# L

## *Labiosimplex*

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A genus of nematodes (Strongylida, Chabertiidae) parasitizing macropodid marsupials in Australia

### Further Reading

Smales LR (2011) New species and new locality records of the nematode genus *Labiosimplex*. Rec West Aust Mus 26:183–190

## Labium

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Latin: *labium* = lip; this term describes a portion of the mouthparts of ▶ insects.


H. Mehlhorn (ed.), *Encyclopedia of Parasitology*,
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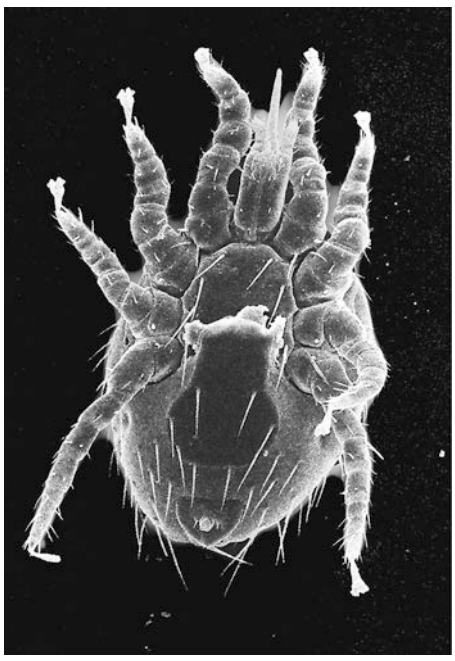
## Labyrinthomorpha

Phylum of ▶ Protozoa that form cysts and ameba-like stages on marine organisms.

## *Laelaps agilis*

About 2 mm long bloodsucking mite in the fur of mice (Fig. 1).



***Laelaps agilis*, Fig. 1** SEM of the ventral side of an adult; note the stiletto-like chelicerae

## Laelaptidae

Family of mites, that are found on insects (e.g., genus *Myrmonyssus*), while others parasitize mammals (genera *Echinolaelaps, Haemolaelaps, Laelaps*). The larvae and nymphs are mostly lymph feeders, while the adults are hematophagous. The life cycles (including egg, larva, protonymph, deutonymph, and adults) is completed within 8–28 days. During the blood meal the blood parasite ▶ *Hepatozoon* may become transmitted.

## Lagochilascaris

Genus of ascarid ▶ nematodes, which occur in general in wild animals, but which may also enter (as larvae) humans leading to larva migrans interna.

## *Lama branchialis*

Microsporidian species of freshwater fish (*Gluega*).

## Lamarck, Jean Baptiste de Monet (1744–1829)

French zoologist and evolutionist; he believed in the genetic transmission of acquired qualities.

## Lambl, W. D. (1824–1895)

Austrian physician, discoverer of the agents of the giardiasis.

## Lamblia

Old genus name for *Giardia* spp. ▶ Diplomonadida, ▶ Giardia lamblia.

## Lambliasis

### Synonyms

Giardiasis, Man.

## Landsteiner, Karl (1868–1943)

Austrian pathologist, discoverer of the human blood groups and the rhesus factor. Winner of the Nobel prize in 1930.

## Langerhans Cells (LCs)

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This term honours the German pathologist Paul Langerhans (1847–1888) who first described the Langerhans islets (*insula pancreaticae)* inside the pancreas. Langerhans cells, however, act as macrophages inside the epidermis phagocytizing penetrated pathogens and present them to T-cells inside lymph nodes.

## Lapudrine-Dapsone (Lapdap)

▶ Malariacidal Drugs.

## Large Roundworms of Ruminants

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See ▶ *Toxocara vitulorum* = English trivial name for roundworms of cattle.

## Larva

From Latin: *larva* = mask. Non-fertile developmental stage of helminths and arthropods (plural: larvae).

## Larva Currens

Larva 3 of ▶ *Strongyloides stercoralis* which after penetration wanders with a high speed (20 cm/h) inside the skin of humans and leads to serpiginous pruritic eruptions.

## Larva Migrans

Larvae of ▶ nematodes, which have animals as final hosts, wander through the body of humans in case they become infected.

- Larva migrans externa: For example, larva of ▶ hookworms of dogs (▶ *Ancylostoma caninum*) stay within the skin and lead to externally visible channels.
- Larva migrans interna: the larvae, for example, of ascarids of dogs or racoons (▶ *Toxocara canis*, ▶ *Bayliascaris procyonis*) wander through internal organs if eggs are swallowed by humans.
- Spargana: larvae of ▶ tapeworms of fish-predating birds wander as a so-called ▶ sparganum inside the body of humans if they have eaten raw fish meat containing ▶ plerocercoid larvae.

▶ Cestodes.

## Larval Tapeworms

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### Name

Greek: *kystis* = bladder, cyst; *kerkos* = tail; *koinos* = together, common; *ura* = tail; Latin: *tenuis* = thin; *ovis* = sheep; *bos* = cattle; *collis* = protrusion; *multiceps* = with many heads.

### Geographic Distribution/Epidemiology

Worldwide.

### Morphology/Life cycle

(a) ***Cysticercus bovis*:** 10 × 4.5 mm sized bladder = larval stage of the tapeworm *Taenia saginata* of humans. This stage occurs in muscles of cattle.
(b) ***Cysticercus tenuicollis*:** 5–15 cm long, thin-necked larvae of the dog's tapeworm *T. hydatigena*, which is mostly situated in the ommentum of its intermediate hosts (ruminants).
(c) ***Cysticercus ovis*:** 10 × 5 mm sized larva of the dog's tapeworm ▶ *Taenia ovis* being situated often in heart, diaphragm, and masseter of intermediate hosts (e.g., sheep).
(d) ***Coenurus cerebralis*:** Up to 5 cm sized translucent larva of the dog's tapeworm *Taenia*

(syn. *Multiceps*) *multiceps*; at its inner side several protoscolices are formed. This parasite is found in the brain of sheep but occasionally also in humans.

(e) **Hydatids of *Echinococcus*:** These very large cysts contain many daughter cysts within which thousands of protoscolices are produced. This larval stage is formed due to infections with *Echinococcus granulosus*. It occurs in a broad spectrum of intermediate hosts including humans.

(f) **Alveolar cysts:** This type of larvae, which is formed due to an infection with the tapeworm ▶ *Echinococcus multilocularis*, occurs mainly in rodents but also in humans. It grows tumor-like with the help of undifferentiated cells.

## Symptoms of Disease

Organ-specific dysfunctions, which may also lead to death.

## Diagnosis

In humans: investigations with computer tomography or MRT. In animals, these larvae are mostly only found after slaughter. Serological tests are also available.

See *Taenia* species; ▶ *Echinococcus* species.

# Larvicidal and Repellent Effects of Essential Oils

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Essential oils besides ▶ repellent effects on mosquitoes also have larvicidal activity against their larvae (see Table 1). These effects depend on the

**Larvicidal and Repellent Effects of Essential Oils, Table 1** Percentages of mortality rate of *Aedes aegypti* third-instar larvae in 50-ppm oil solutions after 1, 12, and 24 h (Amer and Mehlhorn 2006)

| No | Name of plant material | % of dead larva[a] | | |
|---|---|---|---|---|
| | | After 1 h | After 12 h | After 24 h |
| 1 | Citronella (*Cymbopogon winterianus*) | 6.67 | 43.3 | 60 |
| 2 | Rosewood (*Aniba rosaeodora*) | 0 | 33.3 | 60 |
| 3 | Lavender (*Lavandula angustifolia*) | 3.3 | 40 | 63.3 |
| 4 | Camphor (*Cinnamomum camphora*) | 93.3 | 100 | 100 |
| 5 | Catnip (*Nepeta cataria*) | 0 | 40 | 40 |
| 6 | Geranium (*Pelargonium graveolens*) | 0 | 63.3 | 73.3 |
| 7 | Thyme (*Thymus serpyllum*) | 36.7 | 100 | 100 |
| 8 | Eucalyptus (*Eucalyptus globulus*) | 10 | 16.7 | 16.7 |
| 9 | Jasmine (*Jasminum grandiflorum*) | 0 | 6.7 | 6.7 |
| 10 | Broad-leaved eucalyptus (*Eucalyptus dives*) | 43.3 | 83.3 | 96.7 |
| 11 | Lemongrass (*Cymbopogon citratus*) | 0 | | 0 |
| 12 | Lemon-scented eucalyptus (*Eucalyptus citriodora*) | 0 | 43.3 | 76.7 |
| 13 | Fichtennadel (*Picea excels*) | 60 | 90 | 96.7 |
| 14 | Amyris (*Amyris balsamifera*) | 0 | 90 | 100 |
| 15 | Lemon *(Citrus limon)* | 96.7 | 100 | 100 |
| 16 | Narro-leaved eucalyptus *(Eucalyptus radiata)* | 6.7 | 46.7 | 50 |
| 17 | Carotin oil *(Glycina soja)* | 3.3 | 43.3 | 53.3 |
| 18 | Cedarwood *(Juniperus virginiana)* | 6.7 | 100 | 100 |

(*continued*)

**Larvicidal and Repellent Effects of Essential Oils, Table 1** (continued)

| No | Name of plant material | % of dead larva[a] | | |
|---|---|---|---|---|
| | | After 1 h | After 12 h | After 24 h |
| 19 | Frankincense *(Boswellia carteri)* | 66.7 | 100 | 100 |
| 20 | Dill *(Anethum graveolens)* | 93.3 | 100 | 100 |
| 21 | Myrtle *(Myrtus communis)* | 86.7 | 96.7 | 100 |
| 22 | Chamomile *(Anthemis nobilis)* | 0 | 0 | 3.3 |
| 23 | Cinnamon *(Cinnamomum zeylanicum)* | 0 | 86.6 | 90 |
| 24 | Juniper *(Juniperus communis)* | 73.3 | 100 | 100 |
| 25 | Sage *(Salvia sclarea)* | 3.3 | 43.3 | 46.7 |
| 26 | Peppermint *(Mentha piperita)* | 0 | 36.7 | 53.3 |
| 27 | Basil *(Ocimum basilicum)* | 3.3 | 70 | 86.7 |
| 28 | Cajeput *(Melaleuca leucadendron)* | 0 | 3.3 | 3.3 |
| 29 | Soya *bean (Glycina max)* | 0 | 0 | 0 |
| 30 | Rosemary *(Rosmarinus officinalis)* | 6.7 | 10 | 16.7 |
| 31 | Niaouli *(Melaleuca quinquenervia)* | 13.3 | 13.3 | 30 |
| 32 | Olive *(Olea europaea)* | 0 | 26.7 | 43.3 |
| 33 | Black pepper *(Piper nigrum)* | 86.7 | 100 | 100 |
| 34 | Verbena *(Lippia citriodora)* | 63.3 | 100 | 100 |
| 35 | Tagetes *(Tagetes minuta)* | 0 | 3.3 | 3.3 |
| 36 | Violet *(Viola odorata)* | 3.3 | 86.7 | 86.7 |
| 37 | Helichrysum *(Helichrysum italicum)* | 6.7 | 100 | 100 |
| 38 | Litsea *(Litsea cubeba)* | 0 | 50 | 50 |
| 39 | Sandalwood *(Santalum album)* | 83.3 | 100 | 100 |
| 40 | Galbanum *(Ferula galbaniflua)* | 6.7 | 13.3 | 13.3 |
| 41 | Chamomile *(Chamamelum nobile)* | 40 | 20 | 50 |

The species in rows presented in bold have a 100 % efficacy. [a]Each percentage was calculated for 30 larvae in three replicates

test species, on the dosage used, and on the time of exposure. The environment friendly dosage of 50 ppm shows good effects by use of some plant oils.

## Larvicidal Fly Insecticides

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Among several local larvicidal products acting against houseflies (*Musca domestica*), Naga® 505, Neporex® 505, and Starycide® are worldwide available.

### Further Reading

Ong SQ et al (2015) Comparative effectiveness of insecticides for use against the house fly (Diptera: Muscidae): determination of resistance levels on a Malaysian poultry farm. J Econ Entomol 109:352–359

## Larviparous

### Name

Latin: *larva* = mask, *parere* = giving birth.

Producing larvae instead of eggs (▶ Oviparous) from within the body, e.g., in ▶ mites, ▶ *Trichinella spiralis*, and ▶ Filariidae.

## Lasiohelea

Genus of ▶ Ceratopogonidae, ▶ Midges, ▶ *Culicoides*.

## Latency

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### Name

Latin: *latere* = hide.

This term describes the period during which an infection is not discernible, e.g., the incubation period of an outbreak of a virosis after mosquito bites.

## Latidectin

### Chemical Class

Macrocyclic lactone (16-membered macrocyclic lactone, milbemycins).

### Mode of Action

Glutamate-gated chloride channel modulator. ▶ Ectoparasiticides: Antagonists and Modulators of Chloride Channels.

## *Latrodectus mactans*

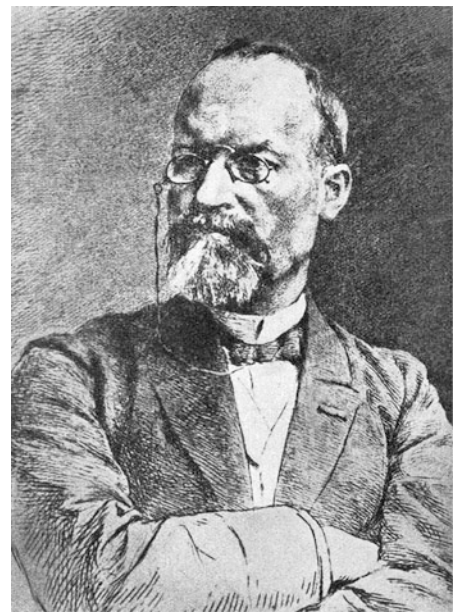
Black widow spider, may harm humans.

## Laurer's Canal

Found in some digeneans, it probably represents a vestigial vagina that no longer functions but may be used as an excretory system for superfluous sperm, etc. (▶ Platyhelminthes/Reproductive Organs).

## Laveran, Charles-Louis Alphonse (1845–1922)

French military physician (Fig. 1), who won the Nobel Prize in 1907 for the discovery of malaria due to *Plasmodium malariae*.



**Laveran, Charles-Louis Alphonse (1845–1922), Fig. 1** Painting of Prof. Alphonse Laveran, the great French malaria researcher at his zenith of fame

**Lazear, Jesse William, Fig. 1** Photo of Dr. Jesse W. Lazear just before his death in a self-infection experiment with yellow fever

## Lazear, Jesse William

American entomologist (Fig. 1, page 694), discoverer (together with ▶ Reed) of the transmission of yellow fever by *Aedes* (*Stegomyia*)-mosquitoes, died in 1900, during a self-experiment with yellow fever.

## $LD_{50}$

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Dose of a medicament which kills 50 % of the actually present parasites.

## Lecithodendriidae

Family of flukes with spined tegument parasitizing the gut of insectivorous vertebrates. However, *Phaneropsolus* sp., *Prosthodendrium* sp., or *Paralecithodendrium* also live in humans. Intermediate hosts are aquatic insects.

## Leeches

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### Synonyms

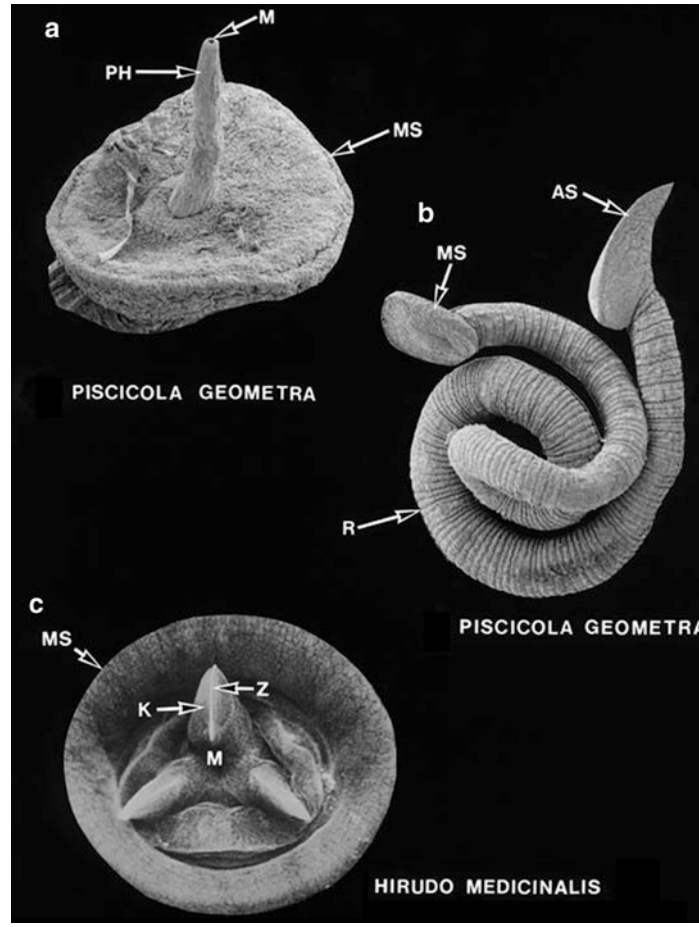
Hirudinea, from Latin: *Hirudo* = leech

### Classification

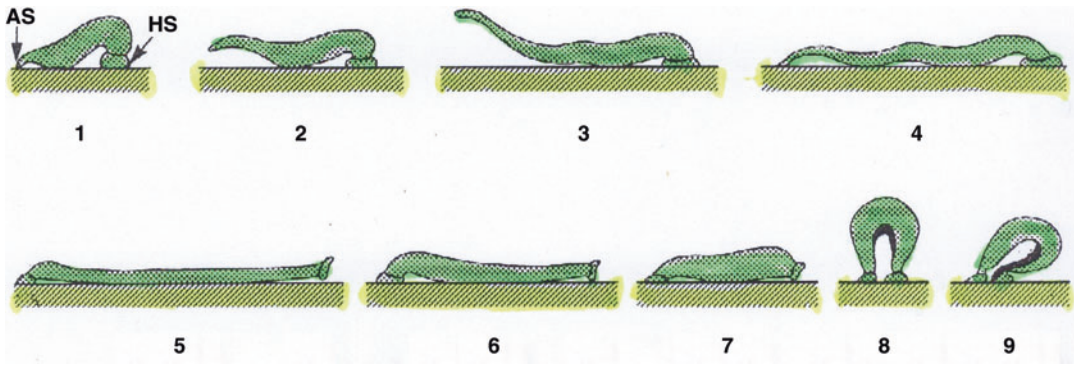
Hirudinea is a subclass of ▶ Annelida.

### General Information

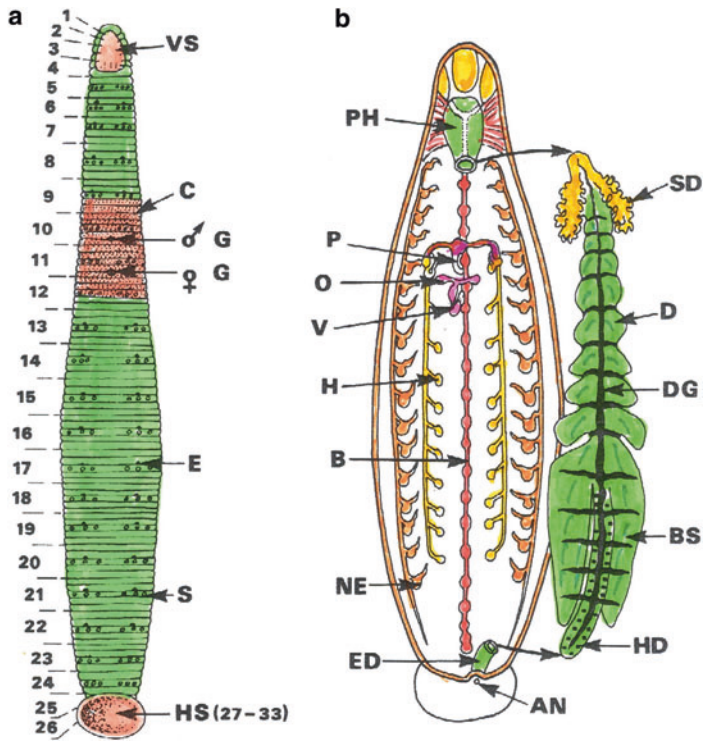
In general, members of the Hirudinea, which are endowed with a complete intestinal tract, look like platyhelminths and are dorsoventrally flattened monoecious animals (▶ Hermaphrodites). Mostly they develop 32 inner segments (except for 29 in *Acanthobdella*), which each corresponds to 2–14 outer annuli (some authors count 34 segments). Except for *Acanthobdella*, the Hirudinea, parasitic or not, are characterized by an oral sucker and a posterior disklike ▶ acetabulum, which act as strong holdfast organs supporting movements on the surface of animal hosts, plants, etc. (Figs. 1, 2, 3, 4, and 5, ▶ *Hirudo medicinalis*/Figs. 1 and 2). Bloodsucking leeches produce enzymes (e.g., hirudin) preventing coagulation of blood during feeding. Typically, closed circulatory vessels and a definitive respiratory system are lacking in most



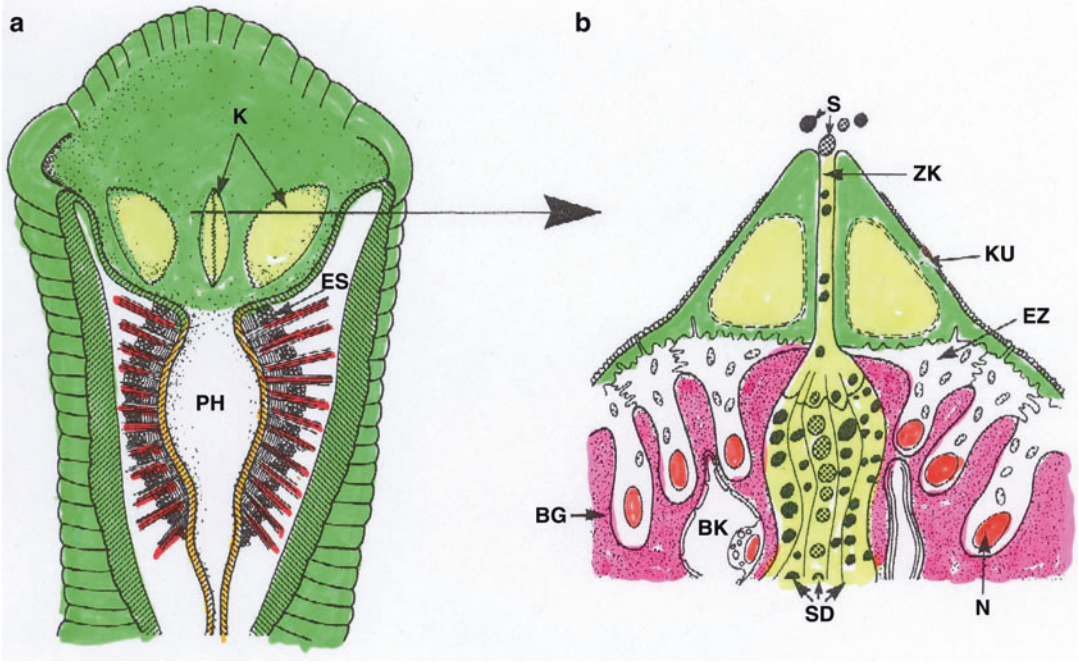

**Leeches, Fig. 1** SEMs on leeches. (**a**) Anterior pole of the fish leech *Piscicola geometra* with the protruded pharynx (×80). (**b**) Total lateral view of *P. geometra* (×8). (**c**) Mouthpart of the medical leech ▶ *Hirudo medicinalis* (×15). *AS* anal sucker, *K* jaw, *M* mouth, *MS* oral sucker, *PH* pharynx, *Z* row of teeth



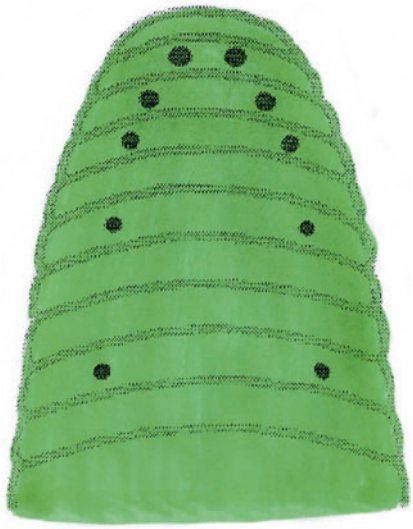

**Leeches, Fig. 2** Diagrammatic demonstration of typical movements of leeches on soil




**Leeches, Fig. 3** Diagrammatic representation of the outer and inner morphology of the leech *Hirudo medicinalis*. (**a**) Ventral side and (**b**) organs seen from dorsal (after Mann (1962) and Barnes (1982)). In Fig. (**a**) only the segments are numbered. Today it is believed that there are only 32 segments. *AN* anus, *B* ventral nerve strand, *BS* last stomach, *C* clitellum, *D* intestine, *DG* dorsal blood vessel, *E* excretion porus (= 17 pairs inside segments 6–22), *ED* terminal portion of the gut, *G* genital porus, *H* testis, *HD* hindgut, *HS* posterior sucker, *NE* nephridium, *OV* ovary (paired), *P* penis, *PH* pharynx, *S* sense papilla, *SD* salivary gland, *V* vagina, *VS* anterior sucker




**Leeches, Fig. 4** *Hirudo medicinalis*. Diagrammatic representation of the anterior portion (**a**) and a section through the jaw (**b**) along the line shown by the *arrow* in Fig. (**a**). *BG* connective tissues, *BK* blood capillary, *ES* terminal pole of the unicellular salivary gland cells, *EZ* epithelial cells, *K* jaw, *KU* cuticle, *N* nucleus, *PH* pharynx, *S* saliva, *SD* salivary gland (unicellular), *Z* tooth channel



**Leeches, Fig. 5** *Hirudo medicinalis*. Location of eyes

species, and the coelom cavities are restricted to a few blood-transporting lacunae. The ontogenesis of the Hirudinea proceeds directly, without involving any larval stages (such as the ▶ trochophora larva which is characteristic for other annelids). Thus, juvenile worms hatch immediately from eggs which are joined in packs of 1–200 into a ▶ cocoon; the latter is secreted 2 days to months after copulation of two individuals by their ▶ clitellum region (segments 9–11).

## System

The classification of the Hirudinea is still a matter of debate; however, the following groups are widely accepted:

Subclass: Hirudinea (some parasitic species).
Order: ▶ Acanthobdellida.
Unlike other orders, they show only the posterior ▶ acetabulum, are endowed with some surface bristles, and are composed of 29 inner segments (each with four outer annuli).
Order: ▶ Rhynchobdellida.
The anterior part of the intestine forms a large, protrusible, and retractile ▶ proboscis without teeth; specimens suck blood and thus may transmit several endoparasites; they are eyeless, their blood is colorless, and host location occurs by body contact.
Order: ▶ Gnathobdellida.
The anterior part of the intestine is noneversible, but is armed by three pairs of ▶ jaws with varyingly strong cuticular teeth; the members of this group that are up to 25 cm long are characterized by five pairs of eyes, five annuli per segment, and red blood in a lacunar system; ▶ host finding occurs by means of olfactory systems.
Order: Pharyngobdellida.
Specimens have no teeth and a nonprotrusible pharynx; they suck blood by means of their strong muscular pumping pharynx (armed with one or two stylets but no teeth), are provided with three or four pairs of eyes, and contain red blood in lacunae.

## Important Species

See Table 1.

## Integument

As in other members of the phylum ▶ Annelida, the leeches are covered by a unilayered, cellular epidermis which excretes to its surface a thin ▶ cuticle consisting of a proteinaceous ground substance including collagen fibers. ▶ Chitin is only present in the rigid bristles (chaeta) which are, however, absent in most hirudineans except *Acanthobdella*. This ▶ cuticle remains very elastic and is molted several times (not at definite intervals) in Hirudinea, but not in other annelids.

## Intestine and Food Uptake

The intestine of parasitic leeches consists of a frequently armed mouth, a pharynx, an esophagus, a stomach, an intestine with 6–7 large paired diverticles, a hindgut, and the rectum ending with the anus (▶ *Hirudo medicinalis*/Fig. 1). In the medicinal leech *H. medicinalis*, the teeth of the

**Leeches, Table 1** Some common species of leeches (Hirudinea)

| Family/species | Length (mm) | Main hosts/habitat |
|---|---|---|
| **Acanthobdellidae** | | |
| *Acanthobdella peledina* | 35 | Salmonid fish/skin |
| **Rhynchobdellidae** | | |
| *Piscicola geometra* | 70 | Freshwater fish/skin |
| *Theromyzon tessulatum* | 50 | Waterbirds/nose, pharynx, trachea |
| *Haementeria ghilianii* | 500 | Many vertebrates/skin |
| *Glossiphonia* spp. | 20 | Snails, oligochaetes/skin |
| **Gnathobdellidae** | | |
| *Hirudo medicinalis* | 170 | Mammals, **humans**/skin |
| *Haemadipsa* spp. | 70 | **Humans**, mammals, birds/skin |
| *Xerobdella* spp. | 50 | Amphibia/skin |
| *Limnatis nilotica* | 120 | Horses, mammals/nose, pharynx |
| *Haemopis sanguisuga* | 100 | Feeds on oligochaetes |
| **Pharyngobdellidae** | | |
| *Erpobdella octoculata* | 20 | Predacious leeches, feed on insect larvae |

three jaws are pored by the canaliculi of unicellular glands, which produce, besides anesthetic and vasodilatory compounds, an anticoagulant (hirudin) which acts as an antithrombokinase. Due to this fact, a large leech may ingest about 15 g blood (i.e., tenfold his own body weight) within a few minutes. This phenomenon was used for centuries in human medicine as a general remedy (Introduction). The blood cells are stored in the intestinal diverticles, while the fluid compounds are rather quickly excreted. This amount of blood allows the leeches to survive starving periods of up to 2 years. The blood cells inside the intestine are retained due to the activity of the hirudin in full shape for a long time and become digested bit by bit due to the activity of a particular bacterium (*Pseudomonas [Aeromonas] hirudinis*) instead of its own digestive enzymes (which, however, are not completely absent). The bacteria are packed by the adult worm on its eggs and are thus transmitted to the next generation. Investigations of our group prove the long (half year) survival of many agents of diseases (viruses, bacteria, protozoan parasites) inside the stored blood. Furthermore, the antibodies of HIV and hepatitis B viruses were found in African leeches, so that leeches pose a considerable danger for their hosts.

## Excretory System

The excretory system of leeches consists of 10–17 pairs of ▶ metanephridia (▶ *Hirudo medicinalis*/Fig. 1) which each opens with a porus at the ventral body surface. They start with a ciliated funnel that opens into the body cavity or into a spherical nephridial capsule (depending on the species) and collect materials to become excreted.

## Nervous System

The nervous system of leeches (▶ *Hirudo medicinalis*/Fig. 1) corresponds in principle to that of other annelids while being composed of a ventral chord system with a typical broad fused ganglion in each segment. From there 3–4 ringlike running pairs of nerves extend to the periphery. The ganglia of the segments of the posterior sucker are fused to form a large terminal ganglion. Anteriorly, a supraesophageal ganglion is developed innervating sensillae of various types. This epi- = supraesophageal ganglion is connected to the subesophageal ganglion which innervates the mouth and the anterior intestine.

# Leeuwenhoek, Antony van (1632–1723)

Developer and user of the first type of microscope, described, e.g., human sperms, Giardia, etc.

## Leidy, Joseph (1823–1891)

German-American anatomist, discoverer of the muscle stages of *Trichinella* (1846) and recommending to eat only cooked meat. In 1886 Leidy described the hookworm of cats.

## *Leidynema appendiculata*

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Oxyurid nematode in the intestine of cockroaches.

## Leishman, W. B., Sir (1865–1926)

English tropical physician, honored by genus ► Leishmania.

## Leishman, William Boog (1865–1926)

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Scottish pathologist and medical officer of the British Army in overseas (mainly in India), finally ranked as general manager of the Army Medical Services during the last 3 years of his life (Fig. 1). While he stayed in India, he studied patients suffering from enteric fever and kala-azar (= the Indian name for the disease, which ► Ross later called "leishmaniasis," honoring Leishman's merits in the discovering of this parasitosis. In 1903, he published tiny ovoid stages seen in tissues of kala-azar patients. They were later called Leishman-Donovan bodies (since ► Donovan detected similar ones). Today, it is known that these bodies are the amastigote (= micromastigote) stages of the *Leishmania* species. Ronald Ross ( = the winner of the second Nobel Prize in Physiology or Medicine) as well as Leishman and Donovan were honored by the English Court by the award of the title "Sir." Leishman's amendment of the so-called Romanowsky stain by adding methylene blue and eosin to color the *Leishmania* stages is still used today.

**Leishman, William Boog (1865–1926), Fig. 1** W.B. Leishman

### Further Reading

Leishman WN (1901) A simple and rapid method of producing Romanowsky staining in malarial and other blood films. Br Med J 1901:757–758
Manson P, Low GC (1904) The leishman-donovan body and tropical splenomegaly. Br Med J 1904:183–187
Ross R (1903) Note on the bodies recently described by Leishman and Donovan. Br Med J 1903:1261–1262

# *Leishmania*

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## Classification

*Leishmania* is a genus of ▶ Trypanosomatidae, named after Sir William Leishman (1865–1926).

## Important Species

See Table 1 and Figs. 1, 2, 3, and 4.

## Life Cycle

See Fig. 1.

## Surface Coat

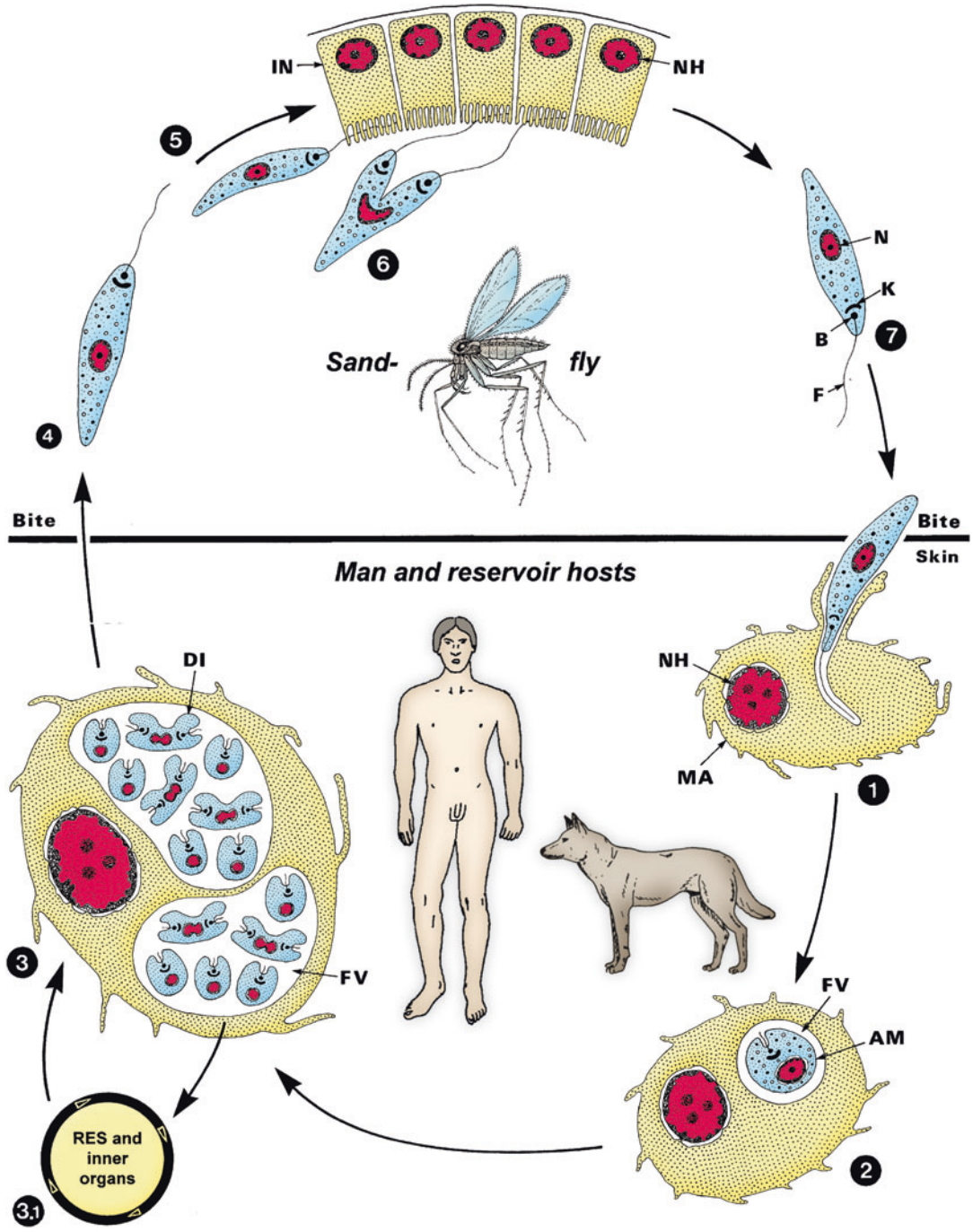
Besides several GPI-anchored glycoproteins on the surface of *Leishmania* spp., the major component of the ▶ surface coat in these parasites is represented by a ▶ lipophosphoglycan which is also a ▶ GPI-anchored family of molecules harboring a large glycanic moiety mostly made of repeats of a disaccharide phosphate motif that differs in size and terminal ▶ capping sugars among developmental stages. LPG stage-specific differences are responsible for the specific interaction of the developmental stages with their respective target cells or organs.



***Leishmania*, Table 1** Important *Leishmania* spp. parasitizing humans

| Species | Type of disease | Reservoir hosts | Geographic distribution | Vector |
|---|---|---|---|---|
| **Cutaneous leishmaniasis**[a] | | | | |
| *L. tropica minor* | Dry cutaneous | Rodents, dogs | Southern Europe, Middle East | *Phlebotomus* spp. |
| *L. tropica major* | Wet cutaneous, oriental sore | Rodents, dogs | Southern Europe, Africa, Middle East | *Phlebotomus* spp. |
| *L. aethiopica* | Diffuse or dry cutaneous | *Hyrax* sp. | Ethiopia, Kenya | *Phlebotomus* spp. |
| *L. braziliensis braziliensis* | Espundia, mucocutaneous | Rodents | Mexico, Brazil | *Lutzomyia* spp., *Psychodopypus* spp. |
| *L. peruviana* | Uta, cutaneous | Dogs | Peru | *Lutzomyia* spp. |
| *L. mexicana mexicana* | Chiclero ulcer, cutaneous | Rodents | Central America | *Lutzomyia* spp. |
| *L. mexicana amazonensis* | Diffuse, cutaneous | Rodents | Amazonas region | *Lutzomyia* spp. |
| *L. mexicana pifanoi* | Cutaneous, mucocutaneous | Rodents | Venezuela | *Lutzomyia* spp. |
| **Visceral leishmaniasis** | | | | |
| *L. donovani donovani* | Kala-azar, dumdum fever, visceral | Dogs, foxes | Africa, Asia, Middle East, southern Russia, South America | *Phlebotomus* spp. |
| *L. donovani infantum* | Visceral, infantile | Dogs | Mediterranean countries | *Phlebotomus* spp. |
| *L. donovani chagasi*[b] | Visceral | Foxes, cats, dogs | South America | *Lutzomyia* spp. |

[a]Some cutaneous species may also initiate visceral leishmaniasis
[b]Some authors keep this species synonymous to *L. infantum*

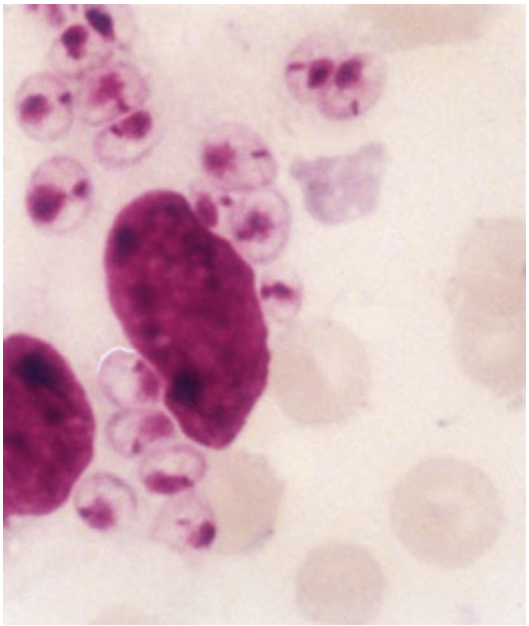



***Leishmania*, Fig. 1** Life cycle of *Leishmania* spp. (see Table 1). *1* After the bite of the ▶ vector, the injected promastigote stage is engulfed by macrophages in the skin of the vertebrate host. *2* Transformation of ▶ promastigotes into amastigote stages (2–4 µm in diameter) requires 1–4 h; reproduction proceeds as ▶ binary fission inside a ▶ parasitophorous vacuole, which later breaks down. *3* When macrophages are closely filled with ▶ amastigotes (after 48 h), they finally burst and set free the parasites which may enter other macrophages in the skin, leading to a *cutaneous leishmaniasis* (▶ Leishmaniasis, Man/Fig. 2). *3.1* Amastigotes of the

## Host Cell Invasion

In this group, two forms of the parasite are invasive: the promastigote (due to extracellular multiplication in the vector) and the amastigote (due to intracellular development). The target of these parasites is essentially a phagocyte (monocyte, macrophage). They have been described as entering the host cell via phagocytosis (► Host Cell Invasion/Fig. 1) although some participation of the parasite cannot be completely excluded. The *Leishmania*-containing phagosome then acquires properties of late endosomes-lysosomes and is therefore a particular compartment of the host cell, partly connected to the vesicular traffic of the cell. This compartment has a low pH (around 5), and its membrane contains the major lysosomal glycoproteins (LGPs) and the proton ATPase. The vacuole is readily accessible to the fluid-phase ► endocytosis pathway of the host cell, but accessibility to receptor endocytosis markers is not universal, showing that this vacuole is not simply a lysosome. Promastigote-to-amastigote transformation occurs in this compartment before parasite multiplication. An intriguing feature of *Leishmania* invasion is that the ► vacuoles formed by the different species do not possess the same properties with regard to their size and their interaction with the endosomal compartment of the host cell, and this may have consequences for the respective pathogenicity of these parasites.

Adaptation of *Leishmania* amastigotes to optimal survival at low pH under the adverse conditions of a lysosome is not fully explained; high levels of glycoinositol phospholipids and glycosphingolipids may be in part responsible for this unusual resistance.

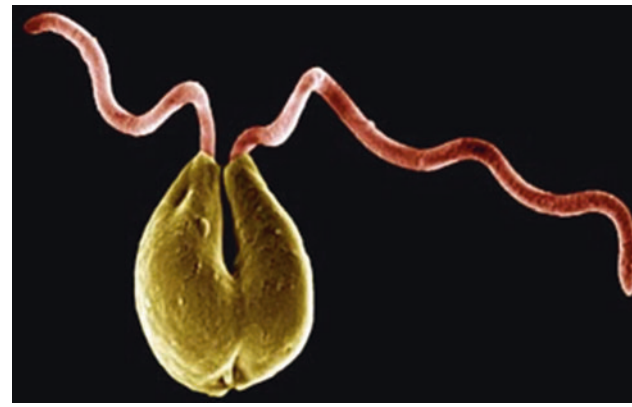


***Leishmania*, Fig. 2** LM of a Giemsa-stained blood smear. Several amastigotes of *Leishmania* spp. are situated closely to two red host cell nuclei, the cells of which were disrupted. Note inside the amastigote, the small red-colored kinetoplast and the larger nucleus

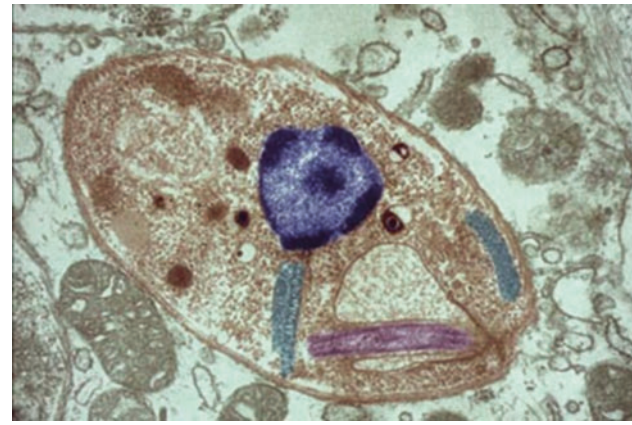
## Transformation Inside the Vector

If a female *Phlebotomus* has taken up amastigotes of *Leishmania*, they are transformed within 24–48 h in the foregut into procyclic stages,

***Leishmania*, Fig. 1** (continued) L. donovani group are carried to inner organs and may enter various host cells, where they are reproduced by repeated binary fissions and lead to a *visceral leishmaniasis* within 4–6 months (*kala-azar*, *dumdum* fever; ► Leishmaniasis, Man/Fig. 1). *4–7* When a sand fly (genera ► *Phlebotomus*, ► *Lutzomyia*) ingests amastigotes along with its blood meal, the latter are transformed into slender ► promastigotes (10–20 μm in length) in the midgut, where they multiply by repeated ► binary fission (*6*). Quickly they block up the gut of the vector and move to the pharynx and buccal cavity, where they are injected into a new host with the fly's next bite (*7*). All stages have a slight ► surface coat. *AM* ► amastigote stage, *B* basal body of flagellum, *DI* dividing stage, *F* free flagellum, *FV* food vacuole, *IN* intestinal cell, *K* ► kinetoplast, *MA* macrophages, *N* nucleus, *NH* nucleus of host cell



***Leishmania*, Fig. 3** SEM of a dividing promastigote (= infectious stage)



***Leishmania*, Fig. 4** SEM of an amastigote stage of *Leishmania* in a host cell

which transfer inside the terminal midgut (enclosed within the ▶ peritrophic membrane) to nectomonads (= swimming promastigotes) within 48–72 h. Later (within 4–7 days) leptomonads (= slender promastigotes) and haptomonads (wall-attached forms) occur prior to the occurrence of the transmissible metacyclics, which are found around days 6–7 at the inner side of the stomodeal valve. During the next sucking activity of the *Phlebotomus*, these stages are regurgitated into the wound.

## Diseases

▶ Leishmaniasis, Animals and ▶ Leishmaniasis, Man.

# *Leishmania Donovani* Complex: Survey

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## Name

The genus name honors W.B. ▶ Leishman (1863–1926); the genus name is dedicated to his English colleague Charles Donovan (1863–1951). Both contributed most essential knowledge on these parasites.

## Geographic Distribution/Epidemiology

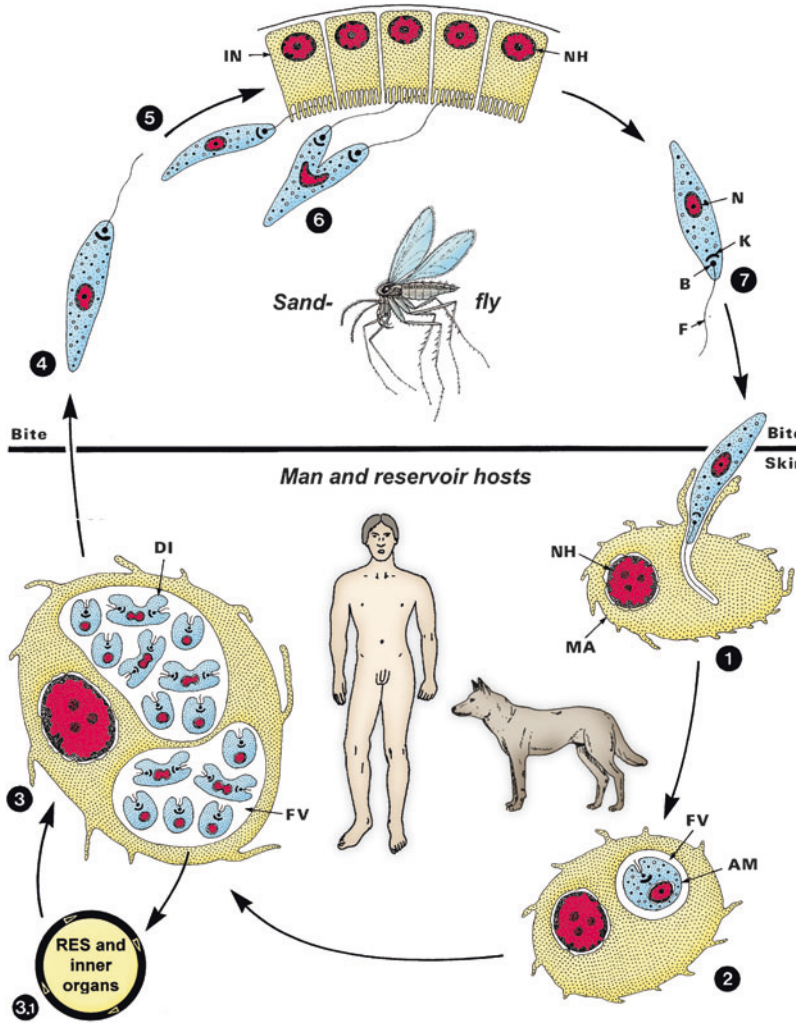
The parasites and the induced disease are found in dry, sandy, and mountainous regions. ***Leishmania donovani donovani***: India, China, Central Asia, East Africa from Egypt to Kenya and Uganda, West Africa: Senegal, Mali, Nigeria; ***L. donovani infantum***: Balearic Islands, Corsica, Sardinia, Coasts of the Mediterranean Sea, regions of the Black Sea; oriental countries: Saudi-Arabia, Yemen, Iraq, Iran, Emirates, Ethiopia. ***L. donovani chagasi***: Middle and Central South America: local spots from Mexico until South Brazil. In total more than 100 millions humans are infected.

## Morphology/Life Cycle

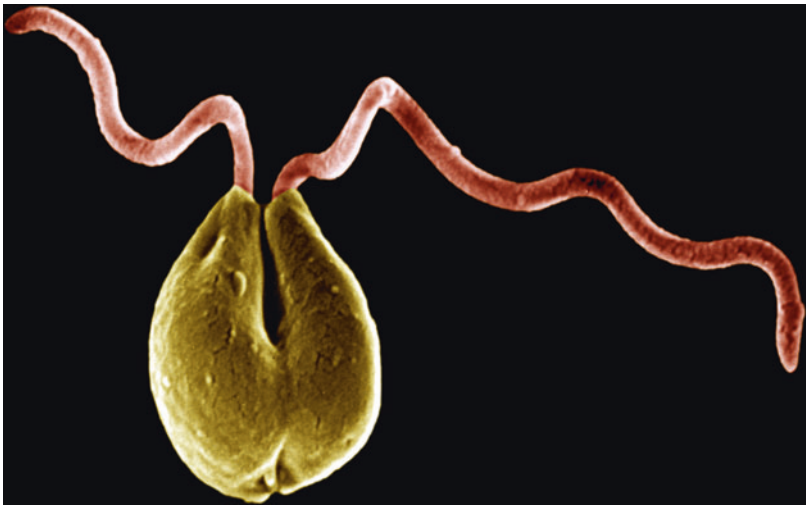
It is still finally not solved, whether the *L. donovani* complex consists of three true subspecies or whether there are three different species. However, there is no possibility to decide by means of morphological criteria nor by significant molecular biological facts. The infections start by bites of infected sandfly (e.g., ▶ *Phlebotomus* species in the case of *L. d. donovani, L. d. infantum* respectively ▶ *Lutzomyia* species in *L. d. chagasi*). During these bites promastigotes (sized 8–10 μm in length; Figs. 1 and 2) are transmitted. Within the skin region they were ingested by macrophages and included within food vacuoles (Figs. 3 and 4). Therein they are transformed during binary fissions to ovoid amastigotes = micromastigotes with a length of about 2–4 μm. Their tiny, short flagellum, which originates in a short invagination, never surmounts the cell surface, so that it becomes only visible in electron micrographs (Fig. 4). The parasitized host cell finally ruptures and sets free these micromastigotes, which either enter other cells in the skin region (so that also lesions may occur there) or are transported by lymph or blood to inner organs, where the characteristic further development occurs. Thus shortly after the skin reproduction phase the parasites are found in the reticuloendothelial system of the intestine, liver, spleen, lymph nodes, and bone marrow. In case a female sandfly ingests in such micromastigote stages they are transformed in the anterior portion of the intestine into promastigotes, which divide themselves repeatedly by longitudinal binary fission. During each of the following sucking acts the sandflies inject some of these promastigotes into the new host, so that a new cycle may start. Besides humans many reservoir hosts are known. Several live close to humans and thus are the main source for human infections. In the case of *L. d. infantum* dogs, wolves, foxes, raccoons, and rats are most important, while *L. d. chagasi* apparently only appears in foxes and dogs in larger amounts. Infections with *L. donovani* apparently induce a strong immunity after the infection had been cured by treatment using medicaments.

## Symptoms of Disease

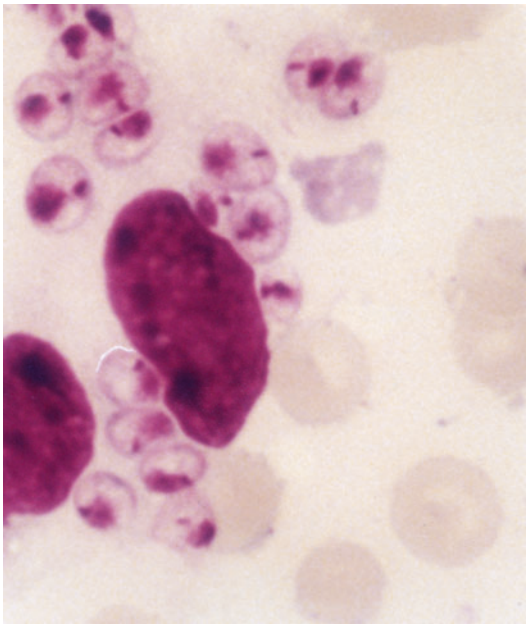
Depending on the region of occurrence the disease due to *Leishmania donovani* has got different names: Kala Azar, e.g., in India, Dum-dum fever, black disease, visceral or intestinal leishmaniasis. In most cases – although the parasites divide themselves constantly and become increased in number – significant symptoms do not occur for a long period after the infection. Thus there appear often first symptoms only after weeks or even after several months. Then start long lasting fever (for weeks with only short interruptions), which reach 39–40 °C (without chills). After weeks fever declines to a subfibrile status. During the phase of high fever mostly two peaks occur within 24 h. Another **leading symptom** of the visceral leishmaniasis is besides the long lasting fever the increasing splenomegaly (increase of spleen), occasionally accompanied by lymph node swellings and hepatomegaly (liver swelling). In the following period of disease anemia occurs as well as leucopenia with decreasing numbers of 2,000 leucocytes per $mm^3$ (found in up to 75 % of the cases). The number of thrombocytes decreases also significantly, while eosinophilia does not belong to the criteria of this type of leishmaniasis! When looking at the results of electrophoresis the amount of gammaglobulines is strongly increased, while albumin has



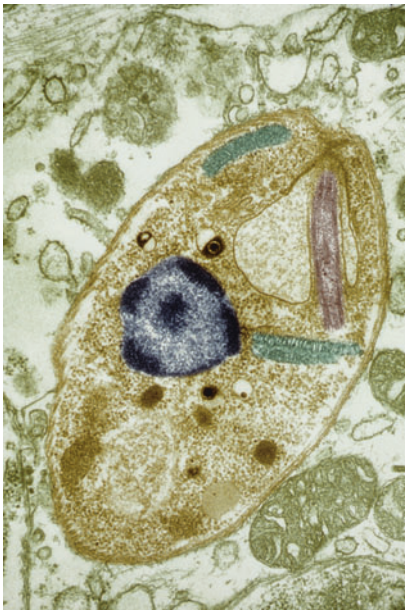

***Leishmania Donovani* Complex: Survey, Fig. 1** Life cycle of *Leishmania* spp. *1* After the bite of the ▶ vector the injected promasitigote stage is engulfed by macrophages in the skin of the vertebrate host. *2* Transformation of ▶ promastigotes into amastigote stages (2–4 µm in diameter) requires 1–4 h; reproduction proceeds as ▶ binary fission inside a ▶ parasitophorous vacuole, which later breaks down. *3* When macrophages are closely filled with ▶ amastigotes (after 48 h), they finally burst and set free the parasites which may enter other macrophages on the skin, leading to a cutaneous leishmaniasis. *3.1* Amastigotes of the *L. donovani* group are carried to inner organs and may enter various host cells, where they are reproduced by repeated binary fissions and lead to a visceral leishmaniasis within 4–6 months (kala-azar, dum-dum fever). *4–7* When a sandfly (genera ▶ *Phlebotomus*, ▶ *Lutzomyia*) ingests amastigotes along with its blood meal, the latter are transformed into slender ▶ promastigotes (10–20 µm in length) in the midgut, where they multiply by repeated ▶ binary fission (*6*). Quickly they block up the gut of the vector and move to the pharynx and buccal cavitiy, where they are injected into a new host with the fly's next bite (*7*). All stages have a slight ▶ surface coat. *AM* amastigote stage, *B* basal body of flagellum, *DI* dividing stage, *F* free flagellum, *FV* food vacuole, *IN* intestinal cell, *K* ▶ kinetoplast, *MA* macrophages, *N* nucleus, *NH* nucleus of host cell



***Leishmania Donovani* Complex: Survey, Fig. 2** Scanning electron micrograph of a dividing promastigote stage in the intestinal tract of a sandfly



***Leishmania Donovani* Complex: Survey, Fig. 3** Light micrograph of a macrophage with disrupted cell membrane containing large numbers of amastigotes. *E* erythrocyte, *K* kinetoplast, *N* nucleus of the parasite, *NH* nucleus of the host cell



***Leishmania Donovani* Complex: Survey, Fig. 4** Transmission electron micrograph through an amastigote = micromastigote stage inside of a macrophage. Note that the flagellum (above nucleus) does not leave the flagellar pocket

decreased. The change in protein composition and the anemia may initiate a sudden erythrocyte sedimentation. The color of the skin – especially of the face of patients – may reach extremely pale aspects. Untreated cases of this type of leishmaniasis end within a period of ½ and 3 years in cachexia and death mostly accompanied by bacterial superinfections. For **differential diagnosis** other diseases which induce also symptoms like splenomegaly (and/or leucopenia and anemia) must be considered in the first phase of *L. donovani* infection: e.g., malaria, typhus, miliar tuberculosis, sepsis, brucellosis, schistosomiasis. In the second phase of *L. donovani* infections other diseases such as lymphomas or leukemia may start additionally.

In treated cases of a *L. donovani* infection late symptoms may occur beginning 1-10 years after treatment, which are called **"dermal post Kala-Azar leishmanoid" (DPKL)**, which is characterized by the formation of strongly pigmented or erythematoic skin lumps. This late symptom occurs in 20 % of cases in India and in 2 % of the cases in Africa. These lumps are mainly found in the face.

## Diagnosis

In *Leishmania donovani* infected persons tissue probes taken from spleen, bone mark, lymph nodes, or liver contain the micromastigote stages, which can be seen microscopically in Giemsa stained smear preparations. However, in case of probes of the spleen there is a high risk, since leishmaniasis is linked with thrombopenia and thus there exists a decreased blood cell coagulation. Probes can also become inoculated in tissue cultures and in golden hamster. Positive reactions in hamsters, however, only occur after 6–8 weeks. PCR tests and/or serological examination (IFT, ELISA, and other methods) show mostly high levels of antibodies. General symptoms are hypergammaglobulinanemia, anemia, and pancytopenia. **Attention:** false positive results may also occur when using serological methods, since cross reactions with cutaneous and/or mucocutaneous leishmaniasis respectively Chagas disease are possible in the final stage of the disease or in case of immunosuppressed persons.

## Infection

Percutaneous injection of promastigote stages during bites of sandflies in endemic regions.

## Prophylaxis

Use repellents (Viticks®, Autan®); spray them onto skin and clothes in endemic regions. **Attention:** repellency lasts only a few hours!

## Incubation Period

Ten to sixty days, in rare cases also 1 year or more.

## Prepatency

One to three weeks.

## Patency

Months until years. However, self-healing is extremely rare. Thus without treatment this type of leishmaniasis ends mostly fatal for the patient.

## Treatment

Glucantime (20 mg/kg bodyweight) i.v. twice at intervals of 28 days. Alternatives in cases of antimony resistance or intolerance are pentamidin and amphothericin B. Paromomycin (i.m.) and allopurinol and combinations of antimony preparations together with gamma-interferon had also been used successfully. Miltefosin (Impavido®) is used orally: 3 doses per day of a total of 1.5–2.5 mg per kg bodyweight are given for 25–30 days.

## Further Reading

Abass E et al. (2015) Hepatogenenity of *Leishmania donovani* parasites complicates diagnosis of visceral leishmaniasis: comparison of different serological tests in three endemic regions. PLoS One DOI 10.1371/journal.pone.011408

Alam MZ et al. (2014) Genetic diversity of *Leishmania donovani/infantum* complex in China. Inf Genetics Evol 22:112–119

Chappuis F et al (2006) Field validity, reproducibility and feasibility of diagnostic tests for visceral leishmaniasis in rural Nepal. Trop Med Int Health 11:31–40

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# *Leishmania* Species of Skin: Survey

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## Name

The genus name honors the English scientist W.B. Leishman (1865–1926). The species names show regional relations, honor the English scientist Charles Donovan (1863–1951) or refer to main hosts: Latin: *infans* = child.

## Geographic Distribution/Epidemiology

The different species of the genus *Leishmania* have entered different regions:

*Leishmania donovani infantum* (found in dry, sandy mountain regions of countries around the Mediterranean Sea)

*L. tropica* (found in countries of the Southern Balcony, Greece, Turkey, Caucasian region, Arabian coasts, Afghanistan, Pakistan)

*L. major* (Northern Africa, anterior oriental regions, Lebanon, Syria, Iraq, Iran, Northern Saudi Arabia. Southern Afghanistan, Pakistan, Black Sea region, Western Africa between 10th and 13th°, local regions in Central and Western Africa)

*L. aethiopica* (Ethiopia, Kenya, Tanzania, Namibia)

*L. mexicana*-complex (Texas, Mexico until northern Argentina respectively Peru)

*L. braziliensis* (like *L. mexicana*)

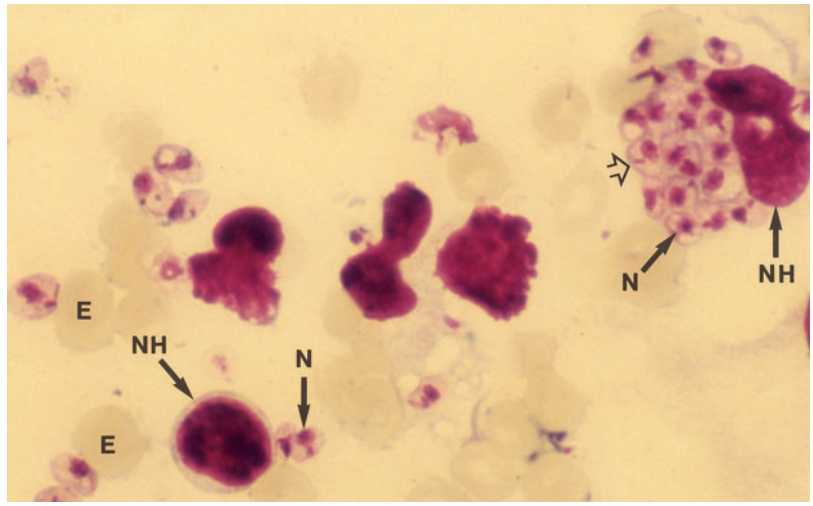
In these countries at least 100 million humans are infected, although high cure rates have been reached by medications. However, new and repeated infections lead to constant high numbers of infected people (plus reservoir hosts), so that travelers have a constant infection risk and should therefore protect themselves by use of significantly acting repellents (e.g., Viticks®) Autan based on icaridin. Table 1 shows further species of the genus *Leishmania*.

## Morphology/Life Cycle

The infections of humans and reservoir hosts start by bites of the females of the sandfly genera ▶ *Phlebotomus* (worldwide), ▶ *Lutzomyia* or ▶ *Sergentomyia* (in South America). During bites saliva is injected that contains so-called promastigote stages (Figs. 1 and 2), which are characterized by an anterior single flagellum. They have been reproduced by longitudinal binary fission while being attached at the wall of the proventriculus of the vector sandflies. Inside the skin these stages become situated within vacuoles of macrophages, histocytes, and endothelial cells. There the promastigotes become transformed to so-called amastigote (syn. micromastigote) stages, which have a size of only 2–4 µm, possess a tiny flagellum, a typical

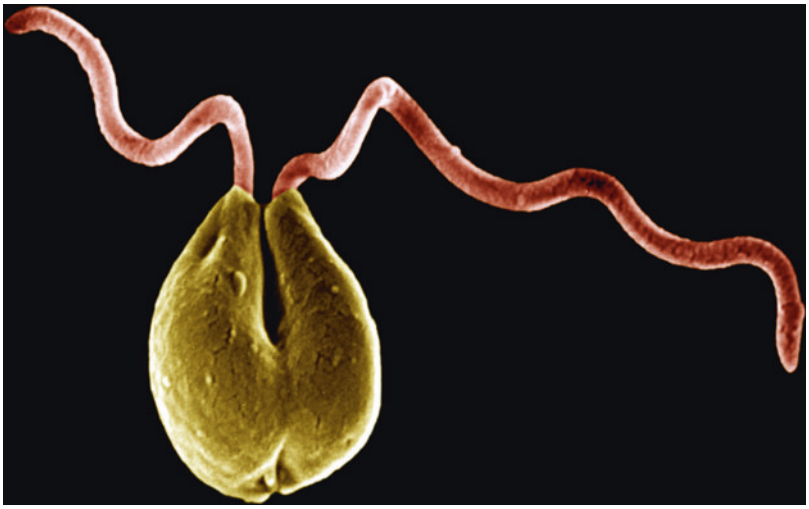
***Leishmania* Species of Skin: Survey, Table 1** *Leishmania* species of skin and their regional distribution

| Species | Type of disease | Reservoir host | Geographic distribution | Vector |
|---|---|---|---|---|
| Cutaneous leishmaniasis | | | | |
| *L. tropica minor* | Dry cutaneous | Rodents, dogs | Southern Europe, Middle East | *Phlebotomus* spp. |
| *L. tropica major* | Wet cutaneous, oriental sore | Rodents, dogs | Southern Europe, Africa Middle East | *Phlebotomus* spp. |
| *L. aethiopica* | Diffuse or dry cutaneous | *Hyrax* sp. | Ethiopia, Kenya | *Phlebotomus* spp. |
| *L. braziliensis braziliensis* | Espundia, mucocutaneous | Rodents | Mexico, Brazil | *Lutzomyia* spp., *Psychodopypus* spp. |
| *L. peruviana* | Uta, cutaneous | Dogs | Peru | *Lutzomyia* spp. |
| *L. mexicana mexicana* | Chiclero ulcer, cutaneous | Rodents | Central America | *Lutzomyia* spp. |
| *L. mexicana amazonensis* | Diffuse, cutaneous | Rodents | Amazonas region | *Lutzomyia* spp. |
| *L. mexicana pifanoi* | Cutaneous, mucocutaneous | Rodents | Venezuela | *Lutzomyia* spp. |

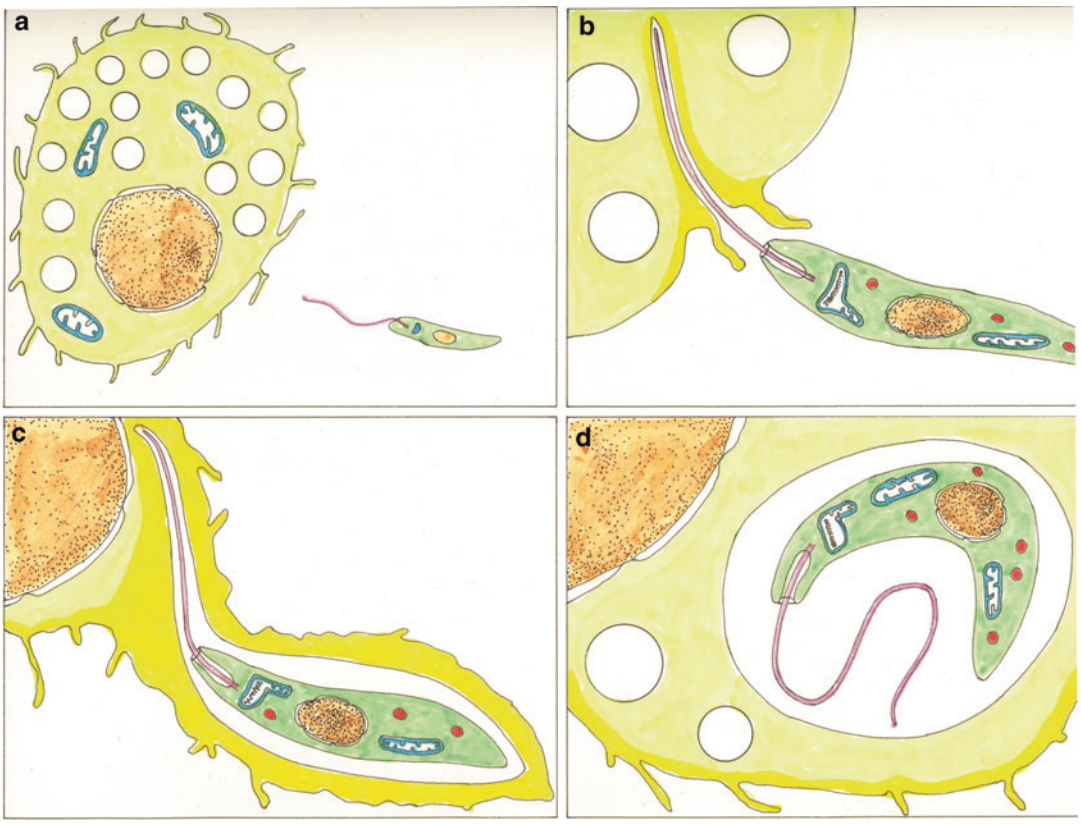



***Leishmania* Species of Skin: Survey, Fig. 1** Giemsa-stained smear preparation of macrophages containing *Leishmania* amastigotes. *E* erythrocyte, *N* nucleus of the parasite, *NH* nucleus of host cell

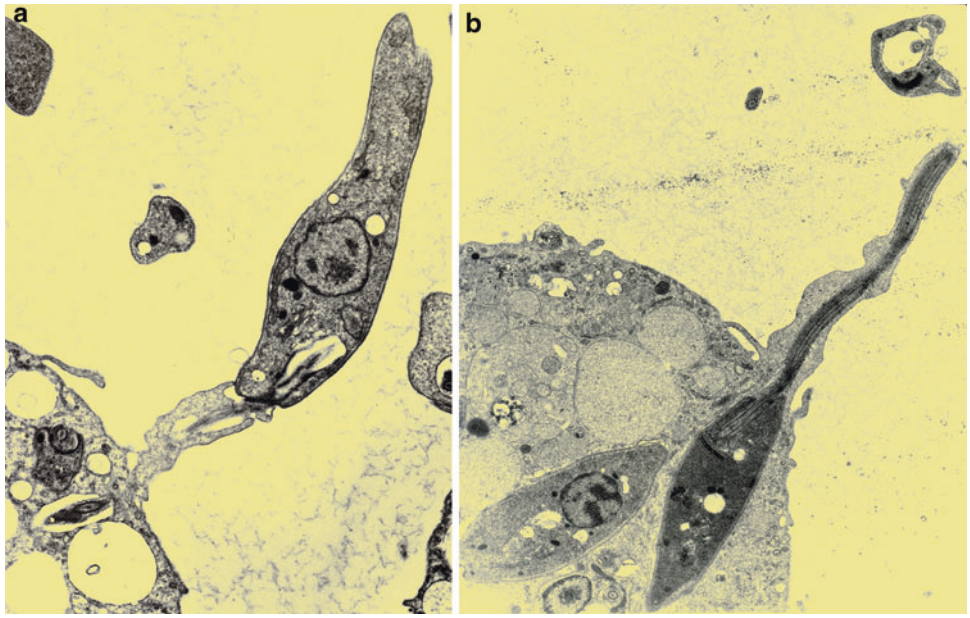
kinetoplast, divide themselves by binary fission, and finally destroy the host cell so that they are able to enter neighboring cells (Fig. 3). Therefore larger regions of destruction occur leading in the case of *L. tropica* to badly healing wounds in the skin. In the case of *L. donovani* stages the parasites are transported by macrophages to inner organs (e.g., spleen, lymph nodes, center of bones, etc.), where life-threatening damages may occur. In the case that sandflies suck blood they ingest those tiny amastigotes, which are transformed to promastigotes in their anterior intestinal regions. These stages are then transmitted to other hosts during further blood meals. All



***Leishmania* Species of Skin: Survey, Fig. 2** Dividing stage of a promastigote




***Leishmania* Species of Skin: Survey, Fig. 3** Diagrammatic representation of the process how macrophages engulf promastigotes (**a**–**d**)




***Leishmania* Species of Skin: Survey, Fig. 4** Transmission electron micrographs of promastigotes attracted by a protrusion of a macrophage

*Leishmania* species use besides humans a wide spectrum of reservoir hosts, so that eradication is practically excluded. Common reservoir hosts are *L. tropica*: dogs, rodents; *L. aethiopica*: cape hyrax; *L. mexicana* complex: rodents. Since the leishmaniases are distributed among reservoir animals as well as among humans and since they are transmitted by sandflies the leishmaniasis is considered as a true zoonosis.

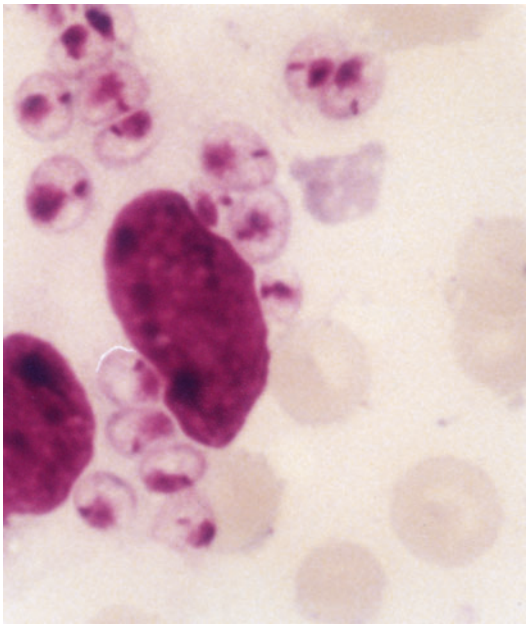
## Symptoms of Disease

The skin leishmaniasis is a common term to describe a wide spectrum of clinically different diseases, which are caused by a related group of agents.

(a) **Old World skin leishmaniasis**
- Dry skin leishmaniasis: (*L. tropica, L. d. infantum*)
- Wet skin leishmaniasis, Oriental sore, Aleppo sore: *L. major*
- Diffuse skin mucosa leishmaniasis: *L. aethiopica*

(b) **New World skin leishmaniasis**
- Chiclero disease along the ear: *L. mexicana mexicana.*
- Espundia, leishmaniasis of mucous layers (*L. braziliensis braziliensis),*
- Uta (dry skin leishmaniasis): *L. braziliensis peruviana,*
- Diffuse skin leishmaniasis: *L. mexicana amazonensis, L. mexicana pifanoi*

In general the following symptoms occur: after an incubation period of about 2–4 weeks (rarely also after several months) the biting sites develop itching reddish papulae and skin nodules, which slowly enlarge into ulcerations. Their final appearance depends not only on the injected species but also on the immune system of the host. In the case of the Oriental sore of the Old World (i.e.,



***Leishmania* Species of Skin: Survey, Fig. 5** Light micrograph of a destroyed host cell containing numerous reproduced amastigotes

infections with *L. tropica*) self-healing may occur within 1 year (i.e., 1 year sore) if there are not superinfections with different bacteria. As remnants of the Oriental sore a flat scar occurs. In the cases of the South American skin leishmaniasis different prognoses exist depending on the species (Fig. 4):

- *L. mexicana* leads to sores comparable to *L. tropica.*
- *L. braziliensis* leads to infections of mucous layers (Espundia) introducing to destruction of the lips, mouth, or the nasal cartilage, thus producing aspects described as tapir nose and other malformations of the skin (Figs. 4 and 5).

## Diagnosis

The agents of diseases (i.e., amastigote respectively micromastigote stages) can be obtained, when smear preparations or punctate probes are fixed and colored according to Giemsa. Serological tests are common, e.g., IFT, ELISA, etc., which act well in mucocutaneous leishmaniasis but deliver poor results in cutaneous leishmaniasis. For clear species differentiation PCR techniques are most successful and can be recommended as golden standard for high-quality laboratories.

## Infection

*Leishmania* promastigotes are transmitted during bites of sandflies of the genera *Phlebotomus, Lutzomyia,* or *Sergentomyia*.

## Prophylaxis

Repellents based on ▶ icaridin (▶ saltidin) (e.g., Viticks®, Autan®) or DEET offer protection for up to 6 h from attacks of sandflies, while pure plant products protect for less than a half hour. Sleeping below mosquito nets in endemic regions is recommended.

## Incubation Period

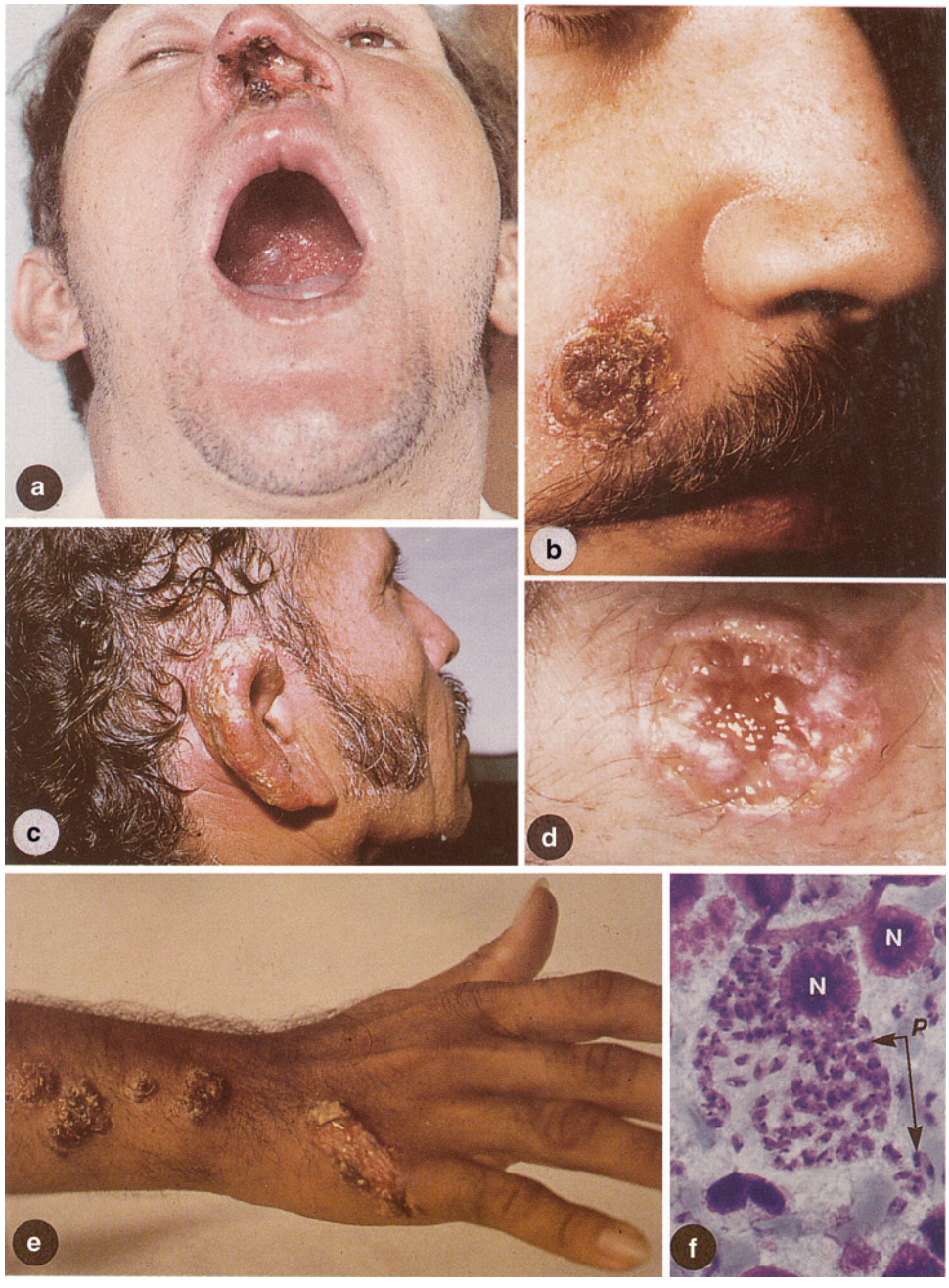
Two to four weeks.

## Patency

Months up to years.

## Therapy

In cases of uncomplicated cutaneous leishmaniasis treatment is not recommended, since drug toxicity is high and wounds will heal after a while. Only symptomatic cure is recommended by use of




***Leishmania* Species of Skin: Survey, Fig. 6** (**a**–**f**) Skin leishmaniasis in humans. (**a**) Mucocutaneous Espundia of nose and throat. (**b**) Espundia of lip region. (**c**) Chiclero's sore at the ear (*L. mexicana*). (**d**) Oriental sore due to *L. tropica.* (**e**) Uta sore due to *L. peruviana*. (**f**) Skin smear preparation of a disrupted macrophage containing numerous macrophages (*N* nucleus of host cell)

injections with 1–3 ml (=100–300 mg) sodium stibogluconate. In cases of complicated mucocutaneous leishmaniasis the same methods are recommended as in cases of internal leishmaniasis (▶ *Leishmania donovani*).

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# *Leishmania* Species: Dog Infections

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Table 1 presents the most important *Leishmania* species, which worldwide may infect dogs.

***Leishmania* Species: Dog Infections, Table 1** *Leishmania* species (infecting dogs) and their local vectors

| *Leishmania* spp. | Vectors | Geographical distribution |
|---|---|---|
| *L. amazonensis* | *Lutzomyia flaviscutellata* | Brazil |
| *L. arabica* | *Phlebotomus papatasi* | Saudi Arabia |
| *L. braziliensis* | *L. intermedia* | South America |
| *L. colombiensis* | *L. hartmanni* | Venezuela |
| *L. guyanensis* | *L. anduzei* | Colombia |
| *L. infantum* | *P. perniciosus* | Africa, America, Asia, Europe |
| *L. major* | *P. papatasi* | Egypt, Saudi Arabia |
| *L. mexicana* | *L. ayacuchensis* | Ecuador, USA |
| *L. panamensis* | *L. panamensis* | Colombia, Ecuador, Panama |
| *L. peruviana* | *L. peruensis* | Peru |
| *L. pifanoi* | *L. flaviscutellata* | Ecuador |
| *L. tropica* | *P. sergenti* | India, Iran, Morocco, Syria |

## Further Reading

Danhas-Torres F et al (2012) Canine leishmaniosis in the old and new world. Trends Parasitol 28:531–538

# *Leishmania*: Taxonomy

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Many scientists working with different *Leishmania* species feel that it is needed to reconstruct the interrelationships of *Leishmania* species and already propose changings (e.g., Schönian et al. (2010)). Others warn that it might be too early for a fundamental revision, if not all full

genome sequences of well-chosen reference strains are available – and this will need time. Thus the present status (2014) of naming ▶ *Leishmania* species is shown in the present edition of the Encyclopedia of Parasitology.

## References

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### Further Reading

Fraga J et al (2010) Phylogeny of *Leishmania* species based on heat-shock protein 70 gene. Infect Genet Evol 10:238–245

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# Leishmaniacidal Drugs

## General Information

▶ *Leishmania* spp. are intracellular parasites (amastigote stages) that affect mainly humans, dogs, and rodents (Table 1). The parasites are transmitted to various hosts by bites of sand flies (▶ *Phlebotomus* spp. and ▶ *Lutzomyia* spp., small in size). *Leishmania* invades resting macrophages and reaches cells of the reticuloendothelial system in various organs causing inflammatory processes and immune-mediated lesions. *Leishmania* can cause various disease patterns. Leishmaniasis comprises a variety of syndromes ranging from asymptomatic and self-healing infections (e.g., single cutaneous lesions caused by *L. major* or *L. tropica*) to those with a significant ▶ morbidity and mortality. The lesions may be confined to skin or disseminated to various tissues as in the case of the potentially fatal ▶ visceral leishmaniasis (VL). This zoonotic form (Kala-azar, Dum Dum Fever, or ▶ Black Sickness) is produced by *L. donovani* in China, India, the Middle East, and Africa, by *L. infantum* in North Africa and the Mediterranean region, and by *L. chagasi* in Latin America. Various clinical signs referring to the Old World ▶ cutaneous leishmaniasis (CL) are due to *L. major*, *L. tropica*, *L. aethiopica*, and certain zymodemes of the *L. infantum* complex. *L. mexicana* complex and *L. braziliensis* complex cause the New World cutaneous leishmaniasis and mucocutaneous leishmaniasis (MCL) ("Espundia"); they focally occur from Texas (USA) and Mexico, southwards throughout Central America and South America as far south as São Paulo state of Brazil. All species except *L. tropica* are essentially ▶ zoonoses that occur in scattered foci primarily rural and suburban, but there is a trend towards urbanization. Annually, about 500,000 clinical cases of VL occur worldwide and more than 200 million people are exposed to infection.

Zoonotic VL in **dogs** is a progressive systemic disease characterized by chronic wasting. Initial clinical signs are vague and may be ▶ weight loss, fever, ▶ anorexia, and exercise intolerance. Clinical signs indicative of systemic involvement include nonpruritic skin lesions, peripheral lymphadenopathy, lameness, and epistaxis. However, there may be different clinical features depending on individual variations, species of *Leishmania*, and phase of the disease. CL is a localized skin disease, which can show cutaneous, or mucocutaneous ▶ nodules and ulcerations but does involve other organs. Canine leishmaniasis in the Old World is mainly due to *L. infantum* endemic in parts of Spain and throughout the Mediterranean basin where its incidence may be up to 40 %. In the New World, *L. chagasi* (reservoir crab eating "fox", *Cerdocyon*, possibly others, dogs, serve as domestic reservoir) is the causal agent for American VL in dogs.

## Drugs Acting on Leishmaniases of Humans and Animals

For 50 years, pentavalent antimony compounds (sodium stibogluconate, identical to sodium

**Leishmaniacidal Drugs, Table 1** Drugs used against *Leishmania* sp. in humans

| **Parasite, disease**, distribution | **Stages** affected (location) | CHEMICAL CLASS, **nonproprietary name** (*Trade name), dose regimens (adult = pediatric) | **Miscellaneous comments** on drug characteristics |
|---|---|---|---|
| **Old World and the New World Leishmaniasis**: are transmitted by sand flies and caused by various *Leishmania* occurring in the Old World and the New World; in humans and animals, *Leishmania* produce numerous clinical manifestations attributed to them; thus leishmaniasis comprises a variety of syndromes ranging from asymptomatic and self-healing infections (e.g., single cutaneous lesions caused by *L. major* or *L. tropica*) to those with a significant morbidity and mortality. The lesions may be confined to skin or disseminated to various tissues as in the case of the potentially fatal visceral leishmaniasis (VL); post-kala-azar dermal leishmaniases (PKDL) is a relatively common consequence of therapeutic cure from VL caused by *L.* (*L.*) *donovani*; amastigote (intracellular) stages can be diagnosed clinical, parasitologic, serologic, and by isoenzyme electrophoresis, and DNA-based detection; however, it may be difficult to detect amastigotes in impression smears or in biopsy material (e.g., from bone marrow); these very small spherical to ovoid stages characterized by large nucleus and a prominent ovoid or rod-shaped kinetoplast may be differentiated from organisms such as *Histoplasma* or *Toxoplasma*; *Leishmania* has recently been divided into two subgenera, *Leishmania* (*Leishmania*) (most species) and *Leishmania* (*Viannia*), e.g., *L.* (*V.*) *braziliensis* and related species, taking into consideration many factors, including morphology, biochemical, and genetic characteristics of the organisms as well as their geographic distribution, clinical manifestations, and epidemiological factors; drugs used in humans may be also used in dogs | | | |
| DRUGS MAY BE USED FOR TREATMENT OF ALL LEISHMANIASES IN HUMANS AND ANIMALS | | | |
| SPECIES OCCURRING IN THE OLD WORLD | | | |
| **Cutaneous leishmaniasis (=CL)** (oriental score) *L.* (*L.*) *tropica, L.*(*L.*) *major, L.*(*L.*) *aethiopica*<br>**Visceral leishmaniasis (=VL)** (kala-azar) *L.* (*L.*) *donovani L.* (*L.*) *infantum* complex (certain strains may also cause CL; PKDL is not associated with this species) | **amastigote** (parasites invade resting macrophages of the skin; infection is often confined to the dermis and subcutaneous tissue)<br>**amastigote** (parasites initially invade resting macrophages of the skin and subsequently cells of RHS in liver, spleen, lymph nodes, and, bone marrow) | **CL:** *DRUGS OF CHOICE*<br>PENTAVALENT ANTIMONIALS<br>**sodium stibogluconate** (*Pentostam GSK) or **meglumine antimonate** (*Glucantime, Sanofi-Aventis): (20 mg Sb/kg/d i.v. or i.m. x20d, may be repeated or continued)<br>*ALTERNATIVES*<br>DIAMIDINES<br>**pentamidine isethionate** (*various): (*L. panamensis*, Columbia: 2–3 mg/kg i.v. or i.m. daily or every second day x4–7 doses)<br>AMINOGLYCOSIDE ANTIBIOTIC<br>**paromomycin** (*various): (topically 2x/d x10–20d may be repeated or continued) or *Leshcutan, a special formulation with methylbenzethonium HCl in soft white paraffin | **Sb compounds** are generally toxic: frequent fatigue, nausea, muscle and joint pain, increased transaminases, changes in ECG (T wave inversion), occasionally hepatic and renal dysfunction; shock sudden death (rare); **pentamidine** may cause frequent hypotension, hypoglycaemia often followed by diabetes mellitus, renal damage, pain at injection site, GI disturbance, vomiting; it proved effective in CL patients (Columbia) where likely organism was *L. panamensis* (its effect against other species is not well established) **paromomycin** should be used only in regions where CL species have low potential for mucosal spread; *Leshcutan proved effective against *L. major* in Israel and Guatemala (*L. mexicana*, |
| SPECIES OCCURRING IN THE NEW WORLD | | | |

(*continued*)

**Leishmaniacidal Drugs, Table 1** (continued)

| | | | |
|---|---|---|---|
| **American visceral leishmaniasis** (=AVL) *L.* (*L.*) *chagasi* (on rare occasions it may cause CL) | **amastigote** (location in host see above) clinical features in children closely resemble those of 'infantile' VL due to *L.* (*L.*) *infantum* of Old World | **VL:** *DRUGS OF CHOICE* **sodium stibogluconate** (*Pentostam GSK) or **meglumine antimonate** (*Glucantime, Sanofi-Aventis): (20 mg Sb/kg/d i.v. or i.m. x28d, may be repeated or continued) or POLYENE MACROLIDE ANTIBIOTICS **amphotericin** B (*various) (0.5–1 mg/kg i.v. daily or every second day for up to 8 weeks) or **liposomal amphotericin** B (*AmBisome FDA approved): (3 mg/kg/d i.v.: d1–5, and 3 mg/kg/d i.v. d 14 and d21) *ALTERNATIVES* **pentamidine** (*various) (4 mg/kg/d i.v. or i.m. daily or every second day for 15–30 doses) ALKYL PHOSPHOLIPID **miltefosine** (*Miltex, *Impavido Zentaris, Frankfurt Germany) (2.5 mg/kg/d x28d per os: children suffering from kala-azar in India) | *L. braziliensis*); for other effects of the drug cf. Antidiarrhoeal and Antitrichomoniasis Drugs, or Cestodocidal Drugs); **amphotericin B**, an antibiotic with extreme toxicity: generalized pain, convulsions, anaphylaxis, flushing chills, fever, phlebitis, anemia, thrombocytopenia, nephrotoxicity; there are various lipid formulations of the drug: *AmBisome (see dosage regimen), or *Abelcet (lipid complex of amphotericin B) and *Amphotec (amphotericin B cholesteryl sulfate) investigational drug products with good results in patients infected with *L. infantum*; **miltefosine** proved effective (97 %) against kala-azar in adults in India (100 mg/d orally) after 6 months; GI disturbances are common, drug is contraindicated in pregnancy; the drug was also effective against CL caused by *L. panamensis* in patients (≥12 years old) in Colombia but not *L. braziliensis* in Guatemala (2.5 mg/kg/d per os for 28d: frequent adverse effects: 'Motion sickness', nausea, headache and increased creatinine) |
| **Mucocutaneous leishmaniasis** (=MCL) *L.* (*V.*) *braziliensis, L.* (*V.*) *guyanensis* (and others) may also cause CL *L.* (*L.*) *amazonensis* (and others) **Cutaneous leishmaniasis (CL)** *L.*(*L.*) *mexicana L.*(*V.*) *lainsoni L.*(*V.*) *guyanensis* (and others) | **amastigote** (parasites invade resting macrophages of the skin and then they may spread to mucocutaneous junctions to cells of RHS; extensive destruction of dermis and other tissues **amastigote** (location in host see above; some species may spread to mucocutaneous junctions) | **AVL/MCL:** *DRUGS OF CHOICE* **sodium stibogluconate** (*Pentostam GSK) or **meglumine antimonate** (*Glucantime, Sanofi-Aventis): (20 mg Sb/kg/d i.v. or i.m. x28d, may be repeated or continued) **amphotericin** B (*various) (0.5–1 mg/kg i.v. daily or every second day for up to 8 weeks) | |

Dosages listed in the table refer to information from manufacturer, literature, and The Medical Letter, "Drugs for parasitic infections"

More information on adverse effects, manufacturers of drugs and brand names are given in The Medical Letter and partially in → Trypanocidal Drugs, Animals

Data Given in this Table have no claim to full information

antimony gluconate and meglumine antimoniate) have been the first-line drugs for the treatment of leishmaniasis in humans. The precise chemical structure of these drugs is difficult to identify. Thus quality control relies on chemical analysis for **pentavalent antimony** ($Sb^{5+}$) rather than sugar component, and other physicochemical analyses. Drug tolerance to antimonials in human and

canine leishmaniasis is known and there may be considerable rates of treatment failure and relapsing patients; drug tolerance may also be due in part to long-term treatment. Besides unresponsiveness, these drugs may show marked toxic effects such as arthralgia, nephrotoxicity, and cardiotoxicity leading in rare cases to sudden death. Antimonials are administered either by intralesional infiltration in simple single cutaneous lesions or by intramuscular injection in all cases with systemic involvement. The parenteral administration may be associated with unpleasant side effects. However these drugs seem to be safe if administered in the correct doses. Antimony is excreted quickly from the body so that daily treatment is necessary throughout each course for patients with VL (regimen see Table 1). The polyene antibiotic, **Amphotericine B**, is known to be effective in the treatment of VL, MCL (South America), and systemic mycoses but because of its toxicity it has so far been used only as a second-line drug (regimen see Table 1). There are now lipid formulations of amphotericine B with lower toxicity on the market and all have been on clinical trial for leishmaniasis. Thus the unilamellar liposome formulation, AmBisome, proved highly active against VL in Europe, Africa and India. *L. donovani* resistant to pentavalent antimony compounds may respond to lipid-encapsulated amphotericin B (NexStar is partner of TDR, WHO). In the search for nontoxic antileishmanials, attention has been directed toward currently used oral antifungal drugs such as the allylamine, terbinafine, N-substituted azoles, ketoconazole, and itraconazole. This is also true for the oral purine (hypoxanthine) analogue, **allopurinol** (see Table 1, also ▶ Trypanocidal Drugs, Man/Drug Acting on American Trypanosomiasis (Chagas' Disease) of Humans) or parenteral and topical formulations of the aminoglycoside **paromomycin** (= monomycin = aminosidine, Table 1). Most of these drugs and the 8-aminoquinoline WR6026, including synergistic combinations of antimonials either with paromomycin, allopurinol, or interferon-γ, which are or were on clinical trial for VL and CL have proved variably effective so far and well-tolerated. VL/HIV coinfections present special problems. Indirect methods of diagnosis (▶ Serology) frequently fail in treated and relapsing patients and direct invasive methods and skilled microscopy are then required. DNA-based identification of parasites by means of PCR method appears to provide a solution to diagnosis of persistent infections. Standard treatment of VL with conventional drugs gives poor results with HIV patients (about 40 % relapsed or showed persistent ▶ chronic infections) demonstrating the importance of the immune response during chemotherapy.

Current treatment of **leishmaniasis in dogs** with pentavalent antimony derivatives and/or allopurinol does not always provide complete elimination of parasites and in most cases clinical remission. If treatment period is too short clinical relapses are common. Oral long-term treatment with **allopurinol** for 4 weeks or longer (up to several months) may lead to clinical remission after intermittent administration of the drug. Dose used is usually 10–20 mg/kg b.w. twice daily or higher (up to 30 mg/kg b.w./day) and well-tolerated (sometimes vomitus). Simultaneous administration of **meglumine antimoniate** and allopurinol resulted in maintaining clinical remission in dogs. Dose regimen for Sb was 100 mg/kg b.w. s.c. for 20 days, followed by discontinuation of treatment for 15 days and repetition of the same regimen for 10 days, and that for allopurinol 30 mg/kg b.w. p.o. for 3 months, followed by 20 mg/kg b.w. for 7 days each month. Another intermittent regimen, which has successfully been used in treating canine leishmaniasis, is the intravenous (i.v.) administration of meglumine antimoniate, alone or in combination with, oral allopurinol. The intermittent regimen with meglumine antimoniate was 50 mg/kg b.w. (diluted with 0.9 % NaCl solution) for 2 days, followed by 100 mg/kg b.w. for 8 days. After discontinuation of treatment for 14 days, the same dosage regimen was repeated. The overall maintaining clinical remission was satisfactory in most patients but bone marrow continued to be PCR positive in the majority (11 of 16) of treated dogs.

## Leishmaniasis, Animals

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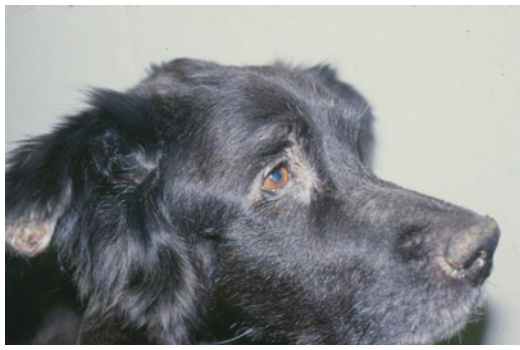
### Synonyms

Leishmaniosis

### Pathology

Leishmaniosis is caused by ▶ protozoa of the genus ▶ *Leishmania* that affect various mammalian hosts, but disease occurs most commonly in humans and dogs. The disease in dog is caused by *L. infantum*. The parasite is obligatory intracellular. It multiplies within macrophages and other cells of the mononuclear phagocytic system and causes chronic inflammatory processes. Clinically, the disease in dogs is characterized by a chronic loss of weight, nonregenerative ▶ anemia, intermittent pyrexia, and generalized or symmetrical lymphadenopathy. Cutaneous lesions are very common and include dry exfoliative dermatitis, ▶ nodules, ulcers, onychogryposis (clawlike curvature of the nails), and diffuse, symmetrical, or periorbital ▶ alopecia (Fig. 1). Ocular lesions such as keratoconjunctivitis, uveitis, and panophthalmitis may be present. Other signs include intermittent lameness, epistaxis, arthropathies, ascites, and intercurrent ▶ diarrhea. During postmortem examination, generalized lymphadenopathy and hepato- and splenomegaly are also observed.



**Leishmaniasis, Animals, Fig. 1** Dog showing typical skin signs of leishmaniasis

### Immune Responses

▶ Leishmaniasis, Man/▶ Immune Responses.

### Therapy

▶ Leishmaniacidal Drugs.

## Leishmaniasis, Man

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### Synonyms

*Skin Form*: Aleppo Boil, Chiclero's ulcer, Delhi Boil, French Bouton; Orient, Oriental sore
*Visceral Form*: Kala azar
*Mucocutaneous Form*: Espundia

### General Information

Leishmaniasis is a disease corresponding to a large spectrum of clinical symptoms, including visceral (VL), cutaneous (CL), diffuse cutaneous (▶ DCL), and mucocutaneous (MCL) forms. Recent estimations indicate that more than 400 million people are at risk of catching VL and ▶ CL and the annual number of cases of VL or CL has turned into hundreds of thousands. The

different species are responsible for various clinical manifestations and exhibit peculiarities of their natural cycle such as animal reservoirs or species of vectors as well as epidemiological features. Therefore a universal control strategy is not possible. Species such as *L. major, L. tropica, L. braziliensis, L. mexicana*, and *L. aethopica* cause mostly single, self-healing cutaneous ▶ ulcers in humans while chronic diffuse cutaneous forms or progressively destructive mucocutaneous forms occur after infection with *L. mexicana* and *L. amazonensis* or *L. braziliensis*, respectively. The most severe, visceral form (kala-azar), which is fatal, if left untreated, and affects spleen, liver, and bone marrow, is caused by *L. donovani* and *L. infantum* (▶ *Leishmania*).

The infections usually start in the skin after the bite of a phlebotomid sand fly which inoculates ▶ Promastigotes. In all clinical forms of leishmaniasis (see below) ▶ amastigotes multiply in monocytes. Parenchymal cells appear rarely to be involved, suggesting that organisms are phagocytized. Although the organisms are capable of multiplying extracellularly, such as in the gut of the sand fly or in culture, there appears either to be little or no extracellular multiplication in the mammalian host, where such organisms are destroyed by the processes of immunity. Traditionally *L. major, L. tropica, L. aethiopica, L. mexicanum, L. peruviana, L. brasiliensis*, and *L. pifanoi* have been recognized, with several subspecies. The classification of the various leishmanial groups by zymodemes and serodemes and the correlation with clinical forms is in progress.

## Pathology

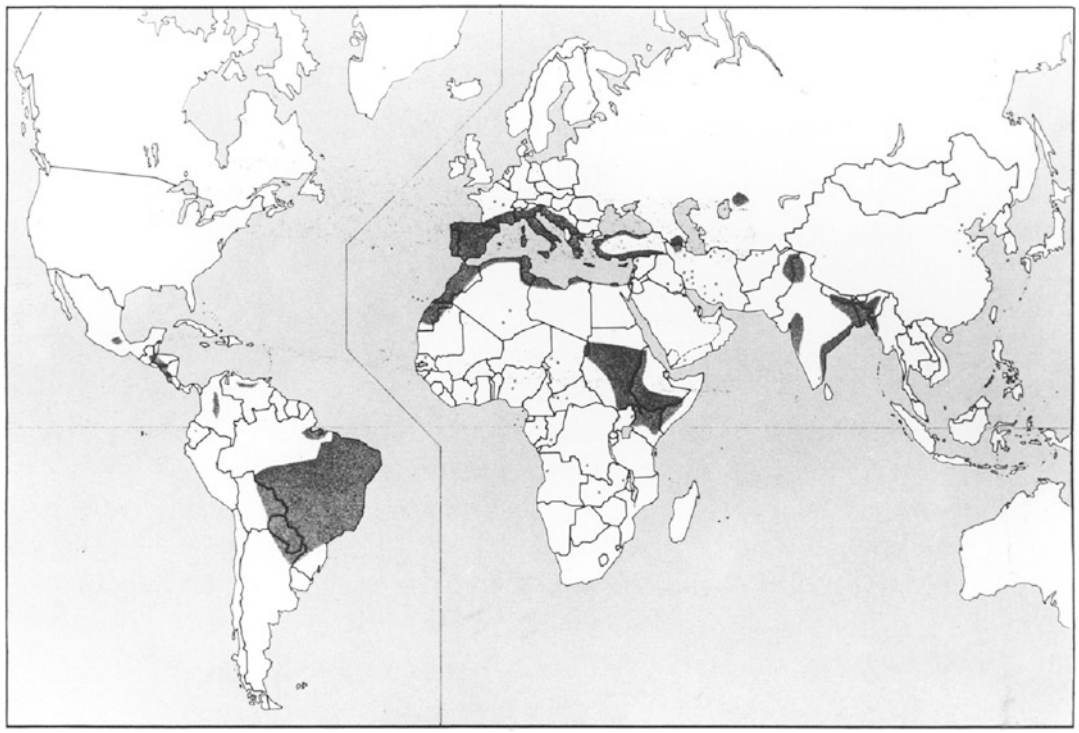
The primarily cutaneous forms of leishmaniasis may be limited to the skin and adjacent tissues, possibly because the temperature optimum of the causative organisms is 33–35 °C, i.e., as in the skin; also the expression of cellular immunity is impaired at lower skin temperatures. A similar situation appears to account for the superficial localization of leprosy. In contrast to this, the organisms causing ▶ visceral leishmaniasis infect the deep tissues even though they are inoculated by ▶ *Phlebotomus* spp. bite into the skin.

### Cutaneous Leishmaniasis (CL)

▶ Cutaneous leishmaniasis occurs in both the Old and the New Worlds, produced by ▶ *Leishmania tropica* and *L. mexicanum*. Lesions start as papules composed of proliferating histiocytes (macrophages) which contain numerous amastigotes (▶ Pathology/Fig. 1). The lesions are usually found on the exposed areas of the face or extremities, at the presumed inoculation site. Satellite lesions develop sometimes on skin surfaces with intact epidermis. Diagnosis is easily accomplished in histological sections or impression smears; however organisms may be sparse. The lesions become infiltrated by varying numbers of lymphocytes and plasma cells and eventually become granulomatous, containing fewer amastigotes after several weeks or months. With the development of delayed hypersensitivity the lesions ulcerate. They become secondarily infected with bacteria and the base of the ulcer contains neutrophils. The amastigotes remain in the epidermally covered areas peripheral to the ulcer and can best be isolated by aspiration from there for diagnosis in culture.

With developing immunity, the ulcers heal with granulation tissue and fibrosis, often leaving a slightly depressed scar. However, chiclero ulcers, typically on the earlobes, do not heal readily in Mexico and Central America, a fact believed to result from the lower body temperature which impairs the expression of cellular immunity.

**Main clinical symptoms**: Skin ▶ nodules, papulae, ulceration, necrosis.
**Incubation period**: 2–4 weeks up to 1 year.
**Prepatent period**: 1–3 weeks.
**Patent period**: Months.
**Diagnosis**: Microscopic determination of amastigotes in skin biopsies, serodiagnostic methods, ▶ serology, ▶ *Leishmania*/Fig. 2.
**Prophylaxis**: Avoid the bite of the vector.
**Therapy**: See ▶ Leishmaniacidal Drugs.



**Leishmaniasis, Man, Fig. 1** Distribution map of skin leishmaniasis (according to WHO)

### Mucocutaneous Leishmaniasis (MCL)

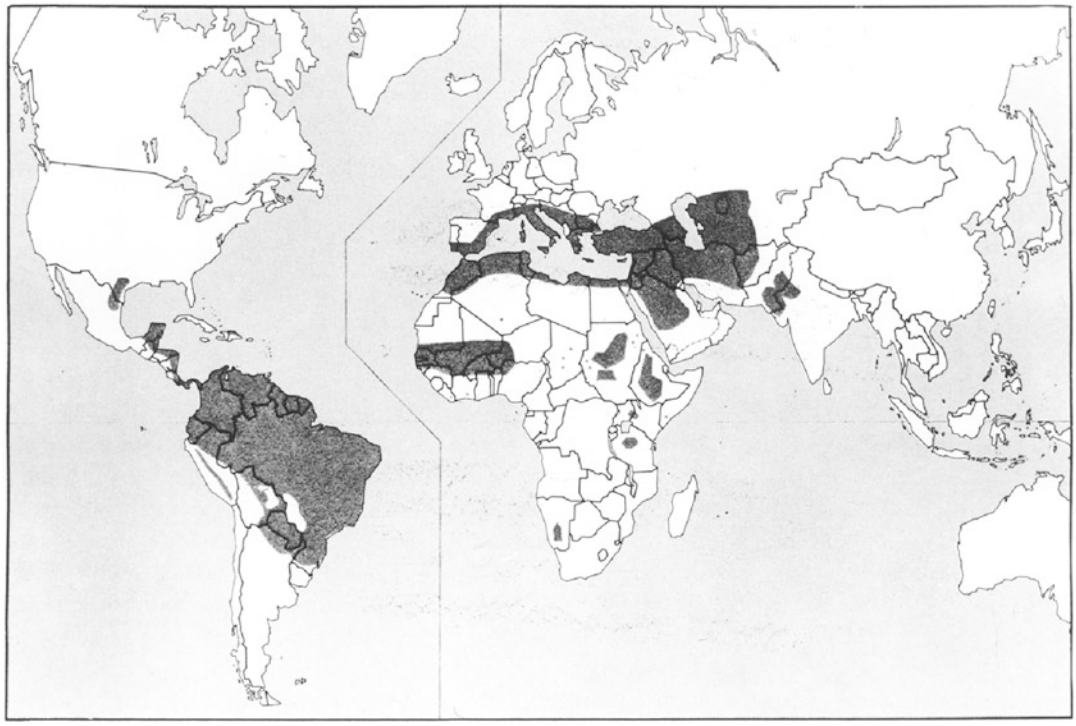
Mucocutaneous leishmaniasis, or espundia, caused by *Leishmania brasiliensis* complex is also transmitted by sand fly bite in South America. However, skin lesions often metastasize from the site of inoculation to other areas of skin and the mucous membranes, especially of the oro- and nasopharynx. Histologically the lesions are granulomatous with relatively few amastigotes and numerous lymphocytes and plasma cells. The lesions ulcerate, become bacterially infected, and often persist for months or years, at times destroying the cartilaginous nasal septum.

### Diffuse Cutaneous Leishmaniasis (DCL)

Diffuse cutaneous leishmaniasis may be produced by a distinct species of *Leishmania*, or it may be an individual reaction, as occurs in lepromatous leprosy. It occurs in the Caribbean, Brazil, and Ethiopia (Fig. 1). Huge numbers of macrophages filled with amastigotes accumulate and develop into nodular cutaneous lesions without necrosis, ulceration, or the formation of granulomas and accompanied by only few lymphocytes and plasma cells (► Pathology/Fig. 14).

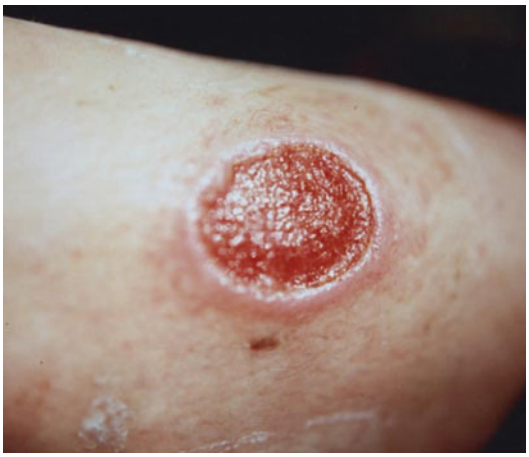
### Visceral Leishmaniasis (VL)

Visceral leishmaniasis, or kala-azar, occurs in South Europe, the Middle East, India, Africa, and focally in Central and South America (Figs. 2, 3, 4, and 5). It is produced by several forms of *Leishmania* which can be arranged into several groups according to results of isoenzyme analysis, antibody tests, and nucleic acid analysis; these groups may include species other than the classical species, *L. donovani, L. infantum*, in the Middle East, and *L. chagasi* in Latin America. The reticuloendothelial cells of the viscera are parasitized by amastigotes and multiply greatly, resulting in hepatomegaly and splenomegaly (up to 3,000 g) which is palpable through the abdominal wall. Splenomegaly leads to hypersplenism with erythrophagocytosis, anemia, and is accompanied by hyperglobulinemia and hypoalbuminemia. The

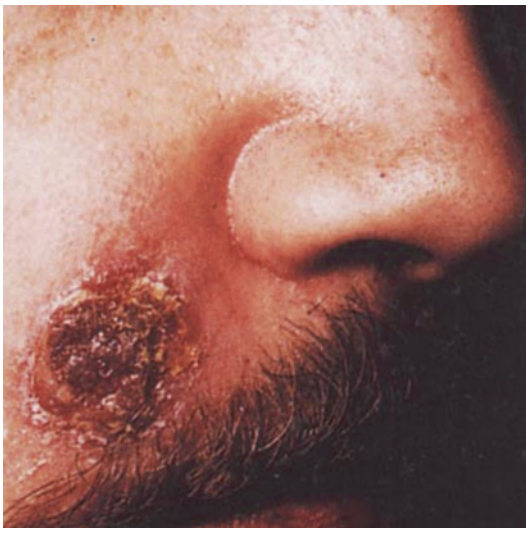


**Leishmaniasis, Man, Fig. 2** Distribution map of visceral leishmaniasis (according to WHO)



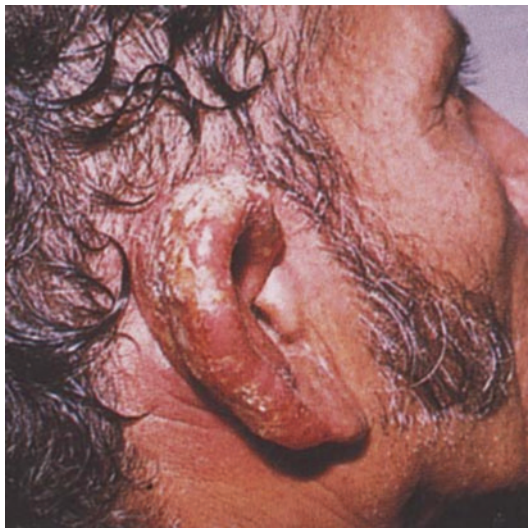


**Leishmaniasis, Man, Fig. 3** Nonhealing leishmanial wound at the arm



**Leishmaniasis, Man, Fig. 4** *Leishmania* sore in the face

lymph nodes and bone marrow are usually also involved. Impaired hematopoiesis, leucopenia, and thrombocytopenia are commonly found. Histological examination shows that the Kupffer cells of the liver and the histiocytic cells of the spleen are filled with large numbers of amastigotes; the hepatic parenchymal cells often show steatosis and atrophy and the splenic follicles are also



**Leishmaniasis, Man, Fig. 5** *Leishmania* sore at the border of the ear

atrophic. Immunoglobulins (IgA, IgM, and IgG) are deposited in the glomerular mesangia and around the tubules in the kidney. A long febrile course with progressive cachexia and secondary infection often precedes death. An unknown number of patients recover spontaneously and many do after timely chemotherapy with a regression of the reticuloendothelial ▶ hyperplasia. Some of these patients develop post-kala-azar dermal leishmaniasis with amastigote-laden histiocytes accumulating in the skin and producing nodules covered by thin epidermis similar to an anergic cutaneous leishmaniasis (▶ Pathology/Fig. 14). Apparently, effector mechanisms of cellular immunity, which operate in the viscera, were not effective in the cooler skin.

**Main clinical symptoms**: Fever of 39–40 °C, with two peaks in 24 h, ▶ anemia, leucopenia, pale skin, kachexia, bacterial superinfections.
**Incubation period**: 10 days to 1 year.
**Prepatent period**: 1–3 weeks.
**Patent period**: Months to years.
**Diagnosis**: Serologic tests and microscopic determination of smear preparations of bone marrow, ▶ Serology.
**Prophylaxis**: Avoid the bite of phlebotomids in endemic regions.
**Therapy**: Treatment see ▶ Trypanocidal Drugs, Man and ▶ Leishmaniacidal Drugs.

## Immune Responses

In their mammalian host, *Leishmania* typically reside within macrophages, dendritic cells, and fibroblasts which not only serve as potentially safe habitats for the parasite but may also possess antigen-presenting and/or antimicrobial functions. Experimental infections of mice with either *L. major* or *L. donovani* have greatly attracted many immunologists over the last decades to study the role of innate or acquired immune mechanisms to control an intracellular microorganism. In particular, the existence of inbred mice which either cure or succumb to the infections has helped to define protective and nonprotective functions of the immune system.

### Innate Defense Mechanisms

An initial study has demonstrated the ability of *L. major* promastigotes to activate the IL-1 promoter in macrophages via a MyD88-dependent pathway. Consistently, three studies have shown that mice lacking functional MyD88 adapter protein are very susceptible to infection with *L. major*. Contrasting with the WT mice, in the MyD88 KO mice infected with *L. major*, the Th responses were characterized by the production of high levels of IL-4 and low levels of IFN-γ. Importantly, upon treatment with exogenous IL-12 or anti-IL-4 antibodies, MyD88 KO mice develop Th1 responses and become resistant to infection. Additional studies have demonstrated that the lypophosphoglycan (LPG), a dominant molecule that covers the surface of the promastigote stage of *Leishmania*, is a TLR2 agonist. The lipid moiety was shown to be essential for TLR2 signaling by LPG, suggesting the involvement of the GPI anchor. Together, these results indicate that LPG is an agonist for TLR2 and that induction of IL-12 synthesis and protective immunity during infection with *L. major* in mice involves the TLR signaling pathway. While noninfective, procyclic *Leishmania* promastigotes are sensitive to complement-

mediated lysis, the infective stages transmitted by ► sand flies (metacyclic promastigotes) are relatively resistant to direct serum killing. As shown recently by Dominguez and Torano, *Leishmania* promastigotes bind natural anti-Leishmania IgM antibodies within 30 s, which then activate the classical complement pathway resulting in opsonization by the third component of complement. The opsonized promastigotes then bind quantitatively to erythrocyte CR1 receptors. Progression of infection implies promastigote transfer from erythrocytes to monocytes/macrophages where the parasite uptake is predominantly mediated by CR3. Since cross-linking of the CR3 does not elicit an oxidative burst in monocytes, complement components of the host are used by Leishmania for silent invasion of host macrophages. Macrophages harbor Leishmania and allow the parasite to replicate or when activated by appropriate stimuli such as IFN-γ kill and destroy the parasites. Toxic nitrogen products, predominantly ► nitric oxide, which are synthesized by iNOS, are the main parasitocidal molecules produced by activated macrophages. Mice genetically deficient for iNOS or treated with iNOS inhibitors are unable to restrict parasite replication and reactivation of latent leishmaniasis occurred after treatment of long-term-infected C57BL/6 mice with the specific iNOS inhibitor L-iminoethyl-lysine (L-NIL). In addition, iNOS appeared to have important immunoregulatory functions during the early phase of a Leishmania infection. At day 1 of infection genetic deletion or functional inactivation of iNOS abolished the IFN-γ and NK cell response, increased the expression of TGF-β, and caused systemic parasite spreading. Since neutralization of IFN-α/β in vivo inhibited iNOS expression and mimicked the phenotype of iNOS-deficient mice, type I interferons and iNOS are critical regulators of the innate immune response to *L. major*.

More than macrophages, dendritic cells are extraordinarily efficient in presenting antigens to naive T cells. Langerhans cells of the skin ingest Leishmania parasites, process native antigen, and express relevant epitopes in context with MHC molecules on their surface. The Langerhans cells move to the draining lymph nodes where they activate parasite-specific naive T cells. Evidence suggesting that this takes place not only in experimentally infected mice but also in humans comes from immunohistochemical investigations of biopsy material from patients with cutaneous leishmaniasis: Langerhans cells containing Leishmania antigens have been found in the epidermis and dermis at the site of an oriental sore.

Homogeneous populations of mouse mast cells released preformed mediators such as b-hexosamidase or TNF in response to living Leishmania promastigotes. By local cutaneous reconstitution of mast-cell-deficient mice, it was found that the presence of mast cells augmented the lesion size caused by *L. major*. However, there was no influence of mast cells on the cytokine response in the draining lymph nodes or the ultimate outcome of the infection.

Studies with *L. major*-infected mice pointed at NK cells as an important source of IFN-γ during the early course of infection. Genetically resistant mice had a higher NK 7activity after infection than susceptible mice and the depletion of NK cells resulted in less IFN-γ production and a transient increase in lesion size. On the contrary, activation of NK cells in susceptible mice by injection of poly I-C enhanced IFN-γ synthesis and led to lower parasite burdens. However, the effects of NK cells appeared to be transient and did not influence the ultimate outcome of experimental *L. major* infections. C57BL/6 mice deficient in NK cell activity due to the beige mutation were less able to control *L. donovani* infection compared to normal control mice and reconstitution with NK cells restored this defect. While in lesions of patients with cutaneous leishmaniasis high numbers of NK cells have been detected, impaired NK activity has been found in the blood of patients with visceral leishmaniasis, which could be restored in vitro by incubation with IL-2.

### B Cells and Antibodies

In vivo, B cells respond to Leishmania infections by production of parasite-specific antibodies, which are generally considered not protective against the intracellular Leishmania. The levels of Leishmania-specific antibodies may be very

high and in most severe infections an unspecific polyclonal B cell activation leading to hypergammaglobulinemia occurs additionally.

Although B cells cannot be infected by Leishmania parasites, activated B cells are able to process and present leishmanial antigens to T cells. It has been proposed that antigen presentation by B cells is involved in the generation of a Th-2 response. In fact, BALB/c mice treated neonatally with anti-IgM were resistant to *L. major*, and BALB/c X-linked immunodeficient (Xid) mice, which lacked the B1 subset of B cells, displayed enhanced resistance to *L. major*. In line with these findings, the cotransfer of B cells converted resistance into susceptibility in T cell-reconstituted, *L. major*-resistant scid mice. However, more recent experiments with mice harboring a targeted disruption of the IgM locus (μMT mice) and therefore lacking B cells showed no influence of B cells on the polarization of T helper cells: μMT mice on the BALB/c background were susceptible to *L. major* infection and developed a Th2 response.

### T Cells and Cytokines

A significant increase of γ/δ T cells was found in skin lesions of patients with cutaneous leishmaniasis. Similarly, expansion of γ/δ T cells has been observed in genetically resistant mice following *L. major* infection, indicating that γ/δ T cells may be involved in host defense against this parasite. However, C57BL/6 knockout mice lacking γ/δ T cells (TCR δ-/-) effectively controlled the infection and produced similar levels of IFN-γ when compared with control mice, strongly arguing against an essential protective role of this T cell subset in *Leishmania* infection. In contrast, mice depleted of or genetically deficient for conventional α/β T cells were unable to control leishmania parasites. While ample evidence has demonstrated the central role of $CD4^+$ Th cells in the control of a *L. major* infection, the role of $CD8^+$ T cells in cutaneous leishmaniasis is less well defined. Although $CD8^+$ T cells appear to be important for resistance to a secondary challenge with *L. major*, there appears to be no essential function of $CD8^+$ T cells in primary infection. Both, mice genetically deficient for β2-microglobulin and CD8 thus lacking $CD8^+$ T cells were able to mount an effective and long-lasting immune response against *L. major*.

Unlike the *L. major* model, resolution of primary *L. donovani* infection requires not only $CD4^+$ T cells but also $CD8^+$ T cells. Acquisition of resistance involves the secretion of IL-2, IFN-γ, and TNF. Similar to cutaneous leishmaniasis, resistance of *L. donovani*-immune mice to rechallenge was strongly dependent on $CD8^+$ T cells.

Mice from the majority of inbred strains (C3H/He, B10.D2, C57BL/6, Sv129/Ev, etc.) are resistant to infection with *L. major*, while only mice of a few strains such as BALB/c develop progressive lesions and succumb to the infection. Healing of lesions induced by *L. major* requires the induction and expansion of specific $CD4^+$ Th1 cells that are restricted by MHC class II and produce IFN-γ, while susceptibility was found to be associated with the development of a predominant Th2 cell immune response. However it has been shown that susceptibility is not an absolute trait but one conditional on parasite dose, since infection with low numbers of parasites (about 1000-fold lower than the number employed ($10^5$) to define the susceptible phenotype of BALB/c mice) induced long-term protective Th1 immunity in BALB/c mice. Thus in addition to host factors the parasite dose determines the Th1/Th2 nature of the response to *L. major*, and this was found to occur independently of the infection route and parasite strain. A large number of studies has focused on the immunoregulatory mechanisms determining the Th1/ Th2 decision and the role of these different Th cells in *L. major*-infected mice.

The role of IFN-γ in the control of infection with *L. major* was firmly established by experiments showing that genetically resistant mice with disrupted genes for IFN-γ or its receptor failed to resolve their lesions. More recently, the additional importance of the Fas-Fas-L pathway in the elimination of parasites has been demonstrated. In contrast to wild-type C57BL/6 mice gld or lpr mice lacking either a functional Fas or Fas-L were unable to resolve *L. major*-induced lesions although they mounted a normal Th1 response

and their macrophages produced normal levels of NO in response to IFN-γ in vitro. Since IFN-γ upregulated the expression of Fas on *L. major*-infected macrophages, thereby rendering these cells susceptible to apoptotic death by Th1 cells, IFN-γ might contribute by at least two mechanisms to the defense against intracellular Leishmania.

Th1 and Th2 cells develop from a common native precursor. Both accessory molecules and cytokines are known to influence the differentiation of $CD4^+$ T cell precursors in vivo. CD80 (B7-1) and CD86 (B7-2) as well as the CD40 molecule and its ligand have been shown to influence the Th cell differentiation and thus the clinical outcome after infection with *L. major*. Deficiency in either CD40 or its ligand resulted in the inability of mice to generate a Th1 response and to control *L. major* or *L. amazonensis* infections. While the blockade of CD86 by mAb treatment ameliorated the infection and inhibited Th2 development in BALB/c mice, BALB/c mice deficient for CD28, a ligand of CD80 and CD86, remained susceptible to infection. In contrast, the interaction of the CD4 molecule with MHC class II appeared to be of importance for the development of a Th2 cell immune response. There is ample evidence that IL-4 is essential for the development of Th2 cells after infection with *L. major*. The neutralization of IL-4 by mAb or recombinant soluble forms of the IL-4 receptor resulted in Th1 development in BALB/c mice which thereby controlled primary *L. major* infection and became resistant against secondary challenge infections. Confirmatory evidence came from experiments with mice deficient for either IL-4 or STAT-6 (one of the major IL-4 signal-transducing molecules) which were more resistant against *L. major* or *L. mexicana*, respectively, when compared with their control littermates. Only in susceptible BALB/c mice there was a very early IL-4 production by activated $CD4^+$ T cells during the first day after infection with *L. major*. A highly restricted subpopulation of $CD4^+$ T cells expressing the TCR Vβ4 and Vα8 chains specific for a single immunodominant antigen called LACK (Leishmania-activated C kinase) was identified as source for the early IL-4. Interestingly, mice deficient in Vβ-4 mounted a polarized Th1 response and were fully resistant to infection, suggesting that a single epitope of the LACK antigen drives the early IL-4 response and instructs subsequent Th2 differentiation and susceptibility to infection in BALB/c mice. In agreement with this concept, transgenic BALB/c mice expressing the LACK antigen in the thymus were tolerant to this antigen and resistant to infection with *L. major*. However, since LACK appears not to be the dominant antigen in MHC haplotypes other than $H\text{-}2^d$ (N. Glaichenhaus, personal communication) it remains to be determined which antigen(s) or mechanism(s) are responsible for the susceptible phenotype of BALB congenic mice.

The essential role of IL-12 for the development of a protective Th1 cell response against *L. major* has been demonstrated by several experimental approaches. Neutralization with antibodies or disruption of the IL-12 gene in resistant mice resulted in susceptibility, while treatment of BALB/c mice with recombinant IL-12 during the first week of infection enabled these mice to develop a Th1 response and allowed the resolution of lesions. In line with this, mice deficient for the transcription factor IRF-1 (Interferon regulatory factor 1) were susceptible to *L. major*, most likely due to the impaired ability of their macrophages to produce IL-12. While in resistant C3H mice an enhanced expression of the IL-12 receptor subunits β1 and β1 was detected after *L. major* infection this was not the case in lymph nodes of BALB/c mice unless these mice were rendered resistant by neutralization of IL-4 or treatment with IL-12. Thus, the upregulation and maintenance of IL-12 receptor molecules or its counterregulation by IL-4 on $CD4^+$ T cells may be critically involved in the generation of a protective Th1 cell response. The nonhealing lesions caused by *L. major* in mice were associated with enhanced IL-10 production and $T_{reg}$ presence at the site of infection. Enhancement in the number of natural $T_{reg}$ in mice chronically infected with *L. major* was sufficient to trigger disease reactivation and to inhibit the effector memory response. Thus, enhancement of $T_{reg}$ regulatory function, either from the endogenous pool or

induced by the infection, can clearly become detrimental to the host by allowing excessive parasite expansion. On the other hand in the nonhealing model of *L. major* infection, pathology is also held in check by natural $T_{reg}$. *Leishmania amazonensis* infection in mice is characterized by the accumulation of natural $T_{reg}$ at sites of infection that transiently downregulate immunopathology.

Several other cytokines are additionally involved in the regulation of immunity against Leishmania. It has been shown that leishmanial infection induced the production of active TGF-β, both in vitro and in vivo. Since application of recombinant TGF-β markedly exacerbated the disease while treatment with anti-TGF-β resulted in protection of BALB/c mice after infection with *L. amazonensis*, induction of TGF-β has been regarded as a parasite escape mechanism. TNF, which had no direct toxic effects on leishmania, was found to activate in combination with other cytokines such as IFN-γ the leishmanicidal activity of macrophages in vitro. In vivo, there were no differences in the expression levels of TNF, lymphotoxin (LT), or the TNF receptors I and II (p55 and p75) when susceptible BALB/c and resistant CBA mice were compared. Using knockout mice deficient for either TNFRp55, TNFRp75, or both receptors it was reported that the TNFRp75 plays no essential role in *L. major* infection while the TNFRp55 might be required for optimal macrophage activation. TNFRp55-deficient mice developed larger lesions than control mice and failed to resolve these lesions. However, they were able to eliminate parasites within these lesions. Migration inhibitory factor (MIF), granulocyte-macrophage colony stimulating factor (GM-CSF), and IL-7 were found to enhance leishmania killing by macrophages in vitro. While MIF delivered via a Salmonella-based expression system in vivo enhanced resistance of mice, application of GM-CSF or IL-7 surprisingly caused aggravation of lesions in *L. major*-infected mice. Cytokines such as IL-10, TGF-β (see also above), and IL-13 have been found to deactivate macrophages and to enhance intracellular survival of leishmania. With the exception of TGF-β, the role of these proteins during an immune response against leishmania in vivo remains to be determined.

The expression of chemokines has been analyzed in lesions of patients with localized cutaneous leishmaniasis and diffuse cutaneous leishmaniasis. While high levels of macrophage chemoattractant protein 1 (MCP-1) and moderate levels of macrophage inflammatory protein 1 α(MIP-1a) were detected in the localized forms of leishmaniasis, the pattern was reversed in diffuse cutaneous leishmaniasis, suggesting a functional role of these chemokines in the differential recruitment and activation of macrophages in the different forms of cutaneous leishmaniasis.

It is important to emphasize that susceptibility or resistance to *L. major* most likely involves several mechanisms since it appears to be controlled by several genes. Six loci located on the mouse ▶ chromosomes 6, 7, 10, 11, 15, and 16 were found to be associated with resistance to *L. major* in BALB/c × B10.D2 backcross mice. Another study analyzing (BALB/c × C57BL/6) F2 mice showed a linkage to the h2 region on chromosome 17 and to chromosome 9.

Although *L. donovani* and *L. chagasi* also readily parasitize and cause noncuring visceral infection in inbred mice, these leishmania species do not regularly provoke an active, functional Th2 response in experimental infection as they seem to induce in human disease. The one reported exception was in mutant C57BL/6 ep/ep (pale ear) mice in which noncuring *L. donovani* infection was related to multiple host defense defects including an active Th2 response. In most other cases noncuring *L. donovani* infection has been ascribed to the failure to properly express a Th1-associated cytokine response rather than to dominant activity of Th2 cells.

In mice the susceptibility to infection with intracellular parasites such as *Salmonella*, *Mycobacteria*, and *L. donovani* is controlled by the Nramp1 locus (also known as *Bcg, Ity*, or Lsh) on chromosome 1. The integral membrane protein Nramp1 is expressed exclusively on professional phagocytes in the late endocytic compartments. Since a single nonconservative amino acid exchange at position 169 of this protein resulted in enhanced susceptibility of mice to *L. donovani*, the

Nramp1 protein may alter the intravacuolar environment of the parasite-containing phagosome.

### Evasion Mechanisms of Leishmania

The complement resistance of metacyclic leishmania promastigotes was explained by the spontaneous shedding of the lytic membrane attack complex from the parasite surface, which might be causally linked to the elongation of the phosphoglycan chain of the surface ► lipophosphoglycan (LPG). In addition, leishmanial protein kinases have been reported to phosphorylate components of the complement system, thereby inhibiting the classical and alternative complement pathway. The 63 kDa surface metalloprotease (gp63) accelerated the conversion of C3b to a C3bi-like molecule, which acts as an opsonin and facilitates the uptake of leishmania into macrophages. *Leishmania* parasites are able to invade not only macrophages but also host cells devoid of important defense mechanisms such as iNOS. Langerhans cells of the skin as well as cells negative for all classical macrophage and dendritic cell markers, presumably reticular fibroblasts, might function as safe habitats for the parasite enabling its long-term persistence. *Leishmania* parasites are able to survive in the phagosome and phagolysosome. LPG is able to inhibit phagosome-endosome fusion and scavenge hydroxyl radicals and superoxide anions which are rapidly produced during phagocytosis. In addition, the protease activity of gp63 has been shown to protect the parasites from intraphagolysosomal degradation and is required for virulence of leishmania. Leishmania parasites are able to interfere with both main antimicrobial effector mechanisms, the release of superoxide, and the synthesis of NO. LPG, gp63, and GIPLs, a group of glycolipids related to LPG, have been shown to mediate these suppressive effects, at least in part by inhibiting the translocation and activation of the protein kinase C (PKC) of the host cell.

A further, important mechanism by which leishmania influence the host immune response is the modulation of cytokine production. As discussed above, different leishmania species induce the production of TGF-β which has been found to inhibit antileishmanial defense mechanisms of macrophages and to aggravate the disease in vivo. The selective suppression of IL-12 p40 synthesis by macrophages mediated by phosphoglycans of the parasite occurring on the transcriptional level appears to be an important mechanism by which leishmania avoid or delay the development of a host-protective Th1 response. Interestingly, this effect appears to be cell type specific, since uptake of *L. major* amastigotes by skin-derived dendritic cells results in activation of these cells and IL-12 release.

The processing and presentation of antigen is also targeted by the parasite. It has been demonstrated that *L. donovani* amastigotes interfered with upregulation of MHC class II molecules on the transcriptional level. Downmodulation of MHC class II occurs additionally on the posttranslational level, most likely by an enhanced internalization and degradation of these molecules. In contrast to other intracellular microorganisms, *L. donovani* prevents the upregulation of costimulatory molecules like CD80 on macrophages. The recently reported finding that gp63 selectively cleaves CD4 molecules from T cells is intriguing, as CD4 via binding to MHC class II stabilizes the interaction between antigen-presenting cells and T helper cells. A phenomenon called antigen sequestration not allowing the transport of sufficient numbers of MHC-peptide complexes to the cell surface may let infected macrophages go unnoticed by T helper cells. The molecular mechanism of this phenomenon is not yet defined, and prevention of intracellular protein degradation appears only partially responsible.

In addition to the numerous ► evasion mechanisms of *Leishmania* species summarized above, the saliva of the parasite-transmitting sand fly exerts various immunmodulatory functions. Saliva components, such as the peptide maxadilan, inhibited killing of *Leishmania* by suppressing the production of NO. Furthermore, sand fly salivary gland lysates were found to downregulate a Th1 but to upregulate a Th2 response in mice infected with *L. major*. Interestingly, the salivary gland lysates directly upregulated expression of IL-4 mRNA also in the absence of infection with *L. major*.

## Vaccination

Although a treatment for leishmaniasis exists, it is costly and difficult to apply because it requires daily injections for weeks. Moreover, resistance against the classical antimonial treatment has been increasing and increased doses, prolonged hospitalization, and needs for second treatment can be necessary. Thus, an effective and affordable vaccine remains the only realistic hope of controlling such a parasitic disease. This has been the goal for many years of the tropical disease research program of the WHO, which plays a major role in *Leishmania* vaccine development and several formulations are currently under trial with encouraging results.

The use *L. major* mouse model of *Leishmania* infection has been helpful for the understanding of mechanisms involved in immunity to leishmania. It was first observed that genetically different mice presented a different degree of susceptibility to the *L. major* infection, with some strains such as C57BL/6 being resistant (spontaneous healing of controlled cutaneous lesion) while others such as Balb/c are susceptible and present progressive disease. It was further demonstrated that the difference in the susceptibility was linked to the expansion of $CD4^+$ T cells secreting different patterns of cytokines. Th1 cytokines such as IFN-γ in conjunction with the IL-12 and TNF-α secretion by macrophages/dendritic cells are essential for the induction of the inducible nitric oxide synthase (iNOS) leading to large amounts of NO which play a major role in the killing of intracellular *Leishmania*. In contrast, expansion of $CD4^+$ T cells secreting Th2 cytokines such as IL-4, IL-5, and IL-10 but no IFN-γ in conjunction of macrophage-deactivating factors such as TGFβ and/or PGE2 is commonly associated to nonhealing infection.

Recent studies have shown that the activation/differentiation of one of the Th types inhibits the induction or expansion of the reciprocal subset, via reciprocal feedback inhibition by Type 1 or Type 2 cytokines. For instance, IFN-γ inhibits the induction/expansion of TH2, and, IL4 and IL10 inhibit the induction of TH1 cells. The mechanisms leading to the expansion of Th1 or Th2 depend on early events, IL-12 secretion in the first case and IL-4 secretion in the last case. IL-12 injection has been shown to induce protection against cutaneous leishmaniasis in susceptible Balb/c mice leading to expansion of a Th1 cell response. From these experiments, the use of IL-12 has been proposed as an adjuvant eliciting a Type 1 response for the delivery of a *Leishmania* vaccine in particular, but also in general for vaccine against other pathogens.

If these new concepts emerging from the mouse model have allowed important progress in the comprehension of the induction of anti-*Leishmania major* immune response in humans, there is still much to do in understanding the reasons why *L. major* induces generally cutaneous lesions whereas *L. donovani* leads to visceral leishmaniasis and *L. braziliensis* to mucocutaneous disease. Therefore vaccine development against leishmaniasis has proceeded, so far, entirely within empirical approach. The observation that *L. major* induces usually benign infections with spontaneous healing after 6–9 months protecting from pathogenic reinfections was the starting point of vaccine strategies known as ▶ leishmanization. It consists in injecting viable parasites to produce a controlled lesion in a nonvisible area of the skin. This induces a significant protection against reinfection. This immunity is essentially T-cell mediated. Leishmanization was used for a long time and was until recently used in the former USSR, in Israel, and in Iran. However, the use of live organisms can induce persistence of parasites in the immune host able to cause serious diffuse or mucocutaneous lesions in cases of change of the immune status. This program has now been abandoned. With the development of *Leishmania* transfection techniques, the production of an avirulent strain lacking the dihydrofolate reductase/thymidilate synthetase gene infecting and persisting in the macrophage is an interesting alternative for attenuated vaccine. This vaccine does not induce side effects but, so far, very little is known about the long-term consequences of such vaccine in particular in HIV-infected individuals. Killed parasites have thus renewed interest. Several trials using whole killed parasites with BCG as adjuvant are under evaluation in South America (*L. braziliensis*, *L. guyanensis,* and *L. amazonensis*) and in Iran (*L. tropica* and *L. major*) and are encouraging even if they are inferior to live vaccine.

Recently significant progress has been obtained using subunit vaccines. Molecules such as gp63, gp46, PSA-2, and LACK have given interesting results in mouse models using adjuvant not appropriate to humans. Other delivery systems using recombinant bacteria such as *Salmonella typhimurium* or BCG or recombinant vaccinia virus are under study. Besides proteins, the lipophosphoglycan (LPG) seems to be an interesting candidate. It can protect mice from infection with *L. major*. Despite the prevailing dogma that only peptide can induce T cell responses, LPG is presented by Langerhans cells to the T cells, not in the context of classical MHC molecules but by the new CD1 pathway. Because of possible genetic restriction as well as their partial protective effect, such vaccine candidates have to be mixed in a cocktail vaccine and tested as one vaccine. Subunit vaccine also has the disadvantage of inducing a usually short-lived immune response. One possible solution is to use the vaccine candidates not as proteins or peptides but as their encoding DNA. Indeed DNA vaccine is particularly attractive because it can induce a long-lived immune response. The antigen is constantly produced at low doses inducing an immune response similar to the situation of natural infection. gp63, PSA-2, and LACK delivered as plasmid DNA have already demonstrated efficient protection in mice.

The first generation of *Leishmania* vaccine against CL has already shown a relative efficacy (killed parasites) that needs to be improved by use of appropriate adjuvant. However, because the preparation of such a vaccine is difficult to standardize, research on a second generation against the different forms of leishmaniasis using defined molecules is more than ever necessary.

## Leishmanin Test

This test of leishmaniasis is also called Montenegro-skin-test and often used in epidemiological studies, but less important in clinical diagnosis.

## Leishmaniosis: Treatment of Canines

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First-line treatment is a combination of meglumine antimonate and allopurinol. Other options are offered by a combination of miltefosine and allopurinol or allopurinole alone.

### Further Reading

Oliva G et al (2010) Guidelines for treatment of leishmaniasis in dogs. J Am Vet Med Assoc 236:1192–1198
Solano-Gallego L et al (2011) LeishVet guidelines for the practical management of canine leishmaniosis. Parasite Vectors 4:86–90

## Leishmanization

The observation that *Leishmania major* induce a usually benign infection with spontaneous healing after 6–9 months protecting from pathogenic reinfections was the starting point of vaccine strategies known as leishmanization. It consists of injecting viable parasites to produce a controlled lesion in a nonvisible area of the skin. This immunity is essentially T-cell-mediated. Leishmanization was used for a long time and was until recently used in the former USSR, in Israel, and in Iran (► Leishmaniasis, Man/ ► Vaccination).

## Lemming Disease

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Trivial name of the disease due to infections with *Francisella tularensis*.

## Lemniscus

String-like organ at the apical pole of ▶ Acanthocephala.

## *Lemuricola pongoi*

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Syn. *Protenterobius pongoi*. Pinworm of *Pongo* monkeys in Sumatra.

## Leopard Skin

Type of depigmentation of skin in patients with onchocerciasis.

## *Lepeophtheirus salmonis*

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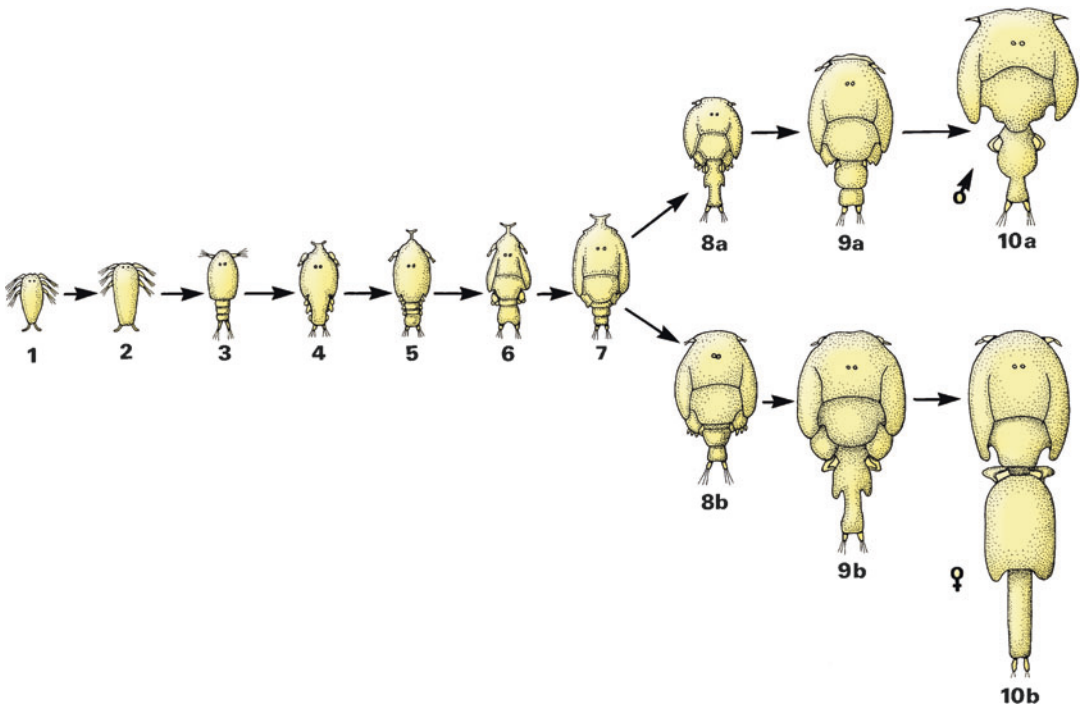
### Classification

*Lepeophtheirus salmonis* is a species of ▶ Crustacea, an order of ▶ Copepoda.




***Lepeophtheirus salmonis*, Fig. 1** Life cycle of *Lepeophtheirus salmonis* (order Copepoda), the so-called louse of salmons. *1, 2* ▶ Nauplius stages (0.54–0.85 mm), free swimming. *3* ▶ Copepodit stage (invasive stage, 0.7 mm). *4–7* ▶ Chalimus stages I–IV (1.2–2.8 mm long), engorging stages. *8a*, *9a* Preadult males – motile on the skin. *8b*, *9b* Preadult females – motile on the skin. *10a*, *10b* Adults (male 5 mm, female 10 mm). One generation needs about 6 weeks at a water temperature of 10–12 °C

### Life Cycle

See Fig. 1.

### Disease

Salmon disease: due to wounds in the skin, superinfections with bacteria or viruses occur, which – together with the sucking activity of the parasite – weaken the fish, delay growing, and even may lead to death.

### Treatment

Its treatment is monthly medical bath with insecticides, Argulol™ (emamectine), Sera/Alpha-Biocare.

## *Lepidapedon*

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Genus of digenean trematodes that parasitizes mainly deep sea water fish (e.g., *L. sereti* in Gadiformes: Macrouridae).

## *Lepidapedon sereti*

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Digenean fluke parasitizing deepwater fish (e.g., *Coelorinchus sereti*, Gadiformes in Vanuatu).

### Further Reading

Bray RA et al (2013) *Lepidapedon sereti* n. sp. in *Coelorinchus sereti* from deep waters of Vanuatu. Parasitol Res 112:3981–3990

## Leptoconops

Genus of ▶ Ceratopogonidae, which attack warm-blooded animals, suck blood all 3–5 days and are known vectors of agents of diseases (viruses, protozoans, worms).

## Leptomyxid Amoebae

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### Name

Greek: *leptos* = tiny; *myxa* = slimy.

These unicellular protozoans belong to the amoebian order Leptomyxida (class Tubulinea). Members of this group are in general free-living, soil inhabiting organisms. For humans and animals, they turned out to be harmless. However, some few species of leptomyxid amoebae (e.g., ▶ *Balamuthia mandrillaris*) are opportunistic pathogens.

### Further Reading

Amarel-Zettler LA et al (2000) A molecular reassessment of the leptomyxid amoebae. Protist 151:275–282
Lorenzo-Morales J et al (2013) Is *Balamuthia mandrillaris* a public health concern world-wide? Trends Parasitol vol 29:483–488

## *Leptosphyra*

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Institut für Zoomorphologie, Zellbiologie und Parasitologie, Heinrich-Heine-Universität, Düsseldorf, Germany

Genus of feather mites of birds belonging to the family ► Analgidae.

## Leptotheca

Myxozoan species parasitizing in the urinary system of freshwater fish.

## *Leptotrombidium akamushi*

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Asian mite species; the larvae of this species suck lymph on the skin of humans and animals. During this process the agents of the "► tsutsugamushi fever" might be transmitted.

## Lernaeidae

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**Name:** Greek: *lerna* = muddy water.

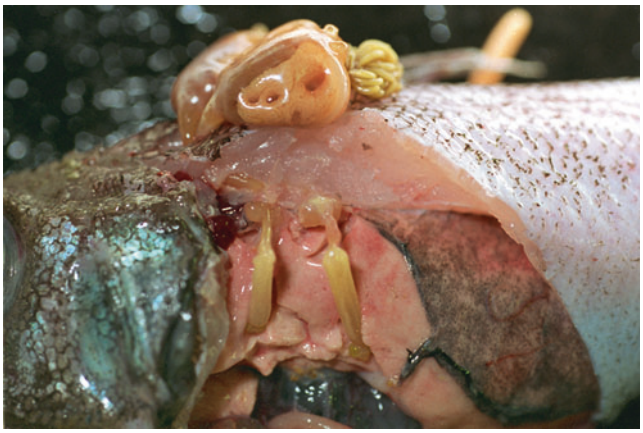
This term describes a family of copepod crustaceans, which measure as adults 5–40 mm in length, appear slender wormlike, and are anchored by help of their anterior portion deeply inside the bodies of fish (Figs. 1, 2, and 3), where they suck blood or lymph. Only the females (Fig. 3) appear crustacean-like due to the fact that they bear two egg sacs, which are typical for

**Lernaeidae, Fig. 1** Diagrammatic representation of an adult female stage of *Lernaea* sp.

**Lernaeidae, Fig. 2** Freshwater fish, which is parasitized by two female lernaeids. Note the long egg sacs

**Lernaeidae, Fig. 3** Antarctic fish with large lernaeids

**Lernaeidae, Fig. 4** Sectioned fish showing how deep the lernaeids enter





those primitive crustaceans. The species of the genus *Lernaea* develops via four free-living nauplius stages, one metanauplius, and five so-called copepodit stages (which are part time = temporary parasites) into adults. Fertilization occurs between female copepodit stage 4 and males which die afterward. The fertilized females penetrate the body wall of the fish with their anterior part. The time needed for maturation is temperature dependent and needs more than 100 days at 14 °C but only 7–13 days at 28 °C. Eggs are released from the egg sacs, when the nauplius stage is formed inside the egg.

**Disease:** Lernaeidae introduce large loss of blood and inflammations of the skin, gills, and even of inner organs and thus may lead to death (Fig. 4).

**Treatment:** Masoten® was shown to bring good healing effects, if 0.2–0.4 mg/l water is applied. Filtering with active charcoal cleans the water after an exposition of the fish for 3–5 days at around 20–23 °C.

## Further Reading

Mehlhorn B et al (1992) Health for ornamental fish. Springer, Heidelberg
Reichenbach-Klinke HA (1980) Diseases and damages of fish. Fischer, Stuttgart
Schubert G (1988) Diseases of fish. Frankh'sche Verlagsbuchhandlung, Stuttgart

## Letality

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### Name

Latin: *letalis* = deadly.

This term describes the amount of dead victims due to an infection in relation to the total sum of infected persons/animals.

## Lethality

Number of dead individuals in relation to sick people.

## Leuckart, Friedrich Andreas Sigismund (1794–1843)

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Rudolf Leuckart (Fig. 1) was a German physician and zoologist, who was Professor for Zoology at the University of Giessen (at a time when also the famous chemist **Justus Liebig** taught there). Later he became Professor for Zoology and Comparative Anatomy at the University of Leipzig. Leuckart worked on a broad spectrum of parasites, e.g., on *Trichinella spiralis* and showed its transmission cycle in pigs as well as the life cycle of *Ancylostoma caninum* and the transmission of trematodes by stages in snails. His famous books "*Die menschlichen Parasiten und die von ihnen herrührenden Krankheiten*" (Vols. 1, 2) = engl. "*The human parasites and the related diseases*" presented combined knowledge on parasites being important for veterinarians, human physicians, and zoologists at the same time (Fig. 1). Thus he created the basis for the new research field **Parasitology** as an own science line. Therefore he was selected by the German-Swiss-Austrian Society of Parasitology as a symbol. The awarding of the **Leuckart medal** honors researchers in any field of parasitology (Fig. 2).

### Awarded Scientists

1974: Robert-Philippe Dollfus† (Paris, France)
1974: P. C. C. Garnham† (England)
1974: R. Geigy† (Basel, Switzerland)
1974: G. Poljanski† (Moscow, Russia)
1974: H. W. Stunkard† (New York, USA)
1974 P. H. van Thiel† (The Netherlands)
1980: W. Peters† (London, England)
1982: R. M. Cable† (Indiana, USA)
1982: W. Trager† (New York, USA)
1982: J. Weiser† (Prague, Czechoslovakia)
1984: S. Willmott† (Albans, England)
1986: K. Enigk† (Hannover, Germany)
1986: R. Supperer† (Vienna, Austria)
1987: L. J. Bruce-Chwatt† (London, England)
1992: G. Piekarski† (Bonn, Germany)
1996: J. Eckert (Zürich, Switzerland)
2000: T. Hiepe (Berlin, Germany)
2002: M. Röllinghoff (Erlangen, Germany)
2002: M. Rommel (Hannover, Germany)
2004: H.Mehlhorn (Düsseldorf, Germany)
2006: H. Aspöck (Vienna, Austria)
2008: J. Boothroyd, Stanford, USA
2010: K. Becker (Gießen, Germany)
2012: R. Lucius (Berlin, Germany)
2014: K. Lingelbach† (Marburg, Germany)
2016: Heidrun Moll (Würzburg, Germany)


DIE

MENSCHLICHEN PARASITEN

UND

DIE VON IHNEN HERRÜHRENDEN

KRANKHEITEN.

Ein Hand- und Lehrbuch

für

Naturforscher und Aerzte.

Von

Rudolf Leuckart,

Dr. phil. et med., o. ö. Professor der Zoologie und vergleichenden Anatomie in Giessen.

Erster Band.

Mit 268 eingedruckten Holzschnitten.

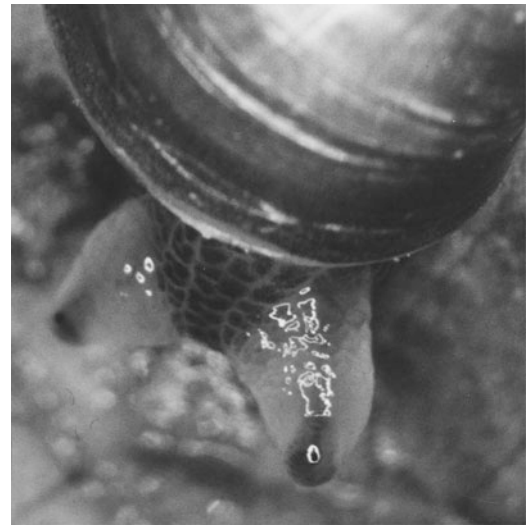
LEIPZIG UND HEIDELBERG.

C. F. WINTER'SCHE VERLAGSHANDLUNG.

1863.

**Leuckart, Friedrich Andreas Sigismund (1794–1843), Fig. 1** Title page of the first volume of the book "Human Parasites and Their Diseases" which appeared in the year 1863


**Leuckart, Friedrich Andreas Sigismund (1794–1843), Fig. 2** Head of Leuckart on the **Leuckart medal** of the German Society of Parasitology



***Leucochloridium macrostomum*, Fig. 1** The tentacles of this amber snail are filled each with a metacercaria of the trematode, which initiates active movements, thus attracting the final hosts (birds)

## Further Reading

Leuckart R (1863/1876) Die menschlichen Parasiten und die von ihnen herrührenden Krankheiten, vols 1, 2. C.F. Winter'sche Verlagsbuchhandlung, Leipzig/Heidelberg

## *Leucochloridiomorpha lutea*

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This small, up to 2 mm long digenean trematode (family Brachylaimidae) is a common parasite of the bursa fabricii of ducks. First intermediate hosts are *Viviparus* sp. snails, which release furcated cercariae. These cercariae enter exclusively male snails of the same species, where they develop inside the testes into metacercariae. If this snail is ingested by ducks, the life cycle is completed.

## *Leucochloridium macrostomum*

Syn. *L. paradoxum*. ▶ Digenea. The colourful sporocysts of this trematode of the ▶ cloaca of birds enter the tentacles of their vector snail, form ▶ cercariae and metacercariae (Fig. 1), which pulsate, and thus attract the final host (▶ Behavior).

## *Leucochloridium* Species

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The name comes from Greek *leukos* = white, *chloros* = slightly green. Tiny digenetic trematodes reaching about 1.5–2.6 mm in length and 1.2–1.4 mm in width. Their eggs are also very tiny (~24–30 μm × 16 μm) and are excreted within the feces of birds (e.g., tits, other singing birds). The adults are hermaphrodites and live attached at the cloacal wall of their hosts. The excreted eggs are ingested by so-called amber snails (*Succinea*

*putris*) living in terrestric biotopes. Insides the snail's gut a miracidium larva hatches from each egg and transforms into a sporocyst, inside which infectious cercariae are formed. The whole brood sacs containing the sporocysts or their protruding ends penetrate into the snail's tentacles and initiate there strong pulsating movements which attract attention of the final hosts (birds). This induced pulsation is interpreted by some scientists as "active" manipulation of the parasite in order to enhance its chances to reach the final host and thus to become an adult worm.

In Europe two common species are found among others:

- *L. paradoxum* (1.5–1.9 mm × 1.0–1.3 mm); their brood sacs inside the snails are green-banded.
- *L. pertubatum* (2–2.6 mm × 1.4 mm); their brood sacs appear brownish-banded.

## Further Reading

Rietschel G (1972) Investigations on colour patterns of *Leucochloridium* sporocysts. Parasitol Res 40:61–68

Rzad P, Hofsoe P, Panicz R, Nowakowski JK (2013) J Helminthol. doi:10.1017/S0022149x13000291

# Leucocytes

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## Name

Greek – *leukos* = white, *kytos* = cell.

This term comprises the so-called "white" cells in the blood, e.g., granulocytes, lymphocytes, etc. In case of an infection, the body increases their total numbers.

# *Leucocytozoon quynzae*

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Species described from hummingbirds in South America.

## Further Reading

Matta NE et al (2013) Description of *Leucocytozoon quynzae* n. sp. from hummingbirds with remarks on distribution and possible vectors of leucocytozoids in South America. Parasitol Res 113:457–468

# *Leucocytozoon simondi*

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## Synonyms

*L. anseris*

## Classification

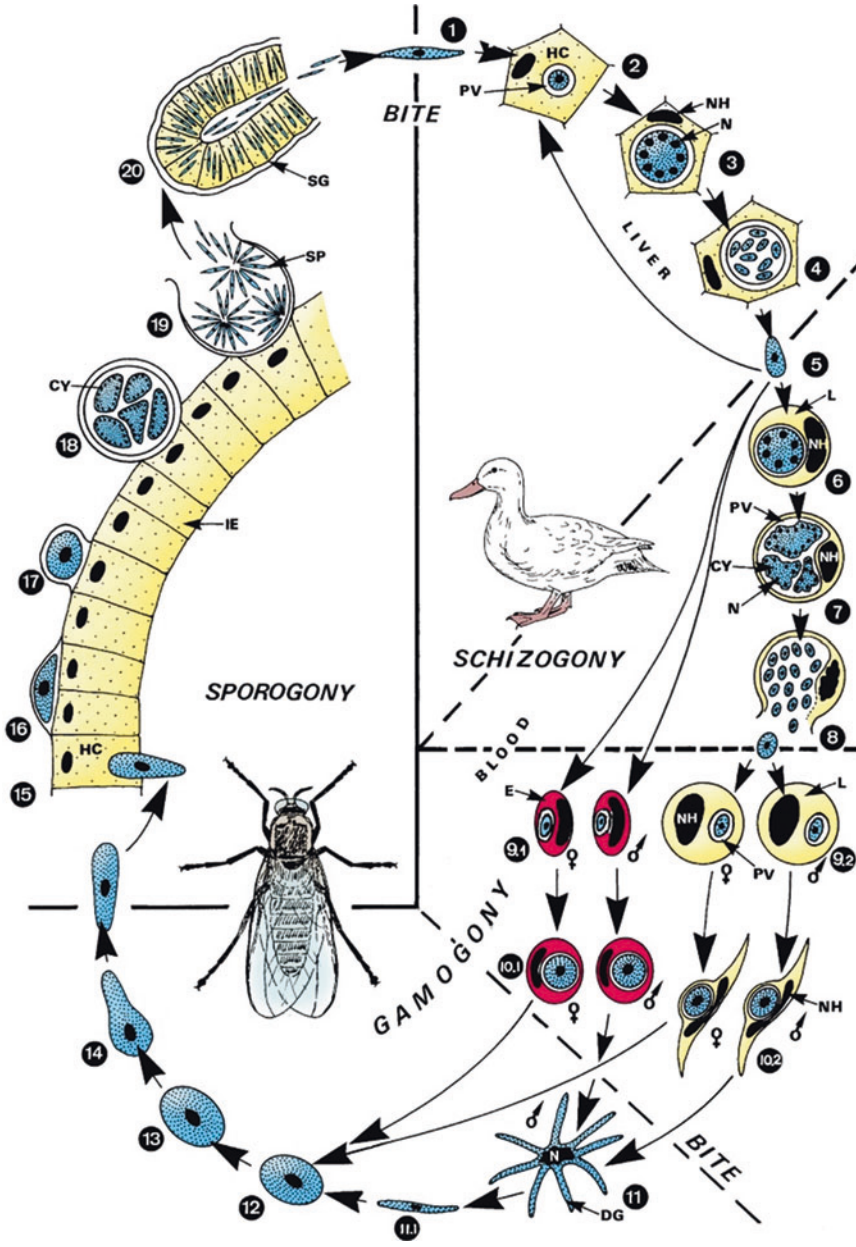
Species of ▶ Coccidia.

## Life Cycle

Fig. 1.

## Disease

▶ Leucocytozoonosis.




***Leucocytozoon simondi*, Fig. 1** Life cycle of *Leucocytozoon simondi* in its vertebrate hosts (domestic and wild ducks and geese) and in its vector (▶ *Simulium* spp. blackflies). *1–5* Sporozoites injected by the *Simulium* fly are carried by the bloodstream to the liver, where they enter Kupffer cells and form the multinucleate first-generation schizonts. The latter give rise to small merozoites (*5*) which may reinfect other hepatic cells (*2*) or invade lymphoid cells (*6–8*) or erythrocytes (*9.1*). *6–8* After invasion of lymphoid cells or macrophages, 4–6 days after infection, large schizonts (megaloschizonts) of 60–150 μm diameter are formed, which via cytomeres (*7*) produce numerous merozoites (*8*). *9–12* Having entered lymphoid cells, the majority of merozoites probably develops into gamonts (*9.2*), but it is thought that some may initiate further asexual reproduction. During the formation of the finally elongate or ovoid gamonts (20 × 5 μm), the host cells become distorted and appear elongated spindle shaped (*10.2*). Occasionally, spherical gamonts appear (*10.1*) which are thought to originate from hepatic merozoites (*5*) that have penetrated erythrocytes instead of lymphoid cells. However, there is no evidence

## Leucocytozoonosis

Disease due to ▶ *Leucocytozoon simondi* in domestic and wild ducks and geese transmitted by bite of *Simulium* spp. (North America, Central Europe). *L. smithi* is found in turkeys in Europe. *L.* (syn. *Akiba*) *caulleryi* is transmitted by ▶ *Culicoides* spp. and occurs also in red blood cells.

### Symptoms

The most important symptom is anaemia, which may lead to death. Initial symptoms are: loss of weight, uncontrolled turning of the head, problems when moving, reduction of egg production.

### Diagnosis

Microscopical analysis of Giemsa-coloured blood smears.

### Treatment

Pyrimethamine plus sulfonamides as prophylaxis; in clinical cases: Furazolidon or pyrimethamin.

## Leupeptin

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This term describes an antimalarial toxin, which needs an uptake by a so-called plasmodial surface anion channel (PSAC).

## Levineia

Genus of ▶ Coccidia, synonymous to ▶ *Cystoisospora*.

## *Levinsenilla*

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Genus of digenetic trematodes of the family Microphallidae that parasitize in the intestine of shore birds.



***Leucocytozoon simondi*, Fig. 1** (continued) that these differ functionally from the elongate forms. When the vector has sucked blood, the formation of gametes (*11, 12*) is initiated inside the gut, leading, after fertilization, to an extracellular ▶ zygote (*13*). *13–17* The immobile zygote is transformed into a motile ▶ ookinete, which enters the intestinal wall (*15*), migrates through the ▶ cytoplasm of a gut cell, and begins its transformation into an ▶ oocyst, situated between basal membrane and epithelial cells of the gut (*17*). *18–20* Formation of multinucleate sporoblasts (*18*) which give rise to numerous sporozoites (*19*; *SP*). The latter are released into the body cavity and migrate to the salivary glands (*20*). These slender sporozoites are finally injected into the next host. *CY* cytomere, *DG* developing microgamete, *E* erythrocyte, *HC* host cell, *IE* intestinal epithelium, *L* lymphoid cell/macrophage, *N* nucleus, *NH* nucleus of host cell, *PV* ▶ parasitophorous vacuole, *SG* salivary gland, *SP* ▶ sporozoite

## LF

Short for ▶ Lymphatic filariaris, disease due to infections with *Wuchereria bancrofti* or *Brugia malayi*. 120 million people are infected, 40 million with severe symptoms of disease; it is the world's leading cause of disability. ▶ Filariidae.

## Lice

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### Synonyms

Phthiraptera

### Name

Greek: *phtheir* = louse, *a* = non, *pteron* = wing.

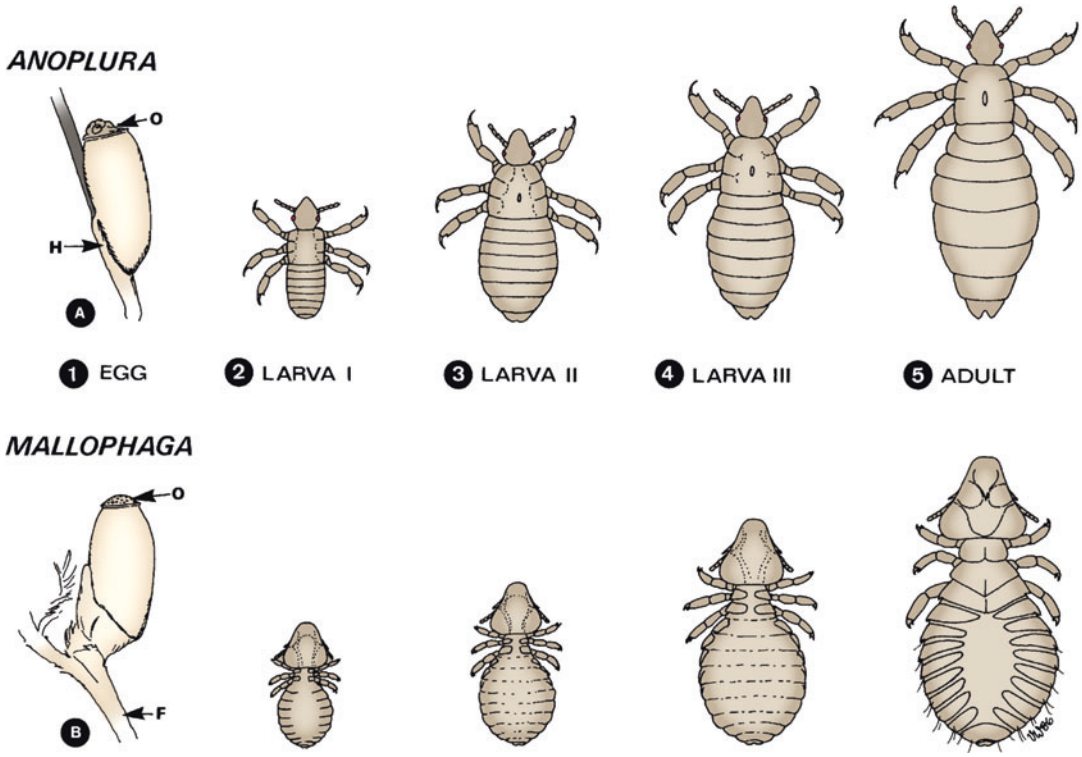
### Classification

Order of ▶ Insects.

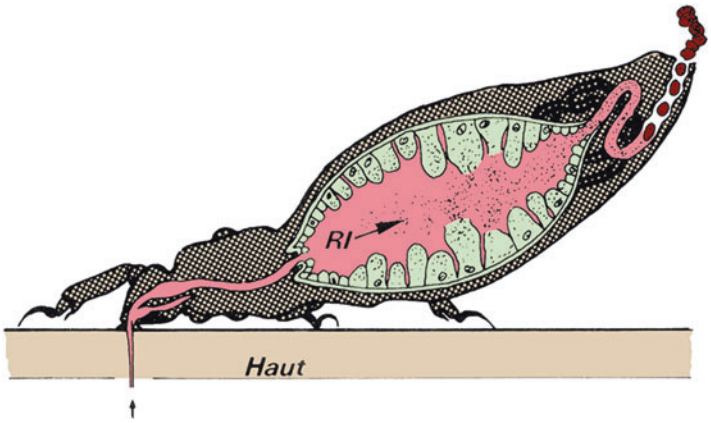
### General Information

The order Phthiraptera is subdivided into two suborders: ▶ Anoplura (bloodsucking lice) and ▶ Mallophaga(feeding on skin, keratinous substances of feathers and hairs, and dermal secretion fluids). Both groups show the following common features:

- They have very short antennae (often in grooves).



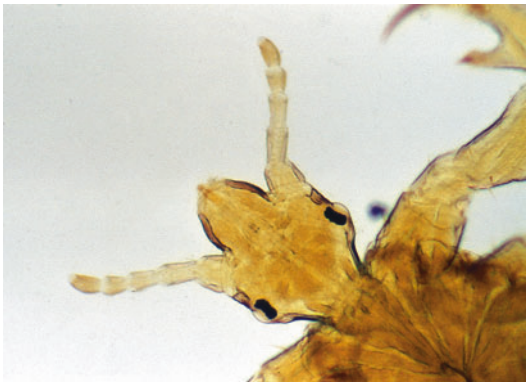

**Lice, Fig. 1** Diagrammatic representation of the life cycle stages of Anoplura and Mallophaga lice




**Lice, Fig. 2** Diagrammatic representation of a sucking body louse, which excretes feces during sucking. These feces may contain agents of diseases. Haut = skin; RI = rickettsial stage

**Lice, Fig. 3** Scanning electron micrograph of a female body louse and several eggs attached at clothes.

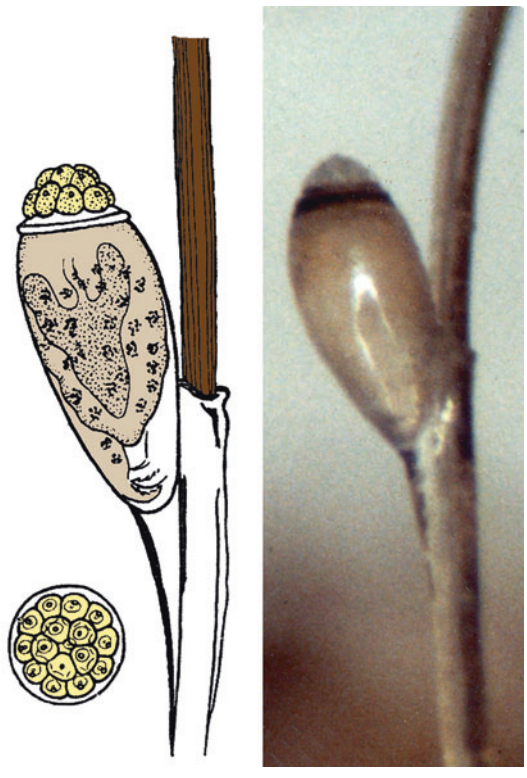
**Lice, Fig. 5** Scanning electron micrograph of an egg of the human head louse (*Pediculus humanus capitis*). Note the pores at the operculum.



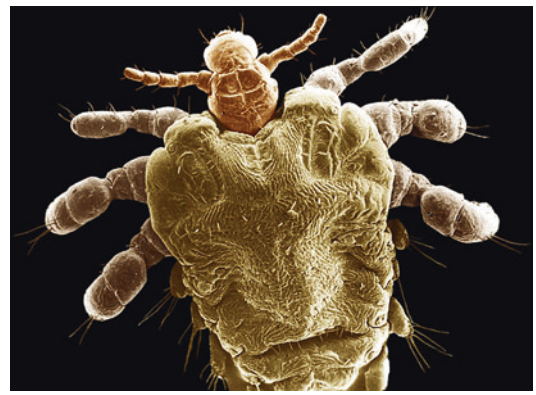
**Lice, Fig. 4** Light micrograph of the head region of a head louse. Note the two lense eyes.

- They are always wingless.
- Their eyes are reduced; they are eyeless or have 1 or 2 ommatidia.
- Their feeding (on keratin or blood) always requires the aid of endosymbionts in mycetomes (which are transmitted to progeny).
- Their life cycle constantly proceeds ▶ hemimetabolous development; the relatively large eggs are always attached to hairs, feathers, etc.
- All developmental stages stay on their hosts permanently; host-to-host transmission occurs by body contact.

**Lice, Fig. 6** Photos of two females of head lice (left) with protruding eggs and a male (right). Note the claws at the feet, which are used to clutch at hair.



**Lice, Fig. 7** Diagrammatic representation (left) of an egg of a head louse and its cover (operculum). Right: Light micrograph of a head louse egg attached at a hair.



**Lice, Fig. 8** Scannin electron micrograph of *Phthirus pubis*

**Lice, Fig. 9** Light micrograph of two pig lice.

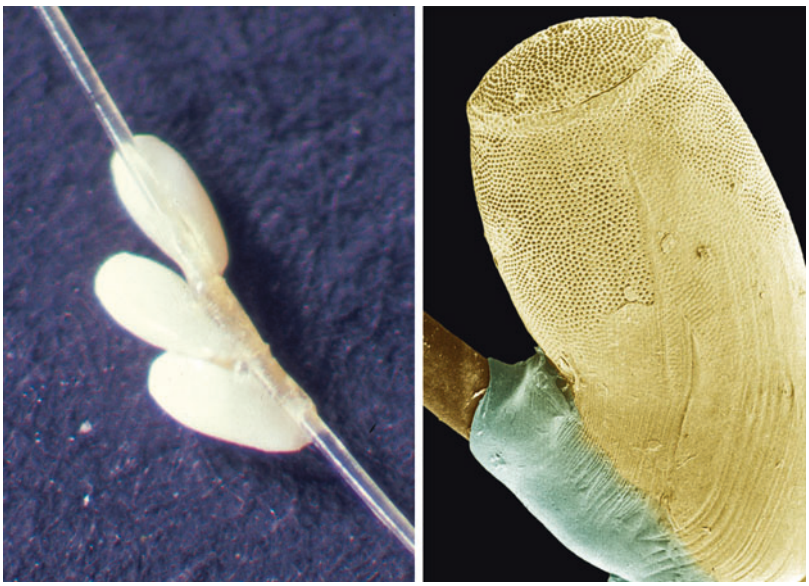
Members of the ▶ Mallophaga (Fig. 1b) are furthermore characterized by a head which is broader than the thorax and by visible chewing mouthparts, whereas the bloodsucking mouthparts of members of the Anoplura are hidden inside their short and stumpy ▶ proboscis (Fig. 1a,4).

Of the about 500 known species of the suborder Anoplura, only three species are ectoparasites of humans: ▶ *Pediculus humanus capitis* (head louse), living in head hair; *P. humanus corporis* (body or clothing louse), occupying the clothes and visiting the body only to feed (Figs. 2–7); and ▶ *Phthirus pubis* (▶ Crab Louse), developing mainly in the hairs of the genital region, but regularly also colonizing the other coarse hairs of the head and body, e.g., the eyelashes (Fig. 8). These lice are highly host-specific, obligate parasites, spending their entire life cycle on the host, and only infesting humans and monkeys. Animal lice (Figs. 9–11) only occasionally attack humans (▶ *Haematopinus suis*). Lice are even common in cold water when parasitizing, e.g., seals. (▶ *Antarctophthirus*). Only *P. h. corporis* transmits rickettsial or bacterial diseases.

**Lice, Fig. 10** Scanning electron micrograph of a pig louse.

## Life Cycle

For details of the life cycle of biting lice (Fig. 1b), see ▶ Mallophaga. In human lice (Fig. 1a), after a temperature-dependent embryonic development of about 8 days, the first



**Lice, Fig. 11** Light (left) and scanning micrographs of eggs of the pig louse (*Haematopinus suis*)

**Lice, Table 1** Some common species of the Phthiraptera (lice)

| Species | Length (mm) of adults (females) | Host/habitat | Transmitted pathogens |
|---|---|---|---|
| **Mallophaga** | | | |
| *Trichodectes caninum* | 2 | Dogs/hairs | *Dipylidium caninum* |
| *Felicola substrostratus* | 1.3 | Cats/hairs | *Dipylidium caninum* |
| *Werneckiella equi equi* | 1.8 | Horses/hairs | Virus of anemia |
| *Bovicola bovis* | 2 | Cattle/hairs | – |
| *Lepikentron ovis* | 1.5 | Sheep/hairs | – |
| *Eomenacanthus stramineus* | 3.2 | Turkeys, chickens/ feathers | – |
| *Menopon gallinae* | 1.8 | Chickens/feathers | – |
| *Lipeurus caponis* | 2.3 | Chickens/feathers | – |
| *Columbicola columbae* | 2.3 | Pigeons/feathers | – |
| **Anoplura** | | | |
| *Pediculus humanus capitis*[a] | 3.4 | **Humans**/head | – |
| *P. h. corporis*[b] | 4.5 | **Humans**/body, clothes | *Rickettsia prowazekii*, *Borrelia recurrentis*, *Rochalimaea quintana* |
| *Phthirus pubis* | 1.7 | **Humans**/hair of genitalia, eye lashes | |
| *Linognathus setosus* | 2.5 | Dogs, cats/hairs | – |
| *Haematopinus suis* | 6 | Pigs/Skin, hairs | Rickettsiae: *Eperythrozoon suis* |
| *H. asini* | 3.5 | Horses/hairs | – |
| *H. eurysternus* | 3 | Cattle/hairs | – |
| *Linognathus* sp. | 2.5 | Sheep, goats/hairs | – |
| *Haemodipsus ventricosus* | 1.5 | Rabbits/hairs | *Pasteurella (= Francisella tularensis)* |

[a]Some authors name this species *P. capitis*
[b]Also named *P. humanus*

instar nymphs (1 mm long) hatch and within 7–10 days after two additional nymphal stages, the adults. (The term larva is used by scientists in Central Europe, but the term nymph by other scientists.) The whole developmental cycle (egg to egg) lasts about 2–3 weeks. Bacterial and fungal symbionts, which are restricted to special organs (▶ Mycetomes) near the gut or ovaries and transmitted transovarially to the eggs, are necessary for larval development and adult reproduction.

## Important Species

See Table 1.

## Distribution

Human lice occur worldwide, clothing lice regularly in poor regions where people possess only one set of clothes. In the USA, white people are more frequently infested with head lice than

Afro-Caribbean people, probably because of the better adaptation of the claws of the lice to hairs which are round or oval in cross section, respectively.

## Morphology

The relatively small, narrow head of lice has very short antennae (five segments), and eyes are strongly reduced to two big ommatidia. The mouthparts are hidden inside the head. The labrum ensheaths the four long, thin stylets made from the two maxillae, the labium and the hypopharynx, the latter containing the salivary channel, whereas blood is ingested through the tube formed by the maxillae. The thoracic segments are fused, and the short legs bear strong claws that are optimally adapted to the diameter of the hairs of the host and cling onto hairs or fibers. The ▶ cuticle is very tough. The *Pediculus* spp. (Figs. 3–6) are slender insects of about 2–4 mm length, much longer than wide. Males and females can be distinguished by the body and claw sizes, patterns on the thorax, the shape of the abdomen, and the sclerotized penis-like genitalia of males. *P. pubis* is about twice as long as wide and about 1.5–2 mm long. The eggs (so-called ▶ nits) are about 0.8–1 mm long and about 0.3 mm wide and glued onto hairs or cloth fibers. After eclosion of the nymphs, the eggs appear white and remain glued. Eggs of the genera *Pediculus* and *Phthirus* can be distinguished by the shape and the appearance of the pores on the ▶ operculum, those of *P. h. capitis* show similar pores as *P. h. corporis* (Figs. 3–7), but are more intensively glued to hairs. The pores (▶ Aeropyls) are needed for the oxygen supply of the embryo.

Crossbreeding of the 2 *Pediculus* spp. is possible (therefore regarded as subspecies by different authors), but both can be distinguished by their tibial lengths, habitat preference, i.e., cloth or hair, and temperature preference, 28–29 °C for head lice and 31–33 °C for clothing lice. The individual color is genetically determined, darker clothing lice occurring more often in association with inuits and other dark-skinned humans.

## Reproduction

Only *P. h. corporis* colonies breed in the laboratory after adaptation to feeding on rabbits. Other species are fed on volunteers.

Adults copulate shortly after emergence or at a later point in time. About 24 h after mating, ▶ oviposition begins. Females of *P. h. corporis*, *P. h. capitis*, and *P. pubis* live about 5, 3, and 4 weeks and lay about 300, 90, or 30 eggs, respectively. *P. h. capitis* prefers to deposit eggs singly onto hairs in the neck and behind the ears, *P. h. corporis* in clusters on the fibers of clothes, e.g., on the seams, and *P. pubis* lays several eggs on a single hair.

## Transmission

Lice are transmitted by interhost contact and/or by shared use of combs, hats, clothes, etc. Usually less than 10 lice per person occur, but more than 20,000 *P. h. corporis* or several hundred *P. h. capitis* have been collected from one person.

## Feeding Behavior and Transmission of Disease

Lice are attracted to the host by warmth and odors. They are permanent ectoparasites, capillary feeders who suck blood about every 2–3 h. The ingested blood is stored and digested by trypsins and chymotrypsins in a capacious anterior midgut, followed by digestion of peptides in the narrow posterior midgut, and formation of feces in the hindgut. The saliva causes itching and the resulting scratches secondary bacterial infections. However, louse feces usually induces the first irritations.

Only *P. h. corporis* can transmit classic epidemic typhus, ▶ trench fever, and louseborne

► relapsing fever, but experimental transmission of the pathogens is possible using *P. pubis*.

Classical epidemic typhus is caused by *Rickettsia prowazekii* and transmitted only among humans by pathogens present in the deposited feces (Fig. 2). These pathogens invade through skin lesions or are inhaled. The pathogens are infective in the feces for up to 3 months. The disease is prevalent in Europe, Africa, and South America, but incidence is declining.

Trench or 5-day fever, occurring in Europe, is caused by ► *Rochalimea quintana*, showing a mode of transmission similar to that of typhus.

Louseborne relapsing fever is caused by ► *Borrelia recurrentis* and transmitted by crushing infected lice between the fingers or teeth. Thereby, bacteria present in the hemolymph or intestinal tract can invade skin lesions or the mucous epithelia. This disease occurs in Europe, Africa, South America, and Asia, but not in Australia.

## Interaction of Vector and Parasite

If the lice suck blood within the first 10 days of illness, *R. prowazekii* is transmitted and multiplies in the lumen of the gut, but also in the cells of the intestinal wall. *R. prowazekii* is pathogenic to lice due to the destruction of gut cells. In the other bacterial infections, no pathogenic effects on the vectors are reported.

*B. recurrentis* invades the hemocoel of the insect about 4 days after ingestion, slowly multiplying there.

## Diagnosis

By regular macroscopic control of hairs for the white eggs, the head- and crab lice, and by use of a fine-toothed comb, the head lice can be detected. In cases of itching of the skin of head and genital regions, a careful control for nits or lice should be performed. In heavy infestations with *P. h. corporis*, skin is darkened and hardened (morbus errora), and in *P. pubis* infestations bluish spots (maculae caeruleae) develop, since these lice prefer to bite repeatedly in the same places. In the latter infestations, black spots of louse feces also occur in the underwear.

## Control

Information beginning with the parents of children in kindergarten and school can strongly reduce the infestations. However, it should be pointed out that usually more than one member of a household is infested.

All lice can be killed using insecticides either as powder (clothing lice) or in lotions or shampoos (head- and crab lice). Malathion, carbaryl, and pyrethroids are used. Lotions left for some hours on the hair are more effective than shampoos. During the last years, head lice have occurred more often, especially on young children, mainly due to the attitude of some parents who do not wish to use insecticide lotions or shampoos. All stages of clothing lice are killed within less than 30 min at 50 °C, and within 1 min at 90–100 °C; using a tumble drier for 15 min and >60 °C is also sufficient. Exposition to −20 °C has not been investigated, but 24 h should be sufficient for killing. Since lice show a relatively weak starvation capacity, *P. h. capitis* and *P. h. corporis* will die after 3 and 4 days at 23 °C, respectively; for the latter, a storage of clothes for 17 days in a polythene bag is recommended. No vaccination is available (Insecticides, ► Arthropodicidal Drugs). However, appropriate neem extracts (WASH AWAY) clean the hair from lice.

## Resistance

In several countries, lice are resistant to DDT, carbaryl, lindane, malathion, and in recent years also to permethrin or similar pyrethroids, while

those products, which suffocate the lice by covering or entering the tracheal spiracles, will not lead to resistance.

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# Lice: Genome

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Genome sequencing of the head and body lice showed that the specimens of both subspecies are equipped with the smallest genomes among insects showing 108 Mb for females and 109 Mb for males. They are diploid organisms which possess in total six chromosomes and a telocentric one. Body lice show a guanine-cytosine (GC) content of 28 %. Thus these animals are unusually AT-rich. Inside the genome, no genes of prokaryotic origin occur so that it can be concluded that the obligatory symbiont *Candidatus Riesia pediculicola* does not transfer genes to its host. Although the genome of lice is very small, it shows full function and shares inner homology. Eighty percent of their genes are orthologic to other sequenced insects.

While in eukaryotes the single mitochondrial chromosome appears typically circular (with a length of about 16 kb and 37 genes), in lice the 37 mitochondrial genes are located on 18 minicircular chromosomes. These minichromosomes of lice are 3–4 kb in length and contain each 1–3 genes. In lice, apparently recombination occurs between the minichromosomes being facilitated by the fact that identical sequences are present on different minichromosomes. Besides these 18 minichromosomes, several types of chimeric minichromosomes had been documented.

Genetic data show that morphological and behavioural differences between head and body lice are probably results of epigenetics, which are due to other processes than changes in the underlying DNA-sequences. Thus in conclusion several authors claim that head and body lice are ecotypes of the same species. They differ with the exception of a single gene only in the expression and not in gene content. It might be speculated that different expression has started when humans reduced their body hair and started to wear clothes. In any way the three clades of lice are genetically nearly identically, but not in behavior, morphology, and physiology. Apparently several genes might have stopped action.

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## Lichenification

Clinical and pathological symptom (dry scrub, small papule exanthem) of infections with skin parasites (► Skin Diseases, Animals, ► Lice).

***Ligula intestinalis*, Fig. 1** LM of a larva (*Ligula*) of a bird tapeworm taken from the muscles of a carp

## *Ligula intestinalis*

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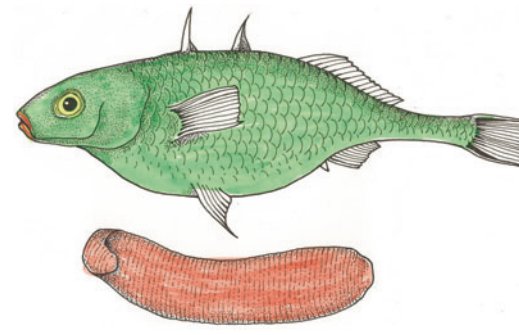
Tapeworm related to the family Diphyllobothriida (► Pseudophyllidea) living in the intestine of fish-eating birds and reaching a length of up to 28 cm. Its ► plerocercoid is found in cyprinid fish, measures 2–60 cm in length, and often represents 25 % of the fish's body weight (Figs. 1 and 2). ► Eucestoda.



***Ligula intestinalis*, Fig. 2** Diagrammatic representation of a fish with a swollen belly due to the included *Ligula* stage, which fills the inner cavity almost completely

## Limax

### Name

Latin: *limax* = slimy.

Genus of free-living ▶ amoebae in not too cold, often polluted waters. The specimens possess a nucleus with a large karyosom and a pulsating vacuole. Some species may become facultative parasites (*Naegleria* spp.).

## *Limnatis nilotica*

Leech species of the family Gnathobdellidae, reaching as adults a length of 8–12 cm. This "large horse leech" parasitizes as adult stage on mammals (inclusive humans), but on insects and frogs as juvenile forms. *Limnatis nilotica* occurs in North Africa and Near East. If present in large numbers in nostrils, pharynx, or oesophagus, they may cause asphyxia and anaemia. The related species *L. africana* is found in Senegal, Congo, India, and Singapore.

## Lindane (γ-HCH, Gamma Benzene Hexacloride)

### Chemical Class

Organohalogenide.

### Mode of Action

GABA-gated chloride channel antagonist. ▶ Ectoparasiticides: Antagonists and Modulators of Chloride Channels, Ectoparasiticidal Drugs.

## *Linguatula arctica*

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This pentastomid species was obtained from dogs and semi-domesticated reindeer in Norway.

### Further Reading

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## *Linguatula serrata*

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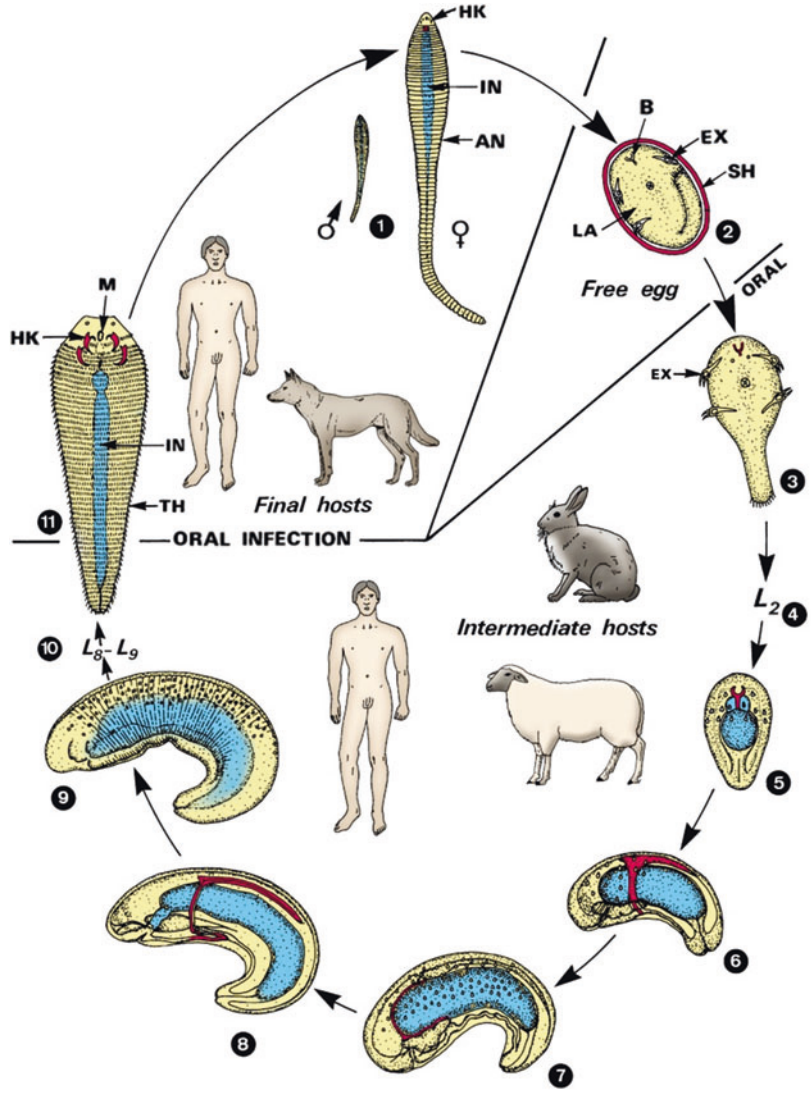
### Name

Latin: *lingua* = tongue, *serratus* = sawlike.

***Linguatula serrata*, Fig. 1** Anterior end of an adult of *Linguatula serrata*




***Linguatula serrata*,**
**Fig. 2** Life cycle of *Linguatula serrata*. *1* Adults live in the nose of dogs (and rarely of man). *2* Embryonated eggs are set free via nasal mucus and/or feces. The thin outer eggshell is left out in drawings, since it disappears soon. *3* If intermediate hosts swallow eggs, the four-legged primary larva hatches and migrates via blood vessels to the inner organs. Humans may also become accidental intermediate hosts. *4–11* Larval stages *2–11* are included in a capsule of host origin and grow after molts. When final hosts ingest raw (or uncooked) meat of intermediate hosts, the adult stages develop inside the nasal tract. Infected humans suffer from the ▶ Halzoun syndrome. *AN* annuli, *B* bore organ, *EX* extremity with a claw, *MK* mouth hooks, *IN* intestine, *LA* primary larva, *M* mouth, *SH* inner eggshell, *TH* thorns

## Classification

Species of ▶ Pentastomida.

## Morphology

Females grow up to 13 cm, while males reach only 2 cm. Both live inside the nasal system of meat-eating mammals (including dogs, man). They keep attached at the wall of the respiratory system by means of their mouth hooks (Fig. 1). Females excrete thousands of (up to 5,000,000) eggs per day. These stages are infectious for plant feeders (including humans), where the larva take them into different organs away from the intestine. If these larvae are eaten by the final hosts, the larvae invade the nasal system and reach maturity within 6–7 months and live for about 15 months (patency period).

## Disease

Halzoun Syndrome or Marrara syndrome are the human diseases described as infection of man,

who can be the final host (with worms in the nose) and intermediate host (with encapsulated larvae in inner organs). The symptoms are nasal infections, blocking of breathing, edema, but also deafness in case of infections with adult worms. In cases of encapsulated larvae, these symptoms depend on the infected organ.

▶ Respiratory System Diseases, Horses, Swine, Carnivores, ▶ Halzoun Syndrome.

### Life Cycle

Fig. 2.

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## Linguatulidae

### Name

Latin: *lingula* = small tongue.

Family of the animal phylum ▶ pentastomida, which comprises important parasites of dogs and even humans.

## Linné, Carl von (1707–1778)

Swedish physician and botanist, introduced the binary nomenclature of species in his books (*Systema Naturae*: 1735–1764).

## *Linognathus setosus*

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▶ Lice, louse species of foxes and dogs (1.8–2.5 mm).

## *Linognathus vituli*

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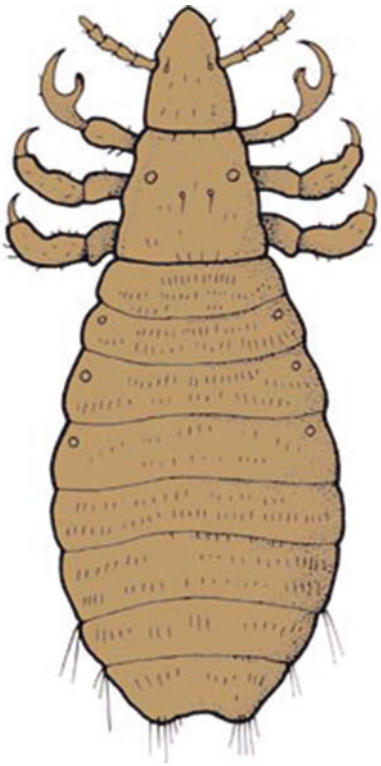
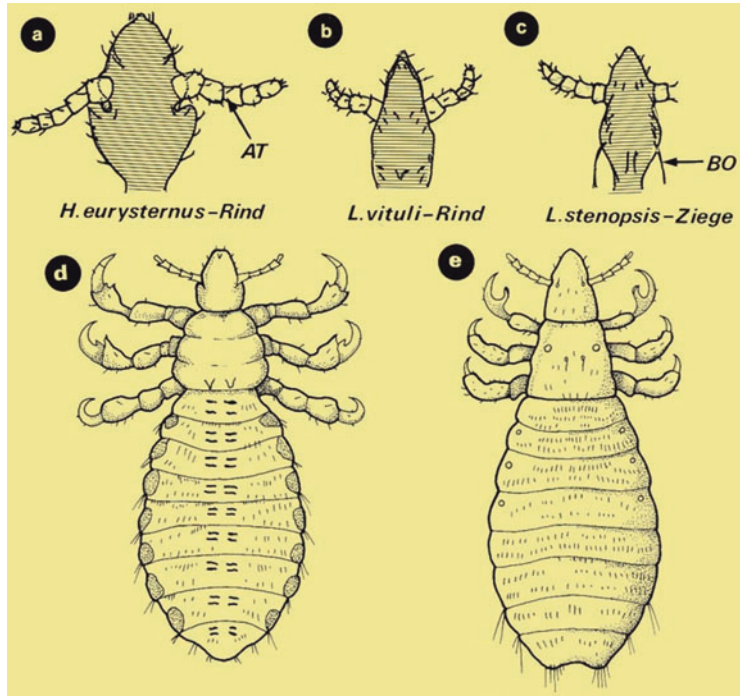
This louse of cattle reaches a length of about 3 mm (Fig. 1) and has, however, no eyes. (Fig. 2)





***Linognathus vituli*, Fig. 1** DR of a female from the dorsal




***Linognathus vituli*, Fig. 2** Diagrammatic representation of different lice of ruminants. (**a**) Head of a female from ventral. (**b**, **c**) Heads of females from dorsal. (**d**, **e**) Adults from dorsal (*d* = *Haematopinus eurysternus*; e = *Linognathus vituli*). *AT* antenna, *BO* bristles; Rind = cattle; Ziege = goat

## *Liopygia ruficornis*

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Syn. *Sarcophaga ruficornis*: sarcophagid fly of forensic importance in South Africa.

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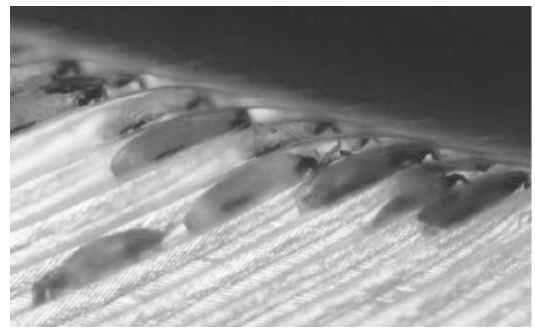
## *Lipeurus caponis*

Species of so-called feather lice or wing lice of chicken birds (Fig. 1). These dorsoventrally flattened ► Mallophaga reach a length of 2.3 mm, whiles their eggs measure about 0.7 mm.



***Lipeurus caponis*, Fig. 1** Feather lice (*Lipeurus* sp.) in a chicken feather

## Lipids

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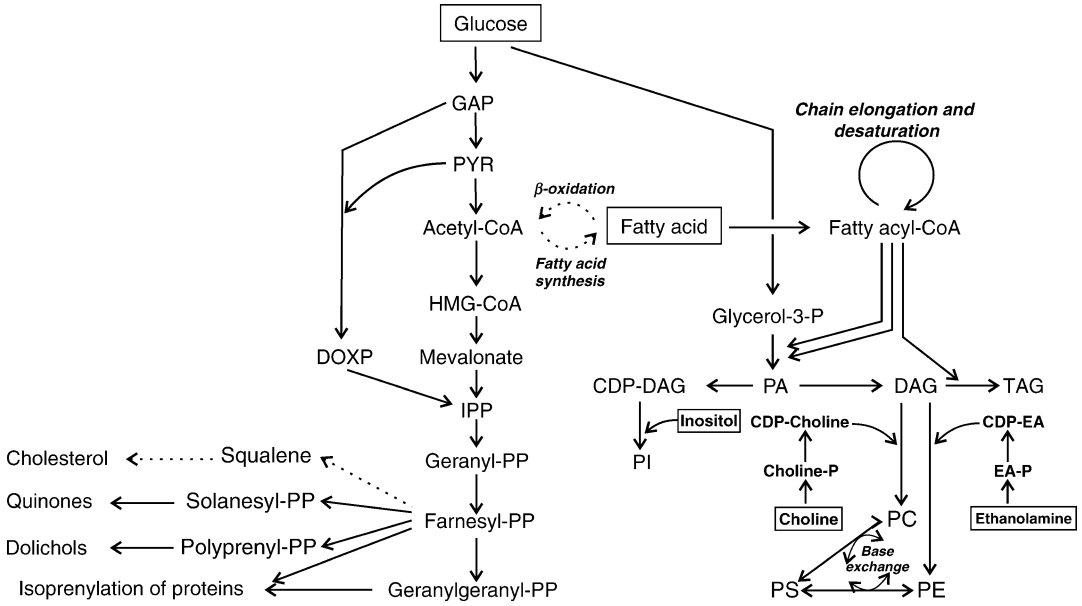
All major classes of lipids found in free-living organisms are also essential biochemical




**Lipids, Fig. 1** Generalized representation of the central pathways for *de novo* biosynthesis of lipids by parasites. Boxed substrates are obtained from the host. Pathways present in the mammalian host, but absent in most parasites, are represented by dotted arrows. For instance, few of the parasites studied appear capable of *de novo* biosynthesis of fatty acids. Abbreviations: *DAG* diacylglycerol, *CDP-DAG* cytidine diphoshodiacylglycerol, *DOXP* 1-deoxy-D-xylulose-5-phosphate, *Farnesyl PP* fernasylpyrophosphate, *GAP* glyceraldehyde-3-phosphate, *Geranyl PP* geranypyrophosphate, *Geranlygeranyl PP* geranylgeranylpyrophosphate, *HMG-CoA* hydroxymethylglutaryl-CoA, *IPP* isopentenylpyrophosphate, *TAG* triacylglycerol, *PA* phosphatidic acid, *PC* phosphatidycholine, *PE* phosphatidylethanolamine, *PI* phosphatidylinositol, *PYR* pyruvate



constituents of parasitic protozoa and helminths. Lipid metabolism in parasites has several unique features and the content, distribution, and requirement of lipids and the synthetic capabilities for these substances show considerable variation between different parasite species. In addition, profound modifications in the lipid composition may occur during differentiation and maturation of a parasite and even in a specific stage, and rearrangements in lipid composition may be central to avoid host defence mechanisms. In addition to their common functions, lipids in endoparasites may be associated with adaptive mechanisms to parasitism. For example, in schistosomes the outer bilayer of the tegumental membrane complex contains lipids which have been suggested to play a major role, through inducible modifications, in modulating the host's effector mechanisms of immunity and in parasite survival. Since lipid metabolism in endoparasites is characterized by substantial limitations of both synthetic and catabolic capabilities, these organisms seem to selectively absorb lipids from the host's diet with subsequent incorporation of these substances into their species- and stage-specific lipid pattern.

In most organisms the oxidation of fatty acids is an important source of ATP. This is, however, not the case in most parasites. In the majority of protozoa and in adult helminths, utilization of lipids as an energy source is either very limited or not feasible at all (Fig. 1). The reason for the absence of a functionally active β-oxidation in those parasites where all the enzymes involved in this process are present, is unclear. A possible explanation for this deficiency could be that sufficiently effective terminal oxidative processes are lacking in most parasite cells and tissues, in particular the tricarboxylic acid cycle and a cytochrome oxidase-linked respiratory chain, for oxidation of reduced coenzymes accumulating in large amounts during fatty acid degradation.

Thus, the role of the β-oxidation enzymes of protozoa and helminths remains unclear, but their action may be associated with biosynthetic processes, such as fatty acid elongation or the formation of volatile fatty acids from carbohydrates. However, some protozoa seem to possess the ability to catabolize lipids to carbon dioxide and water, but even if it occurs, this process is not a significant source of energy. Amongst the helminths, such marked oxidative capacities appear to be restricted to some larval parasitic and most free-living stages.

In accordance with their opportunistic way of living, parasites usually have very limited biosynthetic capacities. Whenever possible they obtain substrates for the synthesis of their structural elements from the host. Most parasites indeed acquire the vast majority of their lipids from the host. Protozoan parasites and helminths are generally unable to synthesize fatty acids *de novo*. However, in common with other organisms, many parasites have the ability to desaturate or to lengthen the chains of fatty acids absorbed from their habitat by the sequential addition of acetyl CoA as two-carbon unit (Fig. 1). Trypanosomatids and apicomplexan parasites can synthesize fatty acids *de novo* using the type II fatty acid synthase (FAS II) machinery found in prokaryotes and plants. This system is composed of multiple proteins rather than being a multifunctional enzyme complex as in higher animals, is membrane-associated rather than cytosolic and is sensitive to the naturally occuring antibiotic thiolactomycin. Surprisingly, *T. brucei* uses mainly, instead of the FAS II system, 3 microsomal elongases in a consecutive way for the stepwise synthesis of fatty acids, for instance in the bloodstream stage for the synthesis of myristate, which is required for the synthesis of GPI anchors in larger amounts than the host can provide.

In trypanosomes, acetyl CoA used in fatty acid elongation is preferentially derived from threonine via a pathway involving threonine dehydrogenase and glycine acetyltransferase. Trypanosomatids are also able to desaturate exogenously supplied fatty acids. Most deficient in lipid metabolism are the anaerobic protozoans, including *Giardia*, amoebae and trichomonads, which cannot synthesize fatty acids, cholesterol, and other sterols from acetate or mevalonic acid. They are also unable to employ fatty acids as energy source, nor are they able to elongate, shorten or desaturate fatty acids. However, they possess the capacity to remodel the fatty acid composition of their phospholipids.

Fatty acids, which are absorbed by parasites from exogenous sources, are rapidly incorporated into their triacylglycerols and phospholipids (Fig. 1), and the pathways responsible for these processes appear to be similar to those found in other animals. Most parasites appear able to manufacture phosphoglycerides and sphingolipids via *de novo* synthetic pathways, provided they have access to suitable precursors, such as fatty acids and sugars. Activation of fatty acids to acyl CoA thioesters is catalyzed by acyl CoA synthetase, which is widely found in parasites. The routes involved in the subsequent steps of synthesis and interconversion of complex lipids are, like the initial step, also similar to those present in higher animals (Fig. 1).

Although sterols, such as cholesterol, are not synthesized *de novo* by parasitic helminths, they do possess a mevalonate pathway (Fig. 1). In most helminths as well as parasitic protozoa, this mevalonate pathway is active and is used for the biosynthesis of dolichols for protein glycosylations, of quinones as electron transporters in the respiratory chain, and of farnesyl and geranylgeranyl pyrophosphates as substrates for the isoprenylation of proteins. Cestodes and trematodes also excrete isoprenoids that act as hormones in the development of insects, notably ecdysteroids. In contrast to helminths, trypanosomatids can synthesize sterols *de novo*. However, they do not synthesize cholesterol, but instead synthesize ergosterol-related sterols, by a biosynthetic pathway similar to that operating in pathogenic fungi, a finding that explains the sensitivity of these protozoans to particular antimycotic drugs, such as ketoconazole. The

bloodstream stages of African trypanosomes cannot synthesize sterols and have to acquire host cholesterol to meet their sterol requirements. A unique feature of apicomplexan parasites is the utilization of a mevalonate-independent route for the biosynthesis of isoprenoid precursors found in many prokaryotes and in the plastids of plants (Fig. 1). In *Plasmodium* and related parasites, this 1-deoxy-d-xylulose-5-phosphate (DOXP) pathway is located within the apicoplast, and because it is not present in the host it provides several attractive targets for chemotherapy.

Several unique lipid structures and pathways have been identified in parasites. A peculiar class of triacylglycerols, which contain esterified volatile fatty acids (2-methylbutyrate, 2-methylvalerate, *n*-valerate), occurs in *Ascaris suum* and a few related nematodes, where they are especially abundant in the eggs. The fatty acids are end products of carbohydrate metabolism in the nematode's muscle tissue and then transported to the ovaries where they are incorporated into triacylglycerols. During egg development, the volatile acids are enzymatically released from the fat storage and serve as an energy-rich fuel for the larval parasite. In nematode eggs, long-chain fatty acids, which also derive from triacylglycerols, are utilized for the resynthesis of carbohydrates through a functional, glyoxylate cycle. The presence of this pathway in developing eggs of some helminths is unusual, as it does not occur in most other animals. A characteristic feature of trypanosomatids is that the entire machinery for the synthesis of ether lipids from glycerol and fatty acids is associated with the glycosomal compartment of the cell. Another unusual feature of many helminths is the presence of the lipid rhodoquinone instead of ubiquinone as a functional constituent of anaerobically functioning mitochondrial respiratory chains in eukaryotes, and it is remarkable that they can synthesize this electron carrier *de novo* (Quinones). In general, parasites have retained only those biosynthetic pathways that are required to modify lipids obtained from the host. Lipids (such as fatty acids and cholesterol) are obtained from the host, but the lipids that are more difficult to acquire because of their low concentration in the host are synthesized by the parasite, usually by modification of more abundant lipid substrates. Other examples of these important unique lipid structures, such as the glycosylphosphatidylinositol anchors and the lipophosphoglycans, are discussed separately.

## Lipophosphoglycan

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Lipophosphoglycan (LPG) is the dominant cell surface glycoconjugate of ▶ *Leishmania* promastigotes. In these protozoan stages, approximately three to five million copies of LPG together with glycoprotein molecules (mainly the promastigote surface proteinase) protrude above a dense cell surface ▶ glycocalyx of about ten million copies of glycosylinositolphospholipids (▶ Glycosylphosphatidylinositols). The molecule consists of four distinct domains, some of which are highly unusual for a eukaryotic glycoconjugate (▶ Glycosylphosphatidylinositols, Fig. 2). This includes the means of membrane anchoring by phosphatidylinositol-linked $C_{24}$ or $C_{26}$ saturated hydrocarbons, a core heptasaccharide, a repeating phosphorylated saccharide backbone containing a unique 4-*O*-substituted mannose, and a terminal neutral oligosaccharide. While the lipid anchor of LPG is highly conserved, the glycan composition shows extensive variability among different *Leishmania* spp. stages and strains, the most striking of which is the increase in size of the phosphorylated saccharide domain as displayed by metacyclic stages. The distinctive structural features of LPG and its developmental modification implicates

important functions for this molecule, including attachment of the parasite to the sandfly vector midgut epithelium and adhesion and entry into the host macrophages.

## Lipoptena

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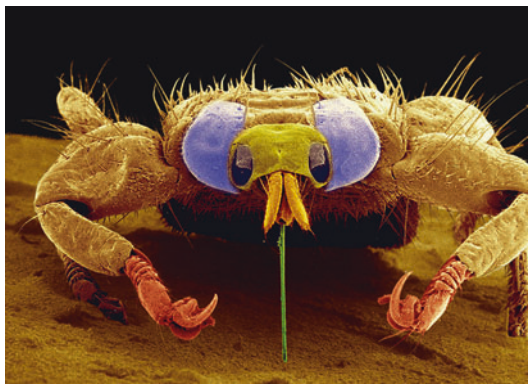
### Name

Genus of louseflies (e.g., *L. cervi*, *L. capreoli* of small ruminants, and wild deer), reaching a length of about 5 mm. ▶ Hippoboscidae, ▶ Diptera, ▶ Keds. The females get rid of their wings after reaching a host. Thus on cervids only wingless stages are seen (Fig. 1). These specimens may also attack humans, where both sexes start bloodsucking, which leads to itching. During their lifespan of 5–6 months, the females produce 10–15 larvae 3 (like tsetse flies), which start pupation when laid on soil. The pupae are brownish red. After about 20–23 days, the adults hatch from the eggs, copulate 4–5 days later after starting bloodsucking on a host, which was reached by help of their wings.



**Lipoptena, Fig. 1** Scanning electron micrograph of the anterior aspect of *L. cervi*. Note the large claws for attachment along the hair

## Lister, Joseph, Lord (1827–1912)

English scientist, discoverer of antisepsis.

## *Listeria*

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Gram-positive bacteriae, which may be transmitted by bites of argasid ticks or fleas but mainly by ingestion of contaminated food (syn. *Listerella*).

## Listeriosis

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### Name

Sir Joseph Lister (1827–1912), English surgeon, described this species of bacteria. The agents of listeriosis (*Listeria monocytogenes*) are transmitted by contact with infected animals, by contaminated food, or during bites of ▶ fleas or argasid ticks.

## *Listrophorus*

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Genus of mites of the family ▶ Demodicidae. *L. gibbus* infects rabbits.

## Litomosoides

### Classification

► Nematode, ► Filariidae.

### General Information

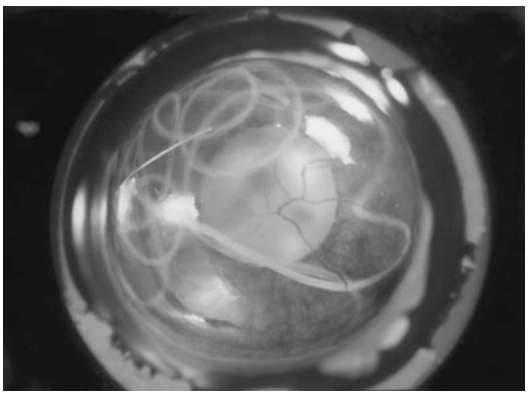
The adults of *L. carinii* (♀ up to 7 cm ♂ 2.8 cm in length) live in general in the pleural cavity of *Sigmodon* rats. However, occasionally they occur also in the eyes of their hosts (Fig. 1). The females produce sheathed microfilariae, which reach a length of 90–120 µm and occur all day in the blood. Blood-sucking mites (*Ornithonyssus*) take up such $L_1$, which grow up to the infectious $L_3$ inside the mite. During blood sucking the transmission occurs and the worms reach maturity within 50–80 days.

### Diagnosis

Giemsa-stained blood smears.

### Therapy

Ectoparasitocidal drugs, diethyl-carbamazine against microfilariae.



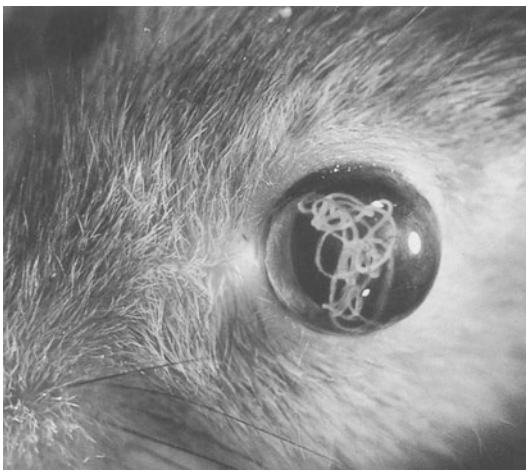
**Litomosoides, Fig. 1** Macrophoto of an eye of a cotton-rat containing an adult worm of *Litomosoides carinii*

## *Litomosoides carinii*

### Synonyms

*L. sigmodonti*.

This nematode species which is kept in laboratory animals (*Mastomys, Sigmodon*) that are imported from desert regions and reared in laboratories, lives in the pleural cavity of mice. The males reach a length of 2.8 cm, the females grow up to 7 cm and are mostly found in coiled crowds (like the other members of the family Onchocercidae). The females produce many sheathed larvae (microfilariae) with a length of 90–120 µm. They are found in the blood, from where they are taken up by bloodsucking mites (► *Bdellonyssus*, *Ornithonyssus*). After two molts the larvae 3 are injected into the mammal during the next blood meal. The adult may also occur accidentally in the anterior chamber of the rodents (Fig. 1). **Prepatent period**: 70–80 days; **Patency** 1–3 years. This worm is used in laboratory as model to develop onchocercidal drugs.



***Litomosoides carinii*, Fig. 1** Macrophoto of the eye of a jird (*Meriones* sp.), within which an adult female is accidentally seen

## Litostomatea

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Group of ciliates (e.g., ▶ *Balantidium coli*).

## Liver Coccidiosis

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Infection of the bilary ducts of rabbits with the coccidian ▶ *Eimeria stiedae* (syn. *E. stiedai*) (Fig. 1).


**Liver Coccidiosis, Fig. 1** Liver of a rabbit infected by *Eimeria stiedai* (syn. *stiedae*). Inset: sporulated oocyst of *E. stiedai*

## Liver Flukes

A variety of digenean ▶ trematodes are very important parasites of the liver of animals and man. They belong to the families Fasciolidae (▶ *Fasciola hepatica*, ▶ *F. gigantica*, and ▶ *Fascioloides magna*), Dicrocoeliidae (▶ *Dicrocoelium dendriticum*, *D. hospes*), and Paramphistomatidae (*Gigantocotyle explanatum*) (▶ Digenea, Table 1). *F. hepatica*, the common liver fluke, is the most widespread and important of the group (▶ Digenea, Fig. 3). *F. gigantica* occurs in the tropics mainly in sheep and cattle, but a patent infection can develop in horses, pigs, wild animals, and in humans, too.

## Liver Penetration

The young ▶ flukes of ▶ *Fasciola hepatica*, when leaving the metacercarial sheath inside the host's intestine, penetrate the intestinal wall, and enter the liver from outside on their way to the bile ducts, their final habitat. Penetration of liver also occurs in ▶ *Ascaris* and ▶ *Schistosoma* spp. as well as in many other parasites (▶ Pathology).

## *Livoneca*

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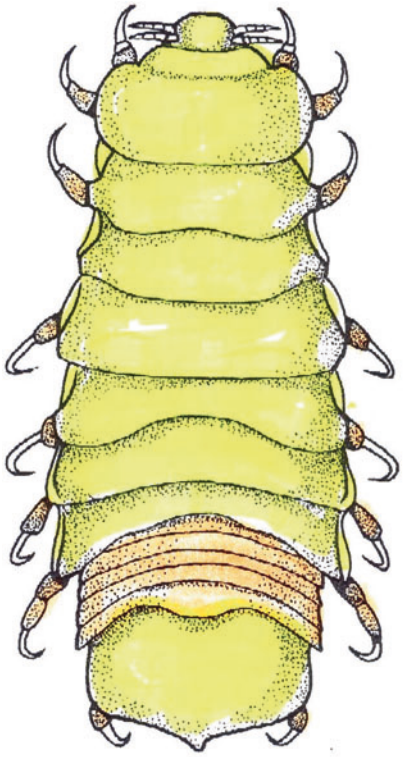
Genus of parasitic isopods (Fig. 1) on the skin of freshwater fish (sucking blood).



***Livoneca*, Fig. 1** Diagrammatic representation of an adult stage from the dorsal

## *Livoneca symmetrica*

Species of isopod crustaceans parasitizing on freshwater fish (▶ Livoneca, Fig. 1).

## Llaga

Common name for the disease due to an infection with *Leishmania* (syn. *Viannia*) *peruviana*.

## LM

Light microscopy.

## *Loa loa*

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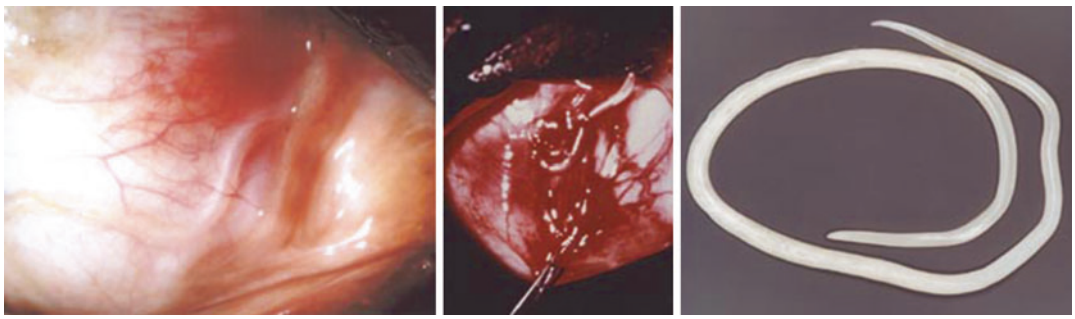
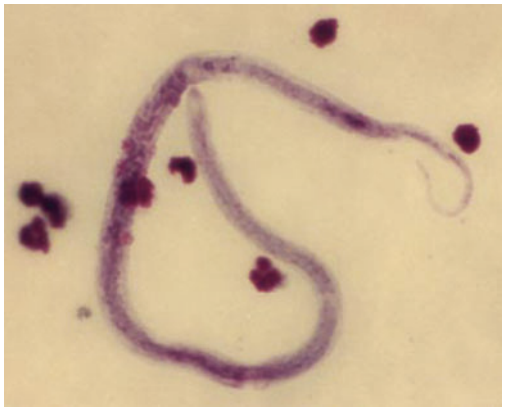
### Synonyms

Eye worm; Old Calabar worm, name comes from a local African state (Gyyot 1778)



***Loa loa*, Fig. 1** Adult worm in the eye (*left*), being surgically removed (*middle*) and taken out from the anterior eye chamber (*right*) (Courtesy Prof. Grüntzig)



***Loa loa*, Fig. 2** Giemsa-stained microfilaria of *Loa loa* with its colorless sheath

## Classification

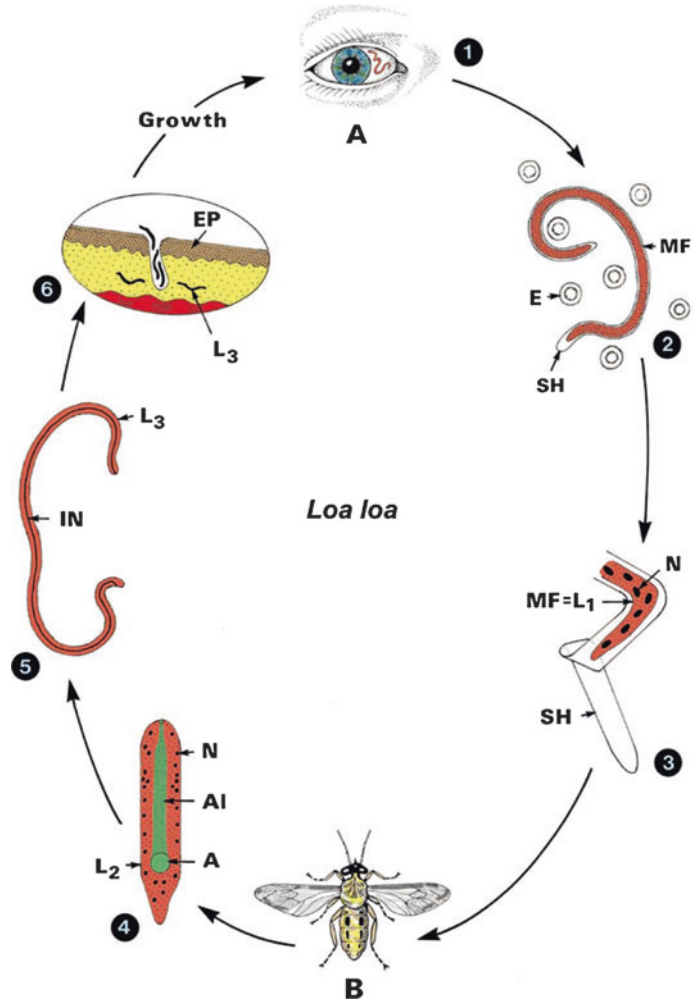
▶ Nematodes, ▶ Filariidae.

## Life Cycle

Figures 1, 2, and 3; ▶ Filariidae.

## General Information

This worm is found in Africa between 10° North and 5° South. The female adults reach a length of up to 7 cm and a width of 0.5 mm, while the males are smaller (3.2 cm × 0.4 mm). It is characteristic that the adult worms wander throughout the subcutaneous tissues and may appear in the anterior




***Loa loa*, Fig. 3** (**A**) Stages in humans: *1*, Adult in the eye chamber; *2*, microfilaria in the blood (= $L_1$); *3* tail of microfilaria. (**B**) Stages in vector (*Chrysops*): *4*, larva 2; *5*, larva 3; *6*, larva 3 penetrating into the skin during bloodsucking of *Chrysops* specimens. After molt to larva 4, molt to adult occurs. *A* anus, *AI* anlage of intestine, *E* erythrocyte, *EP* epidermis, *IN* intestine, *MF* microfilaria, *N* nucleus, *SH* sheath

chamber of the eye (Fig. 1). The microfilariae live in the blood and appear most often between 10 am and 1–3 pm in the peripheral blood. The vectors are biting flies and tabanids) of the genus ▶ *Chrysops*, within which the $L_3$ is developed.

### Diagnosis

Microscopy of Giemsa-stained blood smears showing the unsheathed microfilariae (Fig. 2) (▶ Loiasis).

### *Loa loa*: Genomics

Desjardins et al. (2013) described that the genome of *Loa loa* has a size of 9.4 Mb and predict the existence of 14,907 genes on the basis of microfilarial RNA sequencing. The *Loa loa* genome encodes many immunological relevant genes as well as protein kinases. Despite lacking *Wolbachia* bacteria *L. loa* does not show new metabolic synthesis or transport systems compared to *Wolbachia* bearing filariae.

### References

Desjardins CA et al (2013) Genomics of *Loa loa*, a *Wolbachia*-free filarial parasite. Nat Genet 45:495–500

### Further Reading

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## Lobopodia

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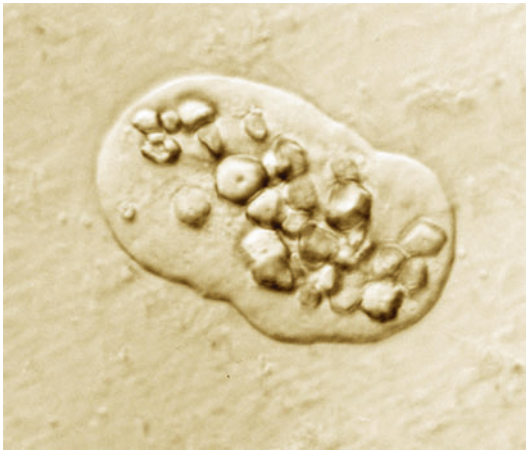
Thick lobe-like ▶ pseudopodia in amoebas (Fig. 1).



**Lobopodia, Fig. 1** *Entamoeba histolytica* magna form producing always an anterior lobopodium

## Local Adaptation

Aubry reports that in 1895, when French armies conquered Madagascar, 5,756 soldiers died during the campaign: 25 died from injuries, the 5,731 others died from local parasitic diseases, mainly ▶ malaria. Such an event (many others could be reported) means that autochtonous human populations are usually better adapted to resist local parasitic diseases than are allochtonous invaders.

This example illustrates an old question, that of "local adaptation," which has been recently the subject of active debates. The question is: which one (the host or the parasite) is locally better adapted to the other?

If the host is better adapted, this means that its defenses are more efficient against local populations of the parasite than against foreign populations (in this case, the reproductive success of the parasite is better in allochtonous than in autochtonous populations of the host). This case is illustrated by the French army in Madagascar.

If the parasite is better adapted, this means that its fitness (reproductive success) is better in local populations of its hosts than in foreign populations. This case is illustrated by many experimental studies. For instance, Xia et al. demonstrate, both by miracidial exposure and microsurgical transplantation of larval stages

(sporocysts), that ▶ *Schistosoma japonicum* develops significantly better in local populations of the intermediate snail host *Oncomelania hupensis* than in populations of the same species collected at another place 1,000 km away. In particular, histological observations show that rejection of grafts is significantly more frequent in allopatric than in sympatric combinations.

Various genetical models predict that better local adaptation of the parasite should be the rule: parasites should stay closer to "optimal virulence" in sympatric populations of hosts than in allopatric ones. This prediction seems to contradict the example cited above of the susceptibility of human populations to allochtonous diseases. In fact, the contradiction is only apparent, because "better adapted" does not mean "more virulent": the dramatic pathogenicity of *Plasmodium falciparum* in European invaders certainly provided less opportunities for transmission than a more lasting disease, so that the parasite, although less virulent, was better adapted to local human populations.

### Related Entry

▶ Virulence.

## Localization of Parasites

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Organotrophy of parasites
Parasites in the blood
Parasites in the bones
Parasites in the brain
Parasites in the eyes
Parasites in the intestine
Parasites in the kidneys
Parasites in the liver and spleen
Parasites in the lung and breathing system
Parasites in the lymph
Parasites in the macrophages
Parasites in/on the mucous layers
Parasites in the muscles
Parasites in the saliva
Parasites in the sexual organs
Parasites in the skin
Parasites in the swim bladder
Parasites on the surface (on the skin, in hair, or among feathers)
Parasites in the urine

### Locomotory Systems

All ▶ Protozoa are motile in at least one stage of their life cycles. During their evolution, the different species have developed distinct locomotory systems such as ▶ pseudopodia (e.g., ▶ Amoeba), ▶ flagella or ▶ cilia. The invasive stages of sporozoans, i.e., the merozoites and sporozoites, have three types of movement: gliding, twisting, and bending (▶ Coccidia, motility). Only the first of these leads to active displacement of the organisms; the other two only change the direction of movement. The gliding form of movement is extremely rare in eukaryotic cells. It is temperature-dependent and cytochalasin B-sensitive, the latter property suggesting the participation of ▶ actin in the process. The gliding movement may be related to the ▶ capping phenomenon in sporozoans. In capping, the organisms aggregate materials on their surfaces and move them towards the posterior pole, from where they release them into the surroundings. A parasite floating in a liquid could move forward

using this type of action. The most studied of the capping phenomena is the circumsporozoite reaction of *Plasmodium falciparum* sporozoites (▶ Micronemes).

## Löffler Syndrome

Hemorrhages and inflammation foci within lungs of humans during the migration phase of larval ascarids (▶ Ascariasis, Man) being accompanied by dyspnea, slight fever, blood ▶ eosinophilia plus coughing.

## Löffler, Friedrich August Johannes (1852–1915)

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Friedrich Löffler was a German physician and a bacteriologist and later a professor at the University of Greifswald. During the years 1879–1884, he was the assistant of Robert ▶ Koch at the Imperial Health Office in Berlin. He became famous due to important discoveries, such as in the year 1894 the determination of the agent of diphtheria (*Corynebacterium diphtheriae*), the virus of food-and-mouth disease of cattle (*Aphthae epizooticae*) together with Frosch, the agent of malleus (*Pseudomonas mallei*) of horses and carnivores together with Schütz (1882), and the agent of erysipelas (*Erysipelothrix rhusiopathiae*). The German Löffler Institute founded in 1910 at its main seat on the Isle of Riems (near Greifswald) and five other dependences in German towns represent today the Central German Institute for Virus Research and register officially all new products on veterinarian immunodiagnostics.

## Löffler's Lung Infiltration

Clinical symptom due to infections with ▶ *Ascaris*, ▶ hookworms, ▶ *Strongyloides*, ▶ *Paragonimus*.

## Loiasis

### Synonyms

Eye worm disease.

Loiasis results from an infection of the subcutaneous and deep tissues with adult ▶ *Loa loa*, transmitted by a biting fly (▶ *Chrysops*; ▶ Filariidae). Larvae enter at the site of the fly bite and slowly develop into adults. Adult worms make their appearance after a year or more, when they give rise to symptoms during their subcutaneous or subconjunctival migration (▶ Eye Parasites). The living worm is not inflammatory, but dead worms give rise to microabscesses (▶ Abscess) with eosinophils. The released microfilariae circulate in the blood and when they die elicit small granulomas with epithelioid and giant cells; these may give rise to symptoms referable to many organs, including the brain.

**Main clinical symptoms**: Swellings (so-called calabar-swellings) of the skin = ▶ oedema of skin, passage of worms through the eye.
**Incubation period**: 2–12 months.
**Prepatent period**: 6 months–4 years.
**Patent period**: 4–17 years.
**Diagnosis**: Microscopic analysis of blood smear, ▶ microfilariae are found at 1–5 clock p.m. in the peripheral blood, ▶ Serology, ▶ Loa loa, Fig. 1.
**Prophylaxis**: Avoidance of *Chrysops*-bites in West Africa.
**Therapy**: Treatment see Nematocidal Drugs, surgical removement of the worm, when passing the eye.

## Longevity, Longvivity

The lifespan reached by larval and adult parasites is species-specific (short: hours – miracidia; weeks – *Enterobius* or long: months – female mosquitos, ► fleas; years: tapeworms, schistosomes, hookworms).

## Long-Lasting Insecticidal Nets

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This term describes mosquito nets consisting of rather strong fibers being impregnated with quick-acting insecticides (e.g., pyrethroids), which repel or kill mosquitoes on contact and thus prevent them from biting for up to 3 years.

## Loop

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Loop mediated isothermal amplification is a method to detect ► *Ehrlichia* infections.

## Looss, Arthur

German parasitologist (Fig. 1), died in 1923, discoverer (1900 in Cairo) of the transmission of the hookworm infections.

**Looss, Arthur, Fig. 1** Photo just prior to his death in 1923. His great discovery was the transmission of the hookworms

## Loperamid

Drug that stops diarrhoea; it is also active against acanthocephalans (e.g., ► *Macracanthorhynchus hirudinaceus*).

## *Lophomonas*

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Genus of hypermastigid flagellates in the intestine of cockroaches possessing several thread-like ► axonemes and two deeply embedded spiral bands bearing single flagella.

## Loss in Performance

The parasitic load often introduces considerable reduction of the fitness of hosts, i.e., they look tired, their skin is pale, their hairs appear dull, their movements are slow, and they grow slowly if at all. Thus several female birds clearly prefer bright, shining, and highly active male mating partners that indicate health.

## Louping Ill

Louping ill is a sheep disease found in North Britain which is caused by the LI virus (▶ *Flavivirus*, group B). It is transmissible to human beings in close contact with sheep (laboratory workers, sheep farmers, veterinarians, and butchers), or those exposed to tick bites; at least one human death has been proven.

## Louse Flies

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### Synonyms

Hippoboscidae; Keds.

These flies received their trivial name from people's observation that they live like true ▶ lice in the hair of their hosts after having infested a host and discarded their two wings. Their thorax is equipped with strong legs armed with thick claws. The horse louse fly ▶ *Hippobosca equina* reaching a length of 8 mm preserves its wings. The deer louse fly *Lipoptena cervi*, which measures 3–5 mm in length, keeps the wings as males, while females lose them. The sheep louse fly *Melophagus ovinus* (∼5 mm long), which is also erroneously named "sheep tick", has in both sexes completely reduced wings and is transmitted during body contacts. Both sexes suck blood on the surface of their hosts. Their bites are painful and lead to loss of body weight of the hosts and hair loss. Females discharge already larvae 3, which start pupation during the next 10 h. The pupal cocoon appears reddish brown and is glued to the hair. During their life span of about 4–7 months, females produce up to 15 larvae.

## Louse-Borne Spotted Fever

Human disease due to infection with ▶ *Rickettsia prowazekii* being transmitted by the feces of ▶ lice.

## LTT

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Lymphocyte transformation test.

## *Lucilia sericata*

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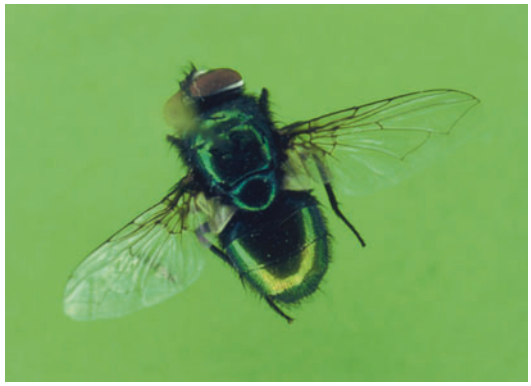
### Name

Latin: *lux* = light, Greek: *serikos* = silk.

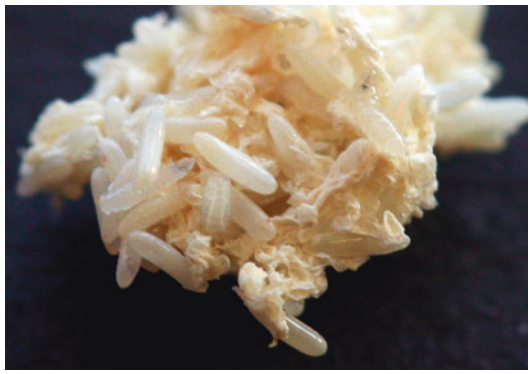


***Lucilia sericata*, Fig. 1** Adult *Lucilia sericata* fly in flight position

***Lucilia sericata*, Fig. 4** Larva of *L. sericata*

***Lucilia sericata*, Fig. 2** Adult *Lucilia sericata* sitting on glass

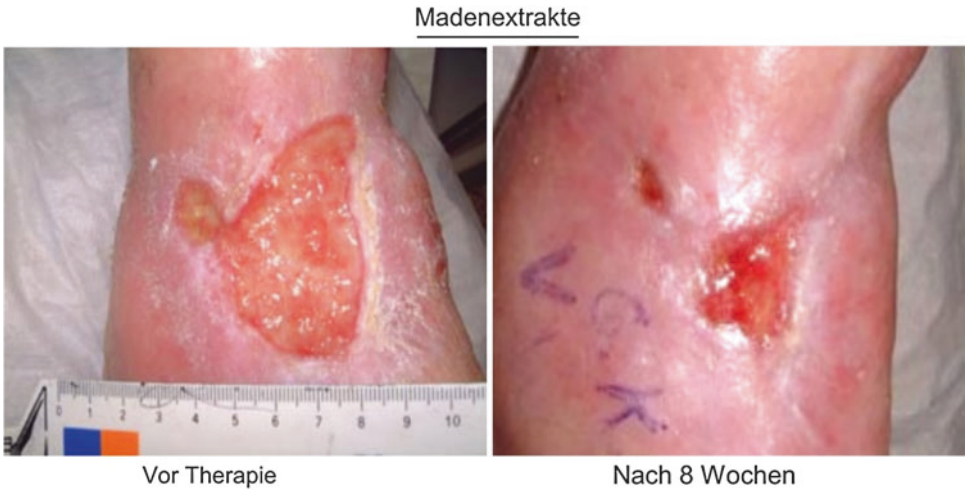
***Lucilia sericata*, Fig. 5** Pupae of *L. sericata*



***Lucilia sericata*, Fig. 3** Eggs of *L. sericata*

The larvae of this fly causing ▶ Myiasis, Man may be used to clean skin abscesses from the bacterial coat, since they feed only from necrotic tissues and not from healthy ones.

The larvae excrete intestinal fluids, which are later engorged again. These fluids lead to a debridement of badly healing wounds. Extracts are used as medicament (Fa. Alpha-Biocare, Düsseldorf, www.alphabiocare.de) to close nonhealing wounds (Larveel®) (Figs. 1, 2, 3, 4, 5, and 6).




***Lucilia sericata*, Fig. 6** Wound before and after use of the Larveel® extract (Dermatological Clinic, Düsseldorf)

## Lufenuron

### Chemical Class

Benzoylphenyl urea.

### Mode of Action

Insect growth regulator (IGR, chitin synthesis inhibitor). ▶ Ectoparasiticides: Inhibitors of Arthropod Development.

## Lumbal Punction

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Method to isolate antibodies against agents of disease from the fluid in the spinal cord (e.g., in cases of a long-lasting ▶ borreliosis due to tick bites.

## Lund's Fly

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Trivial name for *Cordylobia rodhaini*, a myiasis fly in moister parts of tropical Africa infecting humans less frequent than *C. anthropophaga*.

## Lung Fluke

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See ▶ *Paragonimus* species. These worms are often found in the lungs of their hosts being mostly enclosed as pairs in cyst-like compartments.

# Lung Worms

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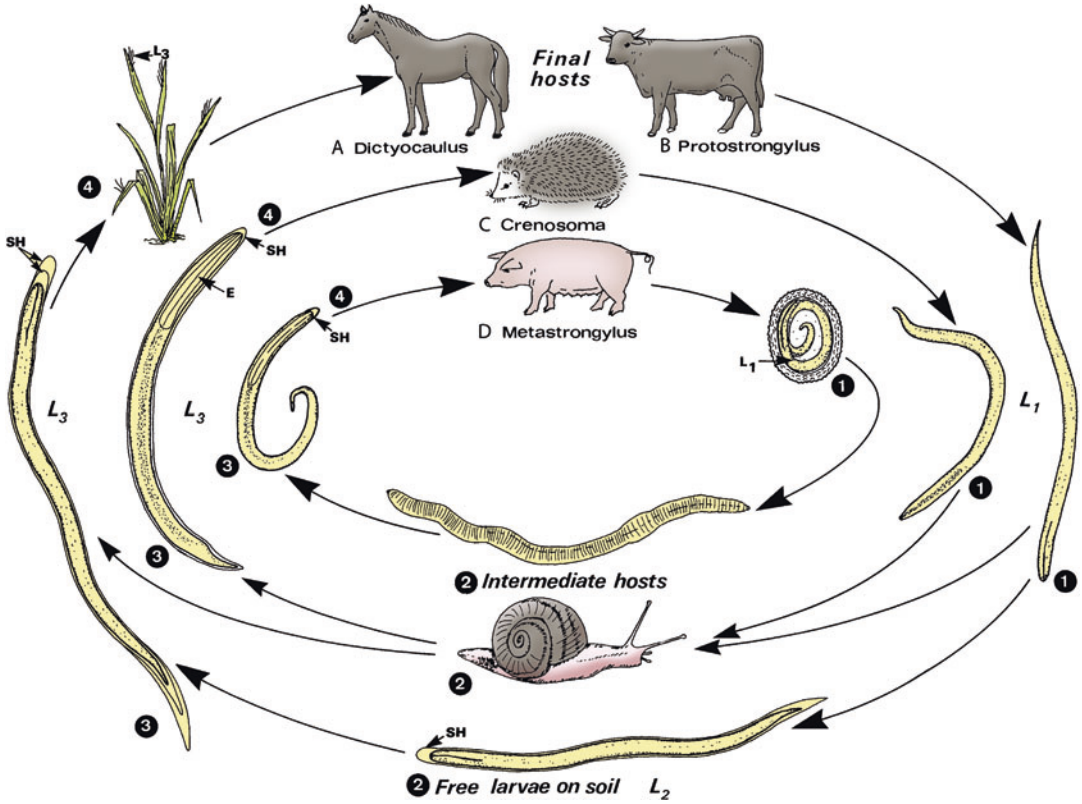
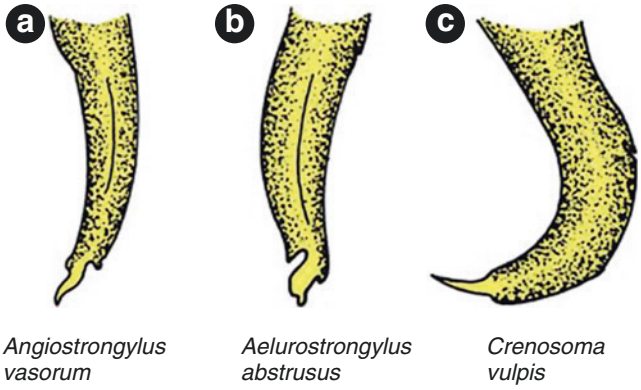
## Systematics

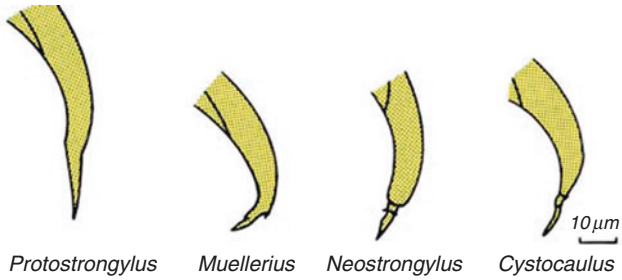
Members of several families of the class ▶ Secernentea (▶ Phasmidea) of ▶ Nematodes, *Dictyocaulus* (Fig. 1).




**Lung Worms, Fig. 1** Life cycles of several lung worms of different hosts. (**a**) *Dictyocaulus* spp. (large lungworms, see Table 4.1). (**b**) ▶ *Protostrongylus* spp. (small lungworms; see ▶ Nematodes, Table 1). (**c**) *Crenosoma striatum* (male 5–7 mm, female 12–16 mm long). (**d**) *Metastrongylus elongatus* (syn. *M. apri*: male 15–25 mm, female 20–55 mm long). *1* Fully embryonated eggs (D) or first-stage larvae are excreted with saliva and/or feces of final hosts. *2*, *3* In *Metastrongylus* spp. ($L_1$ in eggs), in *Protostrongylus* spp. (as in ▶ *Muellerius* spp., *Neostrongylus* spp.), and in *Crenosoma* spp., the $L_1$ is ingested by intermediate hosts (earthworms or various species of land-living snails), inside which the sheathed third larval stage ($L_3$) is formed via two molts. *Dictyocaulus* spp. do not need an intermediate host but develop free-living $L_2$ and $L_3$, which are ensheathed by the molted cuticles of the preceding larval stage. *4* The infection of the final hosts occurs by oral uptake of free larvae ($L_3$) on top of grass blades or by eating infected intermediate hosts with forage. Ingested larvae enter the intestinal wall at species-specific sites, penetrate lymph nodes, molt there, and thus become larvae of the fourth type. The $L_4$ larvae enter the heart via the bloodstream, thus reaching the lung, and passing into the bronchial and tracheal cavities, where it becomes mature (after another molt). If $L_3$ larvae are taken up late in the year, their development proceeds until the preadult stage, then it stops, and they hibernate, reaching maturity in early spring (▶ Hypobiosis). *E* esophagus, $L_{1-3}$, larval stages, *SH* ▶ sheath (formed by larval ▶ cuticle)




**Lung Worms, Fig. 2** DR of the terminal ends of several larvae of lung worms of carnivores




**Lung Worms, Fig. 3** DR of the terminal ends of lung worm larvae of ruminants



## Life Cycle

See Figs. 1, 2, and 3.

## Species

These nematodes parasitize inside the trachea, bronchioles, and/or in the lung alveoles of their hosts which belong (depending on the species) to many groups of vertebrates. There is distinguished between **large** and **small lung worms** (Figs. 1–5).

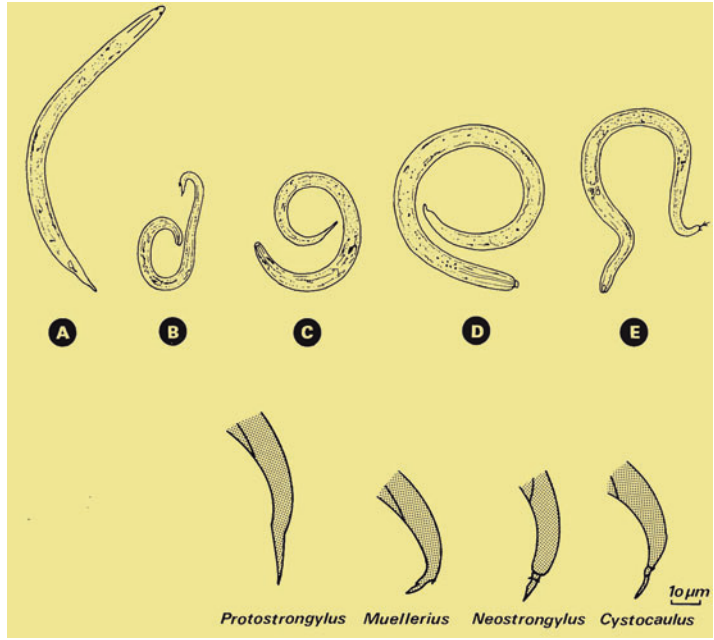
Very important genera are:

- *Aelurostrongylus abstrusus*
- *Angiostrongylus vasorum*
- *Bronchiostrongylus* species
- *Capillaria* species
- *Crenosoma* species
- *Cystocaulus* species
- *Dictyocaulus* species
- *Elaphostrongylus* species
- *Filaroides* species
- *Metastrongylus* species
- *Muellerius* species
- *Neostrongylus* species
- *Otostrongylus* species
- *Protostrongylus* species
- *Troglostrongylus* species
- *Varestrongylus* species

## Disease

► Respiratory System Diseases, Ruminants.

**Lung Worms, Fig. 4** Macrophoto of *Dictyocaulus* worms in the lung of cattle




**Lung Worms, Fig. 5** Diagrammatic representations of several larvae (in toto and their hind ends) of different species of lung worms (after Soulsby). (**a**) *Dictylocaulus viviparus*; (**b**) *Muellerius capillaris*; (**c**) *Protostrongylus rufescens*; (**d**) *Dictyocaulus filaria*; (**e**) *Cystocaulus ocreatus*

## Further Reading

Jabbar A et al (2013) The mitochondrial genome of *Protostrongylus rufescens*. Parasites Vectors 6(6):263–272

Jenkins EJ et al (2006) Climate change and the epidemiology of protostrongylid nematodes in Northern ecosystem. Parasitology 132:387–401

Morrondo P et al (2005) Larval development of *Neostrongylus linearis*. Parasitol Res 97:318–322

Tayce J et al (2008) Minimum sampling effort for reliable non-invasive estimations of excretion of Elaphostrongylus cervi. J Helmithol 82:253–261

Vicente J et al (2007) Sex, age, spleen size and kidney fat of red deer relative to infection intesities of *Elaphostrongylus cervi*. Naturwiss 94:581–587

## *Lutzomyia*

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Genus of ▶ sand flies (Fig. 1) with about 350 different species distributed throughout North, Central, and South America. Most human biters are confined to a few subgenera: *Lutzomyia*, *Helcocertomyia*, *Nyssomyia*, and *Psychodopygus*, which may transmit ▶ *Leishmania* stages to man in those regions. ▶ Diptera, ▶ Sand Flies, ▶ Phlebotomidae, ▶ *Leishmania* (Fig. 2).

***Lutzomyia*, Fig. 1** Adult female of *Lutzomyia* sp., the vector of ▶ *Leishmania* species in South America

***Lutzomyia*, Fig. 2** *Lutzomyia*: diagrammatic representation

## *Lutzomyia*: Subgenera

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- *Helcocertomyia* (e.g., *L. peruensis;* Northern Andes)
- *Lutzomyia* (e.g., *L. longipalpis*; Central, South America)
- *Nyssomyia* (e.g., *L. olmeca*; Central America)
- *Pintomyia* (e.g., *L. pessoai*; Brazil)
- *Psychodopygus* (e.g., *L. amazonensis*; Amazonas region)

## Lycophora

Ten-hooked larva of ▶ Cestodaria (genus ▶ Amphilina).

## *Lycosa tarentula*

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Tarantula spider with long legs has a hairy appearance. It was erroneously believed that its bite introduces extensive dancing in humans (Fig. 1).

***Lycosa tarentula*,**
**Fig. 1** Macrophoto of a tarantula, note the strong claws

## Lyme Disease

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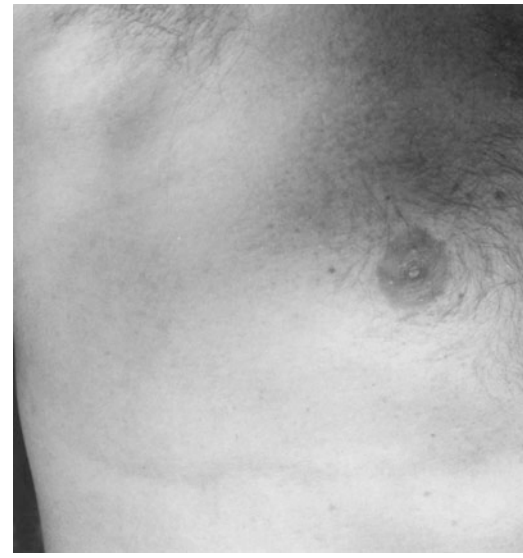
[2]Institut für Zoomorphologie, Zellbiologie und Parasitologie, Heinrich-Heine-Universität, Düsseldorf, Germany

The name Lyme came from the little town in USA, where many cases were first noted and where the first ▶ *Borrelia burgdorferi* bacteria were isolated.

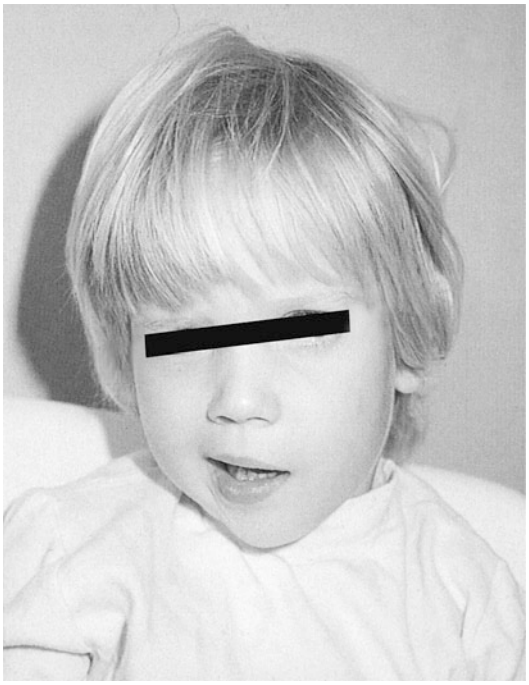
Other names for this disease are tick-borreliosis (▶ ticks as vectors of human diseases).

After a bite of an infected *Ixodes* tick the three phases of disease with the following symptoms may occur:



**Lyme Disease, Fig. 1** Typical *Rosacea migrans* = primary sign of Lyme-borreliosis

1. **Within days up to 6 weeks**: Erythema migrans, myalgia, swelling of lymphnodes, apathy (Fig. 1).
2. **Within weeks to months**: Urticaria, diffuse erythema, meningitis neuritis, radiculitis, myopericarditis, arthritis myositis, myalgia, severe-sickness feeling, affection of the respiratory tractus, osteomyelitis, pain during any movement, pareses (Fig. 2).
3. **Months to years**: Acrodermitis atrophicans, chronical encephalomyelitis, spastic paresis, mental disturbances, chronical arthritis, arthropathy, severe apathy.



**Lyme Disease, Fig. 2** Face of child with a paresis of the Nervous trigeminus (Courtesy of Professor Ackermann, Cologne)

### Diagnosis

Anamnesis: tick bite, erythema migrans (the latter occurs only in 70 % of the cases), serology.

### Therapy

First-stage treatment: oral application of Doxycyclin, Ampilicin or Cefuroxim, later: i.v. Ceftriaxon.

Tick Bites, Ticks as Vectors of Human Diseases, ▶ *Borrelia*.

## Lymnaea

Snail species, vector of many trematodes, e.g., *Fasciola*.

## Lymphadenosis Cutina Benigna

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Symptom of disease during infection with ▶ *Borrelia burgdorferi* transmitted by ▶ *Ixodes* species.

## Lymphocytic Meningoradiculitis Bannworth

Symptom of phase 2 of ▶ Lyme disease.



## Lymphocytome

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This symptom of disease – also described as ▶ Bäverstedt-syndrom – occurs during an infection with a tick-borne borreliosis and appears as benign swelling of the skin at the breast nipples or earlaps.

## *Lynchia maura*

Lousefly (▶ Hippoboscidae) of birds (synonym of = *Pseudolynchia*), e.g., *P. canariensis*.

## Lysosomes

Lysosomes are vesicles measuring 0.2–0.5 µm and bounded by a single membrane. They are derived from the sER and are formed and released from the secretion side of the ▶ Golgi apparatus (the trans-side). They contain enzymes such as phosphatases, ▶ proteinases, lipases, nucleases, etc. and have an internal pH of 4–5. When first released they are called primary lysosomes. After fusion with the endocytotic vesicles their enzymes become active and the vesicle is then called a secondary lysosome. In these secondary lysosomes, or phagolysosomes, the ingested food is dispersed (▶ Endocytosis, Fig. 1B). Another type of secondary lysosome is the ▶ autolysosome, which is involved in the disintegration of cellular waste material, thus providing the function of debris disposal. Defective lysosomes introduce diseases (e.g., mucopolysaccharidosis).

## Lyssa

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### Name

Latin: rage, fury.

This term describes the symptoms of the ▶ rabies, which occurs due to infections with viruses being transmitted during bites, e.g., of dogs and also by bats (▶ vampire bats).

## *Lyssavirus*

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Virus of the so-called rhabdovirus group introducing rabies disease.

See ▶ blood-licking bats.

## Lystropodia

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Genus of the family Nycteribiidae (bat louse-flies).

## Lytta

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### Name

Greek: *lytta* = fury.

This term describes an uncontrolled biting behavior of dogs that have ingested beetles belonging to the genera *Lytta* sp. or *Meloe*, which contain cantharidin that introduces this behavior.