***Leishmania* (mammals)**
(protist: flagellate)

Overview

Protists are single-celled organisms with membrane-bound nuclei (eukaryotes). Flagellates are protists that swim using one or more flagella (undulipodia); each arising from a small centriole (basal body, kinetosome) and having a microtubular axoneme core (2+9 configuration). Rather than forming a monophyletic group, flagellates are divided into several disparate groups: metamonads (amitochondriate flagellates), heteroloboseans (amoeboflagellates), euglenozoans (euglenids and kinetoplastids), stramenopiles (heterokonts), alveolates (dinoflagellates) and cercozoans (biflagellates). Most kinetoplastids are parasitic in vertebrate or invertebrate hosts (some in plants) whereas the remainder are free-living aquatic organisms. All species are characterized by the possession of extranuclear DNA in the form of a kinetoplast, a unique structure formed by massed DNA (circles or lattice) within the single large mitochondrion near the flagellar basal body. The flagellates reproduce by longitudinal binary fission and parasitic species may have simple monoxenous (one-host) or more complicated heteroxenous (two-host) life cycles involving different developmental stages. Trypanosomes have a single flagellum and they form four main developmental stages: trypomastigotes (with a posterior kinetoplast and an emergent flagellum forming a long undulating membrane); epimastigotes (with an anterior kinetoplast and an emergent flagellum forming a short undulating membrane); promastigotes (with an anterior kinetoplast and a short emergent flagellum, but no undulating membrane); and amastigotes (with a kinetoplast but no emergent flagellum or undulating membrane). Many trypanosome species are parasitic only in insects whereas others are transmitted by insect vectors to a wide range of vertebrate hosts. Three main groups infect the blood and/or tissues of humans and animals causing severe clinical diseases: including the leishmanias which develop in the foregut of insect vectors and are transmitted via bite to the tissues of vertebrate hosts (e.g. sand flies transmit *Leishmania* spp. causing cutaneous, mucocutaneous or visceral disease in humans and animals).

Classification:

Domain:	Eukaryota (membrane-bound nucleus)
Supergroup:	Excavata (with conspicuous ventral feeding groove)
Group:	Discoba (diverse group supported robustly by molecular studies)
Phylum:	Euglenozoa (flagella inserted in anterior pocket, some heterotrophs, some autotrophs (with chloroplasts))
Class:	Kinetoplastea (heterotrophs, with extranuclear DNA (= kinetoplast) associated with mitochondrion)
Subclass:	Metakinetoplastina (large polyphyletic group supported by molecular studies)
Order:	Trypanosomatida (parasitic, single anterior flagellum, often forming undulating membrane)
Family:	Trypanosomatidae (monogenetic forms in insects/plants, digenetic forms in vertebrates & arthropods)
Genus:	*Leishmania* (vector-borne tissue parasites)
Species:	various species cause cutaneous, mucocutaneous or visceral leishmaniasis in humans

Parasite biodiversity and host range: Protists are unicellular eukaryotes that move using undulipodia (flagella or cilia), pseudopodia (false-feet) or a unique gliding motion. Flagellated species have one or more flagella with an internal microtubular core (in a characteristic 2+9 configuration comprising 2 single central microtubules and 9 peripheral doublets) anchored to a submembranous protein structure (known variously as a centriole, basal body, kinetosome or blepharoplast). Many types of flagellated cells have been described and recent phylogenetic studies have classified them into several disparate groups: including the metamonads (amitochondriate flagellates), heteroloboseans (amoeboflagellates), euglenozoans (euglenids and kinetoplastids), stramenopiles (heterokonts), alveolates (dinoflagellates) and cercozoans (biflagellates). While most flagellated protists are free-living organisms swimming and feeding in aquatic environments, representatives of several groups have developed symbiotic relationships with various hosts; some being endoparasitic in vertebrates (notably anaerobic metamonads in tubular organs, and heterotrophic euglenozoans occurring in blood or tissues), and some being parasitic in invertebrates (alveolates in crustacean tissues) (representatives tabulated below).

Higher taxonomy	Class or order	Family	Genera	Hosts (tissues)	Trans-mission*
Supergroup: Excavata (with conspicuous ventral feeding groove)					
Group: Metamonad (amitochondriate flagellates with karyomastigonts)					
Phylum: Fornicata (diplomonads)	Order: Diplomonadida (1-2 karyomastigonts)	Hexamitidae (2 karyomastigonts with binary axial symmetry)	*Giardia*	vertebrates (gut)	direct (f-o)
			Hexamita *Spironucleus*	vertebrates (tissues)	direct (f-o, w)
Phylum: Parabasalia (with parabasal body)	Order: Trichomonadida (3-5 anterior flagella plus recurrent flagellum)	Monocercomonadidae (costa absent, most without undulating membrane)	*Histomonas*	birds (gut, liver)	direct (f-o)
			Dientamoeba	vertebrates (gut)	direct (f-o)
		Trichomonadidae (stout axostyle, costa, undulating membrane)	*Trichomonas*	vertebrates (urogenital tract, gut)	direct (f-o, v)
		Cochlosomatidae (anterior adhesive disc)	*Cochlosoma*	birds (gut)	direct (f-o)
Group: Discoba (diverse group supported robustly by molecular studies)					
Phylum: Euglenozoa (flagella inserted in anterior pocket, heterotrophs, autotrophs)	Class: Kinetoplastea (heterotrophs, with extranuclear DNA (= kinetoplast) associated with mitochondrion)	Ichthyobodonidae (flagellar pocket continues as groove)	*Ichthyobodo* (= *Costia*)	fish (gills, skin)	direct (w)
		Parabodonidae (epizoic or endozoic)	*Cryptobia*	fish (gills, skin)	direct (w)
			Trypanoplasma	fish (blood)	indirect (v-b)
		Trypanosomatidae (monogenetic forms in insects/plants, digenetic forms in vertebrates & arthropods)	*Trypanosoma*	vertebrates (blood, tissues)	indirect (v-b)
			Leishmania	vertebrates (blood, tissues)	indirect (v-b)
Supergroup: SAR (Stramenopiles + Alveolata + Rhizaria) (3 groups unified by molecular studies)					
Group: Alveolata (with cortical alveoli)					
Phylum: Dinoflagellata (with unique mesokaryotic nuclei)	Order: Blastodiniales (uninucleate trophonts with chloroplasts)	Oodiniaceae (trophont with rhizoid-like invasive organelle)	*Amyloodinium* *Crepidoodinium* *Piscinoodinium*	fish (skin)	direct (w)
	Order: Syndiniales (multinucleate plasmodial trophonts)	Syndiniaceae (without chloroplasts)	*Haematodinium* *Ichthyodinium*	crustaceans, fish (tissues)	direct (w)
Phylum: Perkinsozoa (parasitic)	Order: Perkinsorida (released trophonts form biflagellated zoospores)	Perkinsidae (incomplete conoid)	*Perkinsus*	gastropods, bivalves (tissues)	direct (w)

*f-o = faecal-oral transmission; v-b = vector-borne transmission, w = water-borne transmission; v = venereal transmission

Euglenozoans comprise a large group of excavates (with ventral feeding groove), most with 1-2 flagella inserted into an anterior pocket. Many species are free-living aquatic autotrophs possessing chloroplasts while others are free-living or symbiotic heterotrophs feeding on solutes, particles and even other organisms. Kinetoplastids are characterised by the possession of a kinetoplast (containing mitochondrial DNA separate from nuclear DNA), a flagellar pocket, basal bodies with three microtubular roots and paraxonemal (paraxial or paraflagellar) rods, and asexual multiplication by longitudinal binary fission. The unique kinetoplast is formed by massed DNA (circles or lattice) usually closely associated with the flagellar basal body (eukinetoplastic) although some species may be polykinetoplastic (with several kinetoplasts) or pankinetoplastic (irregular kDNA) and some mutants even dyskinetoplastic (without a kinetoplast). Two major kinetoplastid groups are recognized: bodonids with two flagella (most being free-living bactivores in aquatic/terrestrial habitats); and trypanosomes with a single flagellum (most being parasites of animals or plants with monoxenous or dixenous life-cycles). Different kinetoplastid assemblages exhibit increasing morphological/ultrastructural complexity in their cellular organization thought to reflect evolutionary grades or clines. Amastigotes are simple non-flagellated cells, choano-, pro- and opistho-mastigotes are flagellated cells with elongate flagella, while epi- and trypo-mastigotes are flagellated cells with undulating membranes. Most kinetoplastids have amastigote and promastigote developmental stages but monoxenous parasites of insects (e.g. *Crithidia*, *Herpetomonas*) do not have more elaborate forms whereas dixenous parasites of plants or animals with invertebrate vectors (e.g. *Trypanosoma, Leishmania*) do have more morphologically complex forms such as epimastigotes and trypomastigotes.

Traditional classification	Molecular classification	Genera	No. spp.	Vertebrate hosts	Transmission (vectors)
F: Trypanosomatidae	SC: Metakinetoplastina F: Trypanosomatidae	*Trypanosoma*	537	mammals, reptiles, frogs, birds, fish	indirect (arthropods, leeches)
		Leishmania	53	mammals, lizards	indirect (sand flies)
F: Bodonidae	SC: Metakinetoplastina F: Parabodonidae	*Cryptobia, Trypanoplasma*	79	fish	direct or indirect (leeches)
	SC: Prokinetoplastina F: Ichthyobodonidae	*Ichthyobodo* (*Costia*)	5	fish	direct

Conventional taxonomic classification systems divide the kinetoplastids into 2 groups: the free-living bi-flagellated Bodonina; and the parasitic uni-flagellated Trypanosomatina. Over 600 species have been described on the basis of multiple phenotypic characters (host occurrence, geographic distribution, vectors, transmission cycles, morphology, development, pathogenicity, culture requirements, etc.). Modern molecular characterization studies, however, have shown that many traditional groups are polyphyletic and composed of numerous clades. Contemporary phylogenetic classifications recognize 2 main lineages: the Prokinetoplastina represented by 2 diverse genera (*Ichthyobodo* biflagellates ectoparasitic on freshwater and marine fishes, and *Perkinsela* (= *Perkinsiella*) aflagellates endosymbiotic (as parasomes or parasome-like organisms (PLOs)) in amoeba *Paramoeba* and *Neoparamoeba*); and the Metakinetoplastina containing 4 groups, including free-living aquatic eu-bodonids (with one genus *Bodo*), free-living neo-bodonids (with 10 genera, including *Rhynchomonas*), free-living or commensal/parasitic para-bodonids (with 5 genera, including *Cryptobia, Trypanoplasma*), and the parasitic trypanosomatids (containing some 39 genera, including *Trypanosoma* and *Leishmania*). Trypanosomatids are dixenous (2-host) parasites with indirect transmission cycles between vertebrates and invertebrate vectors. *Leishmania* spp. form amastigote stages in the tissues of vertebrate hosts, and promastigote stages in invertebrate haematophagous vectors. Infections have been found in a range of vertebrate hosts (mammals and reptiles) with several types of diptera (sandflies) implicated as vectors. Infections in mammals are most commonly found in humans, dogs and rodents. Infections are confined to tropical areas; different parasite species being found in the Old World (Middle-East and Africa) and the New World (Central and South America). However, the recent discovery of *Leishmania* in macropodid marsupials in northern Australia indicates broader zoogeographic boundaries for parasites, hosts and vectors than previously thought.

Infections in humans have been reported for centuries (as early as the 1500s) with Spanish colonists and others describing skin ulcers in South America, the Middle-East and India (conditions known variously as valley sickness, Andean disease, uta, espundia, Chiclero ulcer, Aleppo boil, Delhi boil, salek, forest yaws and dum dum fever). Leishmaniasis is currently endemic in almost 100 countries and some 350 million people are at risk, with around 2 million new cases each year. Most cases of cutaneous leishmaniasis occur in Iran, Afghanistan, Syria, Saudi Arabia, Brazil and Peru, while most cases of visceral leishmaniasis are found in Bangladesh, Brazil, India and Sudan. *Leishmania* spp. were initially identified on the basis of biological (host/vector specificity, geographic distribution), clinical (symptoms/signs, tissue tropism) and immunological (antigenic) variation, as the very small parasites were remarkably similar morphologically. The classification of *Leishmania* species is complex and several systems have been proposed based on phenotypic and genotypic traits (although most do not advocate formal taxonomic ranks).

- Categorization by clinical disease:
  - Cutaneous leishmaniasis (localized, diffuse (disseminated), leishmaniasis recidivans, or post–kala-azar dermal leishmaniasis) arising from infection of macrophages in the dermis;
  - Mucocutaneous leishmaniasis arising from infection of macrophages in the naso-oropharyngeal mucosa; and
  - Visceral leishmaniasis (kala-azar, or black fever) arising from infection of macrophages throughout reticulo-endothelial system of vertebrate hosts.

- Categorization by geographic occurrence:
  - Old World (Eastern Hemisphere) leishmaniasis, caused by species found in Africa, Asia, Middle East, Mediterranean and India (cutaneous or visceral disease caused by various species complexes in the *L. Leishmania* subgenus [e.g. *L.* (*L.*) *tropica*, *L.* (*L.*) *major* and *L.* (*L.*) *aethiopica*, as well as *L.* (*L.*) *infantum* and *L.* (*L.*) *donovani*]; and
  - New World (Western Hemisphere) leishmaniasis, caused by species found in Central and South America (cutaneous, mucocutaneous and visceral disease caused by species belonging either to the *L.* (*L.*) *mexicana* complex [e.g. *L.* (*L.*) *mexicana*, *L.* (*L.*) *amazonensis* and *L.* (*L.*) *venezuelensis*] or to several species complexes in the *L. Viannia* subgenus [e.g. *L.* (*V.*) *braziliensis*, *L.* (*V.*) *guyanensis*, *L.* (*V.*) *panamensis* and *L.* (*V.*) *peruviana*]).

- Categorization by vector:
  - *Phlebotomus* sand fly vectors (in Old World);
  - *Lutzomyia* sand fly vectors (in New World).

- Categorization by vector tissue tropism:
  - Hypopylarian (hindgut) development in sandfly with transmission via vector consumption (comprises 'primitive' species in lizards e.g. *L. agamae, L. ceramodactyli*);
  - Peripylarian (hindgut then foregut) development in sandfly with inoculative transmission (comprises some lizard parasites of Old World (*L. adleri, L. tarentolae*) but dominated by *L.* (*L.*) *braziliensis* complex of Western Hemisphere); and
  - Suprapylarian (midgut and foregut) development in sandfly with inoculative transmission (comprises species causing cutaneous lesions in New World (*L.* (*L.*) *mexicana* and *L.* (*V.*) *hertigi* complexes) and Old World (*L.* (*L.*) *tropica* complex) or visceral disease in New and Old World (*L.* (*L.*) *donovani* complex).

- Categorization by subgenus:
  - Species in mammals with suprapylarian development in sand flies were classified together in the subgenus *L. Leishmania* (generally in the Paleotropics, with the exception of the '*L.* (*L.*) *mexicana'* species complex);
  - Species in mammals with peripylarian development in sand flies were allocated to the subgenus *L. Viannia* (generally located in the Neotropics); and
  - Species in lizards with hypopylarian development in sand flies were grouped in the subgenus *L. Sauroleishmania* (generally confined to the Old World).

- Categorization by molecular characteristics:
  - Protein and isoenzyme characterization studies indicated that infections in humans and some animals were often highly complex consisting of multiple strains or subspecies (possibly even hybrids), therefore infections have been referred to as species complexes (comprising closely related species).
  - Recent phylogenetic studies have identified three major *Leishmania* clades referable to different subgenera: *L. Viannia* species causing New World cutaneous and mucocutaneous leishmaniasis and undergoing peripylarian development in *Lutzomyia* sandflies; *L. Leishmania* species causing New and Old World cutaneous and visceral leishmaniasis and undergoing suprapylarian development in *Phlebotomus* sandflies; and an intermediary *L. Sauroleishmania* group undergoing hypopylarian development in sand flies and infecting Old World lizards when the vectors are ingested.

Most conventional *Leishmania* spp. have been classified within species complexes within these subgenera. In the Old World, four *L.* (*Leishmania*) complexes are recognized: the 'donovani' complex (comprising *L.* (*L.*) *donovani*, *L.* (*L.*) *infantum* and *L.* (*L.*) *archibaldi*); the 'tropica' complex (*L.* (*L.*) *tropica* and *L.* (*L.*) *killicki*); the 'major' complex (*L.* (*L.*) *major*); and the 'aethiopica' complex (*L.* (*L.*) *aethiopica*). In the New World, four *L.* (*Viannia*) complexes are recognized: the 'Brazilian' complex (comprising *L.* (*V.*) *braziliensis* and *L.* (*V.*) *peruviana*); the 'Guayanian' complex (*L.* (*V.*) *panamensis*, *L.* (*V.*) *guayensis* and *L.* (*V.*) *shawi*); the 'naiffi' complex (*L.* (*V.*) *naiffi*); and the 'lainsoni' complex (*L.* (*V.*) *lainsoni*); as well as two *L.* (*Leishmania*) complexes: the 'Mexican' complex (*L.* (*L.*) *mexicana*, *L.* (*L.*) *amazonensis*, *L.* (*L.*) *garnhami*, *L.* (*L.*) *venezuelensis*, *L.* (*L.*) *forattinii* and *L.* (*L.*) *pifanoi*) and a member of the 'donovani' complex (*L.* (*L.*) *chagasi*). A fourth subgenus has recently been added: *L.* (*Mundinia*) comprising the 'enrietti' complex causing cutaneous and visceral lesions in humans and animals and undergoing suprapylarian development in sand flies and biting midges.

***Leishmania* species**	**Vertebrate hosts**	**Disease**	**Vectors**	**Distribution**
CUTANEOUS (and MUCOCUTANEOUS) LEISHMANIASIS				
Subgenus *Leishmania*				
'*mexicana'* complex				
L. (*L.*) *mexicana* (syn. *L. diffusa, pifanoi*)	Primates: hominid (human), Didelphimorphia: didelphid (common opossum, common black-eared opossum, big-eared opossum, Mexican mouse-opossum, Robinson's mouse opossum); Rodentia: caviid (guinea pig), cricetid (short-tailed cane mouse, big-eared climbing rat, Sumichrast's vesper rat, hispid cotton rat, large-headed rice rat, Brazilian pygmy rice rat, Syrian hamster), cuniculid (lowland paca), dasyproctid (Azara's agouti, Central American agouti), echimyid (Guyenne spiny rat, Tome's spiny rat, Atlantic bamboo rat), heteromyid (Gaumer's spiny pocket mouse, Trinidad spiny	chicleros ulcer, cutaneous	Diptera: psychodid (*Lutzomyia anthopora, ayacuchensis, columbia, cruciata, diabolica, migonei, olmeca, ovallesi, panamensis, shannoni, ylephiletor, flaviscutellata*)	Americas

	pocket mouse, Desmarest's spiny pocket mouse), murid (house mouse, wistar rat, Mongolian gerbil)			
L. (*L.*) *amazonensis*	Primates: hominid (human); Didelphimorphia: didelphid (common opossum, white-eared opossum, brown four-eyed opossum, grey four-eyed opossum, Tate's woolly mouse opossum, woolly mouse opossum, Linnaeus's mouse opossum); Rodentia: cricetid (common bristly mouse, scaly-footed water rat, large-headed rice rat, unicolored rice rat, MacConnell's rice rat), dasyproctid (agouti), echimyid (Guyenne spiny rat); Carnivora: canid (crab-eating fox), felid (cat)	diffuse, cutaneous	Diptera: psychodid (*Lutzomyia flaviscutellata, longipalpis, nuneztovari, olmeca, reducta*)	South America
L. (*L.*) *venezuelensis*	Primates: hominid (human); Carnivora: felid (cat)	cutaneous	Diptera: psychodid (*Lutzomyia olmeca, rangeliana*)	Venezuela
L. (*L.*) *garnhami*	Primates: hominid (human); Didelphimorphia: didelphid (common opossum)	cutaneous	Diptera: psychodid (*Lutzomyia youngi*)	Central America
L. (*L.*) *forattinii*	Didelphimorphia: didelphid (big-eared opossum); Rodentia: cricetid (rice rat)	cutaneous	Diptera: psychodid (*Lutzomyia ayrosai, yuilli*)	Brazil
'*tropica'* complex				
L. (*L.*) *tropica*	Primates: hominid (human), Carnivora: canid (dog); Rodentia: murid (dwarf gerbil, unstriped grass mouse, Mullah spiny mouse)	dry cutaneous	Diptera: psychodid (*Phlebotomus aculeatus, arabicus, chabaudi, guggisbergi, rossi, saevus, sergenti*)	Middle-East, India, Aia, Africa
L. (*L.*) *killicki*	Primates: hominid (human); Rodentia: ctenodactylid (common gundi), murid (mouse)	cutaneous	Diptera: psychodid (*Phlebotomus sergenti*)	North Africa
'*major'* complex				
L. (*L.*) *major*	Primates: hominid (human); Carnivora: canid (dog); Rodentia: dipodid (jerboa), murid (great gerbil, Indian gerbil, Indian desert jird, Libyan jird, sand rat, unstriped grass mouse, house mouse), sciurid (ground squirrel)	wet cutaneous, oriental sore	Diptera: psychodid (*Phlebotomus andrejevi, ansarii, caucasicus, duboscqi, mongolensis, papatasi*)	Africa, Asia, India
'*aethiopica'* complex				
L. (*L.*) *aethiopica*	Primates: hominid (human); Hyracoidea: procaviid (rock hyrax, yellow-spotted rock hyrax)	chronic oriental sore, diffuse or dry cutaneous	Diptera: psychodid (*Phlebotomus longipes, pedifer, sergenti*)	Ethiopia, Kenya
unplaced				
L. (*L.*) *arabica*	Rodentia: murid (fat sand rat)	cutaneous		Middle-East
L. (*L.*) *aristidesi*	Didelphimorphia: didelphid (Robinson's mouse opossum); Rodentia: cricetid (large-headed rice rat), cuniculid (lowland paca), echimyid (Tome's spiny rat)	cutaneous	Diptera: psychodid (*Lutzomyia olmeca*)	Panama
L. (*L.*) *deanei* (now *Porcisia*)	Rodentia: erethizontid (Brazilian porcupine, Andean porcupine)	cutaneous	Diptera: psychodid (*Lutzomyia furcata*)	Brazil
L. (*L.*) *gerbilli*	Rodentia: murid (great gerbil)	cutaneous		Eurasia
L. (*L.*) *herreri*	Pilosa: bradypodid (brown-throated sloth), choloepodid (Hoffmann's two-toed sloth)	cutaneous	Diptera: psychodid (*Lutzomyia* sp.)	South America
L. (*L.*) *hertigi* (now *Porcisia*)	Rodentia: erethizontid (Brazilian porcupine, Andean porcupine)	cutaneous		Panama, Costa Rica

L. (*L.*) *turanica*	Primates: hominid (human), and unspecified monkey; Rodentia: murid (great gerbil, Mongolian gerbil, short-tailed bandicoot rat, house mouse), cricetid (golden hamster, Chinese striped hamster)	cutaneous	Diptera: psychodid (*Phlebotomus mongolensis, andrejevi, papatasi, arabicus*)	Eurasia
Subgenus *Viannia*				
'*braziliensis*' complex				
L. (*V.*) *braziliensis* (syn. *L. wrightii*)	Primates: hominid (human); Didelphimorphia: didelphid (common opossum, white-eared opossum, agile gracile opossum, bare-tailed woolly opossum, woolly mouse opossum, Tate's woolly mouse opossum): Pilosa: bradypodid (brown-throated sloth), choloepodid (Hoffmann's two-toed sloth, Linnaeus's two-toed sloth); Rodentia: cricetid (large-headed rice rat, unicolored rice rat, black-footed pygmy rice rat, montane grass mouse), murid (black rat); Carnivora: canid (dog); Perissodactyla: equid (horse)	espundia, cutaneous, mucocutaneous	Diptera: psychodid (*Lutzomyia ayrozai, carrerai, columbiana, complexa, cruciata, davisi, edwardsi, fischeri, gomezi, intermedia, llanosmartini, migonei, neivai, nuneztovari, ovallesi, panamensis, paraensis, pescei, pessoai, pia, shawi, spinicrassa, tejadai, townsedni, trinidadensis, ylephiletor, youngi, yucumensis, wellcomei, whitmani*)	Central and South America
L. (*V.*) *peruviana*	Primates: hominid (human); Carnivora: canid (dog); Rodentia: cricetid (South American field mouse, Andean leaf-eared mouse); Didelphimorphia: didelphid (Andean white-eared opossum, white-eared opossum)	uta, cutaneous	Diptera: psychodid (*Lutzomyia ayacuchensis, peruensis, verrucarum*)	Peru, Bolivia
'*quayanensis*' complex				
L. (*V.*) *panamensis*	Primates: hominid (human), aotid (three-striped night monkey), callitrichid (Geoffroy's tamarin); Pilosa: bradypodid (brown-throated sloth), choloepodid (Hoffmann's two-toed sloth); Carnivora: canid (dog), procyonid (northern olingo, South American coati, kinkajou); Rodentia: echimyid (Tome's spiny rat, armoured rat)	cutaneous	Diptera: psychodid (*Lutzomyia cruciata, gomezi, hartmanni, panamensis, sanguinaria, trapidoi, ylephiletor, yuilli, Psychodopygus panamensis*)	Panama, Costa Rica
L. (*V.*) *guyanensis*	Primates: hominid (human); Pilosa: choloepodid (two-toed sloth), myrmecophagid (southern tamandua); Didelphimorphia: didelphid (common opossum, grey slender opossum)	cutaneous, mucocutaneous, pian bois	Diptera: psychodid (*Lutzomyia anduzei, ayacuchensis, longiflocosa, migonei, shawi, umbratilis, whitmani*)	Brazil, Columbia
L. (*V.*) *shawi*	Primates: hominid (human), cebid (tufted capuchin), pithecid (black-bearded saki); Pilosa: bradypodid (pale-throated sloth), choloepodid (Linnaeus's two-toed sloth); Carnivora: procyonid (South American coati)	cutaneous	Diptera: psychodid (*Lutzomyia whitmani*)	Brazil
'*naiffi*' complex				
L. (*V.*) *naiffi*	Primates: hominid (human); Cingulata: dasypodid (nine-banded armadillo); Rodentia: echimyid (Foster's punare)	cutaneous	Diptera: psychodid (*Lutzomyia amazonensis, antunesi, ayrozai, davisi, gomezi,hirsuta, paraensis, shawi, sordelli, squamiventris, tortura, trapidoi,*	Brazil, French Guiana

			Psychodopygus amazonensis, Nyssomyia anduzei)	
'*lainsoni'* complex				
L. (*V.*) *lainsoni*	Primates: hominid (human); Rodentia: cuniculid (lowland paca)	cutaneous	Diptera: psychodid (*Lutzomyia nuneztovari, ubiquitalis, velascoi*)	Brazil
unplaced				
L. (*V.*) *colombiensis*	Primates: hominid (human); Pilosa: choloepodid (Hoffmann's two-toed sloth); Rodentia: sciurid (red-tailed squirrel)	cutaneous	Diptera: psychodid (*Lutzomyia hartmanni, gomezi, panamensis*)	Columbia
L. (*V.*) *equatorensis*	Primates: hominid (human); Pilosa: choloepodid (Hoffmann's two-toed sloth); Rodentia: sciurid (red-tailed squirrel)	cutaneous	Diptera: psychodid (*Lutzomyia hartmanni*)	Ecuador
L. (*V.*) *lindenbergi*	Primates: hominid (human)	cutaneous	Diptera: psychodid (*Lutzomyia antunesi*)	Brazil
Subgenus *Mundinia*				
'*enriettii'* complex				
L. (*M.*) *chancei*	Primates: hominid (human)	cutaneous		Africa
L. (*M.*) *enriettii*	Rodentia: caviid (guinea pig, Brazilian guinea pig), cricetid (hamster)	cutaneous	Diptera: psychodid (*Lutzomyia longipalpis, gomezi*, *correalmai, migonei, monticula*), ceratopogonid biting midges (*Culicoides sonorensis*)	South America
L. (*M.*) *macropodum (syn. L. australiensis*)	Diprotodontia: macropodid (red kangaroo, northern wallaroo, black wallaroo, agile wallaby)	cutaneous	Diptera: ceratopogonid (*Forcipomyia* (*Lasiohelea*), *Culicoides sonorensis*), psychodid (*Lutzomyia migonei*)	Australia
L. (*M.*) *martiniquensis*	Primates: hominid (human); Rodentia: murid (mouse); Artiodactyla: bovid (cattle); Perissodactyla: equid (horse)	diffuse cutaneous, visceral	Diptera: ceratopogonid (*Culicoides peregrinus, sonorensis),* psychodid *(Phlebotomus argentipes*)	Martinique, Thailand, Africa, Europe, North America
L. (*M.*) *orientalis* (syn. *L. 'siamensis'*)	Primates: hominid (humans)	cutaneous, visceral	Diptera: psychodid *(Phlebotomus argentipes, Sergentomyia gemmea, iyengari*), ceratopogonid (*Culicoides sonorensis),*	Asia
L. (*M.*) *procaviensis*	Hyracoidea: procaviid (rock hyrax)	(from nose)		Africa
VISCERAL LEISHMANIASIS				
Leishmania subgenus				
'donovani' complex				
L. (*L.*) *donovani*	Primates: hominid (human); Carnivora: canid (dog, red fox); Didelphimorphia: didelphid (common opossum, Virginia opossum); Diprotodontia: phalangerid (common brushtail possum, common ringtail possum); Rodentia: murid (black-tailed gerbil, Persian jird, unstriped grass mouse, Guinea multimammate mouse)	kala azar, dum-dum fever, Old World visceral	Diptera: psychodid (*Phlebotomus argentipes, celiae, longiductus, martini, orientalis, rodhaini, vansomerenae*)	India, Asia, Africa, South America
L. (*L.*) *archibaldi* (probable synonym of *L. donovani*)	Primates: hominid (human); Carnivora: canid (dog), felid (serval), viverrid (genet): Rodentia: murid (rat)	visceral	Diptera: psychodid (*Phlebotomus orientalis*)	Africa
L. (*L.*) *infantum*	Primates: hominid (human); Carnivora: canid (dog, raccoon dog,	infantile, visceral, cutaneous,	Diptera: psychodid (*Phlebotomus alexandri,*	Asia, Middle-East, Europe,

	wolf, golden jackal, red fox), felid (cat, European wildcat, Iberian lynx), herpestid (Egyptian mongoose), mustelid (stone marten, pine marten, weasel, European mink, polecat, European badger), viverrid (common genet); Lagomorpha: leporid (European rabbit, European hare, Iberian hare); Eulipotyphla: erinaceid (European hedgehog), soricid (greater white-toothed shrew); Didelphimorphia: didelphid (common opossum, white-eared opossum, big-eared opossum); Chiroptera: miniopterid (Schreiber's bat); Rodentia: cricetid (golden hamster, grey dwarf hamster), glirid (edible dormouse, garden dormouse), murid (house mouse, Algerian mouse, yellow-necked mouse, wood mouse, black rat, brown rat, fat sand rat, thin sand rat, great gerbil, Indian gerbil, Libyan jird, Persian jird), sciurid (red squirrel)	mucocutaneous	*ariasi, balcanicus, celiae, chinensis, galileus, halepensis, kandelakii, langeroni, longicuspis, longiductus, major, martini, neglectus, orientalis, perfiliewi, perniciosus, sichuanensis, smirnovi, syriacus, tobbi, transcaucasicus, turanicus, wui, Lutzomyia almerioi, antunesi, cruzi, evansi, forattinii, longipalpis, mignoei, pseudolongipalpis, sallesi*)	Africa, South America
L. (*L.*) *chagasi* (probable synonym of *L. infantum*)	Primates: hominid (human); Carnivora: canid (dog, hoary fox, crab-eating fox), felid (cat); Didelphimorphia: didelphid (common opossum)	New World visceral, cutaneous	Diptera: psychodid (*Lutzomyia antunesi, andyzei,cruciata, ovallesi, longipalpis, cruzi, evansi*)	South and Central America

Parasite morphology: Two developmental stages are formed: amastigotes and promastigotes. The amastigotes are small spherical cells ranging from 2-5 µm in diameter. They are non-flagellated cells but the cytoplasm contains a flagellar sac and a non-emergent vestigial flagellum. The nucleus and kinetoplast are surrounded by a small ring of vacuolated cytoplasm and the cells are among the smallest nucleated cells known. Promastigotes are thin elongate cells with an anterior kinetoplast and an emergent free flagellum. They are generally lance-like in shape and range in size from 5-20 µm in length by 1.5-3.5 µm in width. Different parasite species are generally not differentiated by morphological differences, but rather on the basis of geographical, biological and clinical features.

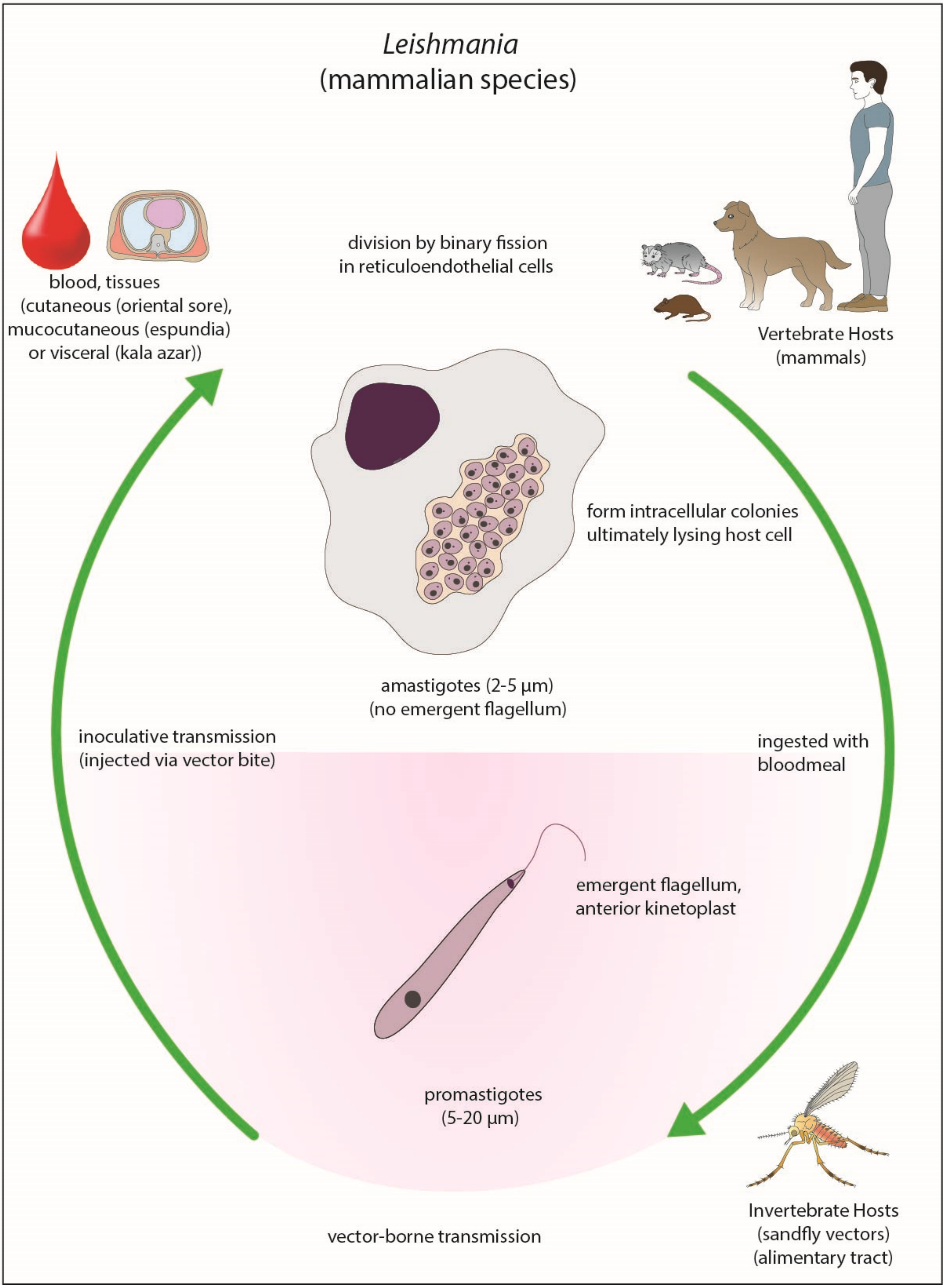
Site of infection: In vertebrates, amastigotes invade macrophage cells of the reticuloendothelial and lymphoid systems of the skin, nasopharynx or viscera depending on the parasite species. The parasites survive within phagosomes in host cells but resist digestion by lysosomal enzymes. They multiply and grow, ultimately rupturing the host cell and releasing stages to infect new macrophages, including those which circulate in the blood (monocytes). Around 36 *Leishmania* spp. have been described from mammals: with 32 species causing cutaneous/mucocutaneous lesions in 90 mammalian species belonging to 28 families in 10 orders (mostly rodents, but also carnivores, artiodactylans, armadillos, opossums, marsupials, hyraxes, horses, sloths and primates), and another 4 species causing visceral infections in 52 mammalian species belonging to 15 families in 8 orders (mainly carnivores and rodents, but also opossums, lagomorphs, marsupials, shrews, bats and humans). In insect vectors, promastigotes develop in the gut undergoing a process known as metacyclogenesis (involving the expression of different surface lipoproteins), with procyclic promastigotes attached to the gut wall, and metacyclic promastigotes maturing as the infective stages. A total of 114 insect species have been found to act as vectors: including 111 species of psychodid sandflies (mainly *Lutzomyia* and *Phlebotomus* spp. and a few *Nyssomyia, Psychodopygus* and *Sergentomyia* spp.) and 3 species of ceratopogonid biting midges (*Culicoides, Forcipomyia* (*Lasiohelea*)).

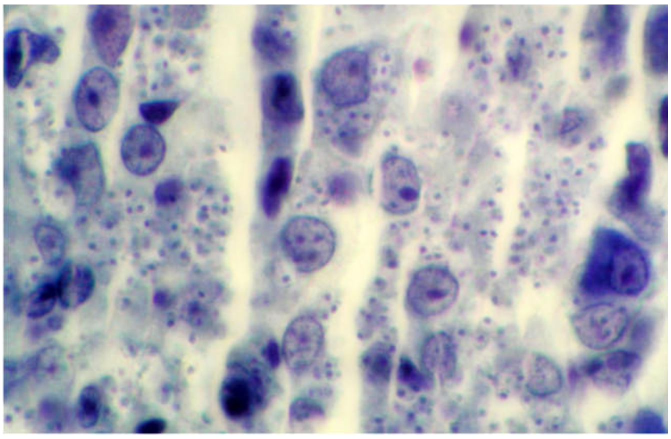
Pathogenesis: *Leishmania* amastigotes live in the reticulo-endothelial cells of vertebrate hosts and are not destroyed by proteolytic enzymes. Here they feed and replicate, ultimately causing host cell lysis. The parasites cause three distinct types of clinical disease: cutaneous, mucocutaneous and visceral leishmaniasis resulting from replication of the parasites in macrophages of the dermis, nasopharynx or visceral tissues. Old World (muco)cutaneous leishmaniasis is caused mainly by *L.* (*L.*) *major*, *L.* (*L.*) *tropica, L.* (*L.*) *aethiopica, L.* (*L.*) *infantum* and *L.* (*L.*) *donovani* (the last 2 species may also cause visceral disease), while New World (muco)cutaneous leishmaniasis is caused primarily *L.* (*V.*) *braziliensis*, *L.* (*V.*) *columbiensis*, *L.* (*L.*) *mexicana*, *L.* (V.) *lainsoni*, *L.* (*L.*) *garnhami*, *L.* (*L.*) *amazonensis*, *L.* (*V.*) *panamensis*, *L.* (*V.*) *guyanensis*, *L.* (*V.*) *peruviana* and *L.* (*L.*) *infantum* (the latter may also cause visceral leishmaniasis). Disease occurs mainly in those living or working in endemic areas, and outbreaks have been associated with military training and infrastructural development projects as well as travellers visiting scenic or remote locations. In the Old World, the disease occurs mainly in semi-arid and desert regions and is known by various common names depending on species and region, including oriental sore, Aleppo boil, Jericho boil, Baghdad boil, Balkh sore, Penjdeh sore, Briska button, Bouton de Crete and Bouton D'Orient. In the New World, the disease occurs mainly in forested areas and is known as uta, espundia, Chiclero'e ulcer, pain bois and forest yaws. Infections generally involve only one or a few lesions at the bite site; they do not spread to other sites. Active lesions appear as open sores or ulcers with raised borders and pronounced inflammation, occasionally developing into nodular and rarely verrucous lesions. The incubation period varies from one week to several months, and most lesions heal spontaneously within 6 months to 3 years, leaving the host with solid protective immunity to re-infection. However, under certain conditions (esp. immuno-compromised hosts), some infections (e.g. *L.* (*L.*) *aethiopica*) may spread giving rise to diffuse (disseminated) cutaneous leishmaniasis (not unlike leprosy in appearance) that does not resolve spontaneously. Infections by *L.* (*V.*) *braziliensis* are also often confined to single skin lesions, but sometimes they spread to the mucocutaneous junction in the pharynx and may cause severe destructive nasopharyngeal lesions developing over 5-20 years. Cutaneous infections by *L.* (*V.*) *guyanensis* may also spread to cause mucocutaneous lesions, and there is evidence to suggest that strains infected with endozoic *Leishmania* RNA virus 1 are more virulent due to their enhanced survival in the face of intense host inflammatory responses. Some patients may also develop a chronic cutaneous form of disease called post-kala-azar dermal leishmaniasis which requires prolonged treatment. Visceral leishmaniasis (known as kala-azar, black fever or dumdum fever) is caused by *L.* (*L.*) *donovani* and *L.* (*L.*) *infantum* when infected macrophages congregate in the viscera, notably the liver and spleen, producing leucopoenia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, oedema, ascites and anaemia. It is a slow but progressive illness, with bouts of irregularly recurring fever, malaise and weight loss and is invariably fatal, unless treated. The incubation period is usually 2-6 months, but has been found to range from as little as 10 days up to several years. Hosts are more susceptible to leishmaniasis when stressed and immunocompromised; due to congenital or acquired immunodeficiencies (esp. HIV-infection), immunosuppressive chemotherapy, and even malnutrition. Hosts are also more prone to concomitant bacterial infections, including tuberculosis, pneumonia and dysentery. The prevalence of leishmaniasis increases initially with host age and then plateaus, likely due to the acquisition of protective immunity. Clusters of disease are also seen within households, likely due to the short flight range of the sandfly vectors. Infections in dogs may be apparent as a progressive wasting disease characterized by weight loss, fever, anorexia, exercise intolerance, non-pruritic skin lesions, lymphadenopathy, lameness and epistaxis.

Developmental cycle and mode of transmission: *Leishmania* spp. undergo vector-borne transmission between vertebrate hosts. Epidemiologically, there are three different cycles of infection involving humans: a primitive or sylvatic cycle involving zoonotic transmission to humans from wildlife; a secondary or peri-domestic cycle involving zoonotic transmission from domestic animals; and a tertiary or anthroponotic cycle between humans. The spread of infections depends not only on the degree of contact between humans and animals, but to a greater extent on the abundance, distribution, specificity and competence of the vectors. Most *Leishmania* spp. are transmitted by blood-sucking sand flies belonging to the subfamily Phlebotominae in the dipteran family Psychodidae. These sand flies are small (2.0-3.5 mm long) and have lanceolate wings and tiny hairs covering their bodies. They occur on all continents (except Antarctica), but only two of the six genera are main vectors for leishmaniasis; the genus *Lutzomyia* in the New World (59 out of some 500 species implicated as vectors) and the genus *Phlebotomus* in the Old World (45 out of some 300 species). Only the females feed on blood which is required for them to complete their reproductive cycles, but they may also take up lymph and other extravascular fluids. Amastigotes ingested during feeding transform to procyclic promastigotes and attach to the midgut-hindgut wall where they multiply by binary fission and develop into metacyclic infective promastigotes over 6-20 days. The parasites migrate forward to the foregut and pharynx where they produce a partial or complete blockage of the sucking apparatus. When the sandfly next attempts to feed, it 'clears its throat' and regurgitates a bolus of metacyclic promastigotes into the bite wound. Promastigotes injected into vertebrate hosts are phagocytosed and develop into amastigotes within 24 hours. The recent discovery of an alternative dipteran vector, *Forcipomyia* (*Lasiohelea*) midges, for the *Leishmania* species found in macropodids in Australia reinforces the need for transmission cycles to be definitively determined for many isolates. Promastigotes injected into vertebrate hosts have numerous lipophosphoglycan molecules on their membranes which enables them to resist lysis as well as adhere to macrophage membranes facilitating their phagocytosis. The parasites are resistant to intracellular enzyme degradation and persist within parasitophorous vacuoles formed by fusion of phagosomes with lysosomes. They transform to amastigote stages which undergo massive asexual multiplication, ultimately lysing the host cell releasing amastigotes which infect other host cells. On occasion, infections can be transmitted horizontally between vertebrate hosts by contaminated needles, blood transfusions, organ transplantation, venereal contact and possibly vertically by crossing the placenta.

Differential diagnosis: Amastigotes may be detected microscopically in biopsy material taken from the dermis, bone marrow, spleen, liver, or lymph nodes (parasites are rarely demonstrated in peripheral blood). Intracellular stages are best visualized in tissue smears using Giemsa's or Leishman's stains, but most microscopic techniques have poor limits of detection, sensitivity and specificity. Infections in vectors may be detected by microscopic examination of gut squash preparations or histological sections. Parasites may be isolated and amplified in number as promastigotes by *in vitro* culture in enriched media (such as nutrient agar-blood mixtures) or by experimental inoculation *in vivo* into laboratory animal models (immunosuppressed or susceptible rodent strains). Such culture techniques, however, are time-consuming, costly, technically demanding and may give false negative results for many reasons. Various immunoserological tests have been developed to detect host antibodies against infection (including immunodiffusion, immunoelectrophoresis, agglutination, immunofluorescence and enzyme immunoassays), but there are difficulties in detecting cutaneous infections (due to poor host responses), establishing the time course of infection (distinguishing between recent and chronic infections) and differentially diagnosing infections (discriminating between different parasite species). A range of crude, subcellular and recombinant antigens have been used with varying sensitivities and specificities. Attempts to develop immunological tests to detect parasite antigens in host samples have been thwarted by considerable cross-reactivity with circulating immune complexes, serum amyloid, rheumatoid factor and reactive immunoglobulins (including auto-antibodies). Delayed hypersensitivity is characteristic of cutaneous forms of leishmaniasis and several skin tests (Montenegro reaction test, leishmanin skin test) have been used to screen populations for exposure, although their use for visceral leishmaniasis has proven contradictory. Parasite isolates have been analysed using various protein characterization techniques, including isoenzyme analyses, polyacrylamide gel electrophoresis and immunoblotting. Modern molecular characterization techniques have used the polymerase chain reaction (PCR) to detect restriction fragment length polymorphisms (RFLP), random amplified polymorphic DNA (RAPD), and to amplify specific gene sequences (parasite DNA) from host samples; including small subunit (18S) ribosomal RNA, internal transcribed spacers, mini-exon gene repeats, microsatellites (maxi- and mini-circles of kinetoplast DNA), beta-tubulin, glycoproteins, heat-shock proteins, cysteine proteases, and mitochondrial cytochrome b.

Treatment and control: Some cutaneous infections require no treatment as lesions may heal within several months. Systemic therapy (intravenous, intramuscular, intralesional) with pentavalent antimonials (sodium stibogluconate or meglumine antimonate) is the treatment of choice for disfiguring and visceral infections. The development of antimonial drug resistance, however, is a growing problem in many endemic areas, including South America, India and the Middle-East. Pentamidine or amphotericin B can be used if antimonials are ineffective, and miltefosine and aminosidine (paromomycin) have shown promise as treatment options, especially when combined with immunotherapy using the tumour-necrosis factor-alpha (TNF-α) inhibitor pentoxifylline. The purine analogue allopurinol has also shown good efficacy against infections in dogs, as many of the others are nephrotoxic. All courses of treatments should be long-term to achieve not only clinical remission but also elimination of the parasites, otherwise relapses may occur. Many human enterprises are conducive to the spread of infections; including urbanization, pet ownership, deforestation, agriculture, migration and tourism. Preventive measures include protection from sand fly bites but this can be difficult as they are so small that they can penetrate most mosquito nets. Reducing the size of reservoir host populations (especially dogs) has proven beneficial in many endemic urban areas. Many cutaneous infections, however, are acquired in forests away from human habitation, as the reservoir hosts are wild animals (esp. rodents). The prevention of sand fly bites in forest areas is almost impossible but may be minimized by the use of protective clothing, insect repellents and insecticidal sprays in houses. In several endemic areas, dogs fitted with deltamethrin-impregnated collars were partly protected from sand fly bites and they exhibited low rates of infection. Considerable research has been conducted on the development of a protective vaccine, prompted by observations that many clinical cases resolve spontaneously leaving the hosts resistant to re-infection. Indeed, vaccination through 'leishmanization' has long been practised around the Middle-East (for centuries according to ancient texts), whereby children are inoculated in innocuous sites with viable *L. major* parasites taken from a mildly infected individual. Several combination vaccines are currently undergoing clinical trials, but research has been hampered by our lack of knowledge about host-parasite immune interactions, particularly with respect to immuno-evasion mechanisms. Results derived from laboratory animal models have implicated both innate and acquired (adaptive) immune responses in the acquisition of protection, particularly cell-mediated responses involving helper (CD4 Th) and cytotoxic (CD8 Tc) T-cells and cytokines stimulating Th1 (pro-inflammatory) responses.


Leishmania
(mammalian species)
blood, tissues
(cutaneous (oriental sore),
mucocutaneous (espundia)
or visceral (kala azar))
division by binary fission
in reticuloendothelial cells
Vertebrate Hosts
(mammals)
form intracellular colonies
ultimately lysing host cell
amastigotes (2-5 µm)
(no emergent flagellum)
inoculative transmission
(injected via vector bite)
ingested with
bloodmeal
emergent flagellum,
anterior kinetoplast
promastigotes
(5-20 µm)
vector-borne transmission
Invertebrate Hosts
(sandfly vectors)
(alimentary tract)



Leishmania amastigotes in liver

Cutaneous leishmaniasis

Leishmania promastigotes in sandfly gut

Phlebotomus sandfly vector for *Leishmania*