Paragonimus
(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 plagiorchidans are varied in appearance, most bearing spines and a median ventral sucker and many producing small eggs which hatch after ingestion by snails (first intermediate hosts). Paragonimids are atypical for the group as their eggs release miracidia to find snails, they form metacercariae in freshwater crustaceans and insects (second intermediate hosts), and crustacean-eating animals may act as paratenic (transport) hosts for metacercariae. *Paragonimus* spp. (lung flukes) are thick oval spiny flukes in the respiratory systems of birds and mammals, and infections have been associated with respiratory and neurological diseases 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:	Xiphidiata (xiphidiocercariae with penetrating stylet in anterior margin of oral sucker)
Superfamily:	Gorgoderoidea (miracidia penetrate gastropod, bivalve IH, sporocysts and rediae formed, simple-tailed cercariae with stylet, encysts in open or in second IH, metacercariae eaten by DH)
Family:	Paragonimidae (thick oval flukes, scale-like spines, miracidia, snail IH-1, crustacean/insect IH-2)
Genus:	*Paragonimus* (parasitic in lungs of carnivores)
Species:	various species cause respiratory and neurological signs 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 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
Haplosplanchnoidea (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. Members of the suborder Xiphidiata are characterized by forming xiphidio-cercariae with a penetrating stylet in the anterior margin of the oral sucker which is used to penetrate second intermediate hosts where metacercariae are formed. Over 1,680 species have been described in 44 families in 4 superfamilies: Allocreadioidea (1,118 spp. in 6 families), Gorgoderoidea (106 spp. in 10 families), Microphalloidea (414 spp. in 12 families) and Plagiorchioidea (47 spp. in 16 families). The superfamily Gorgoderoidea parasitizes fish and tetrapods and the 10 cognate families comprise Atractotrematidae, Cadenatellinae, Haploporidae, Callodistomidae, Dicrocoeliidae, Gorgoderidae, Encyclometridae, Orchipedidae, Paragonimidae and Troglotrematidae. The family Paragonimidae contains 3 genera (*Paragonimus, Euparagonimus, Pagumogonimus*) of thick oval flukes that infect the lungs of carnivores that feed on crustaceans infected with metacercariae. The genus *Paragonimus* contains around 20 species that infect mammals mostly in Asia but also in Africa and the Americas. In particular, *P. westermani* is most prevalent in humans in South-East Asia (including China), *P. kellicotti* in North America, and *P. africanus* in West Africa. Contemporary molecular phylogenetic studies have helped resolve many species-synonymies and have identified major clades comprising species-complexes (species-groups) represented by *P. westermani, P. skrjabini, P. bangkokensis, P. heterotremus, P. mexicanus* and *P. ohirai*. Infection rates in Asia are higher than elsewhere due to the higher consumption of raw shellfish. Several species are considered zoonotic, as many other mammalian species may support completion of the parasite life-cycle through freshwater snails and crustaceans as first and second intermediate hosts. Infections are common in riverine areas with slow-flowing or still waters throughout tropical, subtropical and temperate regions. It is currently estimated that there are some 20 million *Paragonimus* infections per year worldwide and that over 300 million people are at risk of infection.

***Paragonimus* species**	**Definitive hosts (adults in lungs)**	**First intermediate hosts (sporocyst/rediae in tissues)**	**Second intermediate hosts (metacercariae in tissues)**	**Distribution**
***P. westermani* complex**				
P. westermani (syn. *P. edwardsi, P. ringeri, P. philippinensis,* and triploid type, *P. pulmonalis*) (Asian or Oriental lung fluke)	Primates: hominid (human), cercopithecid (crab-eating macaque); Carnivora: canid (dog, fox, wolf, raccoon-dog), felid (cat, leopard, panther, tiger), viverrid (civet cat, palm civet), herpestid (mongoose); Artiodactyla: suid (pig), bovid (cattle); Rodentia: murid (rats)	amphibious and freshwater Gastropoda: pachychilid (*Brotia asperata, Sulcospira quangtriensis*), semisulcospirid (*Semisulcospira libertina, S. bensoni, S. japonica, S. amurensis*), thiarid (*Thiara toucheana, T. granifera*)	freshwater Decapoda: potamid (*Sinopotamon, Potamiscus manipurensis, Geothelphusa, Potamon* (*Ranguna*), *Alcomon superciliosum*), gecarcinucid (*Parathelphusa, Sundathelphusa*), varunid (*Eriocheir japonicus, E. sinensis*), cambarid (*Cambaroides similis*), plus crustacean-eating paratenic hosts (rodents)	Eurasia, India, Pacific Islands
P. siamensis	Carnivora: felid (cat); Rodentia: murid (rats, bandicoot rats)		freshwater Decapoda: gecarcinucid crabs (*Parathelphusa germaini*)	Thailand
***P. skrjabini* complex**				
P. skrjabini (incl. subspecies: *P. s. skrjabini, P. s. miyazakii*) (syn. *P. miyazakii, P. szechuanesis, P. hueitungensis, P. veocularis, P. macrorchis, P. proliferus* (*P. hokuoensis*), *P. heterorchis, P. fukienensis*)	Primates: hominid (human); Carnivora: felid (cat), viverrid (palm civet), canid (dog, raccoon-dog), mustelid (marten, weasel, badger); Rodentia: murid (rats, bandicoot rat); Artiodactyla: suid (boar)	freshwater Gastropoda: pomatiopsid (*Neotricula* (*Tricula*) *cristella*), amnicolid (*Akiyoshia chinensis, Erhaia*, *Bythinella nipponica*), pachychilid (*Sulcospira quangtriensis*)	freshwater Decapoda: potamid (*Potamiscus manipurensis*, *P. mieni*, *Sinopotamon, Geothelphusa*); Anura: ranid (frogs)	China, Japan, Southeast Asia, India
***P. ohirai* complex**				
P. ohirai (syn. *P. sadoensis, P. iloktsuenensis*)	Primates: hominid (human); Carnivora: felid (cat), canid (dog, raccoon-dog); Rodentia: murid (rats); Artiodactyla: suid (pig)	aquatic Gastropoda: assimineid (*Angustassiminea lutea, A. parasitologica*), pomatiopsid (*Oncomelania nosophora, O. hupensis, Tricula minima, T. chiui*)	estuarine Decapoda: sesarmid (*Sesarma* (*Holometopus*) *dehaani*)	South-East Asia

P. bangkokensis (syn. *P. paishuihoensis, P. menglaensis, P. xiangshanensis*)	Carnivora: canid (dog), felid (cat), mustelid (ferret), herpestid (Indian mongoose, Javan mongoose); Rodentia: murid (rats, bandicoot rat)	freshwater Gastropoda: pomatiopsid (*Tricula gregoriana*?)	freshwater Decapoda: potamid (*Potamon smithianus, P. lipkei, Potamiscus mieni, Po. tannanti, Larnaudia beusekomae, Apotamonautes hainanensis, Ranguna smalleyi*)	Asia
P. harinasutai (syn. *P. microrchis*)	Carnivora: felid (cat), canid (dog)		freshwater Decapoda: potamid (*Potamon smithianus, P. lipkei, Larnaudia beusekomae, L. larnaudii, Sinopotamon chekiangenes, Indochinamon ou*), gecarcinucid (*Siamthelphusa paviei, Chulathelphusa brandti*)	Asia
***P. heterotremus* complex**				
P. heterotremus (syn. *P. tuanshanensis*)	Primates: hominid (human); Carnivora: felid (cat, leopard), canid (dog); Rodentia: murid (rats, bandicoot rat)	freshwater Gastropoda: pomatiopsid (*Tricula gregoriana*), assimineid (*Assiminea*)	freshwater Decapoda: potamid (*Sinopotamon*, *Ranguna, Potamiscus manipurensis*, *P. mieni*, *Potamon lipkei*, *Po. smithianus*), gecarcinucid (*Barythelphusa* (*Maydelliathelphusa*) *lugubris, Alcomon superciliosum*), pachychilid (*Sulcospira quangtriensis*)	China, South-East Asia, India
P. pseudoheterotremus	Carnivora: felid (cat)		freshwater Decapoda: potamid (*Larnaudia larnaudii*)	Asia
Unplaced species				
P. africanus	Primates: hominid (human), cercopithecid (drill), lorisid (potto); Carnivora: viverrid (civet cat), canid (dog), herpestid (mongoose)	freshwater Gastropoda: pachychilid (*Potadoma freethii*)	freshwater Decapoda: potamonautid (*Sudanonautes*)	West Africa
P. amazonicus	Didelphimorphia: didelphid (four-eyed opossum, water opossum); Carnivora: felid (margay?)		Decapoda: pseudothelphusid (*Pseudothelphusa chilensis*?)	South America
P. caliensis	Didelphimorphia: didelphid (common opossum, gray four-eyed opossum)		Decapoda: pseudothelphusid (*Strengeria*)	South America
P. compactus	Carnivora: herpestid (Indian mongoose)			India
P. kellicotti (lung fluke) (syn. *P. rudis*)	Carnivora: canid (dog, red fox, coyote), felid (cat, bobcat), procyonid (raccoon), mephitid (skunk, hooded skunk), mustelid (giant otter, mink); Rodentia: cricetid (muskrat); Didelphimorphia: didelphid (North American opossum); Artiodactyla: bovid (goat), suid (pig);	amphibious Gastropoda: pomatiopsid (*Pomatiopsis lapidaria, P. cincinnatiensis*, *Oncomelania hupensis*)	freshwater Decapoda: cambarid (*Orconectes*, *Cambarus*), plus crayfish-eating paratenic hosts (rodents)	Americas, South Africa

	Primates: hominid (human)			
P. mexicanus (syn. *P. peruvianus, P. inca, P. ecuadoriensis*)	Primates: hominid (human); Carnivora: canid (dog, fox), felid (cat, jaguar, ocelot), procyonid (raccoon, coati); Artiodactyla: tayassuid (peccary); Didelphimorphia: didelphid (opossum)	brackish-water Gastropoda: hydrobiid (*Aroapyrgus costaricensis, A. alleei, A. colombiensis*)	freshwater Decapoda: pseudothelphusid (*Pseudothelphusa, Ptychophallus, Potamocarcinus, Strengeria, Hypolobocera guayaquilensis, H. aequatorialis, H. chilensis*), trichodactylid (*Zilchiopsis, Trichodactylus faxoni, Moreirocarcinus emarginatus*)	Central and South America
P. tuanshenensis	Carnivora: canid (dog), felid (cat, leopard); Primates: hominid (human)	freshwater Gastropoda: pomatiopsid (*Tricula gregoriana*)	freshwater Decapoda: potamid (*Potamon*)	China
P. uterobilateralis	Primates: hominid (human); Carnivora: canid (dog), felid (civet cat), herpestid (mongoose); Eulipotyphla: soricid (shrew); Rodentia: murid (rats)	terrestrial and freshwater Gastropoda: achatinid (*Homorus* (*Striosubulina*) *striatella*), ampullariid (*Afropomus balanoides*), pachychilid (*Potadoma sanctipauli*)	freshwater Decapoda: potamonautid (*Liberonautes*, *Sudanonautes*)	West Africa
P. vietnamensis	Carnivora: canid (dog), felid (cat)		freshwater Decapoda: potamid (*Potamiscus tannanti, P. mieni*)	Vietnam
P. yunnanensis	Carnivora: canid (dog)			China

Parasite morphology: *Paragonimus* spp. form 7 different developmental stages in their life-cycles: namely, eggs, miracidia, sporocysts, rediae, cercariae, metacercariae and adults. Eggs are unembryonated, ovoid (70-125 x 40-80 µm), yellowish brown, thick-shelled and operculate with a raised shoulder surrounding the operculum. Miracidia are ovoid (approximately 80 x 30 µm), covered with cilia, and have apical papillae with ducts to penetration glands. Sporocysts are pleomorphic sacs (300-500 µm long) without organs but containing germinal cells which give rise to small rediae. Mature rediae have yellow elliptical bodies (460–850 x 170–360 µm) with a mouth, well-developed pharynx and saccular gut. Cercariae are chaetomicrocercous in type with an ovoid body (160-250 x 65-100 µm) and a very small knob-like tail. The body is covered with tegumental spines and possesses an anterior mouth, a muscular oral sucker, ventral sucker and penetration glands. Metacercariae are white-pink, round-oval (ranging from 200-900 µm in diameter), surrounded by a bilayered cyst wall and contain oral and ventral suckers, saccular intestines and prominent granules. Metacercariae of most *Paragonimus* spp. can be allocated to 3 size groups: < 300 µm in diameter (e.g. *P. heterotremus*); 300-500 µm (e.g. *P. westermani, P. skrjabini*); and > 700 µm (e.g. *P. harinasutai, P. vietnamensis*), and it has been suggested that different species can be differentiated by their internal morphological features, e.g. *P. westermani* with colourless intestines and red dorsal granules, *P. mexicanus* with yellow intestines and red ventral granules. Adult lung flukes are usually found paired in capsules up to 2 cm in diameter in the lungs. Individual worms are thick-bodied, reddish-brown (but often grayish-white in ectopic sites) and are roughly the size of coffee beans (4-16 x 2-8 x 3-6 mm). They are elliptical to concave ovoid in shape and their tegument is covered with tiny thorn-like cuticular spines scattered around the body. The spines may be split distally or develop longitudinal grooves; those on the anterior dorsal surface sometimes forming comb-like groups. The body possesses an oral and a ventral sucker (usually similar in size), a truncated pharynx and oesophagus that bifurcates early into paired caeca, and a posterior excretory bladder. Adult worms are hermaphroditic, possessing both male and female reproductive organs. They contain 2 testes situated side-by-side (the name *Para-gonimus* literally translates to 'side-by-side gonads'). The testes are located posteriorly, irregularly lobed (4-5 lobes) and connected to seminal receptacles (no cirrus pouch). The ovary and uterus are located midbody either side of the midline and the vitelline follicles are located in 2 extensive lateral fields. The single ovary is typically six-lobed and the uterus is tightly coiled into a rosette shape and connects to a genital atrium which opens into a genital pore located posterior to the ventral sucker. The uterus is often dark coloured when packed with heavily tanned unembryonated eggs.

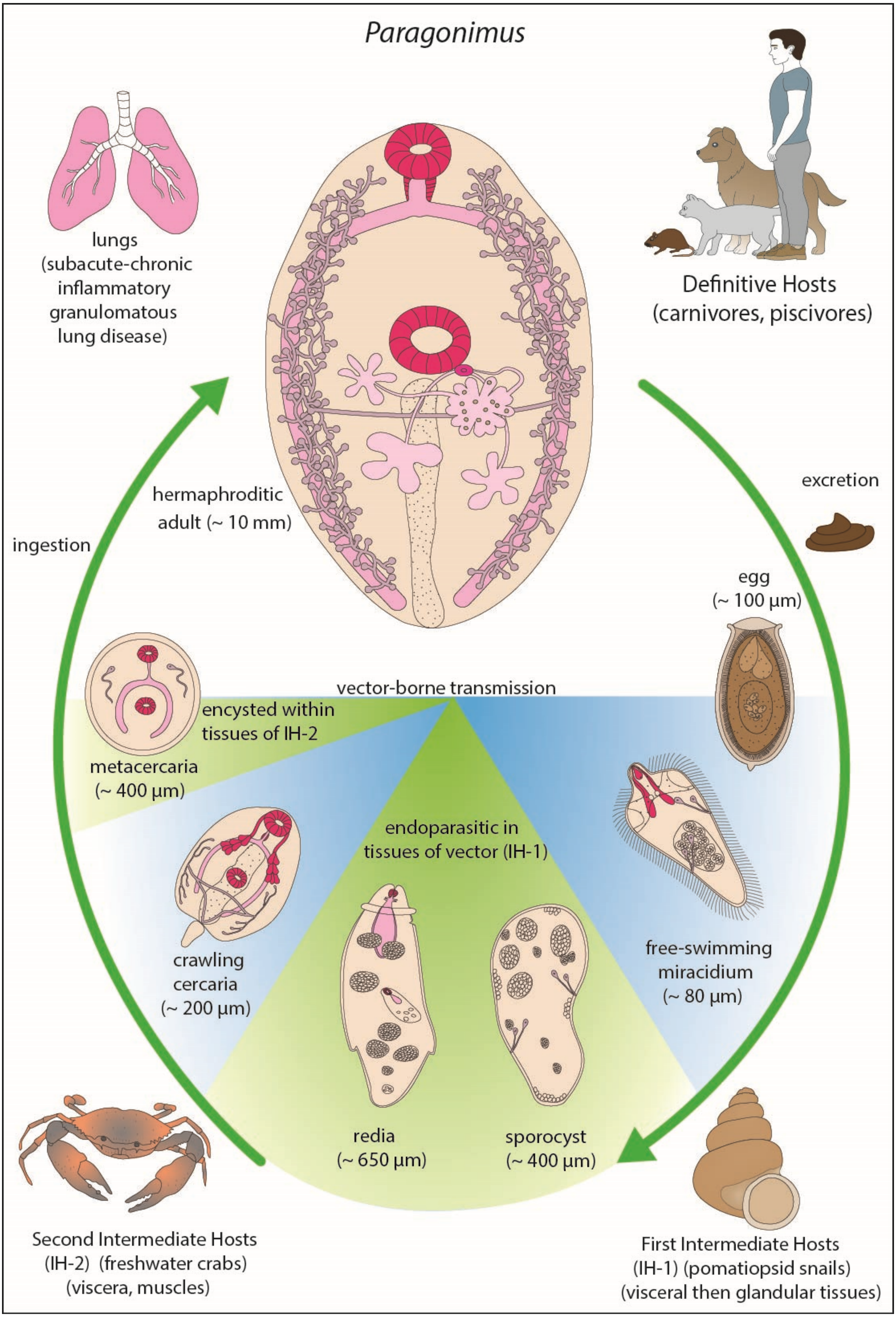
Site of infection: Juvenile worms released in the intestines of their definitive hosts penetrate the gut wall and peritoneum and migrate through the diaphragm and pleura to reach bronchioles in the lungs where they mature as paired adults in capsules. Some flukes may migrate to ectopic sites, including subcutaneous, nervous, muscular, glandular, hepatic, mesenteric and reproductive tissues and organs. Asexual developmental stages (sporocysts and redia) usually form within the digestive gland of their first intermediate hosts (snails), and metacercaria encyst within the viscera and muscles of their second intermediate hosts (crustaceans).

Pathogenesis: Infection by *Paragonimus* spp. may cause a zoonotic disease known as paragonimiasis (sometimes called pulmonary distomatosis or benign endemic haemoptysis) which usually manifests as a subacute to chronic inflammatory granulomatous lung disease. Infections become established when flukes migrate from the gut through tissues to internal organs (typically the lungs) where they mature and produce eggs. Adult flukes feed on host tissues and proteins causing traumatic damage and eliciting host inflammatory, fibrotic and immune responses. Pathological changes vary in severity and type depending on the parasite species/strain, the intensity of infection, the susceptibility of the mammalian host, the route of migration and the site of infection, adult maturation and egg production. Many infections remain asymptomatic or subclinical, while others may produce mild to moderate symptoms for years before medical attention is sought. Clinical infections have been associated with three disease phases: acute (manifestations soon after infection), chronic (pleuropulmonary manifestations) and ectopic (manifestations arising from infections elsewhere than the lungs). The acute phase occurs 2-15 days after infection in response to immature worms migrating through tissues in the abdominal and thoracic cavities to invade the lungs. The mechanical damage and host inflammatory responses result in abdominal pain, diarrhoea, hepatosplenomegaly, fever, leucocytic infiltration, coughing, eosinophilia and urticaria, particularly in patients with heavy worm burdens. Worm migration in the lungs may cause transient haemorrhage, pleuritic chest pain, pleural effusions, bronchiectasis, interstitial pneumonitis and bronchopneumonia. The chronic phase occurs weeks after infection when worms arrive in the lungs, pair up, form capsules and produce eggs. Infections may cause parenchyma-based disease, pleura-based disease, or more usually both (pleuro-pulmonary disease). Capsules usually form in the lung parenchyma near airspaces so eggs may escape in respiratory secretions, but capsules (and eggs) in the pleura lead to pronounced inflammation with cellular infiltrates (neutrophils and eosinophils). Pulmonary manifestations include chronic cough, hoarseness, the expulsion of viscoid bloody or rusty sputum (containing eggs and Charcot-Leyden crystals), haemoptysis, mild anaemia, chronic bronchitis, crepitation/wheezing, pleurisy with dyspnoea, breathlessness, fever, fatigue, anorexia and headache. Immunopathological responses result in pleural thickening, interlobar pleuritis, pleural effusion, and sometimes pneumothorax or haemothorax. Symptoms and chest radiographic abnormalities are similar to those associated with pneumonia and tuberculosis. Inflammatory reactions work to encapsulate worms and eggs producing granulomas which sometimes ulcerate and heal slowly, giving the lungs a peppered appearance. Occasionally complications occur in the form of gross haemorrhages or bacterial superinfections, leading to pneumonia or pulmonary abscesses. Ectopic infections develop when worms migrate not into the lungs but into other tissues and internal organs, such as subcutis, heart, skeletal muscles, liver, brain, spinal cord, mesenteries, adrenal glands, ovary and epididymis. The worms, and sometimes their eggs, provoke serious inflammatory and immunopathological responses with cellular infiltrates, fibrosis, granuloma formation and calcifications. Migrating worms in the brain may cause meningitis or meningoencephalitis, while encapsulated and calcifying worms may cause expansive space-occupying lesions. Symptoms include fever, headache, seizures, convulsions, nausea, vomiting, visual disturbances, motor weakness, decline in cognitive function, personality changes, localized or generalized paralysis, coma and occasionally death. Cerebral paragonimiasis may be confused with other central nervous system diseases such as epilepsy, brain tumours, cysticercosis or echinococcosis. Cutaneous paragonimiasis may present with slow-moving lesions under the skin (especially on the abdomen or chest) but other parasites may cause similar signs (e.g. *Gnathostoma*). Infections have been detected in children and adults, males and females, and immunocompetent and immunocompromised individuals.

Developmental cycle and mode of transmission: *Paragonimus* spp. have indirect heteroxenous life-cycles involving cyclic transmission between definitive hosts (mammals infected with adult flukes), first intermediate hosts (snails infected with asexual stages) and second intermediate hosts (crustaceans infected with metacercariae). Adult flukes release unembryonated eggs into respiratory airspaces from where they are expectorated with sputum or swallowed and excreted with host faeces. Eggs reaching freshwater embryonate over at least 2 weeks and then hatch releasing ciliated miracidia which swim about actively seeking snail hosts by chemotaxis. Free-swimming miracidia do not live long and must find a snail host within 24 hours or die. A range of aquatic, terrestrial and amphibious snails act as suitable first intermediate hosts, including members of the superfamilies Cerithioidea (pachychilids, semisulcospirids, thiarids), Truncatelloidea (pomatiopsids, amnicolids, assimineids, hydrobiids), Ampullarioidea (ampullariids), and Achatinoidea (achatinids) which inhabit habitats as diverse as fast-flowing streams and still ponds. The miracidia penetrate the soft tissues of the snail shedding their cilia and develop into saccular sporocysts in the body cavity where they undergo 2 generations of asexual reproduction. Mother sporocysts give rise to first generation rediae which produce second generation rediae that produce and release cercariae. The prepatent period in snails (time from infection to first release of cercariae) is around 11 weeks. The knob-like tails of the cercariae are ineffective for swimming, so the cercariae crawl over substrates until they encounter crustaceans which they infect by penetrating the exoskeleton using their sharp cuticular stylets. It is thought that some crustaceans may also become infected when they eat infected snails. Once inside, the cercariae encyst in various tissues (muscles, gills, heart, liver and other viscera) forming metacercariae which mature to contain elongate (extended) juvenile worms (rather than ventrally folded juveniles like other flukes). A range of freshwater and estuarine decapod crustaceans act as suitable second intermediate hosts; including members of the crab superfamilies Potamoidea (potamids, potamonautids), Gecarcinucoidea (gecarcinucids), Grapsoidea (varunids, sesarmids), Pseudothelphusoidea (pseudothelphusids), Trichodactyloidea (trichodactylids), and the crayfish superfamily Astacoidea (cambarids). Metacercariae of some *Paragonimus* spp. have also been found in tadpoles of ranid frogs, and a few species apparently utilize paratenic (transport) hosts, such as crustacean-eating rodents and wild boar. Definitive hosts (carnivores, rodents, primates, pigs) become infected by eating raw, undercooked or inadequately cured, dried, salted or pickled freshwater crabs and crayfish containing infective metacercariae. Many countries have local culinary customs supporting the consumption of improperly prepared crustaceans; such as Chinese/Korean kejeng (live crustaceans with soybean sauce), Japanese oboro-kiro (crab juice added to miso (bean paste) soup), Mexican cerviche (uncooked crustaceans), Philippine kilano (raw crab in citrus juice, coconut milk and alcohol), and Asian drunken crab (uncooked crabs pickled in rice wine). On occasion, food handlers have been infected with metacercariae contaminating cooking utensils after being dislodged from crustacean tissues. There are also recorded instances of humans becoming infected as part of traditional folk medicine practices, such as drinking juices from crushed crabs to treat measles in Korea, or eating raw crab to increase fertility in women in Africa. Following ingestion, metacercariae excyst in the small intestines and juvenile worms penetrate the gut wall into the body cavity and begin their migration through abdominal and thoracic tissues to the lungs (or other ectopic sites). Once in host tissues, worms mature, pair, mate and become encapsulated by host connective tissue over 8-12 weeks. If a migrating juvenile worm cannot find a mate, it may continue searching for several weeks, or it may form a single worm cyst. Despite adult worms being hermaphroditic, cross-fertilization between pairs of worms is generally required to produce fertile eggs (although some self-fertilization may occur). Unembryonated eggs released into airspaces are either expectorated in sputum or swallowed and then excreted with host faces. The prepatent period in mammalian definitive hosts (time from infection to first egg release) ranges from 65-90 days and it is thought that worms may live for up to 20 years.

Differential diagnosis: Clinical infections may be suspected on the basis of symptomatology and/or radiographic features, but such indications are not unique or pathognomic for paragonimiasis. Provisional diagnoses must be confirmed by the direct detection of fluke eggs in sputum or faecal samples, usually following their concentration by filtration, sedimentation and floatation techniques. Eosinophils and Charcot-Leyden crystals are commonly found in respiratory secretions and stools, and haematological investigations may reveal eosinophilia, elevated erythrocyte sedimentation rates (ESR) and sometimes leucocytosis. Modern medical imaging techniques, such as X-rays, computed tomography (CT) and magnetic resonance imaging (MRI) scans, often yield nonspecific results possibly attributable to other diseases (e.g. tuberculosis), including calcified spots, nodular shadows, patchy infiltrates, linear streaks (worm tracts), and cystic lesions in the lungs, pleural thickenings, interlobar pleuritis and pleural effusions in the thorax, and various types of calcifications in the brain (punctate, nodular, congregated or 'bubble-like'). More invasive diagnostic procedures may be used to detect parasites in surgical or needle biopsy samples (e.g. decortications and aspirates). Infections by metacercariae in crustaceans may be detected by microscopic examination of dissected tissues, usually in squash preparations or following pepsin-acid digestion. Several immunological tests have been developed to detect host antibodies or parasites antigens in serum or faecal samples, including immunodiffusion, immunoelectrophoresis, immunoblot, intradermal, complement fixation and haemagglutination tests and enzyme immunoassays (polyclonal and monoclonal-antibody based). Several tests were useful for detecting early and ectopic infections, but they do not differentiate between current, recent or past infection. Molecular biological techniques have been used to characterize different developmental stages (adults, eggs, cercariae, metacercariae) of several parasite species by polymerase chain reaction (PCR) amplification of restriction fragment length polymorphisms (RFLP), random amplified polymorphic DNA (RAPD), highly repetitive DNA fragments, and sequencing specific gene fragments (nuclear ribosomal RNA and internal transcribed spacer region 2, and mitochondrial cytochrome c oxidase subunit 1).

Treatment and control: Pulmonary and extrapulmonary infections by *Paragonimus* spp. have been successfully treated using the isoquinoline anthelmintic praziquantel, which was well tolerated, low in toxicity and only produced mild transient side-effects (headaches, dizziness, gastrointestinal upset, blurred vision). The halogenated benzimidazole triclabendazole has also proven to be highly effective, as has the salicylanilide niclofolan despite problems with neurotoxicity and hepatotoxicity. In the past, the halogenated bisphenol bithionol was used but often required extended treatment and side-effects were common (urticaria, rash, abdominal pain, nausea, vomiting, diarrhoea, dizziness). Treatment of individual cases with heavy and/or ectopic infections may involve surgical removal of parasites and infected tissues. Efforts to prevent infections centre around minimizing faecal contamination of water, reducing intermediate host populations (both snails and crustaceans), and rendering crustaceans safe for human and animal consumption. These strategies are difficult, if not impossible, to implement in natural ecosystems where parasites are transmitted between wildlife by free-living aquatic stages or by predator-prey relationships. The chemical control of snail and crustacean intermediate hosts is also impractical and inadvisable due to concerns about toxic residues and untoward ecological consequences. The prevention of infections in humans and domestic animals has been more successful through public health education campaigns designed to raise awareness, improve sanitation, promote safe food preparation and cooking practices, and provide contemporary alternatives to folk medicine treatments. Thorough cooking kills metacercariae in crustacean flesh and consumers should be encouraged to avoid raw or improperly prepared culinary dishes in endemic regions despite local customs. Globally, there has been a reduction in the incidence of paragonimiasis in humans which has been attributed to improved socioeconomic conditions, higher education standards, better sanitation, improved food hygiene, rural industrialization, and restricted intermediate host distribution due to habitat loss through deforestation and environmental pollution.

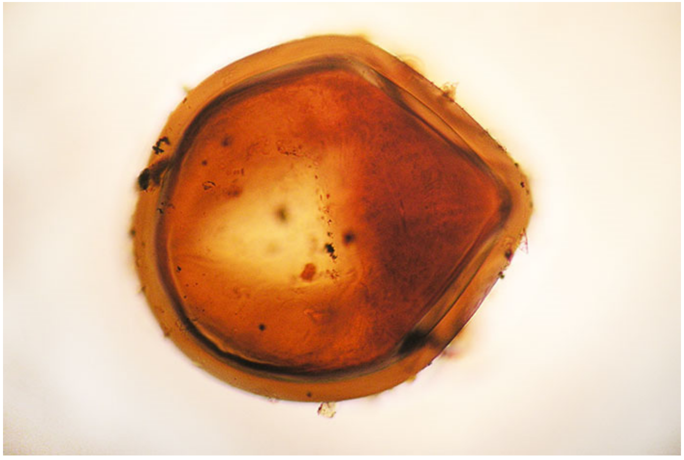


Paragonimus
lungs
(subacute-chronic
inflammatory
granulomatous
lung disease)
Definitive Hosts
(carnivores, piscivores)
hermaphroditic
adult (~ 10 mm)
ingestion
excretion
egg
(~ 100 µm)
vector-borne transmission
encysted within
tissues of IH-2
metacercaria
(~ 400 µm)
endoparasitic in
tissues of vector (IH-1)
crawling
cercaria
(~ 200 µm)
free-swimming
miracidium
(~ 80 µm)
redia
(~ 650 µm)
sporocyst
(~ 400 µm)
Second Intermediate Hosts
(IH-2) (freshwater crabs)
(viscera, muscles)
First Intermediate Hosts
(IH-1) (pomatiopsid snails)
(visceral then glandular tissues)

Paragonimus adult worm

Paragonimus egg

Paragonimus miracidium



Paragonimus metacercaria