Dracunculus
(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. On molecular evidence, the latter is considered to contain the superfamily Dracunculoidea *incertae sedis*. These non-bursate worms have conspicuous phasmids (broad cavities and prominent pores) and indirect life-cycles involving crustacean (copepod) intermediate hosts in which L3 develop. Dracunculids have weakly-developed buccal capsules and the elongate adult females are found in the tissues of reptiles and mammals. Subcutaneous infections of humans by the guinea worm *Dracunculus medinensis* cause painful fiery blisters through which larvae are released into cooling waters to infect copepods. Infections have been described throughout human history; the iconic 'staff-with-serpent' adopted as the official symbol of medicine may even depict the traditional means of worm removal by winding it onto a stick. It is one of the few parasitic nematodes currently brought close to extinction due to effective environmental control measures.

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)
	Incertae sedis
Superfamily:	Dracunculoidea (elongate parasites of vertebrate tissues, freshwater crustacean IH)
Family:	Dracunculidae (buccal capsule reduced, female highly enlarged, filled with L1, copepod IH)
Genus:	*Dracunculus* (parasitic in subcutaneous tissues of humans)
Species:	*D. medinensis* (causes dracunculiasis 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.

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). Two camallaninid superfamilies are recognised: Camallanoidea (buccal cavity well-developed, tiny internal labial papillae, gut parasites); and Dracunculoidea (buccal cavity weakly-developed, prominent internal labial papillae, tissue parasites). Five dracunculoidid families are recognised: Anguillicolidae, Guyanemidae and Philometridae in fishes; Micropleuridae in reptiles; and Dracunculidae in mammals, reptiles and birds.

The family Dracunculidae contains worms with marked sexual dimorphism: small males with pointed tails sometimes with narrow caudal alae; and large females with reproductive organs that atrophy in mature worms so that the body becomes filled with first-stage larvae (L1). Two genera are recognised: *Dracunculus* (syn. *Ophiodracunculus*, *Chelonidracunculus*, *Pesteria*) in mammals and reptiles; and *Avioserpens* (syn. *Oshimaia*, *Petroviprocta*) in marine birds. The genus *Dracunculus* contains around 14 species of worms with weakly-developed buccal capsules, triangular mouths with quadrangular sclerotized plates, thick peribuccal rings, 2 circlets of cephalic papillae and conspicuous phasmids. Adult males are small and non-bursate, while adult females are highly enlarged and ovoviviparous (releasing embryos rather than eggs). They all have indirect life-cycles involving the development of infective (L3) larvae in freshwater copepodid hosts. Infections of humans by *D. medinensis* have been recorded many times in history, being described as 'little snakes' by Greek and Roman scholars, 'fiery serpents' in Biblical texts (Numbers 21:4-8), and colloquially named Medina-worms, guinea-worms or dragon-worms. Infections occurred throughout semi-desert areas of sub-Saharan Africa, India, the Middle-East and Brazil, mainly in rural areas where water was drawn from wells or shallow ponds during the rainy season. However, the amazing successes of preventive campaigns fostered by the World Health Organization

(WHO) have significantly reduced the global prevalence of infections (from 15 million in 1980 to 4 million in 1986, 60,000 in 1997, 1,785 in 2010 and 25 in 2016) and led to its eradication in over 20 countries (as of 2016, small foci persisting only in Chad, Ethiopia and South Sudan). This parasite is facing imminent extinction due to deliberate human intervention. It must be remembered that infections by *D. medinensis* have also been found occasionally in dogs, cats, cattle, horses and other mammals, so some animals may act as reservoirs for zoonotic infection. The species *D. insignis* has been found in raccoons, muskrats, mink, weasels and other carnivores (sometimes humans) in North America, and other species in opossums, otters, snakes and turtles from several continents (Americas, Africa, India, Asia, Australia). The larval stages of all *Dracunculus* spp. use aquatic copepods as intermediate hosts (vectors) and some may even survive in tadpoles/frogs and freshwater fish which subsequently act as paratenic (transport) hosts.

***Dracunculus* species**	**Definitive hosts (DH)**	**Location**	**Intermediate hosts (IH)**	**Distribution**
D. alii	Serpentes: colubrid (checkered keelback snake)	body cavity, mesenteries		India
D. brasiliensis	Serpentes: boid (anaconda), colubrid (brown-banded water snake)	connective tissue, body cavity		Brazil
D. coluberensis	Serpentes: colubrid (trinket snake)	lung		India
D. dahomensis	Serpentes: pythonid (African rock python)	connective tissue		Africa
D. doi	Serpentes: boid (Madagascar boa), pythonid (royal python)	peritoneal mesentery	Copepoda: cyclopid (*Cyclops strenuus*)	Madagascar
D. fuelleborni	Didelphimorphia: didelphid (opossum)	subcutaneous tissue		Americas
D. globocephalus	Testudines: chelydrid (common snapping turtle)	mesenteries, body cavity	Copepoda: cyclopid (*Cyclops bicuspidatus*)	North America
D. houdemeri	Serpentes: colubrid (checkered keelback snake)	cutaneous connective tissue		Vietnam
D. insignis (North American guinea worm)	Carnivora: mustelid (American mink, fisher, river otter, badger, weasel, ferret, American marten, European polecat), procyonid (raccoon), mephitid (striped skunk), canid (coyote, gray fox, dog), felid (cat); Didelphimorphia: didelphid (opossum); Rodentia: cricetid (muskrat); Primates: cercopithecid (rhesus macaque), hominid (human)	subcutaneous tissues	Copepoda: cyclopid (*Cyclops bicuspidatus, vernalis, Cryptocyclops linjanticus, Mesocyclops aequatorialis, leukarti, Thermocyclops emini*) [tadpoles/frogs and freshwater fish may act as paratenic hosts]	North America
D. lutrae	Carnivora: mustelid (river otter)	subcutaneous tissue	Copepoda: cyclopid (*Cyclops*)	North America
D. medinensis (Guinea worm, Medina worm, fiery dragon, fiery serpent) (syn. *D. graecorum, D. aethiopicus*)	Primates: hominid (human); Carnivora: canid (dog, golden jackal), felid (cat, leopard), mustelid (ferret); Artiodactyla: bovid (cattle, chinkara); Perissodactyla: equid (horse); Rodentia; cricetid (muskrat) Serpentes: elapid (cobra)	subcutaneous connective tissue	Copepoda: cyclopid (*Cyclops atter, bisetosus, coronatus* (*fuscus*)*, decipiens, fimbriatus, hyalinus, inopinus, iranicus, karvei, magnus, microspinulous, nigerianus, oithonoides, quadricornis, rylovi, tinctus, varicans, vermifer, vernalis, Eucyclops, Macrocyclops, Mesocyclops aequatorialis, aspericornis, hyalinus, kieferi, leukarti, Metacyclops margaretae, Thermocyclops crassus, emini, incisus, inopinus, kieferi, neglectus, nigerianus, oblongatus, spinosus, vermifer*) [tadpoles/frogs may act as paratenic hosts]	Africa, India, Middle East, South America (range considerably reduced due to control programs)

D. mulbus	Serpentes: pythonid (Papuan python, water python)	connective tissue, body cavity		Australia
D. oesophagea (syn. *D. ricci*)	Serpentes: colubrid (viperine water snake, ringed snake, grass snake)	body cavity	Copepoda: cyclopid (*Macrocyclops fuscus*)	Eurasia
D. ophidensis	Serpentes: colubrid (blackbelly garter snake)	subcutaneous tissue	Copepoda: cyclopid (*Cyclops viridis*) [tadpoles may act as paratenic hosts]	North America

Parasite morphology: Guinea-worms develop through four larval stages prior to the formation of large adult worms; eggs are not produced. First-stage larvae (L1) appear as thin white tubular stages measuring 490-737 by 18-24 µm in size and having a rhabditiform pharynx, long pointed tail, striated cuticle with lateral ridges and a dorsal tooth. The third-stage larvae (L3) are elongate measuring from 240-608 by 12-23 µm in size, and they have a filariform pharynx, intestines containing transparent and brown globules and a genital primordium consisting of 6-8 cells. Adult worms exhibit marked sexual dimorphism: males measuring from 12-40 mm in length with unequal spicules (490-750 µm) and an accessory organ (gubernaculum) in most species; while creamy-white females may grow up to exceptional lengths of 500-1,200 mm by 0.9-2.0 mm in width. In young females, the vulva is located around the midbody but it becomes atrophied and non-functional in adults, as does the intestine due to the high internal pressure generated by the gravid uterus. Mature females are ovoviviparous and contain thousands of developing embryos. The mouth is a triangular opening surrounded by a quadrangular sclerotized plate (lips are absent) with two circlets of cephalic papillae. Although the worms are very long and thin, they differ from filarial worms morphologically (e.g. females only have one uterus rather than 2 like filariae), biologically (aquatic copepodid intermediate hosts rather than terrestrial arthropods) and genetically (phylogenetic studies based on 18S ribosomal DNA sequences group them separately).

Site of infection: Infective larvae (L3) ingested by definitive hosts penetrate the gut and invade subcutaneous connective tissues, migrating mainly to the axillary and inguinal regions. Maturing female worms of *D. medinensis* migrate from deep connective tissues to peripheral subsurface locations, particularly in the extremities of limbs (legs and arms) although they can occur elsewhere. The adults of other *Dracunculus* spp. also develop in subcutaneous locations in their mammalian hosts as well as in the internal tissues and body cavities of their reptilian hosts. Larval stages (L1-3) develop in the haemocoel of their copepodid intermediate hosts.

Pathogenesis: Despite their eventual enormous size, infections by guinea-worms usually do not produce any clinical signs until the mature female worms migrate to the skin and provoke the formation of a papule then a blister. Migration may sometimes produce vague allergic reactions, including nausea, dizziness, fainting, diarrhoea, rash, asthma, local oedema and eosinophilia. Infections then cause disease known variously as subcutaneous filariasis, Guinea worm disease, dracunculosis or dracunculiasis. Infections generally produce two types of lesions: subcutaneous or deep abscesses around dead worms (involving many inflammatory cell types) that tend to calcify; or cutaneous papules that rapidly blister and then rupture to form cup-shaped ulcers through which females release live larvae. Skin lesions may involve local erythema, urticaria, inflammation, ulceration and intense burning pain (fiery serpent of biblical times). In the majority of infections, blisters form on the lower extremities and only occasionally involve other body parts, such as the genitalia, buttocks, torso, upper extremities and head. Patients seek to relieve symptoms by immersing the affected region in cool water. Lesions are initiated by secreted irritants and the deposition of larvae in the tissues and the induction of hypersensitivity reactions which ultimately produce ulcers through which larvae, and parts of the adult worm, emerge (a unique means for tissue-dwelling parasites to seek egress from their hosts). In uncomplicated cases, lesions may only last for several weeks until the worm is completely expelled. However, many cases involve secondary bacterial infection of the worm track with persistence of the lesion, chronic ulceration and possible sequelae, involving abscessation, disseminated infections, phlegma of limbs, contractures of tendons, fibrous ankylosis or arthritis in the joints, or even tetanus.

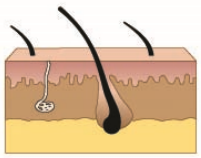
Developmental cycle and mode of transmission: The parasites have a unique indirect life-cycle, involving cyclopoid copepods (water fleas) as intermediate hosts. When adult female worms in the skin mature and become gravid, the high internal pressure causes the body wall to burst forcing through a loop of the uterus. Larvae released into the tissues provoke a violent allergic reaction causing skin blisters which eventually rupture (particularly on contact with water) releasing larvae from the tissues as well as from the exposed and protruding anterior portion of the worm from which the gravid uterus may prolapse. Muscular contractions of the body wall (instigated by cool water) force thousands of larvae out in periodic spurts (up to half a million per day). As exposed portions of the uterus empty, they disintegrate and adjacent portions move into the ulcer. Release of larvae can continue over several weeks if the lesion is repeatedly immersed in water, although the remnants of the female worms die within 2-6 weeks of penetrating the skin. Liberated larvae are infective for less than a week and they actively move about in water attracting copepodid crustaceans which ingest them. Copepods range in size from 0.5-2.0 mm and breed best in standing waters such as ponds, pools, cisterns and open wells, so infections are common in remote rural areas reliant on such water supplies. The larvae penetrate into the haemocoel of the copepods, especially dorsal to the gut, and develop into infective third-stage larvae (L3) over 12-20 days (at 25°C). Humans

become infected by swallowing infected copepods with drinking water. Larvae of several *Dracunculus* spp. (especially those infecting wildlife) have also been found to survive in tadpoles, frogs and even some freshwater fish, which apparently act as paratenic (transport) hosts. When infected copepods (or infected paratenic hosts) are ingested by definitive hosts, the infective larvae penetrate the intestinal wall and migrate for about 3 months through connective tissues where male and female worms develop and mate. The males remain in the tissues and become encapsulated and die in a few months, while the fertilised females migrate to subcutaneous sites and grow to essentially become non-feeding bags full of larvae. Gravid females begin to emerge from the skin around 10-14 months after infection.

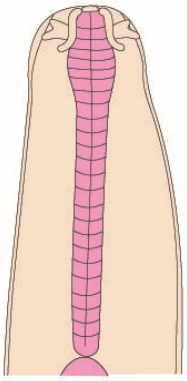
Differential diagnosis: Local itching, urticaria and a burning pain at the site of a small blister are usually the first clear symptoms of dracunculiasis. Infections become obvious once part of the female worm emerges. Milky clouds of larvae can also be seen under low magnification when the lesion is placed in water. X-ray imaging techniques have been used to detect calcified worms. Immunoserological tests (enzyme immunoassays) have been developed to detect host antibodies formed against parasite antigens, but given the persistence of circulating antibodies it can be difficult to discriminate between recent and previous exposure. Molecular tests have been developed to differentiate *Dracunculus* spp. by using polymerase chain reactions (PCR) to amplify specific parasite gene sequences (small subunit (18S) ribosomal RNA).

Treatment and control: Wet compresses may be applied to blistered lesions to relieve pain associated with the emergence of worms (although this may trigger larval release). Occlusive bandages may be used to maintain hygiene, together with topic antiseptics and/or antibiotics to prevent secondary infections and reduce inflammation. The traditional means of curing infections involves the slow extraction of worms by winding them onto a stick a few centimetres a day for several weeks, combined with sterile dressings and acriflavine cream. Excessive force should not be used to avoid breaking the worm which may result in complicated lesions and intense inflammatory reactions. Surgical removal may be successful when worms are restricted to superficial sites, but can be difficult when worms are threaded through tendons or deep fascia. Chemotherapy with conventional anthelmintics has not proven effective, but various compounds, such as albendazole, mebendazole, niridazole, thiabendazole and metronidazole, appear to act as anti-inflammatory agents, thus allowing worms to be extracted more easily. Preventive measures involve breaking the cycle of transmission by reducing contamination of water supplies and eliminating copepod hosts. Public education programmes have been developed to discourage infected persons from entering ponds or wells to collect drinking water or to bath. Local water supplies can be treated with copper sulphate or temephos which kills copepods for several weeks. Improving water supplies by the installation of bores, pumps and reticulated (piped) systems, instead of step-wells, helps reduce contamination by both parasites and copepods. Drinking water can also be purified by chlorination, boiling or filtering through fine-meshed cloth (< 0.15 mm). The World Health Organization has accredited the global decline in the prevalence of infections to the adoption of many of these simple preventive measures.

Dracunculus



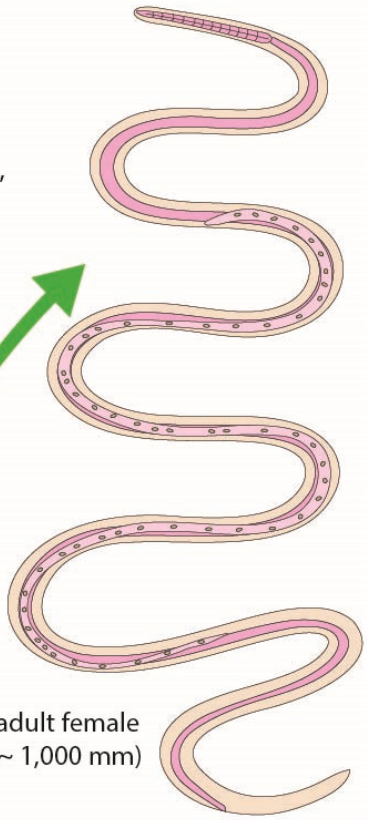
subcutaneous
connective tissue
(painful fiery blisters,
abscesses, allergy)



head

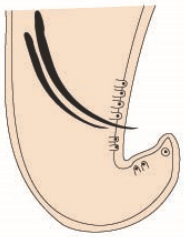
Definitive Hosts
(mammals, reptiles)

larval
migration



adult female
(~ 1,000 mm)

adult male
(~ 20 mm)



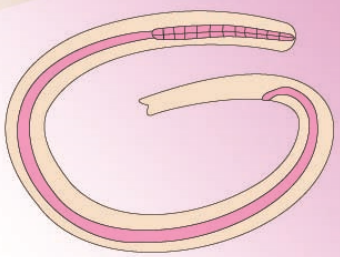
male tail (lateral)

L3/IH/PH
ingested

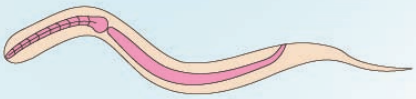
L3 encapsulate in PH?

females ovoviviparous
(release embryos rather than eggs)

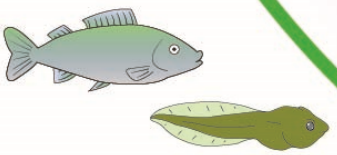
L1
released
through
blisters



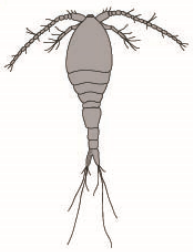
third-stage larvae
(L3) (~ 600 µm)



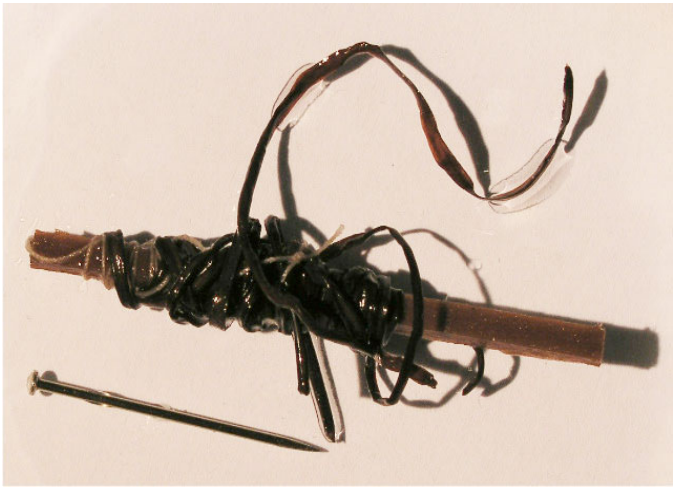
first-stage larvae
(L1) (~ 600 µm)



Possible Paratenic Hosts (PH)
(freshwater fish, tadpoles)
(tissues)



Intermediate Hosts (IH)
(copepods)
(haemocoel)



Dracunculus adult worm

Dracunculus adult worm

Dracunculus larvae

Dracunculus copepod vector