellum disappears and the parasite, now an **amastigote**, starts to reproduce. Visceral and cutaneous forms of the disease are, as yet, still indistinguishable. What is different, however, is the immune response induced by parasites that cause the cutaneous disease (remain locally but inhibit the inflammatory response) from those parasites that cause mucocutaneous disease (disseminate to nasopharynx amid a strong inflammatory response) — Toll-like receptors implicated for each event. Another female phlebotomine sand fly comes along and takes a blood meal, required for egg production. It can take up the dendritic cells from the living edge of a cutaneous wound while taking a blood meal. In visceral disease, circulating macrophages harbouring the parasite are taken up from the blood meal. Either way, the sand fly picks up the amastigotes. The amastigotes then undergo transformation into promastigotes in its gut, ready to be inoculated into another host.

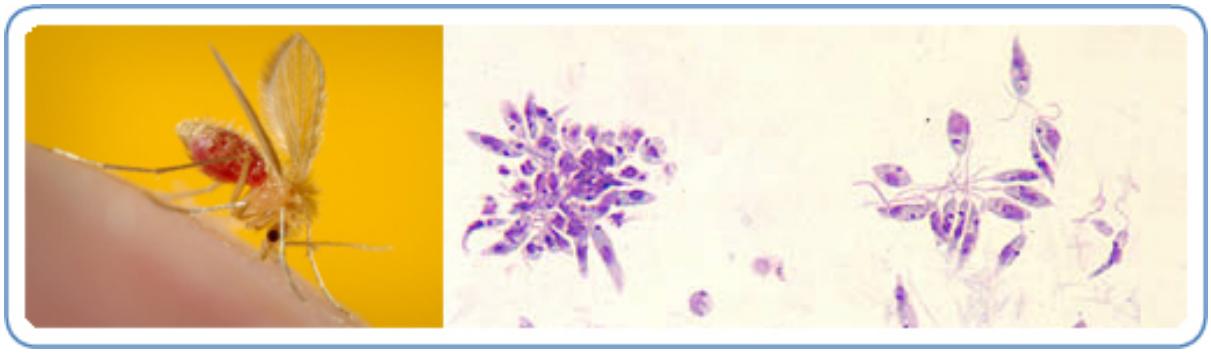

*Image: The sand flies that transmit the parasite are only about one third the size of typical mosquitoes or even smaller. On the left, an example of a vector sand fly (*Phlebotomus papatasi*) is shown; its blood meal is visible in its distended transparent abdomen. On the right,* Leishmania *promastigotes from a culture are shown. The flagellated promastigote stage of the parasite is found in sand flies and in cultures. (Image and text: CDC* ***PHIL****,* ***DPDx****.)*

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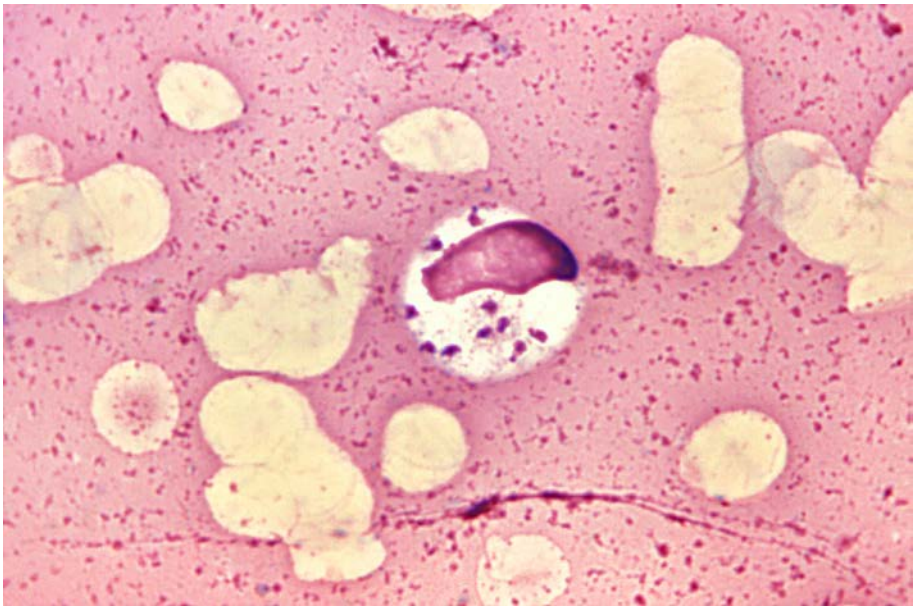
Cases are uncommon in the United States and mostly seen in tourists to southern Europe or expatriates and deployed soldiers to the Mediterranean and Middle East. That apart, the odd case of endogenous cutaneous leishmaniasis has been reported in Texas and Oklahoma. No human visceral leishmaniasis is known to have been acquired from within the United States.

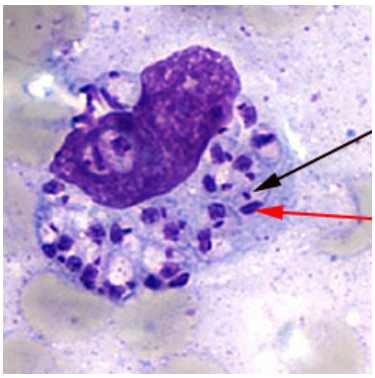
DIAGNOSIS

The index of suspicion should be raised by a clinical presentation in the appropriate context of travel, recent or remote, to endemic areas. Sample suspect tissue for parasite or its DNA. Serology, which is both geographic and host-dependent, is used as corroborative evidence, failing, as it does, to distinguish between active and quiescent infection. Specie identification, by molecular methods or isozyme analysis of culture, will have therapeutic and prognostic implications.

- Serology (including rapid diagnostic tests) — antibody produced against the parasite can be detected in cases of visceral leishmaniasis
- Blood, skin or lymph node biopsy, bone marrow (safer than splenic) aspirate
    - Light Microscopy — of stained tissue smear
    - Molecular methods — PCR for parasite DNA
    - Culture in Schneider's 'insect-cell' medium — amastigotes transform into promastigotes and start to reproduce



Leishmania donovani in bone marrow smear [Wikimedia Commons]



The arrows point to the two distinct parts – nucleus (red) and kinetoplast (black) – of a single amastigote inside the 'parasitophorous vacuole'. Many of these parasite-containing vacuoles can be seen inside this one macrophage. Visualising a kinetoplast helps confirm the diagnosis. (Image: CDC/DPDx)

TREATMENT

Treatment depends on type of disease (not all cutaneous disease needs treatment), parasite specie, geographical location, and host immune status and concomitant illness. An Infectious Disease or Tropical Medicine specialist will individualise therapy of visceral disease, taking into account both host and parasite factors. Traditional drugs used to treat leishmaniasis can be problematic and therapy cannot readily be transferred across geographic regions, clinical disease, or parasite specie. Treatment of visceral disease includes supportive care, such as therapy for malnutrition, treatment of anaemia/bleeding and treatment of any intercurrent infection. Antimonials can be quite toxic but are curative and help to induce a lifelong immunity against visceral disease in most.

- **Liposomal amphotericin B** *(AmBisome),* the drug of choice for visceral leishmaniasis, is given by intravenous infusion and is better tolerated than conventional amphotericin B
    - Visceral disease:
        - Immunocompetent: **3 mg/kg daily IV infusion days 1-5, 14, and 21 (total dose 21 mg/kg)**
        - Immunosuppressed: **4 mg/kg daily IV infusion days 1-5, 10, 17, 24, 31, and 38 (total dose 40 mg/kg)** or higher doses and/or secondary prophylaxis (chronic maintenance therapy) especially HIV positive with CD4 < 200 cells/mm^3.
    - Cutaneous: **3 mg/kg daily IV infusion, for 6-10 or more doses**
- **Miltefosine** *(Impavido*) is an orally active agent (capsule) for cutaneous, mucosal and visceral disease
    - New World species and L. donovani
    - ≥ 12 years of age
    - Not pregnant or breastfeeding
    - weight ≥ 30 kg
        - 30-44 kg: **50 mg BD x 28 days**

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        - ≥ 45 kg: **50 mg TID x 28 days**
- **Sodium stibogluconate** *(Pentostam)* of the pentavalent antimonial (Sb^V) drug class, which have been used to treat leishmaniasis since the 1940s, is available under an investigational new drug protocol. It is less effective in parts of south-east Asia. It is given parenterally (IV/IM):
    - Cutaneous: **20 mg Sb^V/kg for 10-20 days**
    - Mucosal/Visceral: **20 mg Sb^V/kg for 28 days**
- Others
    - Amphotericin B deoxycholate, as
        - rescue therapy for cutaneous (and mucosal) leishmaniasis
        - visceral leishmaniasis (but generally more toxic than liposomal preparation): **0.5 – 1.0 mg/kg daily or every other day IV infusion to a total dose of 15-20 mg/kg** (occasionally longer)
    - Pentamidine isethionate — irreversible toxicity, variable efficacy (mostly in parts of south Asia)
    - Oral azoles
        - Ketoconazole: **600 mg OD x 28 days**
        - Itraconazole: **200 mg BD x 28 days**
        - Fluconazole: **200-400 mg OD x 6 weeks** *(L. major)*; **8 mg/kg x 4-6 weeks** *(L. braziliensis)*
    - Paramomycin sulfate — parenteral or topical
    - Scarification works because infection is protective, with lifelong, although not cross-species, protection
        - Liquid nitrogen
        - Thermotherapy
        - Intralesional Sb^V
        - Topical Paramomycin (15% paromomycin/12% methylbenzethonium chloride in soft white paraffin)

Cutaneous leishmaniasis can be treated to reduce risk of mucosal dissemination, accelerate healing of facial lesions, decrease risk of relapse, and decrease the reservoir of infection. Treated lesions flatten and soften before gradually resolving.

PREVENTION

Immunity

Protective mechanisms against leishmania include both innate and adaptive immune responses. Traditionally, resolving cutaneous leishmaniasis was used to inoculate the non-immune with an attenuated organism, creating a herd immunity. Occasionally recurrent infection is seen with cutaneous leishmaniasis.

Prophylaxis

There are no vaccines or drugs to prevent infection. In some parts of the world, infection in people is needed (anthroponotic) to maintain the cycle (human—

sandfly—human), such as *L. donovani* in the Indian subcontinent. In others the transmission cycle can be sustained through reservoirs such as rodents and dogs alone *(L. infantum/chagasi).*

CDC recommendations are to:

- *Avoid outdoor activities, especially from dusk to dawn, when sand flies generally are the most active.*
- *Wear long-sleeved shirts, long pants, and socks; and tuck your shirt into your pants.*
- *Apply (DEET-based) insect repellent to exposed skin and under the ends of sleeves and pant legs.*
- *Stay in well-screened air-conditioned areas … spraying living/sleeping areas with insecticide … otherwise, use a bed net [ideally one that has been soaked in /sprayed with pyrethroid-based insecticide] and tuck it under your mattress. [Treat] screens, curtains, sheets, and clothing (clothing should be retreated after five washings).*

FUTURE
A kala-azar elimination programmes (South-East Asia) has seen declining cases in the three major endemic countries — Bangladesh, India, and Nepal. Genetically engineered hematophagous (blood-feeding) insects have been used experimentally as the vector of immunisation — the 'flying vaccinator'. Such transgenic anopheline mosquitos, expressing Leishmania Sp15 antigen, have rendered an antibody response in mice, although ethical and feasibility issues may preclude its use.

Summary of Leishmaniasis

- 12 million people affected worldwide
- Transmitted by the bite of a sandfly
- Cutaneous disease
  - 90% occur in Afghanistan, Brazil, Iran, Peru, Saudi Arabia, and Syria
  - Causes disfiguring lesions
  - Available drugs can cure the disease
- Mucocutaneous disease
  - 90% occur in Bolivia, Brazil, Peru
  - causes highly mutilating lesions
  - available drugs can cure the disease
- Visceral disease
  - 90% occurs in Bangladesh, Brazil, India, and the Sudan
  - causes a lethal wasting syndrome with hepatosplenomegaly
  - available drugs can cure the disease

SYNONYMS

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- Kala-azar or "Black fever" (visceral leishmaniasis, India)
- Oriental sore or Button d'orient (cutaneous leishmaniasis in
- Delhi boil (cutaneous leishmaniasis, India)
- Baghdad boil (cutaneous leishmaniasis, Iraq)
- Balkan sore (cutaneous leishmaniasis, Balkans)
- Saldana (cutaneous leishmaniasis, Afghanistan)
- Dumdum fever (visceral leishmaniasis, India)
- Aleppo Evil (leishmaniasis, Syria)
- Jericho Buttons (cutaneous leishmaniasis, Jordan)
- Chiclero's ulcer
- White leprosy
- Andean sickness
- Valley sickness

GLOSSARY

- **Definitive Host:** site of parasite sexual reproduction
- **Intermediate Host:** part of the life-cycle, by definition, must occur here
- **Reservoir Host:** has the same stage of infection as that of humans
- Mastigote refers to the flagellum: a promastigote is the flagellated (motile) stage; an amastigote is the stage without a flagellum (non-motile, replicative).
- **Neglected Tropical Disease (NTD):** a range of tropical and subtropical infections affecting over a billion people and costing developing economies billions of dollars every year. Of some 13 NTDs, Leishmaniasis, Chagas Disease and Sleeping Sickness are the most dangerous.

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FURTHER READING

Downloaded from *The Doctor*

- Cutaneous Leishmaniasis: Recognition and Treatment – American Family Physician
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- Cutaneous leishmaniasis: Disfiguring tropical disease sweeps across Middle East – Independent
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