

Heterophyes

(platyhelminth: trematode)

Overview

Platyhelminths have triploblastic acoelomate soft bodies which are markedly flattened in profile (hence their common name as flatworms). They undergo protostomial embryonic development but do not moult during growth. On the basis of molecular evidence, they are classified within the Lophotrochozoa despite the absence of lophophore mouthparts and trochophore larvae. Three classes are composed entirely of parasitic flatworms (Cestoda, Trematoda and Monogenea), which have prominent attachment organs (suckers or bothria), syncytial teguments, shell glands and vitellaria involved in ectolecithal egg development, and life-cycles involving a variety of larval stages. Trematodes (flukes) have soft leaf-like bodies with oral and ventral suckers, a blind gut (mouth but no anus) and both male and female reproductive organs (hermaphroditic). Digeneans have indirect life-cycles involving alternation of sexual stages in vertebrates and asexual stages in molluscs. Miracidia released from eggs infect snails (obligate intermediate hosts) where they undergo massive asexual proliferation through sac-like sporocyst and redia stages eventually releasing larval cercariae into the water. Vertebrate (definitive) hosts become infected by penetration of the skin by cercariae or by eating encysted stages (metacercariae) on herbage or in second intermediate hosts. Adult opisthorchiideans are small to medium spinose flukes living in the alimentary tracts of mammals, birds, reptiles and fish. They produce embryonated eggs which only hatch after ingestion by snails (first intermediate hosts) and metacercariae develop in fish (second intermediate hosts). Heterophyids are parasitic in the intestines of fish-eating birds and mammals and infections by *Heterophyes* and *Metagonimus* spp. have been associated with enteritis and diarrhoea in cats, dogs and humans.

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: Lophotrochozoa (lophophore feeding structure or trochophore larva or neither)
Phylum: Platyhelminthes (flatworms, acoelomate, most hermaphroditic, prominent attachment organs)
Clade: Neodermata (syncytial tegument = neodermis)
Class: Trematoda (flukes, most with dorsoventrally-flattened bodies, sac-like gut)
Subclass: Digenea (heteroxenous, larval miracidium, sac-like sporocyst/redia stages in mollusc, cercariae/metacercariae)
Order: Plagiorchiida ('echinostomatids', plagiorchiids', mainly fish hosts, some tetrapods, infection by ingestion of cercariae or metacercariae)
Suborder: Opisthorchiata (egg eaten by gastropod IH, rediae formed, simple-tailed cercariae, encysts in second IH, metacercariae eaten by DH)
Superfamily: Opisthorchioidea (small-medium flukes, often spinose, piscivorous DH)
Family: Heterophyidae (tiny pyriform flukes, in intestines of mammals/birds, two IH (snails and fishes/frogs))
Genus: *Heterophyes* (parasitic in intestines of carnivores)
Species: various species cause diarrhoea in dogs, cats and 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 do not moult during their life-cycles are grouped together in the enigmatic clade Lophotrochozoa, including the platyhelminths, rotifers, lophophorates, annelids and molluscs. Platyhelminths (flatworms) have soft acoelomate flat bodies with three-dimensional arrays of muscles that generate a typical writhing motion (cf. longitudinal muscles in nematodes producing a thrashing motion). Flatworms do not have a single unifying characteristic (synapomorphy) but comprise diverse free-living (most Turbellaria) and parasitic (Neodermata) assemblages. Neodermata have non-ciliated syncytial (multinucleate) teguments and 3 classes are recognized, all with prominent attachment organs, namely, Cestoda with anterior bothridia/bothria (true/false suckers), Trematoda with oral and ventral suckers (previously called acetabula), and Monogenea with posterior haptors (opisthaptors). All have shell glands surrounding the ootype, and most exhibit ectolecithal egg development (yolk not present in egg but secreted by accessory glands called vitellaria or yolk glands). Most have indirect life-cycles involving the development of adult worms in vertebrates and larval stages in intermediate hosts (usually invertebrates).

The trematodes (flukes) and monogeneans have blind sac-like guts (lacking an anus) while the cestodes (tapeworms) lack digestive tracts. Trematodes have leaf-like bodies well adapted to living in confined spaces in tubular organs of vertebrate hosts. Two trematode subclasses are recognized: the Aspidogastrea with relatively few species (obligate external parasites of molluscs, fish and turtles, adults possessing a large ventral disc divided with numerous alveoli (suckerlets) or rows of suckers and the

tegument having short protrusions (microtubercles)); and the speciose Digenea (obligate endoparasites of vertebrates, adults bearing undivided ventral suckers (when present) and life-cycles involving alternation of sexual stages in vertebrates and asexual stages in molluscs). The success of digeneans as widespread parasites has been attributed to their ability to proliferate at 2 separate parts of their life-cycles. Adults worms in vertebrate definitive hosts produce numerous eggs which are excreted and release free-swimming miracidia which seek molluscan intermediate hosts. Massive asexual proliferation occurs in molluscs involving unique sporocysts and rediae. Both stages are sac-like structures with almost no anatomical features (no suckers, no reproductive organs). The difference is that sporocysts lack a gut (they absorb their food), whereas rediae have a mouth, a muscular pharynx and a sac-like gut (they browse on molluscan tissues). Sequential development of these stages varies considerably, with mother sporocysts producing daughter sporocysts or rediae over multiple generations, culminating in the production of cercariae. The infected molluscs are typically rendered sterile ('castrated') with parasites replacing their gonads and producing dozens to thousands of infective cercariae every day. The cercariae are larval forms, almost always with tails, and they actively emerge from molluscs and swim around in water. There is enormous variation in cercarial behaviour, but the 3 most important routes of infection for definitive hosts are by penetration of the skin by cercariae (e.g. blood flukes), by ingestion of encysted stages (metacercariae) on vegetation (e.g. sheep liver flukes), or ingestion of encysted metacercariae in the tissues of a second intermediate host (e.g. human liver flukes). Some 6,700 digenean species belonging to 22 superfamilies have been described in fish and tetrapods. The subclass Digenea is divided into 2 orders: Diplostomida characterized by furcocercous cercariae that penetrate definitive hosts; and Plagiorchiida with variable life-cycles but often involving cercariae being ingested by definitive hosts.

Superfamily (+ no. families)	No. spp.	DH ^a	Egg ^b	IH1 ^c	Asexual ^d	Cercaria ^e	IH2 ^f	Mode ^g
Subclass: Aspidogastrea (large ventral disc with numerous alveoli (suckerlets) or rows of suckers, tegument with short protrusions (microtubercles), obligate ectoparasites on molluscs, turtles, fish)								
Aspidogastroidea (4)	65	M,F,C,T	A	G,B	-	-	-	8
Subclass: Digenea (oral and ventral sucker; syncytial tegument; obligate endoparasites of vertebrates)								
Order: Diplostomida (blood flukes, 'strigeids') ~1,480 species								
Brachylaimoidea (2)	250	T	E	G	S	S,F	M	6,7
Diplostomoidea (5)	800	T	P	G	S	F	C,M,A	6
Schistosomatoidea (5)	430	F,C,T	P	G,B,A	R,S	F	-	1,6
Order: Plagiorchiida ('echinostomatids', 'plagiorchiids') ~5,200 species								
Allocreadioidea (6)	1,118	F,T	P	G,B	R,S	S,Y	C,M,R,A	6
Apocreadioidea (1)	94	F	P	G	R	S	M,A	6
Azygioidea (1)	43	F,C	E	G	R	F	C	3,4
Bivesiculoidea (1)	28	F	P	G	R	F	C	3,4
Bucephaloidea (2)	410	F	P	B	S	F	C	4
Echinostomatoidea (10)	112	F,T	P	G	R	S	C,M,R	5,6,7
Gorgoderoidea (10)	106	F,C,T	P	G,B	R,S	S,Y	C,M,R	5,6,7
Gymnophalloidea (4)	200	F,T	P	B	S	F	C,M,R,A,E,N	3,4,6
Haplospalchnoidea (1)	51	F	P	G	S	S	-	5
Hemiuroidea (15)	1,160	F,C,T	E	G,B,S	R,S	F	C,M,R,N	4
Heronimoidea (1)	1	T	P	G	S	S	-	7
Lepocreadioidea (8)	473	F	P	G	R	S	C,M,R,A,E,N	6
Microphalloidea (12)	414	F,T	P	G,B	S	S,Y	C,M,R,A,E	6,7
Monorchioidea (3)	270	F	E	G,B	R,S	S	C,R,A,E	6
Opisthorchioidea (3)	436	F,T	E	G	R	S	C	6
Paramphistomoidea (5)	74	F,T	P	G	R	S	-	5
Plagiorchioidea (16)	47	F,T	P	G	R,S	S,Y	C,M,R,A	6
Pronocephaloidea (6)	131	F,T	E	G	R	S	-	5
Transversotrematoidea (1)	27	F	P	G	R	F	-	2
LEGEND								
^a DH = definitive host: F = teleost fish; C = chondrichthyan fish; T = tetrapod; M = mollusc								
^b Fate of egg: A = larva hatches and attaches to IH1, E = eaten by IH1, P = hatches releasing miracidium which penetrates IH1								
^c IH1 = first intermediate host: G = gastropod, B = bivalve, A = annelid, S = scaphopod								
^d Asexual reproduction involves formation of secondary: R = redia, S = sporocyst								
^e F = fork-tailed cercaria, S = simple tailed cercaria, Y = cercaria with stylet								
^f IH2 = second intermediate host: C = chordate, M = mollusc, R = arthropod, A = annelid, E = echinoderm, N = cnidaria, ctenophore								
^g Mode of infection for DH: 1 = cercaria penetrates DH; 2 = cercaria attaches to DH; 3 = cercaria eaten by DH; 4 = cercaria eaten by IH2; 5 = cercaria emerges, encysts in open and eaten by DH; 6 = cercaria emerges, penetrates IH2, encysts and eaten by DH; 7 = cercaria remains in IH1, encysts and eaten by DH; 8 = no cercarial stage, infected IH1 eaten by DH.								

Thirteen plagiorchidan suborders have been recognized containing 19 superfamilies. The suborder Opisthorchiata contains one superfamily Opisthorchioidea comprising tiny to medium-sized flukes which form rediae without appendages, then simple-tailed cercariae that encyst in second intermediate hosts forming metacercariae. Over 400 species have been described in 90 genera in 3 families (Opisthorchiidae, Cryptogonimidae, Heterophyidae). The family Heterophyidae are found as intestinal parasites in mammals and birds with asexual developmental occurring in gastropods and metacercariae forming in fish and amphibians. The family is characterized by adults with small bodies where the ventral sucker (previously called acetabulum) is usually enclosed in a genital sinus containing a protuberance (gonotyl) and the male and female reproductive tracts fuse terminally to form a hermaphroditic duct. Some 40 heterophyid genera have been described in 8 subfamilies: Heterophyinae (no genital sinus, posterolateral gonotyl with chitinous rodlets, e.g. *Heterophyes*, *Heterophyopsis*); Metagoniminae (lateral ventral sucker in genital sinus, inconspicuous papilla-like gonotyl, e.g. *Metagonimus*, *Metagonimoides*); Cryptocotylineae (median ventral sucker in muscular genital sinus, papilla-like gonotyl, e.g. *Cryptocotyle*, *Seaphanocephalus*); Apophallinae (well-developed ventral sucker in non-muscular genital sinus, 1-2 papilla-like gonotyls, e.g. *Apophallus*, *Euryhelmsis*); Galactosominae (ventral sucker reduced or absent, globular gonotyl usually with spines, e.g. *Galactosomum*, *Acanthotrema*, *Stictodora*); Centrocestinae (circumoral spines present, well-developed ventral sucker in genital sinus, 1-2 papilla-like gonotyls, e.g. *Centrocestus*, *Ascocotyle*, *Phagicola*, *Pygidiopsis*, *Pygidiopsoides*); Haplorchiinae (rudimentary ventral sucker, large gonotyl with chitinous rodlets superimposed on ventral sucker, single testis, e.g. *Haplorchis*); and Stellantchasmae (small lateral ventral sucker, large spiny gonotyl, distal seminal vesicle forms muscular expulsor, e.g. *Stellantchasmus*, *Procerovum*). The genus *Heterophyes* contains some 8 species of small distome flukes found in the intestines of piscivorous mammals which become infected by eating fish or amphibians containing encysted metacercariae. Heterophyiasis is endemic in human populations in Egypt, the Middle-East and East Asia, and an emerging problem in the Philippines. It is difficult to estimate the number of people suffering from heterophyiasis because symptoms are usually mild and similar to other common ailments. People most at risk are those residing next to freshwater sources, particularly where fish consumption is high and sanitation is poor.

<i>Heterophyes</i> species	Definitive hosts [adults in intestines]	First intermediate hosts [sporocysts/rediae in tissues]	Second intermediate hosts [metacercariae in tissues]	Distribution
<i>H. aequalis</i>	Primates: hominid (human); Carnivora: canid (dog, red fox, golden jackal, Indian wolf), felid (cat, jungle cat); Rodentia: murid (rats); Artiodactyla: suid (pig); Pelecaniformes: pelecanid (white pelican), ardeid (reef heron); Accipitriformes: accipitrid (black kite)	brackish-water Gastropoda: potamidid (<i>Pirinella conica</i>)	freshwater/brackish-water Mugiliformes: mugilid (flathead grey mullet, thinlip mullet, golden grey mullet); Cypriniformes: cyprinid (himri); Cichliformes: cichlid (Nile tilapia, redbelly tilapia); Perciformes: serranid (white grouper), sciaenid (croaker), carangid (leerfish); Pleuronectiformes: soleid (common sole)	Asia Minor, Southern Europe
<i>H. bucalis</i> sp. inq.	Pelecaniformes: ardeid (night heron)			South America
<i>H. dispar</i> (syn. <i>H. limatus</i>)	Primates: hominid (human); Carnivora: canid (dog, golden jackal, red fox, Indian wolf), felid (cat, jungle cat); Lagomorpha: leporid (rabbit); Rodentia: murid (rats); Accipitriformes: accipitrid (black kite)	brackish-water Gastropoda: potamidid (<i>Pirinella conica</i>)	freshwater/brackish-water Mugiliformes: mugilid (flathead grey mullet, thinlip mullet, golden grey mullet); Cypriniformes: cyprinid (barbels, himri); Cichliformes: cichlid (Nile tilapia, redbelly tilapia); Perciformes: serranid (white grouper), sciaenid (croaker), carangid (leerfish); Pleuronectiformes: soleid (common sole)	North Africa, Middle-East, Korea, Thailand
<i>H. heroni</i>	Pelecaniformes: ardeid (cattle egret); Columbiformes: columbid (pigeon)		freshwater Cichliformes: cichlid (Nile tilapia)	Egypt
<i>H. heterophyes</i> (syn. <i>H. aegyptiaca</i> , <i>H. fraternus</i> , <i>H. persicus</i> , <i>H. inops</i> , <i>H. palidus</i>)	Primates: hominid (human), cercopithecoid (macaque); Carnivora: canid (dog, red fox, polar fox, golden jackal, Indian wolf), felid (cat, jungle cat), mustelid (badger);	freshwater/brackish-water Gastropoda: potamidid (<i>Pirinella conica</i> , <i>Cerithidea cingulata</i> (syn. <i>Tympanotonus</i>)	brackish-water Mugiliformes: mugilid (flathead grey mullet, thinlip mullet, thicklip grey mullet, golden grey mullet, green mullet, so-iuy mullet, leaping mullet);	North Africa, Middle-East, southern Europe, India, Asia, Hawaii

	Lagomorpha: leporid (rabbit); Rodentia: murid (rats); Chiroptera: rhinolophid (Geoffrey's horseshoe bat); Artiodactyla: suid (pig); Accipitriformes: accipitrid (short-toed eagle, black kite); Pelecaniformes: pelecanid (white pelican); Charadriiformes: larid (gull)	<i>micropterus</i>), <i>Certhideopsilla conica</i>), thiarid (<i>Tarebia</i>)	Cyprinodontiformes: cyprinodontid (Mediterranean killifish), poeciliid (mosquitofish), fundulid (killifish); Gobiiformes: gobiid (tank goby), oxudercid (yellowfin goby, dusky tripletooth goby); Cichliformes: cichlid (Nile tilapia, redbelly tilapia, Mozambique tilapia); Pleuronectiformes: soleid (black sole); Perciformes: sciaenid (croaker), moronid (European bass, spotted seabass), sparid (seabream); and unspecified Decapoda (shrimp), Odonata (dragonfly naiads)	
<i>H. indica</i>	Carnivora: canid (dog)			India
<i>H. nocens</i> (syn. <i>H.</i> <i>katsuradai</i>)	Carnivora: canid (dog, fox), felid (cat); Rodentia: murid (rats, mice, rakali); Primates: hominid (human)	brackish-water Gastropoda: potamidid (<i>Cerithidea cingulata</i> (= <i>Tympanotomus microptera</i>), <i>C. fluviatilis</i>), pleurocerid (<i>Melania obliquegranosa</i>), thiarid (<i>Stenomelania juncea</i> , <i>Melanoides tuberculata</i>)	brackish-water Mugiliformes: mugilid (flathead grey mullet, so-iuy mullet); Gobiiformes: oxudercid (dusky tripletooth goby, yellowfin goby, mudskipper, bluespotted mudskipper), gobiid (goby, tank goby); Perciformes: terapontid (sharpbeak terapon)	Korea, Japan, China, Thailand, Australia
<i>H. pleomorphis</i>	Carnivora: canid (dog)			Africa

Other *Heterophyes* species described from mammals and birds have been assigned to several other heterophyid genera mainly on the basis of the morphological characteristics of adults and metacercariae: e.g. *H. bitorquatus*, *H. chini* and *H. superspinata* transferred to *Alloheterophyes*; *H. continua* to *Heterophyopsis*; *H. lari* returned to *Stictodora*; and *H. reticulatum* assigned variously to *Distomum*, *Mesogonimus* and *Climastomatopsis* before being synonymized with *Clinostomum dictyotum*.

Parasite morphology: *Heterophyes* spp. form 7 different stages in their developmental cycles: eggs, miracidia, sporocysts, rediae, cercariae, metacercariae, and adult flukes. Embryonated eggs are small and ovoid, measuring 19-30 x 13-17 µm, yellow-brown and thick-shelled with an operculum set on thickened opercular shoulders. Eggs contain fully developed embryos in the form of pyriform ciliated miracidia. Sporocysts are pleomorphic non-ciliated sac-like bodies containing few internal elements other than balls of germinal cells. Rediae are elongate sac-like structures, measuring from 0.3-1.2 mm in length by 0.1-0.2 mm in width, and they possess an anterior mouth, tubular pharynx and short simple caecum. Cercariae are pleurolophocercous with ellipsoidal bodies (175-225 x 70-90 µm), eyespots and elongate finned tails (470-510 x 25-30 µm). They have oral and ventral suckers, mouths, guts, numerous glands and tegumental spines. Metacercariae are ovoid encysted stages (130-380 x 80-170 µm), opalescent with scattered brown pigment granules. They have a rounded oral sucker and a larger elliptical ventral sucker, a triangular excretory bladder filled with concretions, a digestive tract and developing genitalia. Adult flukes have small grey leaf-shaped bodies ranging from 0.3-3 mm in length by 0.3-0.9 mm in width. Their forebodies are flatter and narrower than their hindbodies with the junction often demarcated by shoulders. The tegument is covered with scale-like spines which are larger over the forebody and minute over the hindbody. The anteroventral oral sucker is small (around 90 µm in diameter) while the median-located ventral sucker is larger (up to 250 µm in diameter) and contains approximately 70 spines [cf. *Metagonimus* spp. have smaller submedian-located ventral suckers]. The digestive system consists of a mouth in the oral sucker, a short prepharynx, pharynx, long oesophagus, and 2 blind intestinal caeca (no anus). Worms have a conspicuous tubular excretory bladder terminating posteriorly. Adult *Heterophyes* worms are hermaphroditic and have both male and female reproductive organs. They possess 2 ovoid testes located posteriorly in tandem connected to a vas deferens that firstly expands to form a large seminal vesicle and then narrows to form an ejaculatory duct (no cirrus). A single ovoid ovary located mid-body is connected to numerous vitelline follicles. The ovary is also connected to a long tubular uterus which joins the ejaculatory duct leading to the genital pore from where eggs are released. The genital pore is surrounded by a prominent genital sucker (gonotyl) which measures ~150 µm in diameter and is armed with 14-90 toothed or digitate spines (chitinous rodlets) depending on species [cf. *Metagonimus* spp. lack genital suckers]. For example, the gonotyls of *H. heterophyes* have 70-85 chitinous rodlets, *H. nocens* have 50-62, *H. dispar* have 22-35 and *H. aequalis* have 14-25. Genera within the family Heterophyidae (and the 8 subfamilies) differ mostly in adult body morphology: particularly in the number of gonotyl spines; location of the genital pores; extensions of the uterus and vitellaria; structure of the testes; and length of the intestinal caeca.

Site of infection: Adult *Heterophyes* flukes infect the small intestines in their piscivorous definitive hosts, with many species exhibiting some tissue tropism independent of host species or size: e.g. *H. heterophyes* often infects the duodenum and jejunum; *H. dispar* the duodenum; and *H. aequalis* the posterior jejunum and ileum. Asexual developmental stages develop in the intestines and tissues (esp. hepatopancreas) of their first intermediate hosts (freshwater snails), while metacercariae encyst in the muscles, fins or gills of their second intermediate hosts (fish).

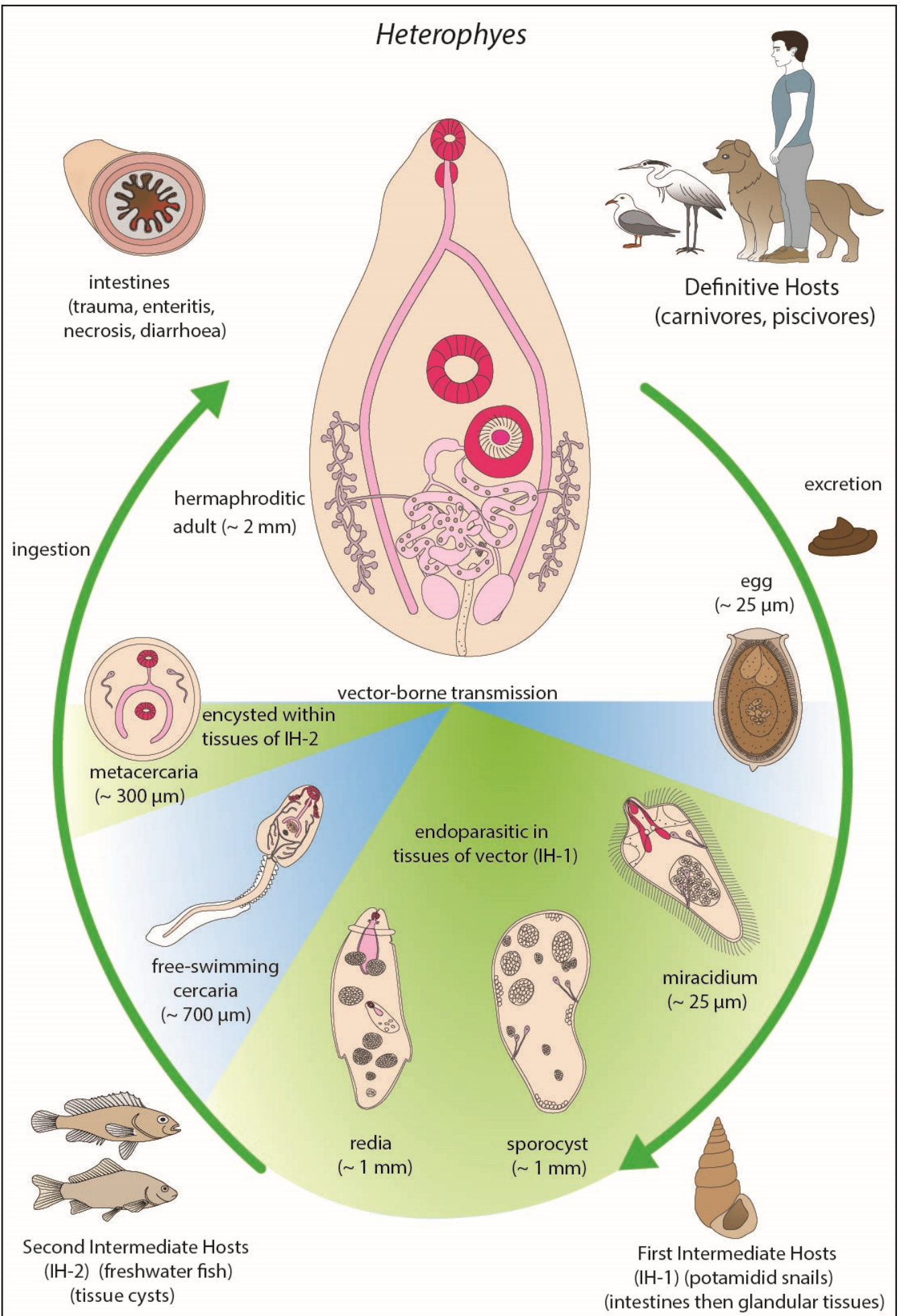
Pathogenesis: These intestinal flukes invade the intervillous spaces, often burrowing into the mucosal layer and crypts of Lieberkuhn and sometimes penetrating the intestinal wall. The resultant pathology arises from traumatic mucosal damage with hyperplasia, villous atrophy, hyperplasia, inflammation and sometimes ectopic granulomas. The severity of disease largely depends on the intensity of the infection but is also influenced by host susceptibility and the degree of acquired protective immunity. Light infections are often asymptomatic although some have been associated with mild enteritis, transient intestinal pain and intermittent diarrhoea. Moderate infections may cause more intense symptoms, such as abdominal tenderness and pain, vomiting and chronic (sometimes blood-tainted) diarrhoea, but these indications are also common in patients with peptic or duodenal ulcers. Heavy infections involving hundreds of worms may cause extensive mucosal necrosis producing severe symptoms including persistent abdominal pain, mucoid (often bloody) diarrhoea, haemorrhages, nausea, indigestion, dyspepsia, vomiting and anorexia. Adult worms and eggs embedded in the mucosa elicit significant inflammatory responses with cellular infiltrates of neutrophils and eosinophils. Complications may arise when eggs in eroded tissues are swept away by the circulatory and/or lymphatic systems and lodge in ectopic sites (such as the heart, lungs, brain and spinal cord) leading to fibrosis and granuloma formation. Lesions in the myocardium and mitral valve have been associated with heart failure, and those in the brain and spinal cord have apparently caused various neurological disorders, sometimes contributing to death. Complications due to disseminated infections appear to be more prevalent in patients with immuno-compromised status due to concomitant diseases, immunosuppression or malnutrition.

Developmental cycle and mode of transmission: *Heterophyes* spp. have indirect life-cycles involving transmission between 3 different types of hosts associated with aquatic environments: adults worms infecting fish-eating mammals and birds (definitive hosts); asexual stages multiplying within aquatic snails (first intermediate hosts); and metacercariae encysting within fish (second intermediate hosts). Gravid adult worms produce embryonated eggs which are excreted with host faeces. Eggs contaminating water sources are ingested by aquatic snails whereupon they hatch releasing the enclosed ciliated miracidium in the snail gut. The miracidium penetrates the gut wall shedding its cilia and developing into a sac-like sporocyst usually within the digestive gland. A small range of snails act as suitable first intermediate hosts for *Heterophyes* spp., notably several amphibious prosobranch (operculate) families, including potamidids (freshwater and brackish-water snails common on mud flats, mangroves, periphyton), thiarids, pleurocerids and semisulcospirids (freshwater snails). Sporocysts undergo asexual multiplication and produce 2 generations of rediae in the snail tissues over 3-5 months, although parasites can survive longer in aestivating snails. The rediae feed on snail tissues and ultimately produce numerous cercariae which emerge actively from the snail. Free cercariae swim up towards the water surface and then slowly descend through the water column. If they contact a fish, they actively penetrate the skin shedding their tails and encyst in the musculature as metacercariae. A range of freshwater and brackish-water fish act as suitable second intermediate hosts, including Mugiliformes (mugilid), Gobiiformes (oxudercid, gobiid), Perciformes (terapontid, sciaenid, moronid, sparid, serranid, carangid), Cypriniformes (cyprinid), Cyprinodontiformes (cyprinodontid, poeciliid, fundulid), Cichliformes (cichlid), and Pleuronectiformes (soleid). Food-borne transmission occurs to piscivorous definitive hosts (mammals and birds) when they consume infected fish. The metacercariae excyst in the intestines, attach to the gut wall and develop into adult worms over several weeks. Infections are transmitted to humans when they eat raw, undercooked or newly salted, pickled or smoked fish in which metacercariae may survive for several days. Adult flukes live for a few months to a year in the final host.

Differential diagnosis: While infections may be suspected on the basis of clinical presentation and history of exposure, the symptoms of heterophysiasis are often similar to those of other gut ailments, notably peptic ulcer disease. Infections by *Heterophyes* spp. are conventionally diagnosed by the microscopic detection of fluke eggs in faecal samples, either in direct smears (Kato-Katz technique) or following concentration (Lumbreras rapid sedimentation or ether-formalin concentration). It is suggested that at least 3 stool samples be examined due to intermittent egg excretion, and that samples be stained with potassium permanganate to accentuate structural features on eggs. Alternatively, adult flukes may be recovered for examination following anthelmintic treatment or by endoscopic biopsy. Infections in fish by metacercariae may be detected by microscopic examination of dissected muscles, usually in squash preparations or following pepsin-acid digestion. Several immunoserological tests have been developed to detect host antibodies in serum samples, including counter-current immunoelectrophoresis, intradermal tests, indirect fluorescent-antibody tests and enzyme immunoassays, but they often exhibited poor specificity presumably due to antigenic cross-reactivity. Molecular techniques have been applied to the characterization of parasite DNA extracted from adult flukes, eggs, sporocysts/rediae, and cercariae; by polymerase chain reaction (PCR) amplification of restriction fragment length polymorphisms (RFLP), random amplified polymorphic DNA (RAPD) and sequencing nuclear (18S, 5.8S and 28S ribosomal DNA, internal transcribed spacers regions 1 and 2) and mitochondrial genes (cytochrome c oxidase subunit 1).

Treatment and control: Clinical infections have been successfully treated with broad spectrum anthelmintics; notably the isoquinoline praziquantel, and the salicylanilide niclosamide. Repeated treatments and community treatments are recommended in endemic regions due to rapid re-infection rates. Patients with suspected ectopic infections should be carefully monitored post-treatment as dying worms and eggs may cause intense reactions. Preventive strategies are centred around breaking transmission cycles but most interventions are only suitable for domestic or peridomestic situations, rather than natural ecosystems. Every effort should be made to reduce faecal contamination of water bodies, by improving sanitation, building latrines, proper waste disposal (human and animal), and treating sewage. While it is desirable to reduce snail populations in which parasites reproduce asexually, the indiscriminate use of molluscicides in aquatic environments may have unintended consequences due to the toxic nature of the chemicals and their effect on other biota. Indeed, snail control is often difficult as they aestivate in the ground during dry conditions and even temporary pools may harbour large snail populations, especially in high rainfall regions. In rural village settings and aquaculture ventures, various physical, chemical and biological control strategies have been integrated with pond management to reduce the suitability of the habitat for snails (e.g. periodic drainage, clearing periphyton, installing screens, small-scale use of molluscicides, introducing predatory crustaceans and/or fish). The most effective means of controlling infections, however, appears to be denying piscivores access to raw fish or improperly cooked fish products. Companion animals should not be fed raw trash fish, and humans should not consume raw or improperly-prepared fish. While metacercariae may survive for days in raw, lightly salted, lightly pickled or lightly smoked fish products, they are killed by cooking at temperatures above 63°C, or by freezing at -20°C for at least 7 days. Public education campaigns should be undertaken in regions where raw or undercooked fish are regarded as traditional cultural cuisine, particularly targeting people who prepare foods or schoolchildren who have not yet been ingrained with dietary customs.

Heterophyes





Heterophyes adult worm



Heterophyes egg



Heterophyes adult worm