ENY-738

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Leishmaniasis[1]

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Leishmaniasis is a disease caused by parasitic protozoans of the genus *Leishmania* that are transmitted to humans by sandflies of the subfamily Phlebotominae (Figure 1). Old World forms of *Leishmania* are transmitted by sandflies of the genus *Phlebotomus*, while New World forms mainly by sandflies of the genus *Lutzomyia*. Sandflies become infected by ingesting blood from infected reservoir hosts (usually small mammals) or from infected people. The disease can attack the skin, mucous membranes, liver, spleen and bone marrow. Over 20 different *Leishmania* species can infect humans and cause a wide spectrum of symptoms that range from self-healing skin ulcers to severe life-threatening disease.

The Trypanosomes

The organisms that cause leishmaniasis belong to the protozoan group known as trypanosomes which are characterized by having a single long whip-like projection known as a flagellum. Members of this group are parasitic, mostly on insects, but several genera have life cycles that involve alternative hosts including plants and vertebrates. The latter group include the species that can cause severe diseases in humans including Leishmaniasis (*Leishmania* spp), African sleeping sickness and Chagas disease (*Trypanosoma* spp.), and others.

Figure 1. Female phlebotomine sandfly. Credits: CDC/WHO

The life cycles of trypanosomes include a variety of different forms, distinguished mostly by the position of the flagellum. All trypanosomes have at least a *promastigote* stage, in which the flagellum occurs anterior to the cell nucleus, and an *amastigote* stage where the flagellum is highly reduced or absent.

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The life cycle of *Leishmania* includes insect (sandflies) and vertebrate phases (Figure 2). The cycle begins when an infected sandfly takes a blood meal from an animal or person and injects the promastigote stage into the skin. The promastigotes are then engulfed by macrophages, specialized white blood cells whose primary function is to engulf and digest (phagocytize) cellular debris and pathogens. In the case of *Leishmania*, however, rather than being digested, the pathogen promastigotes transform into amastigotes and multiply within the host's cells (including the macrophages).

When an uninfected sandfly takes a blood meal from the infected host, cells infected with amastigotes are ingested. The amastigotes transform into promastigotes and multiply in the insect's midgut and then migrate to the mouthparts, where they are ready to infect another host with the next sandfly blood meal.

Most leshmaniases are zoonotic (transmitted to humans from animals), however there are also anthroponotic forms where humans are the only reservoir host.

Forms and Symptoms

Symptoms of infection can be extremely varied. Some common symptoms of the disease include fever, overall malaise, weight loss, anemia and, in the visceral forms, swelling of internal organs.

There are four major forms of human leishmaniasis. The particular presentation of the disease reflects a complex interplay between the individual infecting species and the host's immune response.

- **Cutaneous leishmaniasis** (CL - Baghdad ulcer, Delhi boil, *Bouton d'Orient*) - is the most common form of the disease and produces large numbers of skin lessions that self-heal within a few months but can leave many unsightly and sometimes disabling scars.
- **Diffuse cutaneous leishmaniasis** (DCL) - produces disseminated and chronic skin lessions that do not heal spontaneously and tend to relapse after treatment.

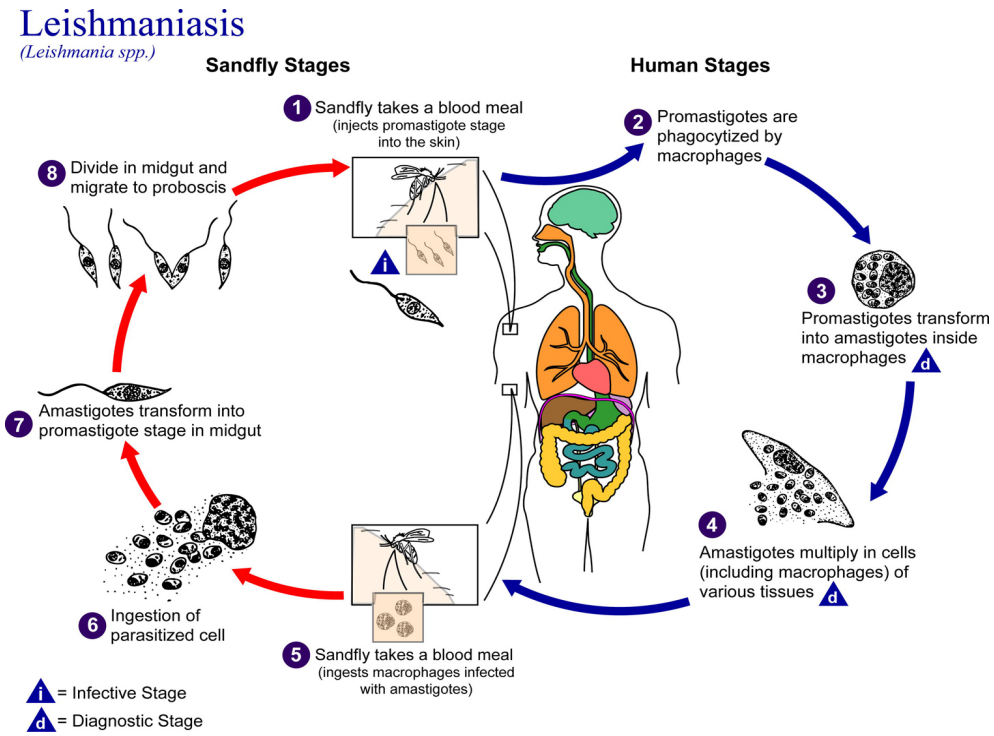

Figure 2. *Leishmania* life cycle. Credits: Centers for Disease Control (US)

- **Mucocutaneous leishmaniasis** (MCL - espundia) - begins with skin ulcers and progresses to lesions which cause massive tissue

destruction of the mouth, nose and throat cavities and severe disfigurement.

- **Visceral leishmaniasis** (VL - *kala azar*, black fever) - is the most serious form of the disease and causes death in almost 100% of the cases if left untreated. Symptoms include significant swelling of the spleen and liver, irregular fever episodes, substantial weight loss, and anemia. Progress of the disease is extremely variable. The usual duration is 12-16 weeks, but individual cases can last from one to more than 20 weeks.

Sometimes a secondary form of the disease called **post kala-azar dermal leishmaniasis** sets in a few months to several years after recovery from VL. The disease starts as small skin lessions on the face which gradually enlarge and spread over the body. The lessions may eventually form disfiguring swollen structures that may cause blindness if they reach the eyes. This condition is distinct from the milder cutaneous leishmaniasis described above.

Distribution

Leishmaniasis occurs in Mexico, Central America, and South America (except Uruguay and Chile), southern Europe, Asia, the Middle East, and Africa, particularly East and North Africa. Approximately 350 million people live in areas vulnerable to the disease. According to the Centers for Disease Control, approximately 1.5 million new cases of cutaneous leishmaniasis and about 500,000 cases of visceral leishmaniasis occur each year (CDC 2004). These figures are probably underestimates, as significant numbers of cases are never reported. A large proportion of the visceral leishmaniasis cases occur in India, Bangladesh, Nepal, Brazil, and Sudan. In Sudan, a decade long epidemic resulted in close to 100,000 deaths from 1984 to 1994.

A sharp increase in numbers of cases has been recorded since the early 1990s. For example, in 1997, the number of confirmed cases in Sudan increased by close to 400% from the previous year. Civil unrest in the region spread the epidemic to Eritea and Ethiopia. A similar increase has been noted in Brazil, where CL increased from 21,800 cases in 1998 to 60,000 cases in 2003. In that year there were also 3000 to 5000 cases of VL (Berman 2006).

Leishmaniasis in the United States

In the United States, rare cases of the cutaneous form of the disease have been reported from southern Texas, but no cases of visceral leishmaniasis are known to have been acquired in the U.S. An enzootic transmission cycle involving *Leishmania mexicana* in Texas has been described, indicating that cutaneous leishmaniasis may be more common than previously thought (Kerr *et al. 1*995).

In 2000, public health authorities in the United States, discovered that hunting dogs in 21 U.S. states and the Canadian province of Ontario were infected with *Leishmania infantum*, a species that can cause visceral leishmaniasis. The infection appears to be widespread in foxhounds, but so far transmission appears to be limited to dog-to-dog mechanisms. However, if the local form of *L. infantum* becomes adapted for transmission by indigenous sandflies, the chances of human infection will be greatly increased.

North American sandflies have not been implicated in transmission of VL, however, four species of North American sandflies of the genus *Lutzomyia* are mammalian feeders. *Lutzomyia anthorpora* and *Lu. diabolica* are found in Texas; *Lu. cruciata* in Florida and Georgia; and *Lu. shannoni* in Alabama, Arkansas, Delaware, Florida, Georgia, Lousiana, Mississippi, North Carolina, South Carolina, and New Jersey (Young and Perkins 1984).

Experimental studies have shown that *Lu.shannoni* became infected with *L. infantum* after feeding on *Leishmania*-infected dogs (Travi *et al.* 2002). The authors hypothesized that these insects were competent vectors and could initiate enzootic (constantly present in animals) cycles of *Leishmania* transmission in new locations if infected animals were present.

The range of some of the North American sandflies mentioned above overlap the locations of many of the locations with *Leishmania*-infected dogs. As the reservoir of infection in canine hosts grows larger and more dispersed, the possibility increases

that conditions will lead to exposure of competent vectors and subsequent vectorborne transmission.

The disease is also of concern to military and other US personnel deployed overseas and to people visiting regions where leishmaniasis is endemic.

Treatment

Some cases of cutaneous leishmaniasis heal without treatment and confer immunity to the affected individual. In some locations in Asia, infections in the buttocks of babies are encouraged to immunize the baby and prevent future disfiguring scars on more visible parts of the body such as the face and arms. Multiple infections in the same individual, however, have been reported.

Other forms of the disease are extremely difficult to treat, and may require long-term treatment with pentavelant antimony drugs. However, resistance to these drugs is high in certain parts of the world, particularly in India (Sundar *et al.* 2000), requiring treatment with more toxic and expensive drugs such as amphotericin, a powerful antifungal agent with some serious side effects that may include kidney damage and severe allergic reactions. Other drugs such as miltefosine and fluconazole have shown promise for treatment of leishmaniasis, and still others are currently in clinical trials.

At present there is no approved vaccine against the disease, but several leishmaniasis candidate vaccines are in various stages of development. One promising substance being produced in Switzerland is a carbohydrate vaccine delivered in an influenza virus envelope that has shown strong protective action against leishmaniasis in laboratory studies.

Leishmaniasis and HIV/AIDS

To date, co-infection with leishmaniasis and HIV has been reported in 34 countries in Africa, Asia, Europe, and South America. The impact of this emerging public health problem is readily apparent and increasingly severe. In southern Europe, for example, up to 70% of adult cases of visceral leishmaniasis are associated with HIV infection. Intravenous drug users are the most seriously affected group. When co-infection reporting began in 1998, the number of cases represented by southwestern Europe was two-thirds of the total number and approximately 71% of those co-infected patients were IV drug users.

Physicians for the World Health Organization note that VL hastens the onset of AIDS, especially since *Leishmania* parasites and HIV often destroy the same cells. Currently, geographic information systems and geostatistical techniques are being used to track and analyze trends and to map and monitor patterns of co-infection.

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