Gnathostoma
(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 Gnathostomatomorpha which includes the gnathostomatoids with enlarged head bulbs covered with hooks and indirect life-cycles. Gnathostomids are found in the stomachs of carnivores and are transmitted through copepods (acting as first intermediate hosts) and then small mammals, birds, reptiles, fish and amphibians (which act as second intermediate hosts or paratenic hosts). Infections by *Gnathostoma* spp. may cause cutaneous lesions and acute abdominal signs, perforation and peritonitis in their definitive hosts.

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:	Gnathostomatomorpha (‘jaw-mouthed’ due to unique bulbous armed heads)
Superfamily:	Gnathostomatoidea (first IH copepod, often use paratenic hosts)
Family:	Gnathostomidae (swollen anterior head bulb, covered with rows of hooks, two lateral lips, four cervical sacs)
Genus:	*Gnathostoma* (parasitic in stomach of cats/pigs)
Species:	various species cause gut lesions in carnivores

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.

Molecular phylogenetic studies have grouped a variety of superfamilies into the infraorder Spiruromorpha whose members are parasites of vertebrates with indirect life-cycles involving larval development within invertebrate intermediate hosts. Most members were previously classified within the order Spirurida: either within the suborder Camallanina (worms with conspicuous phasmids, uninucleate oesophageal glands, larvae without cephalic hooks, usually with copepodid intermediate hosts); or the suborder Spirurina (worms with inconspicuous phasmids, multinucleate oesophageal glands, larvae with cephalic hooks or spines, usually with non-copepodid intermediate hosts). Ten spirurinid superfamilies are recognised: Gnathostomatoidea and Physalopteroidea (buccal cavity weakly cuticularized, 2 large lateral pseudolabia); Habronematoidea and Acuarioidea (buccal cavity well cuticularized, 2 large lateral pseudolabia); Filarioidea, Rictularioidea, Aproctoidea and Diplotriaenoidea (buccal cavity well cuticularized, without pseudolabia); Thelazioidea (long cylindrical buccal cavity well cuticularized, body without caudal alae); and Spiruroidea (short buccal cavity well cuticularized, body with caudal alae).

The superfamily Gnathostomatoidea is characterised by worms with large complex pseudolabia and 4 cervical sacs and infects the alimentary tracts of vertebrates and using invertebrates as intermediate hosts for larval development and vertebrates as paratenic hosts for larval transport. Only one family (Gnathostomatidae) is recognised with 4 subfamilies: Gnathostominae (cephalic bulb present, parasites of mammals, reptiles or fish); Metaleptinae (cephalic bulb absent, pseudolabia with small teeth, *Metalepus* in sharks); Spiroxyinae (cephalic bulb absent, pseudolabia without posterior appendages, *Spiroxys* in snakes, tortoises, amphibians); and Ancyracanthinae (cephalic bulb absent, pseudolabia with long ramified appendages, *Ancyracanthus* in fishes and chelonians). The subfamily Gnathostominae contains 3 genera: *Tanqua* (cephalic bulb divided into 2 or 4 lobes with transverse cuticular ridges with sharp posteriorly-projecting edges but without hooks, parasites of aquatic reptiles); *Echinocephalus* (cephalic bulb undivided and armed with transverse rows of recurved hooks, body unarmed, parasites of fishes); and *Gnathostoma* (cephalic bulb undivided and armed with transverse rows of recurved hooks, body partially or wholly armed with posteriorly-directed spines, parasites of mammals).

Genus	No. spp.	Definitive Hosts	Location	Adult worms	Eggs	Transmission
Gnathostoma	18	carnivores	stomach	10-55 mm long, bulbous head with 2 lateral pseudolabia covered with spines extending to anterior body	62-79 x 36-42 µm ellipsoidal, thick-shelled, polar cap	indirect (L3 in copepodid intermediate hosts) [small vertebrates acting as second intermediate hosts or paratenic hosts]

Gnathostoma spp. are heteroxenous (multi-host) parasites with adult stages occurring in the gut of vertebrate hosts and larval stages developing in copepods (first intermediate hosts) and then ascending the food chain in a range of small vertebrates (second intermediate hosts or paratenic hosts). Some 18 species have been described in the genus *Gnathostoma,* most infecting the stomach (sometimes oesophagus and rarely kidneys) of carnivores. Several species have been associated with clinical disease in domestic animals, mainly *G. spinigerum* in cats and dogs and *G. hispidum* in pigs. The larval stages, however, have a broad host range and may infect many different species of small vertebrates (fish, amphibians, reptiles, birds and mammals) as paratenic hosts. The larvae may undertake extensive migrations through cutaneous tissues or visceral organs causing traumatic damage and inflammation. Several species are zoonotic (*G. spinigerum, G. hispidum*, *G. doloresi*, *G. nipponicum,* and *G.binucleatum*) as larvae infect humans as accidental hosts when they eat or handle raw or undercooked meat or drink water containing infected copepods.

***Gnathostoma* species**	**Definitive hosts [DH]**	**Location [Clinical signs]**	**First Intermediate Hosts [IH-1] Second Intermediate Hosts [IH-2] Paratenic Hosts [PH]**	**Distribution**
G. accipitris	Accipitriformes: accipitrid (imperial eagle)			Africa
G. americanum	Carnivora: felid (oncilla, Geoffroy's cat)	stomach		South America
G. binucleatum	Carnivora: canid (dog), felid (cat, ocelot), procyonid (Mexican raccoon)	stomach	IH-1: Copepoda: cyclopid (water flea, *Cyclops bicuspidatus, Eucyclops agilis, macrurus, prasinus, Macrocyclops albidus, Mesocyclops edax, leuckarti, tenuis*) [plus IH-2/PH: Characiformes: erythrinid (trahira); Cichliformes: cichlid (three spot cichlid, fenestrated cichlid, Mayan cichlid, blue tilapia, Mozambique tilapia, Nile tilapia, bay snook); Gobiiformes: eleotrid (bigmouth sleeper, spotted sleeper, Pacific sleeper, Pacific fat sleeper); Mugiliformes" mugilid (white mullet); Perciformes: centropomid (fat snook), haemulid (long-spined grunt); Siluriformes: ariid (dark sea catfish, Congo Sea catfish); Pelecaniformes: ardeid (great egret), pelecanid (American white pelican); Testudines: emydid (pond slider), kinosternid (Mexican mud turtle); Primates: hominid (human)]	Americas
G. doloresi	Artiodactyla: suid (pig, wild boar, Japanese boar)	stomach [inappetence]	IH-1: Copepoda: cyclopid (*Apocyclops royi, Cyclops strenuus, vicinus, Eucyclops serrulatus, Mesocyclops leuckarti, Thermocyclops hyalinus, taihokuensis*) [plus IH-2/PH: Urodela: hynobiid (spotted salamander, amber-coloured salamander); Anura: ranid (tiger frog); Serpentes: colubrid (loo-choo big-tooth snake, Japanese forest rat snake, Japanese striped snake, Pryer's keelback, tiger keelback), viperid (elegant pit viper, Okinawa habu, Hime habu, Siberian	Asia, Australasia

			pit viper); Perciformes: centrarchid (bluegill); Salmoniformes: salmonid (masu salmon); Rodentia: murid (mouse, rat); Peramelemorphia: peramelid (northern brown bandicoot); Primates; hominid (human)]	
G. gracile	Osteoglossiformes: arapaimid (pirarucu)	intestines		South America
G. hispidum	Artiodactyla: suid (pig, wild boar), Carnivora: felid (cat)	stomach [inappetence]	IH-1: Copepoda: cyclopid (*Acanthocyclops virides, Apocyclops royi, Cyclops strenuus, varicans, vicinus, Eucyclops serratus, Macrocyclops albidis, Mesocyclops leuckarti, Thermocyclops hyalinus, oithonides, taihokuensis*) [plus IH-2/PH: Anabantiformes: anabantid (climbing gourami), channid (striped snakehead, northern snakehead); Anguilliformes: anguillid (Japanese eel); Cypriniformes: cobitid (pond loach), cyprinid (common carp, predatory carp, goldfish, common bleak, Danube bleak, spotted steed, three-lips, common roach); Cyprinodontiformes: poeciliid (mosquitofish, guppy); Gobiiformes: odontobutid (dark sleeper); Perciformes: percid (European perch, zander), sinipercid (mandarin fish); Siluriformes: bagrid (yellow catfish), silurid (Amur catfish, wels catfish); Synbranchiformes: synbranchid (Asian swamp eel); Anura: dicroglossid (rice field frog), ranid (dark-spotted frog, Indian bullfrog); Serpentes: colubrid (Chinese garter snake, checkered keelback), viperid (short-tailed pit viper); Accipitriformes: accipitrid (northern goshawk); Anseriformes: anatid (duck, smew); Columbiformes: columbid (spotted dove); Falconiformes: falconid (peregrine falcon); Galliformes: phasianid (chicken); Passeriformes: sturnid (crested myna); Rodentia: caviid (guinea pig), murid (brown rat, black rat, mouse, southwestern Asian house mouse, Mongolian gerbil); Eulipotyphla: soricid (Asian house shrew); Lagomorpha: ochotonid (Daurian pika); Primates: cercopithecid (rhesus macaque), hominid (human)]	Asia, Australia, Central America
G. lamothei	Carnivora: procyonid (Mexican raccoon)	stomach		Americas
G. malaysiae	Rodentia: murid (red spiny rat)	stomach	[plus IH-2/PH: Synbranchiformes: synbranchid (Asian swamp eel); Primates: hominid (human)]	Asia
G. minutum	Serpentes: viperid (rhinoceros viper)	connective tissue		Africa
G. miyazakii	Carnivora: mustelid (North American river otter)	kidney		North America
G. nipponicum	Carnivora: mustelid (Japanese mink, American mink, weasel, Japanese weasel, Siberian	oesophagus	IH-1: Copepoda: cyclopid (*Acanthocyclops vernalis, Cyclops vicinus, Eucyclops serrulatus, Macrocyclops fuscus, Thermocyclops hyalinus*)	Japan, Korea

	weasel, ferret)		[plus IH-2/PH: Urodela: hydnobiid (clouded salamander); Anura: ranid (black-spotted frog, American bullfrog); Beloniformes: adrianichthyid (Japanese rice fish); Cypriniformes: cyprinid (big-scaled redfin); Cyprinodontiformes: cobitid (pond loach); Perciformes: centrarchid (largemouth bass); Salmoniformes: salmonid (masu salmon); Siluriformes: silurid (Amur catfish); Serpentes: colubrid (Japanese striped snake, tiger keelback); Rodentia: murid (mouse, brown rat); Primates: hominid (human)]	
G. occipitri	Accipitriformes: accipitrid (unspecified eagle)	subcutis		Russia
G. pelecani	Pelecaniformes: pelecanid (great white pelican)	subcutis, respiratory sacs		Eurasia
G. procyonis (syn. *G. 'neoprocyonis'*)	Carnivora: felid (cougar), procyonid (raccoon); Didelphimorphia: didelphid (common opossum)	stomach	IH-1: Copepoda: cyclopid (*Cyclops bicuspidatus, vernalis, Macrocyclops albidis*) [plus IH-2/PH Amiiformes: amiid (bowfin); Testudines: emydid (common box turtle, pond slider); Serpentes: viperid (water moccasin), colubrid (common kingsnake, common water snake); Testudines: emydid (false map turtle, yellow-bellied slider, common box turtle), kinosternid (eastern mud turtle); Crocodilia: alligatorid (American alligator); Pelecaniformes: threskiornithid (American white ibis); Primates: hominid (human)]	North America
G. socialis	Carnivora: mustelid (American mink)	stomach		Americas
G. spinigerum (syn. *Filaria radula*)	Carnivora: felid (cat, wildcat, Asian golden cat, lion, leopard, tiger), canid (dog, golden jackal), herpestid (Indian grey mongoose), mustelid (mink, ferret), procyonid (raccoon); Didelphimorphia: didelphid (common opossum)	stomach [acute abdominal signs, gut perforation, peritonitis]	IH-1: Copepoda: cyclopid (*Cyclops strenuus, varicans, vicinus, Eucyclops agilis, serrulatus, Mesocyclops leuckarti, Thermocyclops*) [plus IH-2/PH: Decapoda: cambarid (crayfish, *Procambarus clarkii*), parathelphusid (freshwater crab, *Paratelphusa sexpunctatum*), potamid (freshwater crab, *Potamon dehaani, smithanus*), varunid (mitten crab, *Eriocheir japonicus*); Gastropoda: ampullariid (snail, *Pila ampullacea, Pomacea canaliculata*); Anguilliformes: anguillid (Japanese eel); Anabantiformes: anabantid (climbing perch), channid (snakehead murrel, striped snakehead, northern snakehead, spotted snakedhead, blotched snakehead, forest snakehead, giant snakehead, Assamese snakehead, dalug), osphronemid (banded gourami, moonlight gourami, snakeskin gourami, three-spot gourami); Beloniformes: belonid (freshwater garfish); Characiiformes: erythrinid (trahira); Cypriniformes: cyprinid (common carp, predatory carp, Crucian carp, spotted steed, three-lips, slender rasbora); Cyprinodontiformes: cobitid (pond loach), poeciliid (eastern mosquitofish); Gobiiformes: gobiid (tank goby, javelin	Asia, Americas, Africa, Australia

			goby), eleotoid (dark sleeper), oxudercid (yellowfin goby); Osteoglossiformes: notopterid (Asian knifefish); Perciformes: nandid (Gangetic leaf-fish), sinipercid (mandarin fish), terapontid (silver perch, ayungin); Siluriformes: ariid (engraved catfish), bagrid (yellowhead catfish, yellow catfish, pla kayeng), clariid (walking catfish, Hong Kong catfish, broadhead catfish), heteropneostid (Asian stinging catfish), silurid (butter catfish, padbah catfish, Amur catfish, helicopter catfish, pla deng, pla neua on); Synbranchiformes: mastacembelid (spiny eel), synbranchid (Asian swamp eel, Gangetic swamp eel, Bengal eel); Anura: bufonid (common toad, Asian common toad), dicroglossid (Chinese edible frog, Indian bullfrog, rice field frog), hylid (European tree frog), microhylid (banded bullfrog), ranid (common green frog, dark-spotted frog, American bullfrog); Urodela: hynobiid (spotted salamander), salamandrid (Japanese newt); Serpentes: acrochordid (elephant trunk snake), colubrid (checkered keelback, tiger keelback, grass snake, cateye snake, oriental odd-tooth snake, Japanese striped snake), cylindrophiid (red-tailed pipe snake), elapid (Asian cobra, king cobra, banded krait), homalopsid (bockadam snake), pythonid (reticulated python), viperid (green pit viper, Russell's viper); Sauria: agamid (oriental garden lizard, common butterfly lizard), gekkonid (Tokay gecko, Schlegel's Japanese gecko), lacertid (Japanese grass lizard), scincid (Herbert's writhing skink), varanid (Bengal monitor, Asian water monitor, clouded monitor); Testudines: geoemydid (Chinese three-keeled pond turtle), geomyid (snail-eating turtle); Accipitriformes: accipitrid (black kite, black-eared kite, northern goshawk, Eurasian sparrowhawk, pied harrier), pandionid (osprey); Anseriformes: anatid (domestic duck, Eurasian teal, red-breasted merganser); Charadriiformes: jacanid (pheasant-tailed jacana), scoilopacid (Eurasian woodcock); Coraciiformes: alcedinid (common kingfisher); Galliformes: phasianid (chicken, common quail); Gruiformes: rallid (Indian water rail); Passeriformes: corvid (carrion crow, large-billed crow, oriental magpie, Australian raven); Pelecaniformes: ardeid (grey heron, striated heron, great blue heron, cattle egret, eastern great egret, little egret, intermediate egret, black-crowned night heron, bittern), pelecanid (American white pelican, brown pelican, spot-billed pelican); Podicipediformes: podicipedid (little grebe); Strigiformes: strigid (Ural owl); Rodentia: caviid (guinea pig), cricetid (golden hamster), murid (greater bandicoot rat, black rat, brown rat, white rat, Polynesian rat, white mouse, southwestern Asian house	

			mouse), sciurid (Pallas's squirrel); Scandentia: tupaiid (common treeshrew); Dasyuromorphia: dasyurid (northern quoll); Didelphimorphia: didelphid (common opossum, Virginia opossum); Lagomorpha: leporid (rabbit); Artiodactyla: suid (pig); Carnivora: herpestid (Javan mongoose), mustelid (Siberian weasel); Primates: cercopithecid (crab-eating macaque, stump-tailed monkey, silver leaf monkey), hylobatid (lar gibbon), hominid (human)]	
G. turgidum (syn. *G. brasiliense, didelphis*, *oligomucronatum*)	Didelphimorphia: didelphid (common opossum, white-eared opossum, Virginia opossum, lutrine opossum, gray four-eyed opossum); Carnivora: ursid (American black bear)	stomach, liver	[IH-2/PH: Cichliformes: cichlid (Nile tilapia); Primates: hominid (human)]	Americas
G. vietnamicum	Carnivora: mustelid (Asian small-clawed otter)	kidney	IH-1: Copepoda: cyclopid (*Mesocyclops leuckarti*) [plus IH-2/PH: Synbranchiformes: synbranchid (Asian swamp eel)]	Asia

Parasite morphology: *Gnathostoma* spp. form 3 different types of morphological stages during their development: eggs; larvae (moulting through 4 stages, designated L1-L4); and adult worms. Eggs are ovoid-ellipsoidal in shape measuring 62-79 x 36-42 µm in size and vary in colour from yellow-brown to green due to bile staining. They are bound by thick shells with a finely pitted surface and conspicuous polar swellings at one or both ends and a distinctive mucoid cap (plug or protrusion) at one pole. When laid, they are unembryonated and contain a central morula, either unsegmented or cleaved at the 2-4 cell (blastomere) stage. First-stage larvae (L1) have elongated bodies measuring 180-360 µm in length with rounded heads armed with small solid spine-like structures. They are coiled up within eggs apparently within a delicate smooth transparent sheath. L2 have cylindrical bodies ranging from 400-625 µm in length and they have retained the L1 cuticle (exuvium) as a transparent sheath with a smooth cuticle and no visible striations. The larvae have bulbous heads with 3-4 rows of cephalic spines (hooklets), cervical sacs and glands, 2 lateral trilobed lips, a cylindrical oesophagus, tubular intestines, and rounded tails. L3 have elongate red-white bodies measuring 2-4 mm in length (some species measure up to 12.5 mm) and usually coiled up within tissue cysts. The larvae have inflated heads with 3-4 transverse rows of cephalic spines, bodies with incomplete coverings of small spines and they contain tubular alimentary tracts and undifferentiated genital primordia. L4 are transient parasitic stages that have developed most adult features, particularly head and body armature, but the genitalia are still immature. Adults have thick elongate tapering bodies measuring from 10-55 mm in length and ranging from red-beige in colour (sometimes red anteriorly and yellow-grey posteriorly). They have characteristic bulbous heads (cephalic bulb) armed with 8-12 transverse rows of recurved cuticular spines (also called hooks or hooklets) and spinose bodies partly or wholly armed with flat leaf-like posteriorly-directed spines (sometimes absent on hindbody). The cephalic bulb is connected to 4 muscular cervical sacs and 4 ballonets which are used to inflate and deflate the bulb. The anterior mouth has 2 well-developed lateral pseudolabia leading to an elongate undivided oesophagus and tubular intestines, the latter being one cell thick, each cell having 2-6 nuclei depending on the species. Adult worms are sexually dimorphic, with males being smaller than females (10-40 cf. 10-55 mm in length). Mature males have rounded tails with 2 cuticular dilations, 8 peri-cloacal caudal papillae, and 2 long blunt unequal spicules. Mature females have curved tails and are didelphic with 2 ovaries and 2 uteri connected to a distinct vagina and a common vulva opening in near the midbody. Gravid females are oviparous and produce partially embryonated eggs.

Site of infection: Adult worms usually infect the wall of the stomach of their definitive hosts (carnivorous mammals, birds, some reptiles), although some species may also infect the oesophagus, intestines, kidneys or urinary bladder. Larval stages develop in the body cavities of aquatic copepods (first intermediate hosts), and infective larvae may be carried in the tissues of numerous small copepod-eating vertebrates (acting as second intermediate and/or paratenic hosts). Humans are accidental hosts for larval stages which do not mature to adult worms but migrate throughout the body before dying.

Pathogenesis: Many infections are clinically inapparent while others have been associated with a wide variety of conditions ranging from vague abdominal signs to specific cutaneous lesions to gastritis with anorexia, illthrift and sometimes life-threatening peritonitis. The severity of disease depends on many factors, including parasite species (some species are more invasive and

virulent), host susceptibility (especially young animals, although infections may accumulate with age due to repeated exposure and little protective immunity), the site of infection (damage to vital organs more problematic than superficial locations), the intensity of infection (numbers of parasites) and the stage of infection (prepatent period involving larval migration, or patent period involving adult worms). Parasites use their fluid-filled muscular sacs to expand and contract the cephalic bulb armed with rows of recurved hooks thus facilitating their invasion and migration in host tissues. Both larvae and adult worms may cause disease at different stages of infection. Larvae are aggressive migrators and may cause acute clinical signs or more chronic cutaneous and/or visceral lesions. They may infect a wide variety of tissues and organs causing trauma by mechanical and chemical disruption and provoking inflammation with leucocytosis (marked eosinophilia). Larval migration may last for several weeks to several years. In contrast, adult worms remain in the gastric mucosa where they become deeply embedded forming conical fibrous nodules, which sometimes ulcerate or even perforate resulting in peritonitis. Clinical signs may first become evident within 1-2 days as infective larvae penetrate the gut wall and migrate to the liver and other abdominal organs. This stage may last for 2-3 weeks and involve tissue trauma, microlesions, petechial haemorrhages, and the development of sinuous necrotic tracts in the liver and other organs. Signs may include burning abdominal pain (especially epigastric) with fever, nausea, vomiting, salivation, diarrhoea, anorexia, malaise, and urticaria accompanied by marked eosinophilia, all of which gradually subside. Most infections then progress to the development of cutaneous lesions, usually within 3-4 weeks but sometimes delayed for many months. Dermatological manifestations are caused by larvae migrating through subcutaneous tissues resulting in the condition variously known as cutaneous gnathostomiasis, cutaneous larval migrans, creeping eruption (regional variants include Yangtze River oedema, Consular disease or Shanghai rheumatism in China, tuao chid in Japan, paniculitis nodular migratoria eosinofilica in central America, and Woodbury bug in Australia). Lesions are characterised by recurrent or intermittent migratory (wandering) swellings, usually on the trunk and upper limbs, and larvae have been observed to move at 1 cm/hr. The swellings typically last 1-2 weeks and recurrent episodes become less intense and shorter in duration although they can persist for many years if left untreated. The non-pitting oedematous swellings vary in size and are often pruritic, sometimes painful and/or erythematous with a continuous non-linear track appearing beneath the skin due to subcutaneous haemorrhages and localised panniculitis, and occasionally with nodule, pseudofuruncle (boil-like) or abscess formation. Migration of larvae into the viscera may cause a more serious form of disease, known as visceral gnathostomiasis or visceral larval migrans. A wide range of organs may be involved resulting in clinical manifestations unique to that organ system. Larvae migrating through the lungs may cause pleuritic chest pain, cough, haemoptysis, pneumonitis with lobar consolidation, pleural effusions, and hydropneumothorax. Larvae frequently migrate to the eye causing pain, conjunctival erythema, lachrymation, uveitis, ophthalmitis, increased intraocular pressure, ocular haemorrhages and lesions, retinal detachment, diminished vision and sometimes blindness. Occasionally, larvae migrate to the ears causing mastoiditis and sensorineal hearing loss. Invasion of the genitourinary system is uncommon but may result in haematuria with adnexal masses, cervicitis and vaginal bleeding in females and balanitis and haematospermia in males. More often, larvae migrate along nerves to the central nervous system causing serious neurological signs including radiculitis, myelitis, cranial nerve palsies, subarachnoid haemorrhages, eosinophilic meningitis, myeloencephalitis, muscle stiffness and weakness, paresis/paralysis, loss of bladder/intestinal control, headaches, seizures, coma and even death. Adult worms live in tunnels in gastric nodules which appear as thick-walled fibrous growths up to 40 mm in diameter on the stomach wall. The nodules are often cavitated and contain several worms and yellow-green fluid and sometimes purulent material. The gastric mucosa is reddened, swollen and oedematous (catarrhal, haemorrhagic or nodular gastritis) and often covered with easily removable pseudomembranes. The nodules usually open into the stomach, and they sometimes ulcerate and may even perforate the gut wall leading to purulent peritonitis and death. Clinical signs include abdominal sensitivity and intermittent pain (sometimes mimicking acute appendicitis or intestinal obstruction), vomiting, constipation alternating with diarrhoea, excessive thirst, inappetence, and loss of condition with weight loss and growth retardation. Heavy infections in pigs may lead to production losses due primarily to gastritis with inappetence and weight loss, while heavy infections in dogs and cats often cause acute abdominal signs, and sometimes gastric perforation and fatal peritonitis. Humans are accidental hosts in which larvae may migrate throughout the body without maturing to adult worms but eventually dying or spontaneously leaving through the skin. Larvae have been found in association with lesions and disease in the alimentary, respiratory, lymphatic, muscular, cutaneous, genitourinary and nervous systems of human patients around the world.

Developmental cycle and mode of transmission: *Gnathostoma* spp. have indirect heteroxenous life-cycles involving adult stages developing in carnivores (definitive hosts), larval stages developing in copepods (intermediate hosts) and then transported in small vertebrate (paratenic hosts), often ascending the food chain. Gravid female worms in gastric nodules lay unembryonated eggs which pass to the lumen of the stomach and are excreted with host faeces. Eggs deposited in freshwater bodies embryonate and hatch in 7-14 days depending on the prevailing temperature. Most reports state that eggs hatch to release L1 although a few studies indicate they may be L2. The freed larvae are ingested by cyclopoid copepods which act as first intermediate hosts supporting further parasite development. Ingested larvae shed their sheaths and penetrate the intestinal wall to the haemocoel (body cavity) where they moult to form early-stage L3 within 10 days. Many reports indicate that these early-stage L3 are not directly infective to final hosts but require further maturation in small copepod-eating vertebrates, but several experimental studies have infected final hosts by feeding them copepods containing L3. Nevertheless, a variety of aquatic, amphibious or terrestrial vertebrates (freshwater fishes, amphibians, reptiles, birds and mammals) that have consumed infected copepods may act as second intermediate hosts in which further larval development occurs (even if it is limited to L3 maturation). Ingested early-stage L3 penetrate the gut wall of these vertebrate hosts and migrate to the muscles and mesenteries in 6-7 days where they encapsulate and develop to advanced- or late-stage L3. Advanced L3 may also ascend the food chain via predation and scavenging as they are able to re-encapsulate in tissues of numerous paratenic (transport) hosts (including fish, frogs, snakes, lizards, turtles, birds, mammals). Definitive hosts become infected when they consume L3 either in first intermediate hosts (copepods), in second intermediate hosts (small copepod-eating

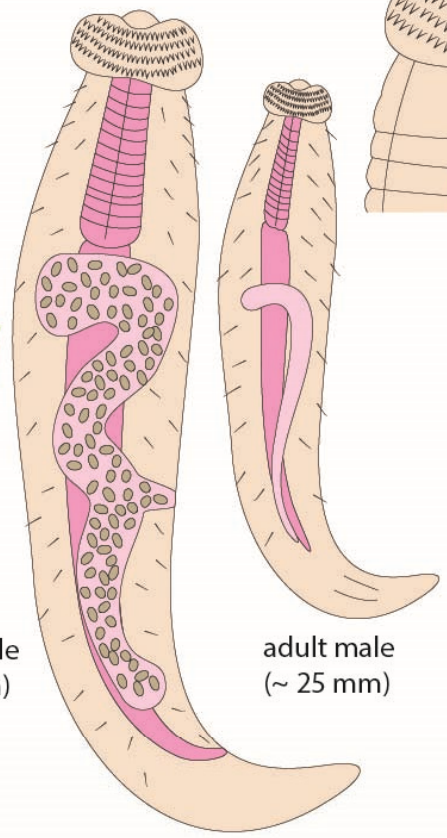
vertebrates), or in paratenic hosts (small predatory vertebrates). Ingested L3 penetrate the stomach wall and migrate to the liver then the muscles and connective tissues over several weeks (prolonged to several months in some species) before returning to the stomach. Larvae moult twice during these migrations forming L4 and then subadults (sometimes called L5) which embed themselves in the stomach mucosa where they mature to adult worms and form nodules over 2-6 months. The prepatent period (time from infection to first excretion of eggs) can be as short as 2 months for some species but is often longer at 5-6 months, and adult worms may live for over 1 year. Humans are non-permissive hosts in which larval migration may occur without developing to sexually-mature adult worms. Humans usually become infected with L3 by eating raw or undercooked meat (fish, frogs, poultry, pork), such as koi pla and som phac in Thailand, sushi and sashimi in Japan, and ceviche in Latin America. Some infections have also been reported in people handling raw meat when larvae penetrate through the skin, and a few infections have been linked to people drinking water contaminated by infected copepods. Several instances of prenatal infection have also been reported in newborn babies.

Differential diagnosis: Infections in animals are rarely diagnosed on the basis of clinical symptomatology as they have been associated with a wide range of nonspecific clinical signs either caused by larvae migrating through tissues and organs or by adult worms developing in the stomach. In contrast, infections in humans are often indicated by intermittent migratory cutaneous swellings in association with a history of travel to endemic areas and the consumption of undercooked foods. Patent infections are conventionally diagnosed by the detection of characteristic eggs in faecal samples, usually following their concentration by sedimentation and/or floatation techniques (but remember that worms do not mature in humans so infections do not become patent). Haematological examinations often reveal leucocytosis (especially eosinophilia) during larval migration, and eosinophils may also be detected in cerebrospinal fluid (which may be bloody or xanthochromic). Medical imaging techniques have been used to assist diagnoses by locating migratory or space-occupying lesions in superficial tissues by ultrasonography or deeper tissues by radiography, computed tomography (CT) and magnetic resonance imaging (MRI). Endoscopy (gastroscopy) has also been used to reveal nodular masses in the stomach wall. Infections may also be diagnosed by the recovery and identification of parasites: either larvae in biopsy samples (some larvae may also emerge spontaneously from the skin, particularly after anthelmintic treatment); or adult worms in surgical or necropsy samples. A range of immunodiagnostic techniques have been evaluated with variable success. Skin tests using intradermal injections of parasite antigens have generally yielded poor results lacking both sensitivity and specificity. Several immunoserological tests have been developed to detect host antibodies in serum samples (sometimes in cerebrospinal fluids), including fluorescent antibody tests, radio-immunoassays and enzyme-linked immunosorbent assays, but some cross-reactivity with other nematodes was observed despite using partially purified antigens and monoclonal antibody reagents. More recently, Western blots have been used to detect parasite antigens in clinical samples with good sensitivity and specificity observed for a small number of parasite species. Molecular biological techniques have been successfully used to characterize larvae and adult worms from a range of piscine and carnivorous hosts following the polymerase chain reaction (PCR) amplification of nuclear (ribosomal RNA and internal transcribed spacers) and mitochondrial genes (cytochrome c oxidase subunit I).

Treatment and control: Infections by adult worms have responded reasonably well to treatment with conventional anthelmintics, including benzimidazoles (albendazole), imidazothiazoles (levamisole), isoquinolines (praziquantel) and macrocyclic lactones (ivermectin, doramectin), but repeated treatments are required to avoid relapses from developing larvae. Many veterinary authorities also recommend chemoprophylactic treatment of livestock at least twice a year (at weaning and before confinement). Anthelmintic treatment has been shown to reduce the severity of cutaneous migratory swellings and dermatitis induced by larvae, but treatment was not effective against neurological infections (drugs unable to access blood-brain barrier). There was also some evidence to suggest that treatment may exacerbate cutaneous and/or neurological symptoms, and that supportive treatment with anti-inflammatory corticosteroids may help alleviate symptoms. In some instances, albendazole treatment was shown to result in the emergence of larvae from the skin. Cutaneous infections in humans have also been treated by the surgical removal of the larvae, sometimes simply by needle manipulation and extraction, but often by deeper excision. Various preventive strategies may be applied in domestic or agricultural situations to curb transmission between hosts, but such interventions are not suitable for broader use in natural ecosystems involving wildlife. The parasites utilize a broad range of definitive, intermediate and paratenic hosts involved in complex predator-prey relationships in the food chain. Improved sanitary practices may reduce environmental contamination by worm eggs, particularly when faeces are not allowed to pollute water sources but are regularly collected and treated. Manure should not be used as fertiliser and wastewater should not be used for irrigation. Animal holding facilities should be kept clean, and drinking water supplies should be treated, even if only by coarse filtration to remove copepods. Wildlife should be excluded from holding facilities and livestock and companion animals should be prevented from hunting and scavenging. Several public education campaigns have been used in endemic regions to help prevent infections in humans, primarily by reducing the risks of food-borne transmission by improved food preparation and hygiene. Cooks should be alerted to the risks of handling raw meat products (from which larvae may emerge) and people should avoid the consumption of raw or undercooked fish, poultry and pork (potentially containing infective larvae). Experimental studies have shown that larvae may survive treatment with lime juice for up to 5 days, pickling in vinegar for up to 6 hours, and salting in soy sauce for up to 12 hours, but they do not survive cooking temperatures > 63°C or freezing at -20°C for 3-5 days or at -4°C for 4 weeks. Nonetheless, it is very difficult to change traditional culinary practices, particularly those promoted as healthy and fresh alternatives to processed foods.

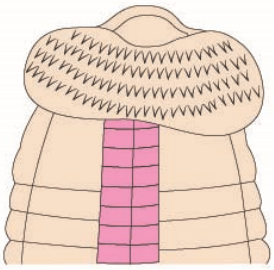
Gnathostoma

stomach
(gastritis, inappetence,
perforation, peritonitis)

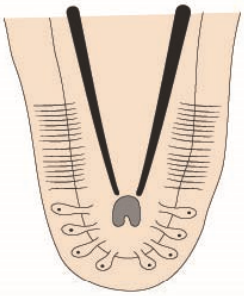


adult female
(~ 40 mm)

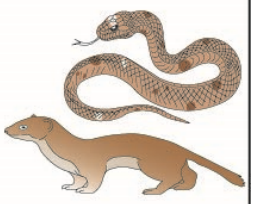
adult male
(~ 25 mm)

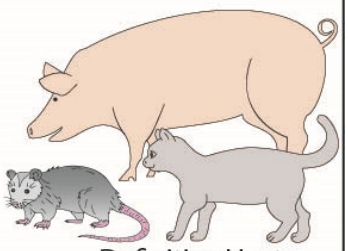


head



male tail





Definitive Hosts
(carnivores, omnivores,
birds, reptiles)

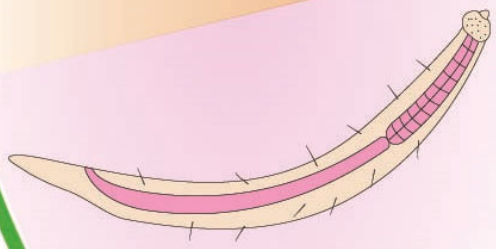
larval
migration

eggs
excreted
in
faeces

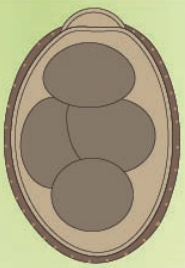
IH/PH
ingested

L3 encapsulate in IH-2/PH

IH-1
ingested
by IH-2/PH

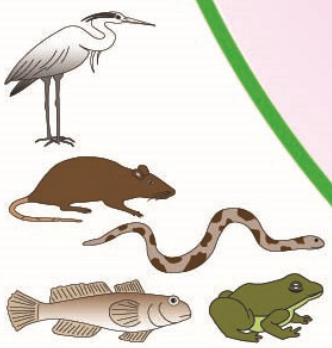


third-stage larvae
(L3) (~ 3 mm)



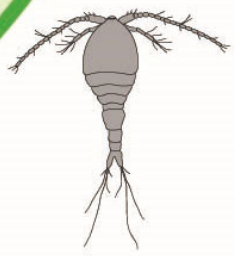
eggs
(~ 70 µm)

first-stage larvae
(L1) (~ 300 µm)



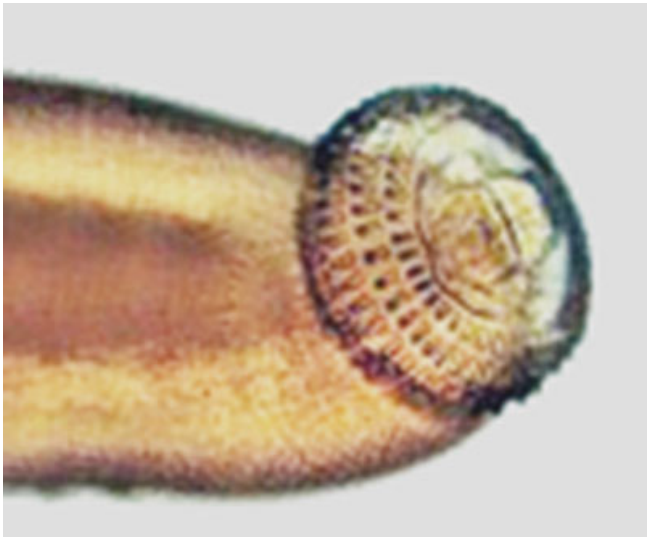
Second Intermediate Hosts
(IH-2) or Paratenic Hosts (PH)
(fish, frogs, reptiles, rodents)
(mesenteries, muscles)

L1 ingested
by IH

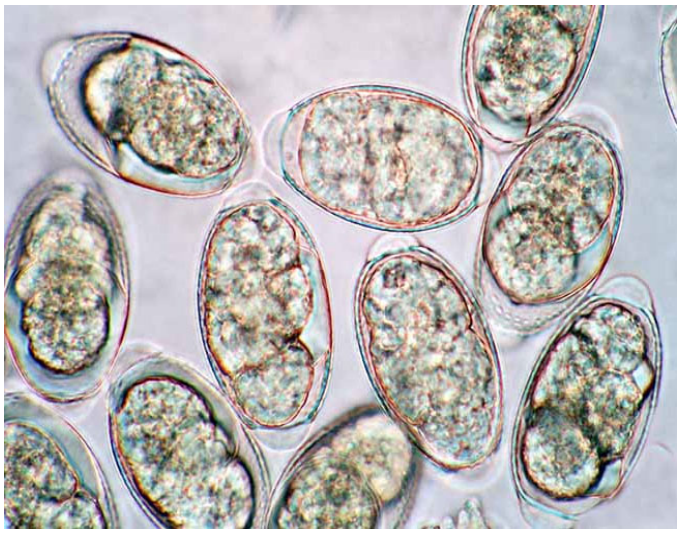


First Intermediate Hosts
(IH-1) (copepods)
(body cavity)

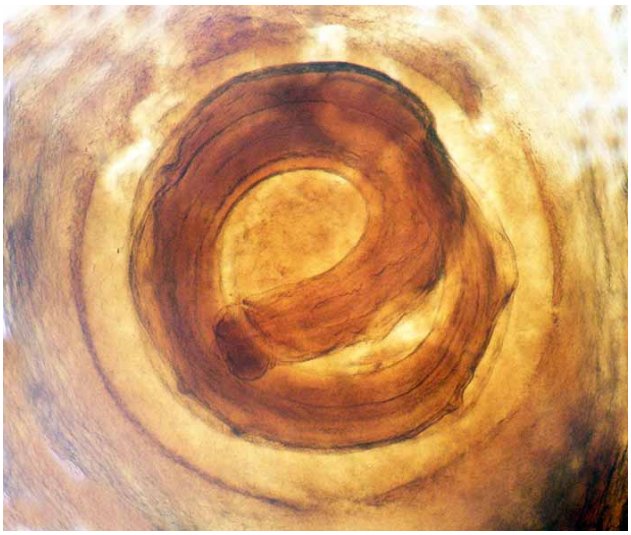
Gnathostoma adult worm



Gnathostoma adult worm, head



Gnathostoma worm eggs



Gnathostoma larva, mouse tissue