Echinococcus vogeli* and *E. oligarthrus

Causative agents of polycystic echinococcosis

These two species, endemic in Central and South America, develop in wild animal cycles (bush dog/*paca* and wild felids/agoutis, paca etc., respectively). In humans, these organisms cause the rare polycystic echinococcosis, which affects the liver, lungs, and other organs.

Hymenolepis

Hymenolepis nana (Dwarf Tapeworm)

Causative agent of hymenolepiosis

Occurrence, morphology, and life cycle. *Hymenolepis nana*, 1–4 cm long (rarely 9 cm) and 1 mm wide, is a small intestinal parasite that occurs worldwide, the highest prevalences being found in warm countries and in children. The final hosts are rodents and humans. Infection results from peroral ingestion of eggs, from which oncospheres hatch in the small intestine, penetrate into the villi, and develop there into larvae (cysticercoids). The larvae then return to the intestinal lumen, where they develop into adult tapeworms within two to three weeks. Alternatively, *H. nana* develops in a cycle with an intermediate host (insects: fleas, grain beetles, etc.). The closely related species *Hymenolepis diminuta* (10–60 mm) is not as frequent in humans. The developmental cycle of this species always involves intermediate hosts (fleas, beetles, cockroaches, etc.).

Clinical manifestations and diagnosis. Infections are often latent, but sometimes cause indeterminate gastrointestinal distress. The eggs (elliptical, about 60 × 50 µm, Fig. 10.**1**, p. 544) are released from the cestode in the intestine and are found by normal stool examination procedures.

Therapy and prevention. Praziquantel or albendazole are the drugs of choice. Preventive measures include general hygiene and treatment of infected persons.

Diphyllobothrium

Diphyllobothrium latum (Broad Tapeworm, Fish Tapeworm)

Causative agent of diphyllobothriosis

Occurrence, morphology, and life cycle. This tapeworm is endemic in lake regions in Europe (above all in Russia, less frequently in Scandinavia, Germany, Switzerland, Italy, etc.), Asia, and America and parasitizes in the small

intestine of humans and fish-eating mammals such as pigs, dogs, and cats. The parasite has two elongated grooves (bothria) on its head, it is 2–15 m long with numerous (up to 4000) proglottids (Fig. 10.**7a, b**, p. 561). The oval, yellow-brown, operculated eggs (approx. 70 × 50 µm) are similar to those of trematodes (Fig. 10.**1**, p. 544). The life cycle includes copepods as primary and freshwater fish as secondary intermediate hosts. Humans acquire the infection when eating raw or undercooked fish containing infective stages (plerocercoids) of the tapeworm. Development of a sexually mature tapeworm can be completed within 18 days.

Clinical manifestations The course of a *Diphyllobothrium* infection is often devoid of clinical symptoms, with only mild gastrointestinal distress in some cases. Anemia and other symptoms due to vitamin B12 uptake by the parasite is observed in about 2% of tapeworm carriers.

Diagnosis, therapy, and prevention. Diagnosis is made by detection of eggs in stool, sometimes proglottids are excreted. Praziquantel is a suitable drug for therapy. Preventive measures include wastewater hygiene and not eating undercooked fish. The plerocercoids can be killed by boiling or deep-freezing (24 hours at –18 °C or 72 hours at –10 °C).

Nematoda (Roundworms)

General. The nematodes (*nema*: thread) are threadlike, nonsegmented parasites, a few mm to 1 m in length, with separated sexes. They possess a complex tegument and a digestive tract. The males are usually smaller than the females and are equipped with copulatory organs that often show features specific to each species. Development from the egg includes four larval stages and four moltings before the adult stage is reached. Some species require an intermediate host to complete development.

10

Intestinal Nematodes

■ *Ascaris lumbricoides* (large roundworm), hookworms (*Ancylostoma* species and *Necator americanus*), and *Strongyloides stercoralis* (dwarf threadworm) parasitize in the small intestine of humans; *Trichuris trichiura* (whipworm) and *Enterobius vermicularis* (pinworm) live in the large intestine. The transmission routes and life cycles of these parasites differ. *S. stercoralis* infections acquired in warm countries may persist in a latent state for many

years and can be activated in response to immunodeficiency and develop into life-threatening systemic infections. Careful diagnostic examinations are therefore necessary if a *Strongyloides* infection is suspected.

Ascaris lumbricoides (Large Roundworm)

Causative agent of ascariosis

Occurrence. The human large roundworm occurs worldwide. The number of infected persons is estimated at 1.38 billion (WHO, 1998). The main endemic regions, with prevalence rates of approx. 10–90%, include countries in Southeast Asia, Africa, and Latin America. Autochthonous infections are rare in central Europe.

Parasite and life cycle. The adult ascarids living in the small intestine (*ascaris*: worm) are 15–40 cm in length, about as thick as a pencil and of a yellowish pink color (Fig. 10.**12**). The sexually mature females produce as many as 200 000 eggs per day, which are shed with feces in the unembryonated state. The round-to-oval eggs are about 60 × 45 µm in size, have a thick, brownish shell and an uneven surface (Fig. 10.**13**). At optimum temperatures of 20–25 °C with sufficient moisture and oxygen, an infective larva in the egg develops within about three to six weeks.

Human infections result from peroral ingestion of eggs containing larvae, which hatch in the upper small intestine and penetrate into the veins of the intestinal wall. They first migrate hematogenously into the liver and then, four to seven days p.i., into the lungs, where they leave the capillary network and migrate into the alveoli. Via tracheopharyngeal migration they finally reach the digestive tract, where they further differentiate into adults in the small intestine. The prepatent period lasts for seven to nine weeks. The lifespan of these parasites is 12–18 months.

Ascaris lumbricoides

Fig. 10.**12** Male and female *Ascaris*.

Epidemiology. Reservoir hosts of the parasite are humans. The excreted eggs remain viable for years in a moist environment (soil), but are sensitive to desiccation. Infective *Ascaris* eggs can be ingested by humans with contaminated foods, soil (geophagia in children!) and, less frequently, in drinking water. In endemic areas, the prevalence and intensity of *A. lumbricoides* infections are highest in children.

Pathogenesis and clinical manifestations. Mild infections frequently remain inapparent. In more severe infections, **larval migration** in the lungs provoke hemorrhages and inflammatory infiltrations, which present as diffuse mot-

***Ascaris lumbricoides* and *Trichuris trichiura:* Life Cycles**

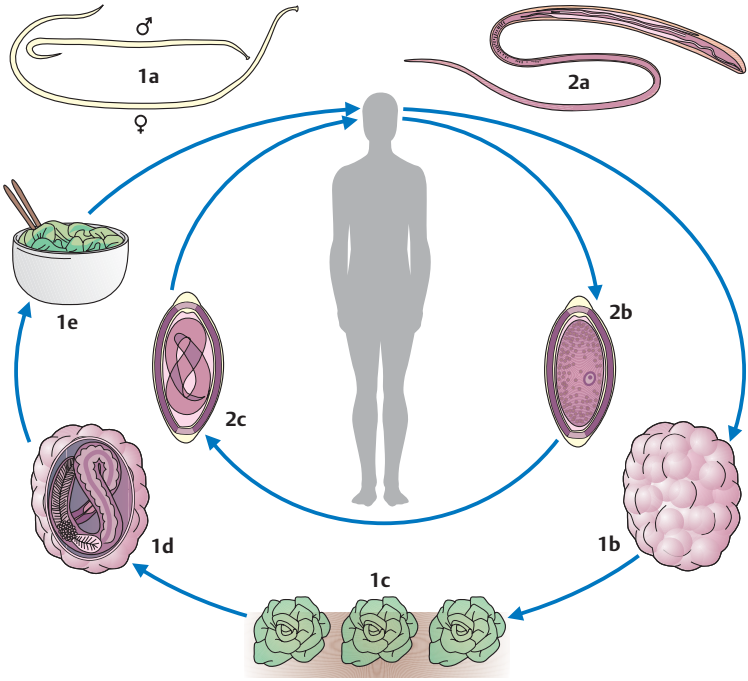


Fig. 10.**13** **1a** Adult stages of *A. lumbricoides*; **1b** freshly shed egg, not yet infective; **1c** contamination of vegetables with eggs; **1d** infective egg with larva; **1e** ingestion of infective eggs with contaminated food. **2a** Adult stage of *T. trichiura*; **2b** freshly shed egg, not yet infective; **2c** infective egg with larva. (The transmission routes of *T. trichiura* are similar to those of *Ascaris*.)

tling and prominence of peribronchial regions in radiographs (Löffler syndrome). Blood eosinophilia is often concurrently observed. This syndrome may be accompanied by coughing, dyspnea, and mild fever. During the **intestinal phase** of the infection, only some patients develop distinct clinical symptoms: abdominal discomfort with nausea, vomiting, pains, and diarrhea. Ascarids sometimes also migrate into the stomach, the pancreatic duct or the bile ducts and cause symptoms accordingly. Infection or frequent contact with volatile *Ascaris* antigens (laboratory staff!) can cause allergies.

Diagnosis. An infection with sexually mature roundworms can be diagnosed by finding eggs in the stool (Figs 10.**1** and 10.**13**). Migrating *Ascaris* larvae can be indirectly detected by means of serological antibody detection (especially specific IgE), but this technique is seldom used in practice.

Therapy and control. Pyrantel, mebendazole, albendazole, and nitazoxanide are highly effective against the intestinal stages of *Ascaris*. Migratory stages are not affected by normal dosage levels. Due to the possibility of reinvasion of the intestine by larvae migrating in the body, the treatment should be repeated after two to three weeks. Preventive measures include sewage disposal, improvement of sanitation, good food hygiene practices (washing fruits and vegetables, cooking foods, etc.) and regular anthelminthic treatment of infected persons in endemic areas (see also filariosis, p. 593).

Trichuris trichiura (Whipworm)

Causative agent of trichuriosis

Occurrence. *Trichuris trichiura* occurs in humans and monkeys. Although this parasite has a worldwide distribution, it is found most frequently, like *Ascaris lumbricoides*, in moist, warm areas with low hygienic standards (prevalence around 2–90%). The number of infected persons worldwide is estimated at one billion (WHO, 1998).

Parasite, life cycle, and epidemiology (Fig. 10.**13**). The name whipworm characterizes the form of this 3–5 cm long nematode with a very thin anterior part reminiscent of a whiplash and a thicker posterior "handle." The adult nematodes live in the large intestine, mainly in the cecum. The females lay 2000–14 000 thick-shelled, yellow-brown eggs per day. The eggs are about 50–55 µm long and are readily identified by their lemonlike shape and hyaline polar plugs (Fig. 10.**1**, p. 544). An infective larva develops in the egg within a few weeks. In moist surroundings, *Trichuris* eggs remain viable for months or even years.

Following peroral ingestion of infective eggs, the larvae hatch in the digestive tract, migrate into the mucosa, and return to the intestinal lumen after a histotropic phase lasting about 10 days. There the adult stages develop and remain with their slender anterior ends anchored in the mucosa. The prepatent period is two and a half to three months, the parasite can live for several years.

A moist, warm climate and unhygienic practices favor infections, which are contracted as described for *Ascaris*.

Pathogenesis and clinical manifestations. The whipworms, with their thin anterior ends anchored in the mucosa, ingest blood. Mild infections are asymptomatic. More severe infections, with hundreds or several thousand whipworms, cause catarrhal or hemorrhagic inflammations of the large intestine.

Diagnosis, therapy, and control. A *Trichuris* infection is diagnosed by detecting eggs in stool (Fig. 10.**1**, p. 544). Effective drugs include albendazole, mebendazole, and oxantel. See ascariosis for appropriate prevention and control measures.

Ancylostoma and Necator (Hookworms)

Causative agents of ancylostomosis and necatorosis (hookworm infection)

Parasites. *Ancylostoma duodenale* and *Necator americanus* are common parasites of the human small intestine, causing enteritis and anemia. Infection is mainly by the percutaneous route. The dog parasite *Ancylostoma caninum* has been identified as the cause of eosinophilic enteritis in humans. Larvae of various hookworm species from dogs and other carnivores can penetrate into human skin, causing the clinical picture of "cutaneous larva migrans" (p. 602).

Occurrence. Human hookworm infections are most frequent in the subtropics and tropics (for instance in southern Europe, Africa, Asia, southern US, Central and South America). The number of persons infected worldwide is estimated at about 1.25 billion (WHO, 1998). In central Europe, hookworm infections are seen mainly in travelers returning from the tropics or in guest workers from southern countries.

Morphology, life cycle, and epidemiology (Fig. 10.**14**). The hookworms that parasitize humans are 0.7–1.8 cm long with the anterior end bent dorsally in a hooklike shape (*ankylos*: bent, *stoma*: mouth, *necator*: killer). The entrance to the large buccal capsule is armed with toothlike structures (*Ancylostoma*) or cutting plates (*Necator*). The thin-shelled, oval eggs (about 60 µm long) containing only a small number of blastomeres are shed with feces. In one

to two days the first-stage larvae leave the eggshells, molt twice, and develop into infective third-stage larvae. Since the shed second-stage cuticle is not entirely removed, the third-stage larva is covered by a special "sheath." Larvae in this stage are sensitive to dryness. In moist soil or water they remain viable for about one month. Higher temperatures (optimum: 20–30 °C) and sufficient moisture favor the development of the parasite stages outside of a host.

Humans are infected mainly by the percutaneous route. Factors favoring infection include working in rice paddies, walking barefoot on contaminated

Life Cycles of Hookworms

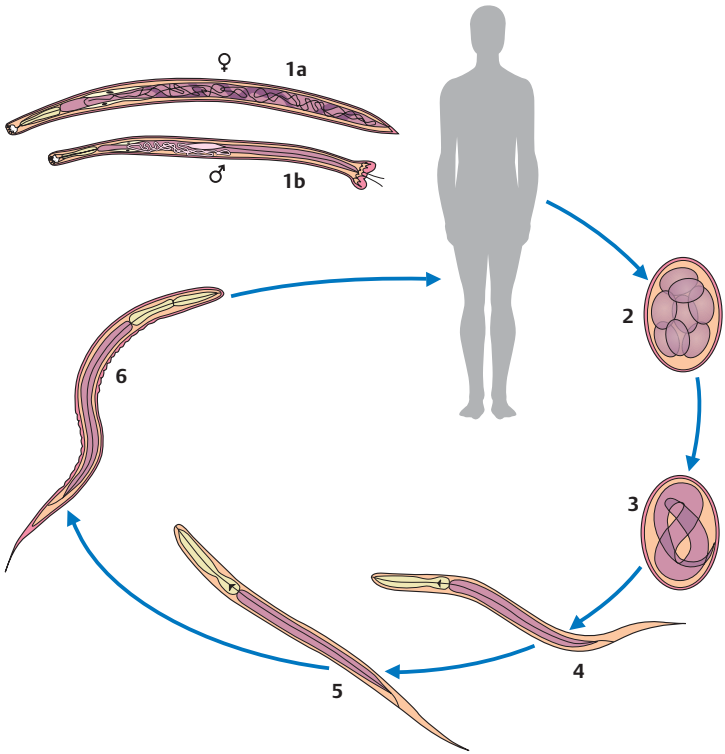


Fig. 10.**14** **1** Female and male hookworms; **2** hookworm egg shed in stool with blastomeres; **3** development of first-stage larva (L1) in egg; **4** hatched L1 larva; **5** L2 larva; **6** L3 larva with sheath, infective stage.

soil, etc. While penetrating the skin the larvae shed their sheaths and migrate into lymphatic and blood vessels. Once in the bloodstream, they migrate via the right ventricle of the heart and by tracheal migration (conf. *Ascaris*) into the small intestine, where they develop to sexual maturity. The prepatent period lasts five to seven weeks or longer (reason: arrested larval development). Following oral infection, immediate development in the intestine is probably possible (i.e., without the otherwise necessary migration through various organs). The parasites can survive in the human gut for one to 15 years.

Clinical manifestations. Hookworms are bloodsuckers. The buccal capsule damages the mucosa and induces inflammatory reactions. The intestinal tissue damage results in diarrhea with bloody admixtures, steatorrhea, loss of appetite, nausea, flatulence, and abdominal pains. General symptoms include iron deficiency anemia due to constant blood loss, edemas caused by albumin losses and weight loss due to reduced food uptake and malabsorption. Blood eosinophilia is often present. Mild infections cause little of clinical note.

Diagnosis. Diagnosis relies on finding of eggs in stool samples. The eggs are thin-shelled and oval; when fresh they contain only two to eight blastomeres (Figs. 10.**1** and 10.**14**). The eggs in older stool samples have already developed a larger number of blastomeres and cannot longer be differentiated from the eggs of the rare trichostrongylid species (*Trichostrongylus* etc.). In such a case, a fecal culture must be prepared in which third-stage larvae develop showing features for a differential diagnosis. Some infected persons produce detectable serum antibodies.

Therapy and control. Drugs effective against hookworms are pyrantel, mebendazole, and albendazole. Practicable preventive and control measures include mass chemotherapy of the population in endemic regions, reduction of dissemination of hookworm eggs by adequate disposal of fecal matter and sewage, and reduction of percutaneous infection by use of properly protective footwear (see also filariosis, p. 593).

10

Strongyloides

Strongyloides stercoralis and S. fuelleborni (Dwarf Threadworms)

Causative agents of strongyloidosis

Parasites and occurrence. *Strongyloides stercoralis*, which parasitizes humans, dogs, and monkeys, occurs mainly in moist, warm climatic zones, and more rarely in temperate zones (e.g., southern and eastern Europe). About 50–100 million persons are infected worldwide (WHO, 1995). *Stron-*

gyloides fuelleborni is mainly a parasite of African monkeys, but is also found in humans.

Morphology, life cycle, and epidemiology (Fig. 10.**15**). Only *Strongyloides* females are parasitic. They are 2–3 mm long and live in the small intestine epithelium, where they produce their eggs by parthenogenesis. During the intestinal passage first-stage larvae (0.2–0.3 mm long) hatch from the eggs and are shed in stool (whereas eggs are shed in *S. fuelleborni* infections). Within a few days first-stage larvae develop into infective third-stage larvae.

***Strongyloides stercoralis:* Life Cycle**

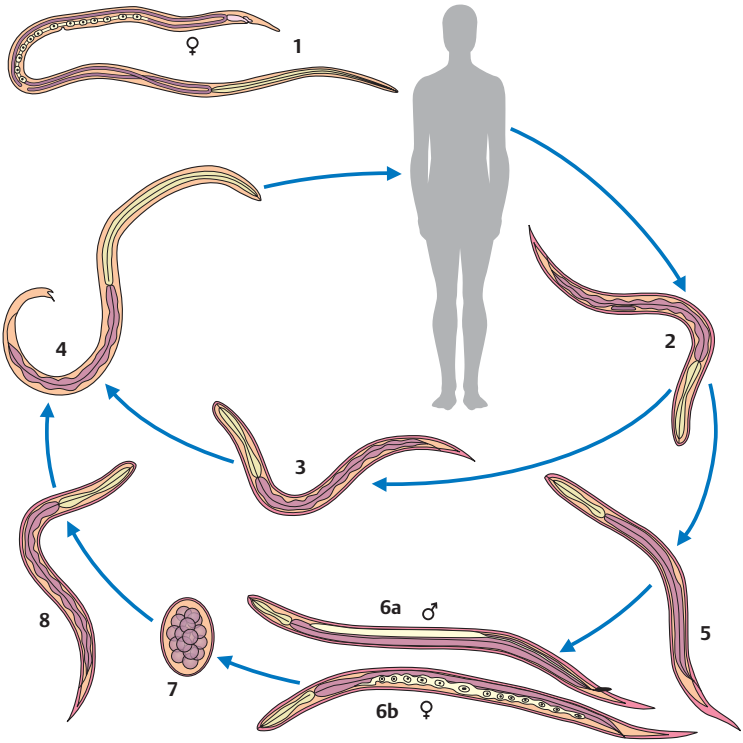


Fig. 10.**15** **1** Female *Strongyloides* from the small intestine; **2** first-stage larva (L1) shed in stool; **3** L2 larva; **4** infective L3 larva; **5** development of L1 larva to adult stages including four moltings (**6**); **6a** free-living male (not host-bound); **6b** free-living female; **7** egg of free-living generation; **8** larva hatched from egg, develops into infective larva including two moltings.

Given certain conditions, the first-stage larvae can develop into a free-living (nonparasitic) generation of males and females. The fertilized eggs laid by the females of this generation develop into infective third-stage larvae. This capacity for exogenous reproduction explains the enormous potential for contamination of a given environment with *Strongyloides* larvae. Third-stage larvae are highly sensitive to desiccation, but remain viable for two to three weeks in the presence of sufficient moisture.

The parasitic part of the life cycle is similar to that of the hookworms in that *Strongyloides* also penetrate the host's skin and the larvae reach their target localization in the small intestine by way of lung and tracheal migration. The prepatent period is at least 17 days. *Strongyloides* larvae can also be occasionally transmitted via mother's milk.

The potential for autoinfection with this organism is worthy of mention. The first-stage larvae can transform into infectious larvae during the intestinal passage or in the anal cleft and penetrate into the body through the large intestine or perianal skin. Continuous autoinfection can maintain an unnoticed infection in an immunocompetent person for many years (see below).

Humans are the main reservoir hosts of *S. stercoralis*; infections can also be transmitted from monkeys or dogs, but this route of infection is insignificant.

Pathogenesis and clinical manifestations

■ **Skin lesions** are observed when the larvae of *Strongyloides* species penetrate the skin, in particular in sensitized persons. Larvae of *Strongyloides* species from animals can cause "cutaneous larva migrans" (p. 602).

■ In the **lungs**, the migrating larvae provoke hemorrhages and inflammatory reactions that manifest clinically as pneumonic symptoms and coughing.

■ During the **intestinal phase**, heavy *Strongyloides* infections cause catarrhal, edematous, or ulcerative forms of enteritis as well as colitis.

■ **Systemic infection**. A *Strongyloides* infection can persist in a latent state for many years due to continuous autoinfection. If immune defense is compromised, for instance by AIDS or immunosuppressive therapy, parasite reproduction can be stimulated, resulting in massive systemic infections (hyperinfections) in which *Strongyloides* larvae are found in the walls of the colon and mesenteric vessels, in the bile ducts and in other organs. In such cases sexually mature female worms are also found in the lungs, and less frequently in other organs as well. A broad spectrum of symptoms is associated with systemic infection.

Diagnosis. Larvae (Fig. 10.**1**, p. 544) of *S. stercoralis* can be detected in fecal samples with the Baermann method and/or larval culture in about 60–70% of infected persons (egg detection with flotation technique for *S. fuelleborni*). Better results can be expected if duodenal fluid is examined.

Serum antibodies are present in about 85% of immunocompetent persons with *S. stercoralis* larvae in their stools (Table 11.**5**, p. 626). In infections with other helminths, especially filariae, cross-reactions occur that can be avoided by using recombinant proteins as antigens in the ELISA.

Therapy and prevention. The main drugs used for therapy are albendazole, mebendazole, and more recently ivermectin. Preventive measures resemble those taken to prevent hookworm infections. Travelers returning from tropical countries should be thoroughly examined for *Strongyloides* infections before any immunosuppressive measures are initiated (e.g., for a kidney transplantation).

Enterobius

Enterobius vermicularis (Pinworm)

Causative agent of enterobiosis (oxyuriosis)

Occurrence. The pinworm occurs in all parts of the world and is also a frequent parasite in temperate climate zones and developed countries. The age groups most frequently infected are five- to nine-year-old children and adults between 30 and 50 years of age.

Parasite, life cycle, and epidemiology. *Enterobius vermicularis* which belongs to the Oxyurida has a conspicuous white color. The males are 2–5 mm long, the females 8–13 mm. The long, pointed tail of the female gives the pinworm its name.

Sexually mature pinworms live on the mucosa of the large intestine and lower small intestine. Following copulation, the males soon die off. The females migrate to the anus, usually passing through the sphincter at night, then move about on the perianal skin, whereby each female lays about 10 000 eggs covered with a sticky proteinaceous layer enabling them to adhere to the skin. In severe infections, numerous living pinworms are often shed in stool and are easily recognizable as motile worms on the surface of the feces.

The eggs (about 50 × 30 µm in size) are slightly asymmetrical, ellipsoidal with thin shells (Fig. 10.**1**, p. 544). With their sticky surface they adhere to skin and other objects. Freshly laid eggs contain an embryo that develops into an infective first-stage larva at skin temperature in about two days. Eggs that become detached from the skin remain viable for two to three weeks in a moist environment.

Infection occurs mainly by peroral uptake of eggs (each containing an infective larva) that are transmitted to the mouth with the fingers from the anal region or from various objects. The sticky eggs adhere to toys and items of

everyday use or are disseminated with dust. In the intestinal tract, larvae hatch from the ingested eggs, molt repeatedly, and develop into sexually mature pinworms in five to six weeks. "Retroinfection" is also conceivable, whereby infective larvae would be released at the anus to migrate back into the intestine.

Pathogenesis and clinical manifestations. The pinworms living on the large intestine mucosa are fairly harmless. Occasionally, different stages of the pinworm penetrate into the wall of the large intestine and the appendix or migrate into the vagina, uterus, fallopian tubes, and the abdominal cavity, where they cause inflammatory reactions.

The females of *Enterobius* produce in particular a very strong pruritus that may result in nervous disorders, developmental retardation, loss of weight and appetite, and other nonspecific symptoms. Scratch lesions and eczematous changes are produced in the anal area and can even spread to cover the entire skin.

Diagnosis. A tentative diagnosis based on clinical symptoms can be confirmed by detection of pinworms spontaneously excreted with feces and eggs adhering to the perianal skin (Fig. 10.**1**). Standard stool examination techniques are not sufficient to find the eggs. Egg detection by the "adhesive tape method" has proved most efficient (p. 622).

Therapy and prevention. The following drugs are effective: albendazole, mebendazole, and pyrantel. Reinfections are frequent, so that treatment usually should be repeated once or more times, extended to include all potential parasite carriers (e.g., family members, kindergarten members), and combined with measures, the purpose of which is to prevent egg dissemination: washing the perianal skin (especially in the morning), covering it with ointments, washing the hands, hot laundering of underwear, and cleaning contaminated objects with hot water.

Nematodal Infections of Tissues and the Vascular System

Filarial nematodes, the Medina worm, and *Trichinella* are discussed in this section along with infections caused by the larvae of various nematode species.

Filarioidea (Filariae)

Causative agents of filarioses

The nematode genera of the superfamily Filarioidea (order Spirurida) will be subsumed here under the collective term filariae, and the diseases they cause are designated as filarioses. In the life cycle of filariae infecting humans, insects (mosquitoes, blackflies, flies etc.) function as intermediate hosts and vectors. Filarioses are endemic in subtropical and tropical regions; in other regions they are observed as occasional imported cases. The most important filariosis is onchocercosis, the causative agents of which, *Onchocerca volvulus*, is transmitted by blackflies. Microfilariae of this species can cause severe skin lesions and eye damage, even blindness. Diagnosis of onchocercosis is based on clinical symptoms, detection of microfilariae in the skin and eyes, as well as on serum antibody detection. Other forms of filarioses include lymphatic filariosis (causative agent: *Wuchereria bancrofti*, *Brugia* species) and loaosis (causative agent: *Loa loa*). *Dirofilaria* species from animals can cause lung and skin lesions in humans (see p. 605).

General. Filariae are threadlike (*filum*: thread) nematodes. The length of the adult stages (= macrofilariae) of the species that infect humans varies between 2–50 cm, whereby the females are larger than the males. The females release embryonated eggs or larvae called microfilariae. These are about 0.2–0.3 mm long, snakelike stages still surrounded by an extended eggshell (sheathed microfilariae) or they hatch out of it (unsheathed microfilariae) (Fig. 10.**17** p. 592). They can be detected mainly in the skin or in blood (Table 10.**4**).

Based on the periodic appearance of microfilariae in peripheral blood, periodic filaria species are differentiated from the nonperiodic ones showing continuous presence. The periodic species produce maximum microfilaria densities either at night (nocturnal periodic) or during the day (diurnal periodic). Different insect species, active during the day or night, function as intermediate hosts accordingly to match these changing levels of microfilaremia.

Life Cycle of Filariae

Insect: → Ingestion of microfilaria with a blood meal → development in thoracic musculature with two moltings to become infective larva → migration to mouth parts and tranmission into skin of a new host through puncture wound during the next blood meal.

Human: → Migration to definitive localizations and further development with two more moltings to reach sexual maturity.

Wuchereria bancrofti and Brugia species

Causative agents of lymphatic filariosis

Parasites and occurrence. About 120 million people in 80 countries suffer from lymphatic filariosis caused by *Wuchereria bancrofti* or *Brugia* species (one-third each in India and Africa, the rest in southern Asia, the Pacific region, and South America), and 1.1 billion people are at infection risk (WHO, 2000). (Table 10.**4**). Humans are the only natural final hosts of *W. bancrofti* and the most widely disseminated *Brugia* strains. There are, however, other *Brugia* strains using also animals as final hosts (cats, dogs, and monkeys).

Life cycle and epidemiology. The intermediate hosts of *W. bancrofti* and *B. malayi* are various diurnal or nocturnal mosquito genera (Table 10.**4**). The development of infective larvae in the insects is only possible at high environmental temperatures and humidity levels; in *Wuchereria bancrofti* the process takes about 12 days at 28 °C. Following a primary human infection, the filariae migrate into lymphatic vessels where they develop to sexual maturity. Microfilariae (Mf) do not appear in the blood until after three months at the earliest (*B. malayi*, *B. timori*) or after seven to eight months (*W. bancrofti*). Tables 10.**4** and Fig. 10.**17** show their specific characteristics. The adult parasites survive for several years.

Pathogenesis and clinical manifestations. The pathologies caused by *W. bancrofti* and *Brugia* species are very similar. The initial symptoms can appear as early as one month p.i. although in most cases the incubation period is five to 12 months or much longer. The different courses taken by such infections can be summarized as follows:

- **Asymptomatic infection**, but with microfilaremia that can persist for years.
- **Acute symptomatic infection:** inflammatory and allergic reactions in the lymphatic system caused by filariae → swelling of lymph nodes, lymphangitis, intermittent recurrent febrile episodes, general malaise, swellings on legs, arms, scrotum and mammae, funiculitis, orchitis.

Table 10.**4** Filarial Species Commonly Infecting Humans

Species and length (cm)	Distribution	Vector	Localization of adults	Microfilariae: characteristics and periodicity	Pathology
Wuchereria bancrofti ♂♂: 2.4–4.0 ♀♀: 5.0–10.0	Southeast Asia, Pacific, trop. Africa, Caribbean, trop. South America	**Mosquitoes:** *Culex*, *Anopheles*, *Aedes*	Lymphatic system	244–296 µm, sheathed, in blood, nocturnal, diurnal or subperiodic[2]	Lymphangitis and lymphadenitis, elephantiasis
Brugia malayi ♂♂: 2.2–2.5 ♀♀: 4.3–6.0	South and East Asia	**Mosquitoes:** *Anopheles*, *Aedes*, *Mansonia*	Lymphatic system	177–230 µm, sheathed, in blood, nocturnal or subperiodic	Lymphangitis and lymphadenitis, elephantiasis
Brugia timori	Indonesia	**Mosquitoes:** *Anopheles*		Nocturnal periodic	
Loa loa ♂♂: 3.3–3.4 ♀♀: 5.0–7.0	Tropical Africa	**Flies:** *Chrysops*	Subcutaneous connective tissue	250–300 µm, sheathed, in blood, diurnal periodic	Skin swellings, infection of conjunctiva
Onchocerca volvulus ♂♂: 2.0–4.5 ♀♀: 23–50	Africa, Central and South America	**Black flies:** *Simulium*	Subcutaneous connective tissue	221–358 µm, unsheathed, in skin, not periodic	Skin nodules, dermatitis, eye lesions
Mansonella perstans ♂♂: 4.5 ♀♀: 7.0–8.0	Africa, South America	**Midges**: *Culicoides*	Peritoneal and pleural cavities	190–200 µm, unsheathed, in blood, nocturnal subperiodic	Normally apathogenic
Mansonella streptocerca ♂♂:[3] ♀[3]	Tropical Africa	**Midges:** *Culicoides*	Subcutaneous connective tissue	180–240 µm, unsheathed, in skin, not periodic	Skin edema, dermatitis
Mansonella ozzardi ♂♂:[3] ♀♀: 6.5–8.1	Central and South America	**Midges:** *Culicoides*	Peritoneal cavity	173–240 µm, unsheathed, in blood (not periodic)	Normally apathogenic

[1] See Fig. 10.**1** for details on differentiation of microfilariae.
[2] Subperiodic: periodicity is not pronounced.
[3] No exact data are available.

■ **Chronic symptomatic infection:** chronic obstructive changes in the lymphatic system → hindrance or blockage of the flow of lymph and dilatation of the lymphatic vessels ("lymphatic varices") → indurated swellings caused by connective tissue proliferation in lymph nodes, extremities (especially the legs, "elephantiasis"), the scrotum, etc., thickened skin (Fig. 10.**16**). Lymphuria, chyluria, chylocele etc. when lymph vessels rupture. This clinical picture develops gradually in indigenous inhabitants over a period of 10–15 years after the acute phase, in immigrants usually faster.

■ **Tropical, pulmonary eosinophilia:** syndrome with coughing, asthmatic pulmonary symptoms, high-level blood eosinophilia, lymph node swelling and high concentrations of serum antibodies (including IgE) to filarial antigens. No microfilariae are detectable in blood, but sometimes in the lymph nodes and lungs. This is an allergic reaction to filarial antigens.

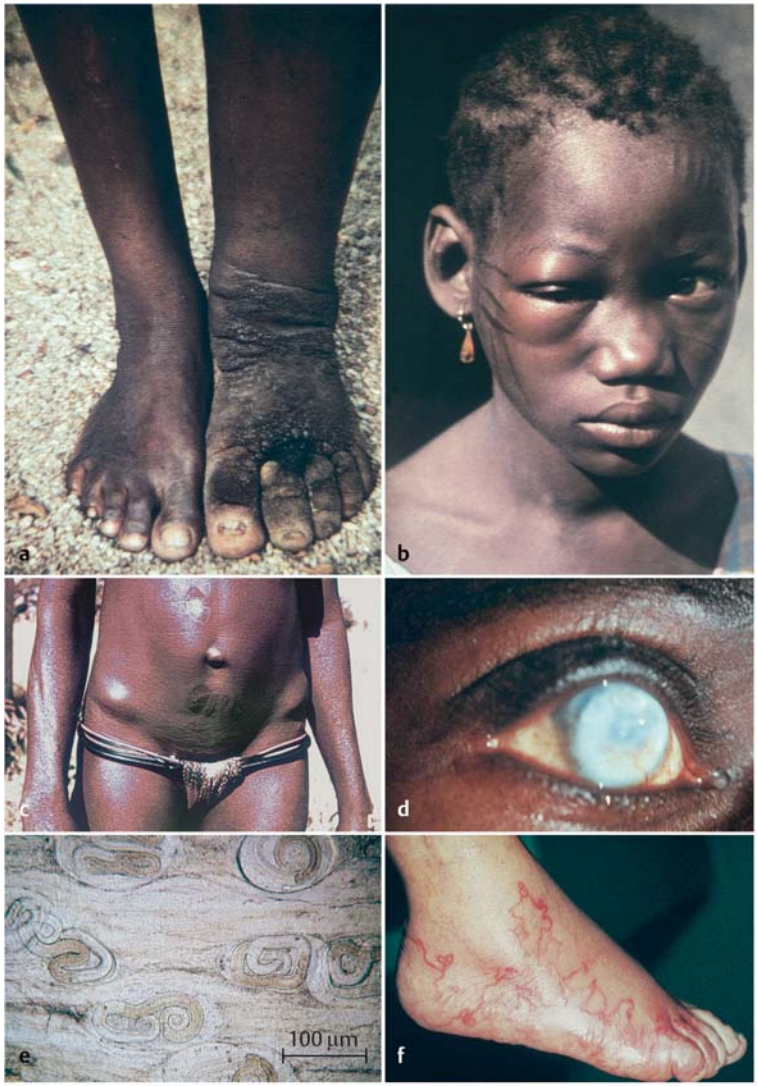
Diagnosis. A diagnosis can be based on clinical symptoms (frequent eosinophilia!) and finding of microfilariae in blood (blood sampling at night for nocturnal periodic species!). Microfilariae of the various species can be differentiated morphologically in stained blood smears (Table 10.**4**, Fig. 10.**17**) and by DNA analysis. Conglomerations of adult worms are detectable by ultrasonography, particularly in the male scrotal area. Detection of serum antibodies (group-specific antibodies, specific IgE and IgG subclasses) and circulating antigens are further diagnostic tools (Table 11.**5**, p. 625). The recent development of a specific ELISA and a simple quick test (the ICT filariosis card test) represents a genuine diagnostic progress due to the high levels of sensitivity and specificity with which circulating filarial antigens can now be detected, even in "occult" infections in which microfilariae are not found in the blood.

Therapy. Both albendazole and diethylcarbamazine have been shown to be at least partially effective against adult filarial stages. However, optimal treatment regimens still need to be defined. Adjunctive measures against bacterial and fungal superinfection can significantly reduce pathology and suffering.

Control and prevention. In 1997, the WHO initiated a program to eradicate lymphatic filariosis. The mainstay control measure is mass treatment of populations in endemic areas with microfilaricides. Concurrent single doses of two active substances (albendazole with either diethylcarbamazine or iver-

Fig. 10.**16** **a** Infection with *Wuchereria bancrofti*: elephantiasis; **b** infection with *Loa loa*: eyelid swelling; **c** onchocercosis: cutaneous nodules caused by *Onchocerca volvulus*; **d** blindness caused by *O. volvulus*; **e** *Trichinella spiralis*; larvae in rat musculature; **f** larva migrans externa. (Images a, b, d: *Tropeninstitut Tübingen*, c: *Tropeninstitut Amsterdam*; f: *Dermatologische Klinik der Universität Zürich*.) ▶

Nematode Infections



Microfilariae of Various Filarial Species

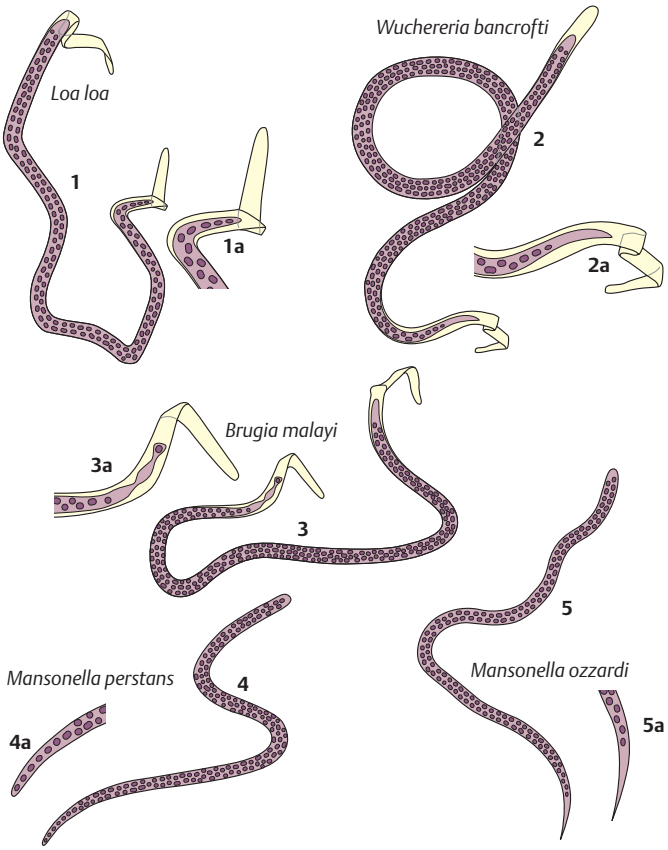


Fig. 10.**17** Differential diagnosis of microfilariae in human blood: sheathed, large: **1** *Loa loa*: tip of tail (**1a**) with several nuclei; **2** *Wuchereria bancrofti*: tip of tail (**2a**) without nuclei; **3** *Brugia malayi*: tip of tail (**3a**) with single nucleus. Unsheathed, smaller: **4** *Mansonella perstans*: tip of tail (**4a**) rounded with densely packed nuclei, often in several rows reaching nearly to the tip of the tail; **5** *Mansonella ozzardi*: tip of tail (**5a**) pointed, tip free of nuclei.

mectin) are 99% effective in removing microfilariae from the blood for one year after treatment. Mass-treatment with albendazole or ivermectin is also expected to have a controlling effect on intestinal nematodes (*Ascaris*, hookworms, *Strongyloides*, *Trichuris*). Measures to avoid mosquito bites are the same as for malaria.

Loa

Loa loa

Causative agent of loaosis (loiasis, *Loa loa* filariosis, African eyeworm)

Occurrence, life cycle, and epidemiology. Thirteen million people are infected with this filarial species in the tropical rainforest areas of Africa (western and central Africa, parts of Sudan) (WHO, 1995).

The adult and pre-adult parasites (Table 10.**4**) live in and migrate through the subcutaneous connective tissues. The microfilariae appear in a periodic pattern during the day in peripheral blood (Table 10.**4**, Fig. 10.**17**). Accordingly, the intermediate hosts are diurnally active horsefly species (Tabanidae: *Chrysops* species). The prepatent period is five to six months. In some cases, microfilariae do not appear in the blood even in older cases of infection. The adult filariae live for several years.

Pathogenesis and clinical manifestations. Clinical symptoms can occur two to 12 months after the infection. They are probably mainly allergic in nature. The filariae migrating through the connective tissues cause edematous swellings in the limbs, face, and body ("Calabar swellings") and itching nodules (Fig. 10.**16b**). The infection is often accompanied by blood eosinophilia. Migration of a parasite beneath the conjunctiva causes lacrimation, erythema, and other symptoms.

Diagnosis, therapy, and prevention. Diagnosis involves observation of typical symptoms, adult parasites in subcutis or conjunctiva and microfilariae in peripheral blood (in blood specimens sampled during the day!) (Table 10.**4**, Fig. 10.**17**). The drug of choice is diethylcarbamazine that kills microfilariae and damages macrofilariae after long-term therapy (N.B.: possible side effects).

Mansonella species

See Table 10.**4** and Fig. 10.**17** for *Mansonella* species that should be taken into account in differential diagnostic procedures.

Onchocerca

Onchocerca volvulus

Causative agent of onchocercosis

This filarial species causes onchocercosis, a disease that manifests mainly in the form of skin alterations, lymphadenopathy, and eye damage, which latter is the reason for the special importance of the disease.

Occurrence. *Onchocerca volvulus* is endemic in 30 countries in tropical Africa (from the Atlantic coast to the Red Sea) and southern Arabia (Yemen) as well as in six countries in Central and South America (Mexico, Guatemala, Columbia, Venezuela, Brazil, Ecuador). About 17.6 million persons are currently infected and 267 000 are blind due to onchocercosis (WHO, 1998, 2000). The WHO has been coordinating successful control programs in 11 African countries since 1974, and in six Latin American countries since 1991 (see below).

Life cycle. The adult *Onchocerca* live in the connective and fatty tissues, usually tightly coiled in connective tissue nodules in the subcutis or deeper tissue layers (Fig. 10.**16c**). Sexually mature parasites can live as long as 15 years.

Female *Onchocerca* produce microfilariae that live in the tissue within the nodules or skin. Starting from the site of the female worms, the microfilariae migrate through the deep corium of the dermis into other skin regions and can also affect the eyes—especially if the nodule is located on the head or upper body. Through the lymphatics, the microfilariae can penetrate into the bloodstream and also appear in urine, sputum, and cerebrospinal fluid. The relatively large microfilariae have no sheath (Table 10.**4**); their lifespan in human hosts is from six to 30 months.

Simuliidae (blackflies) are the intermediate hosts and vectors. The development of the infective larvae, transmitted by a blackfly to a human host, takes many months before the nematodes reach sexual maturity. Microfilariae are usually be detected in skin after 12–15 months (seven to 24 months) (prepatent period).

Epidemiology. Humans are the sole parasite reservoir of *O. volvulus*. Onchocercosis occurs in endemic foci along the rivers in which the larvae and pupae of the blackflies develop. Therefore, the blindness caused by onchocercosis is designated as “river blindness.”

Pathogenesis and clinical manifestations. Pathological reactions are provoked by adult parasites and by microfilariae. These reactions are influenced by the immune status of infected individuals.

■ **Reactions to adult parasites:** enclosure of adult filariae in fibrous nodules (onchocercomas), usually 0.5–2 cm (sometimes up to 6 cm) in diameter in the subcutis along the iliac crest, ribs, scalp, etc., more rarely in deeper tissues. Nodulation occurs about one to two years after infection and is either asymptomatic or causes only mild symptoms (Fig. 10.**16c**).

■ **Reactions to microfilariae:** microfilariae appear in the skin about 12–15 (seven to 24 months p.i.). Initial symptoms occur after about 15–18 months: for example, pruritus, loss of skin elasticity with drooping skin folds, papules, depigmentation, and swelling of lymph nodes; blood eosinophilia may also be present.

■ **Eye changes:** "snowflake" corneal opacities, in later stage sclerosing keratitis, the main cause of blindness, chorioretinitis and ocular nerve atrophy; tendency toward bilateral damage (Fig. 10.**16d**).

Diagnosis

■ **Adult parasites.** Onchocercomas can be identified by palpation and ultrasonic imaging. Presence of the parasites can be confirmed by surgical removal and examination of the cutaneous nodules.

■ **Microfilariae** can be found in skin snips after the prepatent period. A PCR is now available for species-specific detection of *Onchocerca* DNA (Oncho-150 repeat sequence) in skin specimens. Living or dead microfilariae can be seen in the anterior chamber of the eye with the help of a slit lamp or an ophthalmoscope. Various techniques and antigens (e.g., recombinant antigens) can also be used to detect serum antibodies (Table 11.**5**, p. 625).

Therapy. *Onchocerca* nodules can be removed surgically. Suramin—a quite toxic substance effective against macrofilariae—is now no longer used. It was recently discovered that *O. volvulus*, *Wuchereria bancrofti*, *Brugia* species, and several other filarial species contain endosymbionts of the genus *Wolbachia* (order Rickettsiales) that are transovarially transmitted from females to the following generation. Studies in animals and humans have shown that prolonged therapy with doxycyclin damages both the endosymbionts and the filariae. These results could lead to a new therapeutic approach. Ivermectin in low doses is highly effective against microfilariae (see prevention), and has some effect on macrofilariae in repeated higher doses.

Prevention and control. Protective clothing and application of repellents to the skin can provide some degree of protection from blackfly bites (see Malaria). WHO programs involving repeated applications of insecticides to streams and rivers with the aim of selective eradication of the developmental stages of *Simuliidae* in western Africa have produced impressive regional results. Mass treatment of the population in endemic areas with low-dose iver-

mectin (0.15 mg/kg of body weight) administered once or twice a year has been practiced since 1987. This can drastically reduce the microfilarial density in human skin for up to 12 months. Microfilariae in the eyes are also influenced. These measures prevent disease and reduce, or even interrupt parasite transmission. Simultaneous application of vector control measures and mass therapy with ivermectin has eliminated the parasite reservoir in the populations of seven of the 11 African countries participating in the above-mentioned control program (WHO, 2000). The manufacturer of ivermectin is providing the drug at no cost for the WHO-coordinated program. In further disease control campaigns, the vector control measures are to be stopped, but mass treatments with ivermectin or other potent drugs are to be continued once a year over the longer term (WHO, 2000).

Dracunculus medinensis (Medina or Guinea Worm)

Causative agent of dracunculosis (Medina or Guinea worm infection)

Male *Dracunculus medinensis* worms are 1–4 cm long, the females measure 50–100 cm in body length. Humans contract the disease by ingesting drinking water contaminated with intermediate hosts ("water fleas": fresh water crustacea, *Cyclops*) containing infective *Dracunculus* larvae. From the intestine the parasites migrate through the body, females and males mate in the connective tissue, and after approximately 10–12 months p.i. mature females eventually move to the surface of the skin of the legs and feet in 90 % of the cases. There, the female provokes an edema, a blister, and then an ulcer. Skin perforation is accompanied by pain, fever, and nausea; secondary bacterial infections occur in approx. 30 % of cases. When the wound contacts water, the female extends the anterior end out of it and releases numerous larvae. The larvae are ingested by intermediate hosts and develop into infective stages.

Diagnosis is usually based on the clinical manifestations.

The WHO has been running a control program since the early 1980s based mainly on education of the population and filtration of drinking water using simple cloth or nylon filters. Annual infection incidences have been reduced from three and a half million cases in 1986 to about 75 000 in 2000 (WHO, 2004). Dracunculosis now still occurs in 14 sub-Saharan African countries, but has been officially declared eliminated in some formerly endemic countries (including India, Pakistan, and some African countries). Approximately 73 % of all cases are currently reported from Sudan.

Trichinella

Causative agent of trichinellosis

Humans can acquire an infection with larvae of various *Trichinella* species by ingesting raw meat (from pigs, wild boars, horses, and other species). Adult stages develop from the larvae and inhabit the small intestine, where the females produce larvae that migrate through the lymphatics and bloodstream into skeletal musculature, penetrate into muscle cells and encyst (with the exception of *Trichinella pseudospiralis* and some other species which does not encyst). Clinical manifestations of trichinellosis are characterized by intestinal and muscular symptoms. Diagnosis requires muscle biopsies and serum antibody detection.

Parasite species and occurrence. Eight *Trichinella* species and several strains have been described to date based on typical enzyme patterns, DNA sequences, and biological characteristics. The areas of distribution are listed in Table 10.**5**; several *Trichinella* species occur sympatrically, i.e., in the same geographic region (Table 10.**5**).

The most widespread and most important species is *Trichinella spiralis*, which develops mainly in a synanthropic cycle. Despite the generally low prevalence of *Trichinella* in Europe, a number of outbreaks have occurred since 1975 (e.g., in Germany, France, Italy, Spain, England, and Poland) affecting groups of persons of various sizes (the largest about 650). Worldwide, the annual incidences per 100 000 inhabitants (1991–2000) have varied widely, for example between 0.01 in Germany and the USA, 5.1 in Lithuania, and 11.4 in Bulgaria.

Morphology and life cycle (Fig. 10.**18**). Male *Trichinella spiralis* are approximately 1–2 mm long, the females 2–4 mm. A characteristic feature is the subdivided esophagus with a muscular anterior portion and a posterior part consisting of glandular cells ("stichocytes"). The other *Trichinella* species are of about the same length and do not show morphological differences, except *T. pseudospiralis*, *T. papuae*, and *Trichinella zimbabwensis* the muscle larvae of which do not encyst.

The life cycle described here refers to *T. spiralis*. Infection of humans and other hosts results from ingestion of raw or undercooked meat containing encysted *Trichinella* larvae (Fig. 10.**16e**). The larvae are released following exposure to the digestive juices, whereupon they invade epithelial cells in the small intestine, reaching sexual maturity within a few days after four moltings. The males soon die after copulation, the females live for about four to six weeks. Each female produces about 200–1500 larvae (each around 100 µm long), which penetrate into the lamina propria. The larvae disperse

Trichinella spiralis: Life Cycle

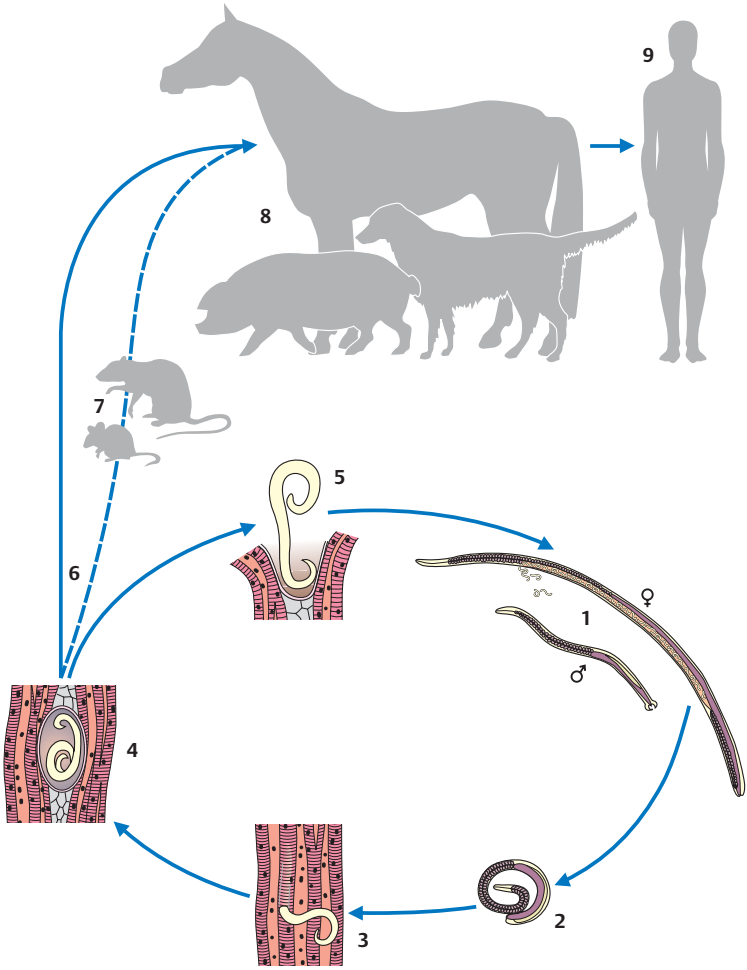


Fig. 10.**18** **1** Male and female in the small intestine of a host; **2** larvae produced by female; **3** larvae penetrating muscle cell; **4** larvae encapsulated in musculature; **5** release of larvae from capsule following peroral ingestion by host; **6** infection of hosts with muscle larvae; **7** rodent hosts; **8** domestic animal hosts; **9** transmission of parasites to humans with trichinellous meat.

into organs and body tissues by means of lymphogenous and hematogenous migration. Further development occurs only in striated muscle cells that they reach five to seven days p.i. at the earliest.

The larvae penetrate into muscle fibers, which are normally not destroyed in the process, but transformed into "nurse" cells providing a suitable environment for the parasite. The muscle cell begins to encapsulate the parasite about two weeks p.i. by depositing hyaline and fibrous material within the sarcolemma. Encapsulation is completed after four to six weeks. The capsules are about 0.2–0.9 mm long with an oval form resembling a lemon. Granulation tissue or fat cells form at the poles (Fig. 10.**16e**). The capsule may also gradually calcify beginning at the poles.

The *Trichinella* larvae at first lie stretched out straight within the muscle cell, but by the third week p.i. they roll up into a spiral form (not observed in *Trichinella pseudospiralis* and some other species, see Table 10.**5**). They differentiate further during this period to become infective. The encapsulated *Trichinella* remain viable for years in the host (demonstrated for up to 31 years in humans). The developmental cycle is completed when infectious muscle *Trichinella* are ingested by a new host.

Epidemiology. In many countries trichinellosis exists in natural foci with sylvatic cycles involving wild animals, in particular carnivores. Such cycles are known to occur in most of the *Trichinella* species but *T. spiralis* is predominantly perpetuated in a synanthropic cycle (Table 10.**5**). Humans can acquire the infection from sylvatic cycles by eating undercooked meat of wild boar, bear etc. containing infective *Trichinella* larvae. Sylvatic cycles may remain restricted to natural foci without spreading to domestic pigs or other domestic animals. This is apparently the case with *T. britovi* in Switzerland, for example. Human infections are most frequently derived from the synanthropic cycle of *T. spiralis*.

Encapsulated muscle larvae are very resistant. They remain infectious for at least four months in rotting meat. Cooled to 2–4 °C, they survive in musculature for 300 days. They are generally killed by deep-freezing to –25 °C within 10–20 days, although muscle larvae of the cold-resistant species *T. nativa* may remain infective for many months at –20 °C (Table 10.**5**). Heat is rapidly lethal, but the larvae can survive drying and pickling.

The sources of human infection are raw and insufficiently cooked or frozen meat products from domestic pigs and wild boars, horses, and less frequently from bears, dogs, and other animal species. Dried and pickled meat containing trichinellae can also be infective.

Clinical manifestations. The severity and duration of clinical manifestations depend on the infective dose and the rate of reproduction of the trichinellae. As few as 50–70 *T. spiralis* larvae can cause disease in humans. The pathogenicity of the other species is apparently lower. Infections run a two-phase course:

Table 10.5 *Trichinella* species

***Trichinella* species and distribution**	**Cycle[1] and important hosts (selection)**	**Characteristics of muscle larvae R: Resistance at –30 °C, 12 h**
T. spiralis Worldwide	*Mainly synanthropic, also sylvatic.* Domestic pig, rat, horse, wild boar, camel, dog, red fox, bear, humans	With capsule R: low
T. britovi Temperate zone of the palaearctic region	*Mainly sylvatic, also synanthropic.* Red fox, wolf, jackal, raccoon dog, wildcat, bears, badger, marten, rodents, domestic pig, wild boar, horse, humans	With capsule R: moderate
T. murrelli Temperate zone in North America (US)	*Sylvatic, also synanthropic.* Bear, raccoon, red fox, coyote, bobcat (*Felis rufus*), horse, humans	With capsule R: low
T. nativa Arctic and subarctic regions (north of the –6 °C January isotherm)	*Mainly sylvatic, also synanthropic.* Polar fox, red fox, polar bear, wolf, raccoon dog, jackal, dog, wild boar, humans	With capsule R: high
T. nelsoni Sub-Saharan Africa, Asia (Kazakhstan)	*Sylvatic.* Hyena, warthog, wild boar, domestic pig, humans	With capsule R: none
T. pseudospiralis Australia, India, Caucasus, Kazakhstan, US	*Sylvatic.* Quoll (Dasyuridae), raccoon, korsak (steppe fox), rodents, bird species, (birds of prey and others), humans	Without capsule R: none
Trichinella papuae Papua New Guinea	*Sylvatic.* Wild boar, domestic pig, humans	Without capsule R: ?
Trichinella zimbabwensis Zimbabwe	*Cycle in farmed crocodiles* Experimental hosts: pig, rat, monkey	Without capsule R: ?

[1] Animals involved: synanthropic cycle: animals living in proximity to human dwellings (domestic animals, rats etc.); sylvatic cycle: wild animals.

Intestinal phase: incubation period of one to seven days. Symptoms: nausea, vomiting, gastrointestinal disorders with diarrhea, mild fever, and other symptoms. An inapparent course is also possible.

Extraintestinal phase: incubation period of seven or more days. Symptoms caused by invasion of body tissues by *Trichinella* larvae: myositis with muscle pain and stiffness, respiratory and swallowing difficulties, fever, edemas on eyelids and face, cutaneous exanthema. Feared complications include mycocarditis and meningoencephalitis. Further characteristic features are blood eosinophilia, raised activity of serum lactate dehydrogenase, myokinase and creatine phosphokinase, and creatinuria. This phase lasts about one to six weeks. It is frequently followed by recovery, but rheumatoid and other symptoms can also persist (e.g., cardiac muscle damage). Lethal outcome is rare.

Diagnosis. Diagnosis during the intestinal phase is difficult and only rarely trichinellae can be found in stool or duodenal fluid. During the extraintestinal phase, *Trichinella* larvae are detectable in muscle biopsies (either by microscopy in press preparations, histologically or by PCR-based DNA detection). Beginning in the third week p.i. serum antibodies appear (Table 11.**5**, p. 626). Clinical chemistry (see above) furnishes further diagnostic data.

Therapy and prevention. The recommended drugs for therapy are mebendazole or albendazole in combination with prednisolone (to alleviate allergic and inflammatory reactions) (WHO, 1995). Heat exceeding 80 °C kills trichinellae in meat. The safest methods are to boil or fry the meat sufficiently (deep-freezing may be unreliable, see above!). Important disease control measures include prophylactic inspection of domestic and wild animal meat for *Trichinella* infection and not feeding raw meat wastes to pig livestock and other susceptible domestic animals.

Infections Caused by Nematodal Larvae

Larva migrans externa and Larva migrans *interna* are diseases caused by migrating nematode larvae. The first (*externa*) is a skin disease, usually caused by zoonotic hookworms or *Strongyloides* species. In the second type (*interna*), nematode larvae migrate into inner organs, e.g., in toxocarosis. In toxocarosis the infection results from peroral ingestion of infective eggs of roundworms of the genus *Toxocara* that are released to the environment in the feces of dogs, foxes, and cats (infection risk for children on contaminated playgrounds!). In humans, migrating *Toxocara* larvae can cause damage to liver, lungs, CNS, and eyes. Additional diseases caused by nematode larvae include anisakiosis, angiostrongylosis, and dirofilariosis.

Larva Migrans Externa or Cutaneous Larva Migrans (CLM) ("Creeping Eruption")

Parasites. CLM designates a syndrome caused by migration of larval parasites in the skin of accidental hosts. Hookworm species of dogs and cats (e.g., *Ancylostoma braziliense*, *Ancylostoma caninum*) and *Strongyloides* species of various hosts (mammalian animals, humans) are mainly responsible for human CLM. Other potential causative organisms include insect larvae (*Hypoderma*, *Gasterophilus*, etc.).

Clinical manifestations. The infective larvae of the above-mentioned hookworm species can penetrate human skin (feet, hands, other body regions) upon contact with contaminated soil (e.g., on bathing beaches) and migrate through the dermis. This results in papules, twisted and inflamed worm burrows, and pruritus (Fig. 10.**16f**). These larvae rarely penetrate further into the body and normally do not reach sexual maturity in the host (however, see also p. 580). The larvae persist in the skin for several weeks to months, and then they die (see p. 617 for causative insect larvae).

Diagnosis and therapy. The clinical presentation with many 1–2 mm wide and centimeter-long worm burrows usually suffices for a diagnosis. Recommended treatments include topical application of thiabendazole ointment (15%), wetting with ivermectin solution, spray-freezing with ethyl chloride and peroral therapy with albendazole or ivermectin.

Larva Migrans Interna or Visceral Larva Migrans (VLM)

Parasites. The main causative agents of this disease are the larvae of various roundworm species from domestic and wild animals, for instance *Toxocara canis* from dogs and foxes, *T. mystax* from cats, *Baylisascaris procyonis* from raccoons as well as roundworm species (Anisakidae) from marine mammals. Toxocarosis and anisakiosis are discussed here as examples from this group. Angiostrongyliosis and dirofilariosis can also be included in this disease category.

Toxocara

Causative agent of toxocarosis

Distribution, life cycle, and epidemiology. Dogs, cats, and foxes all over the world, especially younger animals, are frequently infected with adult *Toxocara* roundworms. The parasites live in the small intestine and in most cases produce large numbers of eggs. An infective larva develops in an egg shed into the environment within two to three weeks. Humans are infected by accidental peroral ingestion of infective eggs (geophagia, contaminated foods). Small children run a particularly high risk. Fairly high levels of contamination of public parks and playgrounds with *Toxocara* eggs (sandboxes >1–50%) have been found in many cities in Europe and elsewhere. Mean antibody prevalence levels of about 1–8% were measured in healthy persons in Germany, Austria, and Switzerland in serological screening based on a specific ELISA, with figures as high as 30% in some population subgroups.

After infection, the *Toxocara* larvae hatch from the eggshells in the small intestine, penetrate the intestinal wall, and migrate hematogenously into the liver, lungs, CNS, eyes, musculature, and other organ systems. Larvae caught in the capillary filter leave the vascular system and begin to migrate through the organ involved. This results in hemorrhages and tissue destruction as well as inflammatory reactions and formation of granulomatous foci. Living larvae are encapsulated in connective tissue in all organs except the CNS, but they can also leave the capsules and continue migrating. The larvae can live for a number of years (at least 10 years in monkeys). Development of adult *Toxocara* stages in the human intestine is a very rare occurrence.

Clinical manifestations. VLM remains inapparent in most cases. Symptomatic cases are most frequently observed in children aged two to five years. The clinical symptoms depend on the localization and degree of pathological changes and include nonspecific and varied conditions such as eosinophilia, leukocytosis, hepatomegaly, brief febrile episodes, mild gastrointestinal disorders, asthmatic attacks, pneumonic symptoms, lymphadenopathy, urticarial skin changes, central nervous disorders with paralyses, or epileptiform convulsions. Eye infections are seen in all age groups and present as granulomatous chorioretinitis, clouding of the vitreous body and other changes. Ocular toxocariosis is often observed without signs of visceral infection.

Diagnosis. Persistent eosinophilia and the other symptoms described above justify a tentative diagnosis. Etiological confirmation requires serological testing for specific antibodies. Highly sensitive and specific techniques are available (ELISA, Western blot) (Table 11.**5**, p. 625). Positive seroreactions can be expected four weeks after infection.

Therapy and prevention. Chemotherapy with albendazole is only indicated in symptomatic cases. Prophylactic measures include control of *Toxocara* infections in cats and dogs, especially in young animals, and reduction or prevention of environmental contamination with feces of dogs, cats, and foxes especially on children's playgrounds.

Anisakis

Causative agent of anisakiosis

Anisakis and related roundworm genera (*Phocanema* [= *Pseudoterranova*], *Contracecum*), live in the intestines of marine mammals or birds. The larvae of these parasites, which are ingested by humans with raw sea fish, are known as the causative agents of eosinophilic granulomas in the gastrointestinal tract ("herring worm disease"). In recent years, most cases reported have occurred in Japan. Reliable prophylactic practices include heating or deep-freezing of fish (–20 °C for at least 12–24 hours).

Angiostrongylus

Causative agent angiostrongylosis

Angiostrongylus cantonensis (syn. *Parastrongylus cantonensis*) occurs in the southern Asian and Pacific area, where it inhabits the lungs of rats. This parasite has been identified as the cause of an eosinophilic meningoencephalitis in humans. Larval stages of the parasite have been found in the brain, spinal cord, and eyes of persons who had previously fallen ill. Infection results from ingestion of raw intermediate hosts (snails) and transport hosts (crustaceans) containing infective larvae of *A. cantonensis*.

Angiostrongylus costaricensis (syn. *Parastrongylus costaricensis*) occurs in the USA, Central and South America, and Africa, where it parasitizes in the mesenteric vessels of cotton rats and other vertebrates. Human infections are caused by accidental ingestion of intermediate hosts (snails) containing larvae, resulting in the invasion of mesenteric vessels by parasites and development of inflammatory intestinal wall granulomas. Larvae are not shed in stool because, although the parasites produce eggs, no larvae hatch out of them.

Dirofilaria

Causative agent of dirofilariosis

The larvae of *Dirofilaria immitis* and *Dirofilaria repens*, which in the adult stages are parasites of dogs, cats, and wild carnivores, are occasionally transmitted to humans by mosquitoes: immature stages of *D. immitis* usually invade the lungs and produce 1–4 cm round foci there, whereas the stages of *D. repens* are usually found in subcutaneous nodules. In Europe, the majority of autochthonous cases are reported from Italy, France, and Greece. Imported infections are reported from other countries as well (Germany, Austria, Switzerland, etc.).