Toxocara
(helminth: nematode)

Overview

Nematodes are triploblastic pseudocoelomate unsegmented worms that undergo protostomial embryonic cleavage and grow by cuticular moulting (ecdysis). Two groups identified by the presence/absence of sensory phasmids have partly been ratified by molecular studies recognising three subclasses: Enoplia and Dorylaimia (both without phasmids) and Chromadoria (most with phasmids). Many phasmidian parasites of vertebrates are grouped in the chromadorian order Rhabditida; including tylenchinids, rhabditinids and spirurinids. The latter contains the infraorder Ascaridomorpha which includes ascaridoid nematodes (roundworms) characterised by their large size, three prominent anterior lips and the absence of a bursa. They occur in the small intestines of many animals (including humans) and most have simple direct life-cycles involving faecal-oral transmission. Female worms produce numerous eggs which are excreted with host faeces and undergo embryonation to contain infective larvae. When ingested, larvae hatch from the eggs and develop into adult worms in the gut. The larvae of ascaridoid species undergo hepato-pulmonary migration before forming adults, whereas those of heterakoid species do not. Two major ascaridoid families are recognised: ascarids in terrestrial mammals; and anisakids in marine mammals. Infections by *Toxocara* spp. are unusual in that larvae may also be taken up by paratenic (transport) hosts (usually rodents and birds), L3 may undergo somatic migration and arrested development (hypobiosis) in definitive host tissues, and infections can be transmitted vertically (transplacental and transmammary). Infections may cause pulmonary and enteric diseases in dogs, and sometimes cats, while the accidental ingestion of larvae by humans may result in visceral and ocular larva migrans.

Classification:

Domain:	Eukaryota (membrane-bound nucleus)
Supergroup:	Amorphea (unikonts with single flagellum, or nonflagellated amoebae)
Kingdom:	Metazoa (multicellular eukaryotes, heterotrophs, notably animals)
Group:	Protostomia (triploblastic, spiral cleavage)
Subgroup:	Ecdysozoa (cuticle moulted = ecdysis)
Phylum:	Nematoda (unsegmented, pseudocoelomate roundworms, tubular digestive tract, dioecious)
Class:	Chromadorea (spiral amphids, three oesophageal glands, usually annulated bodies, free-living and parasitic)
Order:	Rhabditida (Secernentea, Phasmidea) (secretors, with phasmids, bipartite oesophagus, single testis)
Suborder:	Spirurina (mostly parasitic in vertebrate hosts)
Infraorder:	Ascaridomorpha (large roundworms, mouth surrounded by three large lips, numerous caudal papillae)
Superfamily:	Ascaridoidea (ascarids, eggs thick-shelled, direct cycle but larvae undertake hepato-pulmonary migration)
Family:	Ascarididae (large pale roundworms, in terrestrial mammals)
Genus:	*Toxocara* (parasitic in small intestines of dogs/cats/bovids)
Species:	various species cause enteric diseases in dogs, cats and cattle, and larval migrans in humans

Parasite biodiversity and host range: Most Metazoa are multicellular triploblastic animals with differentiated tissues, many being bilaterally symmetrical with a body cavity. Most invertebrate animals are protostomes as their embryonic development involves spiral determinate cleavage. Those that moult their external cuticles during their life-cycles (process known as ecdysis) are grouped together in the unique clade Ecdysozoa, including the nematodes (roundworms), onychophorans (velvet worms), tardigrades (water bears) and arthropods (myriapods, chelicerates, crustaceans and hexapods, all with jointed limbs). Nematodes (roundworms) are unsegmented tubular worms with a fluid-filled body cavity (pseudocoelom) that acts as a hydrostatic skeleton. They have longitudinal muscles and typically exhibit a sideways thrashing motion. They have well developed digestive tracts with various partitions: the foregut comprising the mouth (often with lips and papillae), buccal capsule (sometimes with ridges, rods, plates, spears, stylets or teeth) and oesophagus (glandular, muscular or both); the midgut (nonmuscular absorptive section); and hindgut (rectum) emptying through a subterminal anus (cloaca in males). Most nematodes are dioecious and form separate sexes. Male worms have a single testis (sometimes 2), an elongate vas deferens often equipped with a seminal vesicle and ejaculatory duct (glandular and/or muscular), 1-2 copulatory spicules (sometimes with an accessory gubernaculum), and bursate species with elaborate posterior claspers. Female worms are usually didelphic (some monodelphic or polydelphic) with 2 ovaries, 2 oviducts usually with spermatheca, 2 uteri opening into a common vagina and a vulva often equipped with a muscular ovejector. Female worms are oviparous or viviparous and produce numerous eggs or larvae, respectively. Larval stages undergo several moults (L1-L4) before maturing into adult worms. Some nematodes have direct life-cycles where eggs or larvae infect definitive hosts (per os or per cutaneous), but many have indirect cycles where larvae first develop in invertebrate intermediate hosts before infecting definitive hosts (by ingestion, injection or deposition). Many nematode species are free-living in terrestrial and aquatic habitats, while some species from diverse groups have become plant or animal parasites. Two nematode groups identified by the presence/absence of sensory phasmids have partly been ratified by molecular studies recognising three subclasses: Enoplia and Dorylaimia (both without phasmids) and Chromadoria (most with phasmids). Most Enoplia are free-living marine organisms but

some are found in freshwater, and on land as plant parasites. The Dorylaimia comprise numerous freshwater and terrestrial species, including major groups of plant and animal parasites. The Chromadoria is represented by many marine groups as well as a terrestrial group of plant and animal parasites. The taxonomic ranks of many nematode assemblages vary considerably depending on which classification system has been followed. Molecular phylogenetic studies, however, have supported the separate classification of most groups, particularly at the level of superfamily. Collectively, species from at least 16 superfamilies are considered to pose serious threats to human and animal health as infectious diseases.

CLASSIFICATION* OF SUPERFAMILIES OF PARASITIC NEMATODES
Class: Enoplea (Aphasmidea, Adenophorea) (gland-bearers, cylindrical oesophagus, no phasmids, setae, two testes)
Subclass: Dorylaimia (five or more oesophageal glands, buccal stylet (odontostyle), free-living or parasitic)[clade I(2)]
Order: Trichinellida (Trichocephalida, Trichurida) (single spicule, stichosome oesophagus, L1 with buccal stylet)
Superfamily: Trichinelloidea (oesophagus with short anterior muscular and long posterior glandular portions)
Class: Chromadorea (spiral amphids, 3 oesophageal glands, usually annulated bodies, free-living and parasitic)
Order: Rhabditida (Secernentea, Phasmidea) (secretors, phasmids present, amphids anterior, bulbous oesophagus)
Suborder: Rhabditina (free-living or parasitic in invertebrates/lower vertebrates)[clade V(9)]
Infraorder: Rhabditomorpha (‘rod-shaped’ buccal cavity)
Superfamily: Rhabditoidea (open tube stoma, excretory system with lateral canals)
Superfamily: Strongyloidea (bursate males, prominent buccal capsules, parasites of mammals, birds, reptiles)
Suborder: Spirurina (animal parasites, many use invertebrate intermediate hosts (IH))[clade III(8)]
Incertae sedis Superfamily: Dracunculoidea (elongate parasites of vertebrate tissues, freshwater crustacean IH)
Infraorder: Ascaridomorpha (large roundworms, three large lips, numerous caudal papillae)
Superfamily: Ascaridoidea (ascarids, eggs thick-shelled, larvae may undertake hepato-pulmonary migration)
Superfamily: Heterakoidea (preanal sucker anterior to cloaca in males, direct cycle, infection by egg ingestion)
Infraorder: Gnathostomatomorpha (‘jaw-mouthed’ due to unique bulbous armed heads)
Superfamily: Gnathostomatoidea (first IH copepod, often use paratenic hosts)
Infraorder: Oxyuridomorpha (pinworms, pointed tails, oesophagus with terminal bulb, males with single spicule)
Superfamily: Oxyuroidea (common in mammals, birds, reptiles, amphibians)
Infraorder: Spiruromorpha (enigmatic clade linked by molecular characters, indirect cycles with IHs)
Superfamily: Acuarioidea (small parasites mostly of birds, with cephalic cordons, ptilina or serrated shields)
Superfamily: Camallanoidea (conspicuous phasmids, L1 with dorsal tooth, ovoviviparous, L1-L3 in copepod)
Superfamily: Filarioidea (tissue-dwelling filarial parasites, lack lips, infect tissues/vessels, arthropod IH)
Superfamily: Habronematoidea (unique head structures with small pseudolabia and median lips)
Superfamily: Physalopteroidea (stomach worms in mammals, insect IH)
Superfamily: Spiruroidea (pseudolabia, bipartite oesophagus, infect birds (crop/gizzard), arthropod IHs
Superfamily: Thelazioidea (eye-worms of birds and mammals, transmitted by insects)
Suborder: Tylenchina (fungal, plant and animal parasites)[clade IV(10,11,12)]
Infraorder: Panagrolaimomorpha (free-living or parasitic (insects, reptiles, amphibians, mammals))
Superfamily: Strongyloidoidea (dauer stages, lip region without processes, striated cuticle)

*Contemporary genotypic classification schemes recognize strong monophyletic clades at the level of superfamily and infraorder, while previous phenotypic classification schemes had ranked many as separate orders.

The infraorder Ascaridomorpha is characterised by large roundworms with poorly developed buccal cavity with 3 large lips sometimes separated by interlabia, an undivided oesophagus, numerous caudal papillae, nonbursate males often with pre-anal suckers, and females with complex ovejectors. Five superfamilies (conventionally assigned to the order Ascaridida) are recognised as parasites in vertebrates: Ascaridoidea (cylindrical oesophagus often terminated by swelling without bulb, coelomyarian, eggs thick-shelled); Heterakoidea (oesophagus cylindrical or with claviform corpus, short isthmus and valved bulb, coelomyarian, pre-anal sucker, eggs thick-shelled); Seuratoidea (lips absent, oesophagus short, platymyarian, eggs with delicate shells or hatch *in utero*); Cosmocercoidea (oesophagus with cylindrical corpus, elongate isthmus and valved bulb, platymyarian, eggs with delicate shells or hatch *in utero*); and Subuluroidea (well-developed buccal capsule without lips, coelomyarian, pre-anal sucker, eggs thick-shelled). Adult worms of the superfamily Ascaridoidea inhabit the gastrointestinal tract of vertebrate hosts and generally consume food ingested by the host. They may have simple monoxenous life cycles involving faecal-oral transmission, or more complicated heteroxenous life-cycles involving larval development in vertebrate intermediate hosts and sometimes larval transport in invertebrate paratenic hosts. Female worms produce unembryonated eggs which are passed in host faeces into the external environment where they embryonate to first-stage larvae (L1) which grow and moult to infective L2 or L3. Aquatic species produce thin-shelled eggs which hatch in water releasing sheathed L2 that are taken up by suitable hosts, while terrestrial species produce thick-shelled eggs which hatch releasing L3 when ingested by suitable hosts. Ascaridoid larval stages then undertake unique journeys: most involving pulmonary or somatic migration in their definitive hosts before maturing in the gut, sometimes including vertical transmission (transplacental and/or transmammary); many migrating into the tissues of intermediate hosts, sometimes involving larval migrans or encapsulation in ‘unsuitable’ hosts; and a few undergoing precocious development in invertebrate hosts.

Five ascaridoid families are recognised: Ascarididae (lips often with toothed ridge, oesophagus with or without ventriculus, parasites of mammals, birds, reptiles, amphibians, fishes); Anisakidae (lips with tongue-like prolongations with cuticular thickenings, oesophagus with ventriculus with suture-like depressions, parasites of mammals, birds, reptiles and fishes); Crossophoridae (lips semicircular with toothed combs, fimbriated collar, long oesophagus without ventriculus, parasites of hyracoids); Heterocheilidae (lips with tongue-like prolongations with cuticular thickenings, cylindrical oesophagus without ventriculus, parasites of sirenians); and Acanthocheilidae (lips small with teeth or toothed ridges, oesophagus with ventriculus, parasites of elasmobranchs). The family Ascarididae contains 4 subfamilies: Ascaridinae (oesophagus simple, gubernaculum absent, lips hexagonal with anterior region offset from posterior, parasites of terrestrial mammals); Toxocarinae (oesophagus with globular ventriculus without appendices, gubernaculum absent, parasites of terrestrial or marine mammals or birds); Angusticaecinae (oesophagus simple, gubernaculum absent, lips quadrangular and not divided into anterior and posterior regions, parasites of reptiles and amphibians); and Multicaecinae (oesophagus with globular ventriculus usually with appendices, gubernaculum present, parasites of crocodilians or rarely fish). Ascaridid genera of medical and veterinary significance are compared in the following table.

Genus	No. spp.	Definitive Hosts	Location	Adult worms	Eggs	Transmission
Toxocarinae						
Toxocara	26	carnivores, ruminants, rodents	small intestines	3-30 cm long, 3 lips, long thin cervical alae, oesophageal ventriculus present, males with terminal digitiform appendage, larvae undergo somatic migration, hypobiosis	64-91 µm, spherical, thick-shelled	faecal-oral, ingestion of PH, transplacental, transmammary
Ascaridinae						
Ascaris (roundworm)	2 (+ 150 *nomen dubium*)	primates, suids	small intestines	15-50 cm long, 3 small lips, striated cuticle, males with curved tail, simple spicules, females opisthodelphic, larvae undergo hepato-pulmonary migration	50-87 x 35-60 µm, ovoid, thick-shelled	faecal-oral
Parascaris	3	equids	small intestines	10-50 cm long, 3 large lips each with transverse groove, cuticle striated, males abursate, simple spicules, larvae undergo hepato-pulmonary migration	90-120 µm, spherical, thick-shelled	faecal-oral
Toxascaris	2	carnivores	small intestines	2-15 cm long, 3 lips, long thin cervical alae, oesophageal ventriculus absent, males lack terminal digitiform appendage, larvae do not undergo hepato-pulmonary migration	70-85 x 60-75 µm, ovoid, thick-shelled	faecal-oral (sometimes ingestion of infected PH)

The subfamily Toxocarinae contains 3 genera of large roundworms with well-defined lips and an oesophagus with a globular ventriculus without appendices: namely, *Paradujardinia, Porrocaecum* and *Toxocara* (syn. *Belascaris*, *Neoascaris*). The genus *Toxocara* contains the arrow-headed ascaridoids (cervical alae present) which form rough-shelled (pitted) eggs. Adult worms lack intestinal caeca and interlabia, and some 26 species are found as endoparasites in the intestines of terrestrial mammals. Larval stages migrate extensively (tracheal and/or somatic routes) in host tissues and they may undergo developmental arrest (hypobiosis), notably resuming development in pregnant and lactating hosts thus facilitating transplacental and transmammary vertical transmission. Parasites usually have direct cycles with the faecal-oral transmission of embryonated eggs, but some species also have indirect cycles with the predator-prey transmission of infective larvae encysted with the tissues of invertebrate and vertebrate paratenic (transport) hosts. The species *T. canis* is widely distributed in canids worldwide, with infections being more prevalent in puppies due to their immunological immaturity which favours tracheal migration over somatic migration before the development of adults in the gut. Larvae may encyst in the tissues of older animals and resume development in female dogs during pregnancy facilitating transplacental and transmammary transmission. Larvae may also be carried in a wide range of paratenic hosts further contributing to the high incidence of infections. Humans (especially young children) may act as paratenic hosts for several species and the migrating larvae may cause an enigmatic disease known as visceral larval migrans, sometimes ocular larva migrans.

***Toxocara* species**	**Definitive hosts**	**Location [Clinical signs]**	**Paratenic hosts**	**Distribution**
T. alienata	Carnivora: procyonid (South American coati, white-nosed coati, crab-eating raccoon)			South America

T. anakumae	Carnivora: mustelid (Japanese badger)			Asia
T. apodemi	Rodentia: murid (striped field mouse, Korean field mouse)			Asia
T. canarisi	Carnivora: felid (serval)			Africa
T. canis (syn. *T. marginata*, *Ascaris marginata, Belascaris marginata*)	Carnivora: canid (dog, dingo, African wild dog, raccoon dog, wolf, maned wolf, northwestern wolf, dire wolf, Indian wolf, coyote, golden jackal, red fox, American red fox, Japanese red fox, fennec fox, corsac fox, gray fox, crab-eating fox, Iberian fox, Bengal fox, Arctic fox), hyaenid (spotted hyena), felid (cat, wild cat, ocelot, lion, cougar, Bengal tiger, Eurasian lynx, Iberian lynx), viverrid (common genet, small Indian civet), herpestid (slender mongoose, white-tailed mongoose), mustelid (sable, ferret, European polecat, Siberian weasel, Japanese badger), procyonid (raccoon); Didelphimorphia: didelphid (Virginia opossum); Chiroptera: pteropodid (grey-headed flying fox); Diprotodontia: phalangerid (common brushtail possum); Primates: cercopithecid (macaque), hominid (human)	small intestines [larval migrans, pneumonia, enteritis, illthrift, potbelly]	Rodentia: murid (house mouse, wood mouse, yellow-necked mouse, striped field mouse, Ural field mouse, Eurasian harvest mouse, Mongolian gerbil), cricetid (common vole, bank vole); Artiodactyla: suid (pig), bovid (cattle, sheep); Carnivora: canid (fox); Galliformes: phasianid (chicken, Japanese quail); Blattodea: blattid (cockroach *Periplaneta fuliginosa*); Clitellata: megascolecid (earthworm *Pheretima posthuma*)	worldwide
T. cati (syn. *T. mystax, globulus, brachyoptera*?, *Ascaris globulus, leptoptera*)	Carnivora: felid (cat, wild cat, sand cat, fishing cat, Asian wild cat, Asian golden cat, Pallas's cat, African wild cat, jungle cat, jaguar, jaguarundi, leopard cat, bobcat, serval, ocelot, caracal, cougar, leopard, clouded leopard, snow leopard, cheetah, lion, Bengal tiger, Canada lynx, Eurasian lynx, Iberian lynx), canid (dog, red fox, corsac fox), viverrid (common genet, African civet, small Indian civet), herpestid (common dwarf mongoose), mustelid (beech marten, sable, Siberian weasel); Primates: hominid (human)	small intestines [larval migrans, enteritis, illthrift, potbelly]	Rodentia: murid (house mouse, brown rat, Mongolian gerbil); Artiodactyla: bovid (sheep); Carnivora: canid (dog); Galliformes: phasianid (chicken); Clitellata: lumbricid (earthworm); Blattodea: blattid (cockroach)	worldwide
T. cynonycteridis	Chiroptera: pteropodid (fulvous fox bat)			Asia
T. elephantis	Proboscidea: elephantid (Asian elephant)			Asia
T. genettae	Carnivora: viverrid (South African small spotted genet, common genet)			Africa
T. herpestum	Carnivora: herpestid (Egyptian mongoose)			Africa
T. hippopotami	Artiodactyla: hippopotamid (hippopotamus)			Africa
T. indica	Rodentia: murid (greater bandicoot rat)			Asia
T. lyncis	Carnivora: felid (caracal)			Asia
T. mackerrasae	Rodentia: murid (bush rat, rakali)			Australia
T. malaysiensis	Carnivora: felid (cat)	small intestines [enteritis?]		Malaysia, Vietnam, China
T. manzadiensis	Artiodactyla: bovid (African buffalo)			Africa
T. paradoxura	Carnivora: viverrid (Asian palm civet)			Asia
T. pearsei	Chiroptera: natalid (Trinidadian funnel-eared bat), emballonurid (lesser dog-like bat)		Decapoda: alpheid (shrimp *Synalpheus brooksi*)	South America
T. pteropodis	Chiroptera: pteropodid (black flying fox, grey-headed flying fox, spectacled flying fox, small flying fox, little red flying fox, Gedde's fruit bat); Diprotodontia: phalangerid (common brushtail possum);	small intestines		Australia

	Primates: hominid (human)			
T. sprenti	Carnivora: viverrid (small Indian civet)			Asia
T. suricattae	Carnivora: herpestid (meerkat, banded mongoose)			Africa
T. tanuki	Carnivora: canid (raccoon dog, Japanese raccoon dog), procyonid (raccoon)	small intestines		Asia
T. vajrasthirae	Carnivora: mustelid (hog badger)			Eurasia
T. vincenti	Carnivora: viverrid (African civet)			Africa
T. vitulorum (syn. *Neoascaris*)	Artiodactyla: bovid (cattle, Bali cattle, zebu, water buffalo, Asian buffalo, American bison, sheep, goat, impala); Rodentia: murid (mouse); Primates: hominid (human)	small intestines [diarrhoea]		Africa, Americas, Asia, Australia
T. warreni	Artiodactyla: tragulid (water chevrotain)			Asia

Parasite morphology: *Toxocara* spp. form 3 different types of developmental stages: eggs; larvae (4 consecutive stages encoded L1-L4); and adult worms. Eggs are opaque-brown ovoid-subspherical stages measuring 64-91 µm in maximum diameter and they have thick eggshells with a rough pitted surface due to mammillation of the outer protein layer (cf. *Toxascaris* eggs have a smooth surface). Freshly laid eggs are unembryonated and contain a single central morula. The eggs embryonate forming L1 which then moult while still within the eggshell producing ensheathed L2 (several reports have also suggested that L3 may occasionally be formed within eggs). Irrespective, the emergent larvae are elongate and cylindrical measuring 350-530 x 18-30 µm and they have rounded heads, 3 lips (each composed of a dentigerous ridge), a tubular oesophagus, intestines with 2 excretory canals in the middle, and a short tapering tail. L3 recovered from lung tissues measured 0.8-1.0 mm in length while L4 recovered from the intestines measured 1.0-1.5 mm long. Adults are large round cream-yellow worms ranging in length from 3-30 cm depending on species. They have tubular bodies with pointed ends, the anterior end possessing a pair of prominent cervical alae (making them members of the 'arrow-headed' ascaridoids). The alae are striated in appearance and broad (arrowhead-like) diminishing gradually in width (e.g. *T. canis, T. malaysiensis*) or ending abruptly (e.g. *T. cati*). Worms have 3 prominent lips (broad at the base and narrowing anteriorly with dentate margins), a small buccal capsule, a tubular oesophagus with a posterior muscular bulb known as a ventriculus (absent in *Toxascaris*), and short tapering tails. Adults are sexually dimorphic with females being larger than males (*T. mystax* females 40-120 mm, males 30-70 mm; *T. cati* females 60-120 mm, males 30-70 mm; *T. canis* females 50-180 mm, males 40-120 mm; *T. vitulorum* females 220-300 mm, males 150-260 mm). Mature females have straight tails and are didelphic with 2 ovaries and elongate uteri connected to a common vulva located in the anterior third of the body. Mature males have a single tubular testis, 2 curved alate (winged) spicules subequal in length (ranging from 0.75-1.3 mm long) and curved blunt tails with caudal alae and a terminal digitiform appendage (absent in *Toxascaris*).

Site of infection: Adult worms infect the small intestines of their mammalian definitive hosts, living free within the lumen. Earlier developing larval stages undergo extensive migrations through various host tissues (hepato-pulmonary in young and immunocompromised animals, somatic in older immunocompetent animals). Infective larvae may also encyst within the tissues of various paratenic (transport) hosts (including small mammals, birds, insects, crustaceans, earthworms).

Pathogenesis: Infections are common in domestic and wild carnivores and are a significant cause of morbidity (illthrift, growth impairment) and mortality in companion animals. Young animals are particularly susceptible to disease while adults generally develop acquired immunity leading to the expulsion of most of the adult worm population (concomitant or premunitive immunity rather than sterile immunity as larvae and some adults may persist). Clinical disease may occur at 2 different stages of infection: when larvae migrate through host organs causing disseminated microgranulomas; and when adult worms develop and feed in the small intestines causing digestive disorders, mucosal defects, illthrift, obstruction and occasionally perforation. The severity of disease depends on host susceptibility (age, sex and immune status), the routes of larval migration (hepato-pulmonary or somatic migration), the intensity of infection (numbers of parasites, a few worms are well tolerated), and the behaviour of adult worms (aggregations causing intestinal obstructions, and aberrant migrations to the bile ducts or stomach causing obstructive jaundice or vomiting). The route of migration undertaken by larvae is largely determined by the immuno-competency of the host; with hepato-pulmonary migration occurring in young hosts with immature immune systems; and somatic migration occurring in older animals with competent immune systems. Larvae migrating though the lungs cause traumatic damage with focal haemorrhages, hyperaemia, pneumonitis, pulmonary oedema, eosinophilic infiltrates and sometimes pneumonia. Clinical respiratory signs include coughing, dyspnoea, tachypnoea and frothy nasal discharges. Larvae migrating through other body (somatic) tissues often become encapsulated in dense fibrous tissue, particularly in the muscles, heart, liver, lungs, brain and sometimes the eyes. These larvae exhibit arrested development (hypobiosis) remaining viable for extended periods of time, and may re-awaken and resume development during pregnancy, sometimes invading the placenta or mammary glands to facilitate transplacental or transmammary transmission. In humans, both migrating and encysted larvae may die and degenerate provoking intense inflammatory responses that may cause the disease syndrome known as visceral larval migrans (or ocular larval migrans if in the eye). Clinical signs may include neurological conditions (restlessness, seizures, convulsions), vision disorders, hepatitis, pneumonitis, and myositis. Adult worms in

the intestines feed on luminal content (chyme), consuming large amounts of substances (carbohydrates, lipids, amino acids, vitamins and minerals) resulting in metabolic deficiency disorders (hypoglycaemia, hypocalcaemia, hypochromic anaemia, hyperkeratosis, rickets). Worms and their secretions and excretions provoke intense inflammatory responses (mucoid catarrhal enteritis) contributing to the maldigestion, malabsorption and malnutrition syndromes. Clinical signs include intermittent yellow-pasty diarrhoea alternating with constipation, colic, abdominal distention (pot-belly) sensitive to pressure, vomiting, rough and dull coat, anorexia, weight loss, emaciation, and impaired growth (failure to thrive), sometimes with bone deformities. The presence of balls or tangles of worms in the small intestine may lead to blockage, intussusception and sometimes rupture with peritonitis leading to death. Puppies infected *in utero* with *T. canis* can die a few days after birth (from larvae migrating through alveoli), but most clinical signs appear at 2-4 weeks of age with animals developing digestive symptoms, sometimes with nervous convulsions. Infections by *T. cati* in cats usually cause disease after weaning involving digestive and general disorders. Lactogenic transmission of *T. cati* only occurs after acute infection of the queen during late pregnancy. Infections by *T. vitulorum* in cattle may occasionally cause acute disease in neonates but more frequently chronic digestive disorders in calves up to 6-8 months of age.

Zoonotic infections may occur in humans following the ingestion of infective eggs and the release of larvae which wander throughout the body for extended periods (months to years) but are unable to complete their development in nonpermissive (abnormal) hosts. Three types of disease may develop in humans. The most common form is covert toxocariasis, characterised by nonspecific symptoms and signs (not referable to other conditions). Migrating larvae have been implicated in respiratory conditions (coughing, wheezing, asthma, bronchitis, pulmonitis, sometimes with Loeffler syndrome), dermatological disorders (chronic idiopathic urticaria, eczema), lymphadenopathy and myositis (with limb pain), and pseudorheumatic syndrome (arthralgia). The next most frequent form is known as systemic visceral larval migrans (classical or incomplete) where larvae localize in a range of tissues (muscles, liver, lungs, central nervous system, eyes). The larvae often become encapsulated and slowly degenerate triggering hypersensitive immune reactions characterised by eosinophilia, leucocytosis and granuloma formation. Such infections generally occur on young children (< 5 years) and may be associated with geophagia (pica, soil-eating) and onychophagia (nail-biting). Nonspecific signs develop including hepatosplenomegaly, granulomatous hepatitis, upper abdominal discomfort, lymphadenopathy, oedema, pneumonitis, myocarditis, nephritis, vague neurological signs, fever, headache, anorexia, nausea, vomiting, and malaise. The third form of disease is compartmentalized and includes ocular larval migrans and neurological larval migrans. Ocular disease usually develops in children 5-10 years old and may only involve a few larvae with granuloma formation, optic neuritis, keratitis, irititis and hyphoyon. Common symptoms include red eye, uveitis, leukocoria, eye pain, endophthalmitis or papillitis, strabismus, and granular formation in the retina with macular detachment leading to impaired vision and blindness. Neurological disease occurs more frequently in adults with eosinophilic meningoencephalitis and meningitis associated with idiopathic seizures, neuropsychiatric symptoms (sleep and behavioural changes) and encephalopathy which may lead to death.

Developmental cycle and mode of transmission: Infections may be transmitted to definitive hosts directly (horizontally by faecal-oral transmission or vertically by transplacental and/or transmammary transmission) or indirectly (predator-prey transmission involving consumption of larval stages in paratenic (transport) hosts). Gravid female worms lay unembryonated eggs (up to 100,000 per day) which are excreted into the external environment with host faeces. In suitable warm humid conditions, the eggs embryonate in around 6 days to form L1 which subsequently moult around 12-14 days to form infective L2 still contained within the egg. Some sporadic reports have suggested that an extra moult to L3 may also occur in some eggs. Embryonation and larval development may be substantially delayed in suboptimal conditions, but the thick-shelled eggs are very resistant to adverse conditions (most susceptible to desiccation and direct sunlight). The eggs are dispersed from faecal material by water and wind action and their sticky coats allow them to adhere to plants (including vegetables and fruits), invertebrates (earthworms, insects) and small vertebrates (rodents, birds). Larvated eggs may survive in moist soils for up to 4-5 years and they readily contaminate water sources. Definitive hosts become infected when they ingest infective larvae either contained within eggs contaminating food and water, or encysted within the tissues of paratenic hosts. Depending on the parasite species, larvae may also be transmitted vertically across the placenta or in mothers' milk.

The main mode of transmission is direct via the consumption of larvated eggs which hatch in the intestines releasing L2. The larvae then undertake hepato-pulmonary or somatic migration depending on host resistance/susceptibility, age and sex. *T. canis* undergoes standard hepatopulmonary migration in puppies up to 12 weeks of age (as well as in entire (non-neutered) male or immunocompromised dogs). L2 migrate via the circulation to the liver in 1-3 days and then the lungs in 6-7 days where they enter alveoli and move up the trachea to be swallowed. Some studies have suggested that L2 moult to L3 in the lungs whereas other studies report that it occurs later in the gut. Larvae in the intestines moult to L4 in 13 days and then to subadults (often designated L5) in 19-27 days before maturing to adult worms. The prepatent period (time from infection to first egg excretion) ranges from 28-35 days and adult worms are thought to live for up to 4-6 months. Alternatively, *T. canis* larvae rarely enter the pulmonary alveoli in older immunocompetent dogs (> 6 months) but undergo somatic migration by remaining in the circulation to be distributed throughout the body, particularly to the skeletal muscles, heart, kidneys, brain, liver and lungs. Here the larvae become encapsulated in dense fibrous tissue forming cysts containing arrested (hypobiotic) larvae which may remain viable for extended periods (months to years). In male dogs and spayed bitches, the encysted larvae eventually die, but in pregnant bitches, they may awaken and resume their migration and development. Some larvae may complete normal migration in the bitch produce a few adult worms which lead to a small post-parturient rise in egg production. However, other larvae migrate to the placenta and mammary glands where vertical transmission may occur (over 50% of infected bitches transmit infections vertically to puppies). Prenatal (transplacental) transmission occurs when somatic larvae cross the placenta, invade the liver and lungs of the foetus, and remain there until birth

whereupon they complete tracheal migration and develop into adults in the intestines (prepatent period in newborn pups is 12-21 days). Postnatal (lactogenic/transmammary) transmission occurs when somatic larvae are passed in the milk for up to 35 days post-partum to suckling pups where they develop directly into adults in the gut (prepatent period 21-28 days).

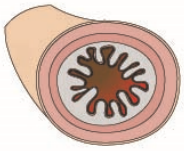
Indirect transmission may also occur by paratenesis when prey animals (earthworms, cockroaches, rodents, birds) consume larvated eggs and develop encysted larvae in their tissues (making them paratenic hosts as the larvae do not undergo further development). Final hosts become infected when they consume paratenic hosts via predation or scavenging, with adult worms developing directly in the intestines (prepatent period 28-35 days). Somatic migration is not a feature of *T. cati* infection in the definitive host. Most *T. cati* infections in felids involve the ingestion of larvated eggs with hepato-pulmonary larval migration before adults form in the gut (prepatent period 35-56 days). Some vertical transmission (transmammary but not transplacental) has been reported involving infection of the queen during late pregnancy (rather than reactivation of arrested somatic larvae). A major source of infection for large predatory felids are paratenic hosts (including earthworms, cockroaches, chickens, mice, lambs, dogs). Similarly, most *T. vitulorum* infections in cattle involve egg ingestion and hepato-pulmonary larval migration (prepatent period ranging from 21-70 days) and some vertical transmission (transmammary but not transplacental). Infections in calves over 6 months rarely become patent, but larvae may remain dormant in host tissues and resume development during pregnancy with transmission in milk for 3-4 weeks post-partum. Humans may act as accidental paratenic hosts for several *Toxocara* spp. (*T. canis, T. cati, T. pteropodis, T. vitulorum*) and develop visceral larval migrans. People become infected by ingesting larvated eggs via contaminated food/water, geophagia or practicing poor hygiene after direct contact with soil or pets. Food-borne transmission may occur not only by the consumption of fruit and vegetables contaminated with eggs, but also by the consumption of raw or lightly cooked meat from paratenic hosts carrying encysted larvae (especially raw livers from chickens, ducks, pigs, rabbits). Risk factors include rural residence (dog ownership, poor hygiene), low socio-economic status (poor sanitation, lack of sewers) and favourable environmental conditions (warm humid climate).

Differential diagnosis: Clinical infections are often indicated in young pets on the basis of clinical symptomatology (respiratory signs then diarrhoea, pot-belly) and relevant history (unhygienic conditions, poor nutrition). However, many other conditions may cause similar clinical signs. Developing worms may occasionally be observed in vomitus or faeces, particularly towards the end of the prepatent period. Haematological assessments often demonstrate marked peripheral eosinophilia, while blood biochemistry may reveal transient elevated levels of liver enzymes. Patent infections are conventionally diagnosed by the microscopic detection of characteristic worm eggs in faecal samples, usually following their concentration by sedimentation in water and floatation in saturated sugar or salt solutions. Infections may be diagnosed at post-mortem by the detection of adult worms within the lumen of the small intestines. Larval infections in humans may be suggested by symptomatology (fever, eosinophilia, vision loss, strabismus) and history (pica, nail-biting) but other diseases or conditions cannot be ruled out. Medical imaging techniques may be used to locate suspect lesions, including sonography (hypoechoic lesions), computed tomography (granulomas) and magnetic resonance imaging (cerebral lesions), but are not confirmatory. Examination of cerebrospinal fluid in neurological cases may reveal the presence of eosinophils, and the histopathological examination of tissue biopsies may occasionally detect sections of nematode larvae. Recourse is therefore often made to the indirect demonstration of infections by a variety of immunoserological tests for specific host antibodies (mostly IgG but sometimes IgM or IgE) against larval and adult worm antigens, including skin tests, immunoprecipitation, agglutination, immunofluorescence, enzyme immunoassays and radio-immunoassays. Most tests yielded good specificity but reduced sensitivity possibly due to cross-reactivity with other helminths. Western blotting has been used to confirm results by detecting reactions against specific antigenic bands. Modern molecular biological techniques have been used to detect parasites in environmental and clinical samples and determine phylogenetic relationships by polymerase chain reaction (PCR) amplification, restriction fragment length polymorphism (RFLP) analyses, single strand conformational polymorphism (SSCP) analyses, and sequencing of nuclear genes (5.8S ribosomal RNA, internal transcribed spacers 1 and 2, repetitive DNA) and mitochondrial genes (protein coding regions). DNA cloning and recombination technologies have also been used to explore parasite immuno-evasion mechanisms involved in the long persistence of larvae in host tissues, including cuticular shedding of secreted mucins, cysteine proteases and other proteins unique to hypobiotic stages.

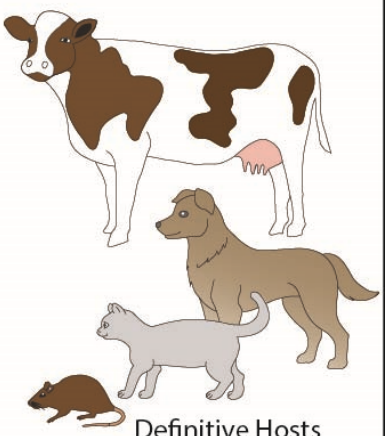
Treatment and control: A broad range of anthelmintic drugs have been used to treat clinical infections in domestic and wild carnivores, including consecutive doses of benzimidazoles (fenbendazole, oxibendazole, flubendazole), probenzimidazoles (febantel), tetrahydropyrimidines (oxantel, pyrantel), macrocyclic lactones (milbemycin, moxidectin, selamectin, eprinomectin), depsipeptides (emodepside), isoquinolines (praziquantel), diethylenediamines (diethylcarbamazine, piperazine), isothiocyanates (nitroscanate) and imidazothiazoles (levamisole). Most drugs were effective against immature and mature worms in the intestines, some (selamectin and moxidectin) were effective against larvae in the circulation, but few were effective against migrating or arrested larvae (other than some reports on levamisole, pyrantel, thiabendazole or febantel in cattle). Repeated treatments should be used to stop infections developing from surviving larvae and to prevent re-infections from contaminated environments or milk from suckling mothers. Several anthelmintics have been found to reduce the burden of vertical and trans-mammary transmission of *T. canis* from dam to pups, including selamectin, fenbendazole and 'off-label' ivermectin. Veterinary authorities recommend treating puppies and kittens at 2 weeks of age, then every 2 weeks until 8 weeks of age, and then monthly until 6 months of age. Nursing bitches and queens should be treated at the same time, and adults should be treated regularly for life every 1-3 months depending on the risk. Post-treatment surgical interventions have also been used to relieve intestinal blockages in heavy infections. Most larval infections in humans resolve spontaneously as the larvae die and degenerate. Some success has been reported in treating infections

with short courses of albendazole, mebendazole or thiabendazole, often with supportive therapy in the form of corticosteroids to suppress intense allergic manifestations and antibiotics to prevent secondary infections. In the case of ocular larval migrans, surgical intervention (vitrectomy) has been used to remove problematic granulomas. Various preventive measures have been applied to domestic and urban situations to reduce parasite transmission, all essentially revolving around improved hygiene (of environment, food/water, animals and people). Environmental contamination may be reduced by the regular removal and disposal of faeces and not using them to fertilise edible crops (note that the tough eggs may survive some biocomposting and sewage treatments), regular cleaning and decontamination of holding facilities (which requires strong disinfectants, flame guns or steam-cleaning), and eliminating moist shaded runs or rest areas which may harbour eggs (by draining, paving or close-crop mowing). Clean water should be provided, giving preference to treated reticulated freshwater sources rather than standing waters. All fruit and vegetables should be thoroughly washed in clean water to remove adherent eggs, and any meat from potential paratenic hosts should be properly cooked to destroy encysted larvae. Animal husbandry practices should include quarantine and isolation procedures when moving or treating animals, particularly in breeding facilities, avoid overcrowding, introduce rodent control, prevent animals from hunting or scavenging, and even hand-rearing or foster-rearing neonates from infected bitches or queens. Improving hygienic practices in human populations often requires intensive education campaigns before people will even adopt simple changes, like hand-washing before eating, preventing children from playing in contaminated soils, covering sandpits in playgrounds, discouraging pica and nail-biting, bathing dogs that roll in soil or faeces, and passing laws requiring the removal of pet faeces from public places.

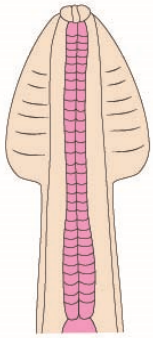
Toxocara



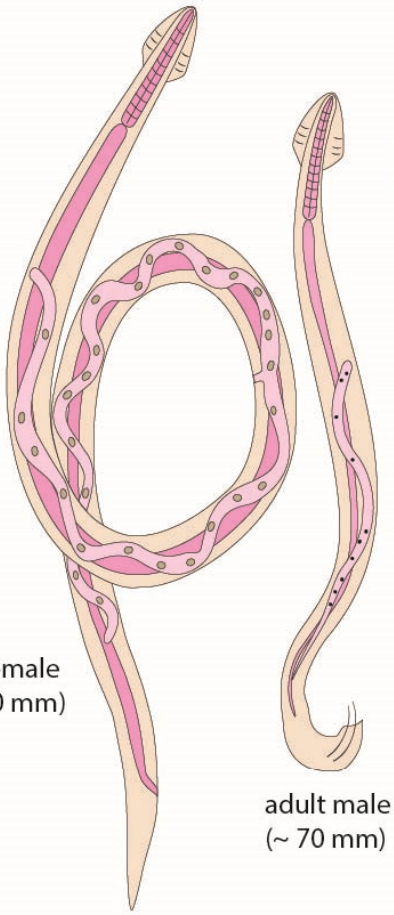
intestines
(larval migrans,
pneumonitis,
enteritis, illthrift)



Definitive Hosts
(carnivores,
ruminants,
rodents)



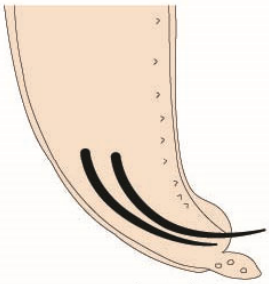
head



adult female
(~ 120 mm)

adult male
(~ 70 mm)

larval migration
(pulmonary/somatic)
hypobiosis,
vertical
transmission



male tail
(lateral)

third-stage larvae (L3)
(~ 500 µm)

eggs,
L2/PH
ingested

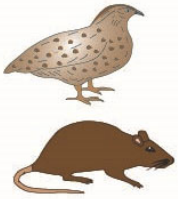
some L2 carried in PH

external
environment

eggs
excreted
in faeces

L2 develop
within eggs

eggs
(~ 80 µm)

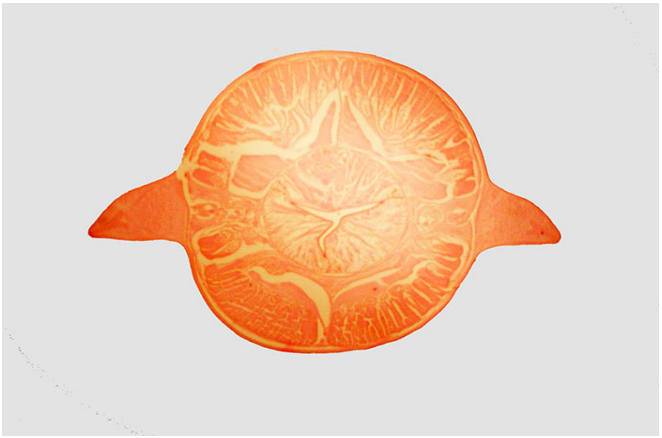


Paratenic Hosts (PH)
(rodents, birds)
(muscles)

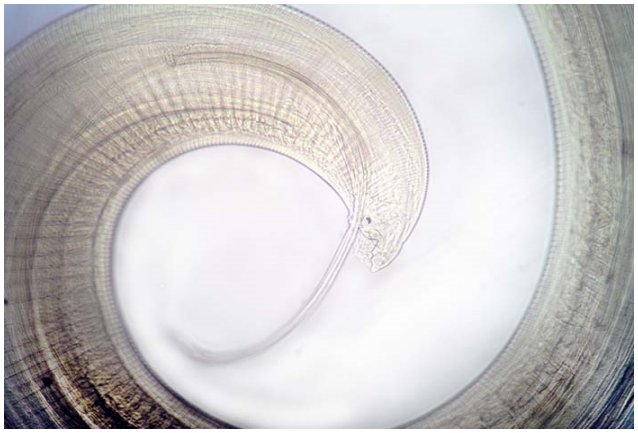
Toxocara adult worms

Toxocara adult worms

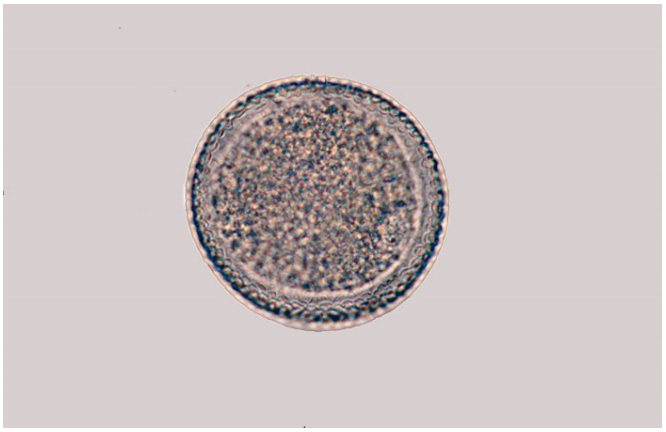
Toxocara adult worm, head



Toxocara adult worm, section through alae



Toxocara adult worms



Toxocara adult worms