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▣ MINI-REVIEW

Foodborne Intestinal Flukes in Southeast Asia

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Abstract: In Southeast Asia, a total of 59 species of foodborne intestinal flukes have been known to occur in humans. The largest group is the family Heterophyidae, which constitutes 22 species belonging to 9 genera (*Centrocestus, Haplorchis, Heterophyes, Heterophyopsis, Metagonimus, Procerovum, Pygidiopsis, Stellantchasmus,* and *Stictodora*). The next is the family Echinostomatidae, which includes 20 species in 8 genera (*Artyfechinostomum, Acanthoparyphium, Echinochasmus, Echinoparyphium, Echinostoma, Episthmium, Euparyphium,* and *Hypoderaeum*). The family Plagiorchiidae follows the next containing 5 species in 1 genus (*Plagiorchis*). The family Lecithodendriidae includes 3 species in 2 genera (*Phaneropsolus* and *Prosthodendrium*). In 9 other families, 1 species in 1 genus each is involved; Cathaemaciidae (*Cathaemacia*), Fasciolidae (*Fasciolopsis*), Gastrodiscidae (*Gastrodiscoides*), Gymnophallidae (*Gymnophalloides*), Microphallidae (*Spelotrema*), Neodiplostomidae (*Neodiplostomum*), Paramphistomatidae (*Fischoederius*), Psilostomidae (*Psilorchis*), and Strigeidae (*Cotylurus*). Various types of foods are sources of human infections. They include freshwater fish, brackish water fish, fresh water snails, brackish water snails (including the oyster), amphibians, terrestrial snakes, aquatic insects, and aquatic plants. The reservoir hosts include various species of mammals or birds.The host-parasite relationships have been studied in *Metagonimus yokogawai, Echinostoma hortense, Fasciolopsis buski, Neodiplostomum seoulense,* and *Gymnophalloides seoi*; however, the pathogenicity of each parasite species and host mucosal defense mechanisms are yet poorly understood. Clinical aspects of each parasite infection need more clarification. Differential diagnosis by fecal examination is difficult because of morphological similarity of eggs. Praziquantel is effective for most intestinal fluke infections. Continued efforts to understand epidemiological significance of intestinal fluke infections, with detection of further human cases, are required.

Key words: intestinal fluke, foodborne, heterophyid, echinostome, epidemiology, Asia

INTRODUCTION

Although 40-50 million people are generally estimated to be infected with foodborne intestinal trematodes worldwide [1], this certainly is an underestimate of the true number of people infected. Most of the infected people live in Southeast Asia, including Korea, China, Thailand, Vietnam, Lao PDR, the Philippines, Indonesia, and India. The number of trematode species, currently known to be involved in this area, is counted at least 59, including *Metagonimus yokogawai, Heterophyes nocens, Haplorchis taichui, Prosthodendrium molenkampi, Phaneropsolus bonnei, Echinostoma hortense, Echinochasmus japonicus, Fasciplopsis buski, Neodiplostomum seoulense,* and *Gymnophalloides seoi* [1-6] (Table 1). They belong to the families Heterophyidae, Echinostomatidae Poche, 1926, Plagiorchiidae Ward, 1917, Lecithodendriidae Odhner, 1911, Neodiplostomidae Shoop 1989, Paramphistomatidae Fischoeder, 1901, Cathaemaciidae Fuhrmann, 1928, Fasciolidae Railliet, 1895, Gastrodiscidae Stiles and Goldberger, 1910, Gymnophallidae Morozov, 1955, Microphallidae Travassos, 1920, Psilostomidae Odhner, 1913, and Strigeidae Railliet, 1919 [1-6]. In this paper, morphology, biology, epidemiology, pathogenicity, clinical manifestations, diagnosis, and treatment of these fluke infections are briefly reviewed.

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SPECIES INFECTING HUMANS

Acanthoparyphium tyosenense Yamaguti, 1939

This echinostome is morphologically characterized by the presence of a characteristic head collar with a total of 23 collar spines arranged in a single row, without ventral corner spines, a long cirrus sac reaching beyond the posterior margin of the acetabulum, and the vitellaria extending to the level of the cirrus sac or the Mehlis' gland [7]. This species was originally described based on worms from the small intestines of the duck

Table 1. Foodborne intestinal flukes and the infection source in Southeast Asia

Parasite species	Source of human or animal infections
Acanthoparyphium tyosenense	Bivalves, *Mactra veneriformis, Solen grandis;* gastropod, *Neverita bicolor*
Artyfechinostomum malayanum	Snail, *Digoniostoma pulchella Echinostoma malayanum, Pila scutata, Lymnaea (Bullastra) cumingiana*
Artyfechinostomum oraoni	Probably freshwater snail
Ascocotyle (Phagicola) longa	Freshwater fish
Cathaemacia cabrerai	Unknown
Centrocestus armatus	Fresh water fish, *Zacco platypus, Zacco temminckii, Rhodeus ocellatus, Gobius similis, Pseudorasbora parva, Pelteobagrus fulvidraco*
Centrocestus caninus	Freshwater fish, *Cyprinus carpio, Hampala dispar, Puntius* spp., *Cyclocheilichthys* sp., *Tilapia nilotica*
Centrocestus formosanus	Freshwater fish
Centrocestus kurokawai	Probably freshwater fish
Cotylurus japonicus	Freshwater snail, *Stagnicola, Lymnaea, Physa, Heligsoma* spp.
Cryptocotyle lingua	Freshwater fish, *Gobius ruthensparri, Labrus bergylta*
Echinochasmus fujianensis	Freshwater fish, *Pseudorasbora parva, Cyprinus carpio*
Echinochasmus japonicus	Fresh water fish, *Pseudorasbora parva, Hypomesus olidus, Gnathopogon strigatus*
Echinochasmus jiufoensis	Probably freshwater fish
Echinochasmus liliputanus	Freshwater fish, *Pseudorasbora parva,* goldfish
Echinochasmus perfoliatus	Freshwater fish, *Carassius* sp.
Echinoparyphium recurvatum	Freshwater snail, *Planorbis planorbis, Lymnaea* sp., *Lymnaea stagnalis;* tadpole and frog of *Rana temporaria*
Echinostoma angustitestis	Freshwater fish
Echinostoma cinetorchis	Freshwater fish, *Misgurnus anguillicaudatus;* freshwater snail, *Radix auricularia coreanus, Physa acuta, Cipangopaludina chinensis malleata*
Echinostoma echinatum	Mussel, *Corbicula lindoensis, Corbicula sucplanta, Idiopoma javanica;* freshwater snail, *Biomphalaria glabrata*
Echinostoma hortense	Freshwater fish, *Misgurnus anguillicaudatus, Misgurnus mizolepis, Odontobutis obscura interrupta, Moroco oxycephalus, Coreoperca kawamebari, Squalidus coreanus*
Echinostoma ilocanum	Large snail, *Pila conica, Viviparus javanicus*
Echinostoma macrorchis	Large snail, *Cipangopaludina malleata, Cipangopaludina japonica, Segmentina nitiella, Viviparus malleatus;* frog of *Rana* sp.
Echinostoma revolutum	Snail or clam, *Corbicula product;* tadpole
Episthmium caninum	Freshwater fish
Fasciolopsis buski	Aquatic plant, including water caltrop, water cress, water chestnut, and water bamboo
Fischoederius elongatus	Aquatic plant
Gastrodiscoides hominis	Tadpole, frog, crayfish, aquatic plant
Gymnophalloides seoi	Oyster, *Crassostrea gigas*
Haplorchis pumilio	Freshwater fish, Cyprinidae, Siluridae, Cobitidae
Haplorchis taichui	Freshwater fish, *Cyprinus carpio, Carassius auratus, Zacco platypus, Pseudorasbora parva, Rodeus ocellatus, Gambusia affinis, Puntius orphoides, Puntius* spp., *Raiamas guttatus, Mystacoleucus marginatus, Henichoryhnchus siamensis*
Haplorchis vanissimus	Freshwater fish
Haplorchis yokogawai	Freshwater fish, *Mugil* spp., *Puntius* spp., *Misgurnus* sp., *Ophicephalus striatus*
Heterophyes nocens	Brackish water fish, *Mugil* sp., *Acanthogobius* sp.
Heterophyopsis continua	Brackish water fish, *Acanthogobius* sp., *Lateolabrax* sp., *Clupadon punctatus*
Hypoderaeum conoideum	Snail, tadpole
Isthmiophora melis	Tadpole, loach *Misgurnus* spp.
Metagonimus minutus	Mullet, *Mugil cephalus*
Metagonimus miyatai	Sweetfish, dace, fat-minnow *Morocco steindachneri,* pale chub *Zacco platypus,* dark chub *Zacco temmincki,*
Metagonimus takahashii	Crussian carp *Carrassius carassius,* carp *Cyprinus carpio,* dace *Tribolodon taczanowskii,* perch *Lateolabrax japonicus*
Metagonimus yokogawai	Sweetfish *Plecoglossus altivelis,* dace *Tribolodon* sp., perch *Lateolabrax japonicus*
Neodiplostomum seoulense	Grass snake, *Rhabdophis tigrina;* tadpole and frog of *Rana nigromaculata*
Phaneropsolus bonnei	Naiad of dragonfly, damselfly
Phaneropsolus spinicirrus	Probably naiads of dragonfly
Plagiorchis harinasutai	Probably insect larva
Plagiorchis javensis	Insect larva
Plagiorchis muris	Insect larval, insect naiad
Plagiorchis philippinensis	Insect larva

(*Continued to the next page*)

Table 1. (*Continued from the previous page*)

Parasite species	Source of human or animal infections
Plagiorchis muris	Freshwater fish, various species, freshwater snail
Plagiorchis vespertilionis	Mosquito larva, caddis-fly larva, mayfly larva, dragonfly nymph; freshwater fish
Procerovum calderoni	Freshwater fish, *Ophiocephalus striatus*, *Glossogobius giurus*, *Mollienesia latipinna*, *Mugil* sp., *Creisson validus*
Procerodum varium	Mullet, *Mugil cephalus*
Prosthodendrium molencampi	Naiad of dragonfly, damselfly
Psilorchis hominis	Unknown
Pygidiopsis summa	Mullet *Mugil cephalus*, goby *Acanthogobius flavimanus*
Spelotrema brevicaeca	Crab *Carcinus maenas;* shrimp *Macrobrachium* sp.
Stellantchasmus falcatus	Mullet and half-beaked fish *Dermogenus pusillus*
Stellantchasmus formosanus	Mullet *Mugil cephalus*
Stellantchasmus pseudocirratus	Mullet *Mugil cephalus*
Stictodora fuscata	Goby *Acanthogobius flavimanus*
Stictodora lari	Goby *Acanthogobius flavimanus*, other estuarine fish

Melanitta fusca stejnegeri and *Melanitta nigra americana* caught in the Republic of Korea [8]. This echinostome is at present known to be distributed in the Republic of Korea and Japan [9]. The first intermediate hosts include marine megagastropods *Lunatia fortuni* and *Glassaulax didyma* in the Republic of Korea [9]. *Cercaria yamagutii* shed from marine gastropods, *Tympanotonus microptera, Cerithidea cingulata,* and *Cerithidea largillierti,* in Japan [10], is now considered to be the cercariae of *A. tyosenense* [9]. Four species of brackish water bivalves, i.e., *Mactra veneriformis*, *Solen grandis*, *Solen strictus*, and *Ruditapes philippinarum*, and a species of brackish water gastropod, *Neverita bicolor*, have been verified to be the second intermediate hosts [7,9]. Chicks [7,11] and sea gulls *Larus crassiostris* [9] were reported to be the experimental definitive hosts. In chicks, worms grew quickly to become ovigerous adults in the jejunum within 5 days and survived at least up to 38 days [11]. The worms fully grew to have a peak number of uterine eggs during day 10 and day 15 after infection [11]. Ten human infections were first discovered in 2 coastal villages of Chollabuk-do Province, Republic of Korea [7]. The patients used to eat improperly cooked marine bivalves and gastropods.

Artyfechinostomum malayanum (Leiper, 1911) Mendheim, 1943

(syn. *Echinostoma malayanum* Leiper, 1911; *Euparyphium malayanum* Odhner, 1913; *Artyfechinostomum sufrartyfex* Lane, 1915; *Artyfechinostomum mehrai* Faruqui, 1930; *Paryphostomum sufrartyfex* Bhalerao, 1931; *Isthmiophora malayana* [48])

This echinostome was first described from a human in Malaysia under the name *Echinostoma malayanum* Leiper, 1911 [12], and then in Singapore, Thailand, Indonesia, India, and the Philippines [6,13-15]. It has a small head collar, with a total of 43 (39-45) collar spines arranged in 2 alternating rows at the dorsal side, 2 deeply lobed testes, and a large and long cirrus sac reaching beyond the ventral sucker [16]. It was noted that *E. malayanum* Leiper, 1911 fits better to the generic features of *Artyfechinostomum* Lane, 1915 [16,17]. A closely related species, *A. sufrartyfex*, was found in an Assamese girl [18] and a boy [19] in India, and also in pigs [20], and cats and dogs [21]. *A. sufrartyfex* (Lane, 1915) was found conspecific with *A. malayanum* (Leiper, 1911) [17]. Another species, *A. mehrai* Faruqui, 1930, which was later synonymized with *A. malayanum* [17,20], was described in 1930 from a Hindu girl suffering from diarrhea, vomiting, anorexia, and loss of weight [22]. *A. mayananum* is now known to be distributed in Malaysia, Thailand, Indonesia, India, and the Philippines [6,12-15]. The first intermediate host is the freshwater snail, *Indoplanorbis exustus* or *Gyraulus convexiusculus*, and cercariae encyst in various species of snails, i.e., *Pila scutata*, *Lymnaea (Bullastra) cumingiana*, and *Digoniostoma pulchella* [6]. Humans, pigs, rats, cats, dogs, mice, hamsters, and house-shrews were reported to be the definitive hosts [6,16,21,23].

Artyfechinostomum oraoni Bandyopadhyay, Manna & Nandy, 1989

This echinostome was first reported from 20 human infections in a tribal community near Calcutta, India [24,25]. The first intermediate host is the freshwater snail, *Lymnaea* sp. [26]. In naturally infected pigs, *A. oraoni* provoked fatal diarrhea [25].

Cathaemacia cabrerai Jueco & Monzon, 1984

This fluke was first reported from a patient in the Philippines [28]. No further information is available.

Centrocestus armatus (Tanabe, 1922) Price, 1932

This heterophyid fluke, having 42-48 circumoral spines, was described from experimental dogs, cats, rabbits, rats, and mice fed on cyprinoid fish infected with the metacercariae [29]. Characteristic morphological features include a small number of intrauterine eggs, the median location of the ovary, and the side-by-side location of the 2 testes [30]. An experimental human infection was reported successful in Japan [29], and a case of natural human infection was reported in the Republic of Korea [30]. The first intermediate host is the fresh water snail, *Semisulcospira* sp. [31], and the second intermediate hosts are freshwater fish, including *Zacco platypus, Zacco temminckii, Rhodeus ocellatus, Gobius similis, Pseudorasbora parva*, and *Pelteobagrus fulvidraco* [32,33]. The natural definitive hosts include the large egret *Egretta alba modesta* [34] and the cat [35].

Centrocestus caninus (Leiper, 1913) Yamaguti, 1958

(syn. *Stephanopirumus longus* Onji & Nishio, 1916)

This heterophyid fluke, armed with 26-30 circumoral spines, was originally described in 1913 based on a single specimen obtained from a dog in Taiwan [4,36], and 2 human infections were diagnosed with this species in Thailand [37]. The freshwater snail, *Melanoides tuberculata*, is the snail host, and freshwater fish, such as, *Carrassius auratus, Cyprinus carpio, Hampala dispar, Puntius* sp., *Cyclocheilichthys* sp., and *Tilapia nilotica*, serve as the second intermediate hosts [37,38]. The validity of this species is now questioned, and this species seems synonymous with *C. formosanus* [36].

Centrocestus formosanus (Nishigori, 1924) Price, 1932

This heterophyid fluke, having 32 circumoral spines, was originally described from an experimental dog fed freshwater fish infected with the metacercariae [39]. An experimental human infection and a natural infection in a fox were also reported [39]. Natural human infections were found in Taiwan and Japan [40, 41]. The distribution of this fluke is known in Taiwan, China, Japan, Philippines, India, Hawaii, Mexico, and Lao PDR [6,36, 41-45]. The snail, *Stenomelania newcombi*, sheds the cercariae [43]. Freshwater fish, including *Cyclocheilichthys repasson, Puntius brevis*, and *Osteochilus hasseltii*, harbor the metacercariae [36,46].

Centrocestus kurokawai (Kurokawa, 1935) Yamaguti, 1958

This heterophyid fluke, having 38-40 circumoral spines, was described from a naturally infected man in Hiroshima Prefecture, Japan [47]. No other information is available on its life cycle.

Cotylurus japonicus Ishii, 1932

This strigeid fluke was originally described from ducks and chickens in Japan by Ishii in 1932 [48]. Later it was reported from a 13-year-old girl in Hunan Province, China [49]. Freshwater snails belonging to the genera *Stagnicola, Lymnaea, Physa*, and *Heligsoma* shed the cercariae, and the cercariae encyst in the same snail hosts to become specialized metacercariae known as 'tetracotyles' [1]. Human infections may occur when tetracotyles in infected snails are ingested [1].

Echinochasmus fujianensis Cheng et al., 1992

This echinostome was originally described from man, dogs, cats, pigs, and rats in Fujian Province, China [50]. The head collar is prominent with 24 spines arranged in a single row, interrupted dorsally [50]. Genetically *E. fujianensis* is distinguished from *Echinochasmus japonicus* by means of random amplified polymorphic DNA analysis (RAPD) patterns [51]. In 5 areas of southern Fujian Province, the prevalence among residents was 3.2% (1.6-7.8% in range), and about two-thirds of the infected people were 3-15 years of age [6,50]. Among the 3 *Echinochasmus* species, *E. fujianensis, E. japonicus*, and *E. perfoliatus*, existing in Hubei, Anhui, and Fujian provinces, China, *E. fujianensis* is the dominant species [51]. Freshwater snails, *Bellamya aeruginosa*, shed the cercariae, and *Pseudorasbora parva* and *Cyprinus carpio* habor the metacercariae [6]. Dogs, cats, pigs, and rats serve as the natural definitive hosts [50].

Echinochasmus japonicus Tanabe, 1926

This echinostome, having dorsally interrupted 24 collar spines, was first described in Japan from experimental animals, including dogs, cats, rats, mice, and birds fed the metacercariae encysted in freshwater fish [52], and is now known to occur in the fae East [2,5]. Its morphological characters include a small and plump body, 2 large and tandem testes, and a very small number of eggs, usually less than 5, in the uterus [2]. An successful experimental human infection was reported in Japan [53], and later natural human infections were found in several provinces of China [54,55] and the Republic of Korea [56]. Fresh water snails, *Parafossarulus manchouricus*, shed the cercariae [57,58], and 18 species of freshwater fish, including *Pseudorasbora parva, Hypomesus olidus*, and *Gnathopogon strigatus*, harbor the metacercariae [58-60]. In the laboratory, its life cycle from cercariae to adults has been successfully completed [58]. Avian species, such as ducks [61] and egrets [34], and mammalian species, such as cats [35] and insectivores [62], have been confirmed as the natural definitive hosts. This echinostome is prevalent among people, as well as animals, in 6 counties of Fujian and Guangdong, China, the prevalence being 4.9% in humans, 39.7% in dogs, and 9.5% in cats [6].

Echinochasmus jiufoensis Yu & Mott, 1994

This echinostome, having dorsally interrupted 24 collar spines, was first described in 1988 at an autopsy of a 6-month-old girl who died from pneumonia and dehydration in Guangzhou, China [63]. This fluke closely resembles *Echinochasmus beleocephalus* Dietz, 1909, but distinguished in several points [6,63]. The life cycle is unknown [63].

Echinochasmus liliputanus (Looss, 1896) Odhner, 1910

This echinostome, having dorsally interrupted 24 collar spines, was originally reported from dogs, cats, and birds in Egypt, Syria, and Palestine [48]. The head collar is reniform, and the vitellarium does not extend anterior to the ventral sucker [64]. Human infections were first discovered in Anhui Province, China in 1991, with the prevalence rate of 13.4% among 2,426 people [65]. The infection rates in dogs and cats living in the same place were 60% and 45%, respectively [65]. Thereafter, more than 2,500 human infection cases have been reported in Anhui Province, China [66]. The freshwater snail *Parafossarulus striatulus* shed the cercariae [6], and the freshwater fish *Pseudorasbora parva* [6] and goldfish [66] harbor the metacercariae. Badgers, foxes, raccoons, dogs, and cats serve as the natural definitive shosts [6,67]. Humans may be infected with this parasite through drinking untreated water containing the cercariae [68]. Cercariae were found to be encysted in the presence of human gastric juice, and this was proposed as the plausible mechanism of cercariae-induced infections [66].

Echinochasmus perfoliatus (Ratz, 1908) Gedoelst, 1911

This echinostome, having dorsally interrupted 24 collar spines, was first recovered from dogs in Rumania by Motas and Straulescus in 1902 under the name *Distoma echinatum*, and then found again by Ratz in 1908 from dogs and cats in Hungary [69]. It is now a common intestinal parasite of dogs and cats in Hungary, Italy, Rumania, Russia, Japan, China, and Taiwan [6, 70], and of red foxes in Denmark [71]. Its body is elongated and larger than the closely related species, *E. japonicus*. An experimental [69] and a natural human infection [72] were successively reported in Japan. A low prevalence (1.8%) of human infections was reported from Guangdong, Fujian, Anhui, and Hubei Provinces of China; however, a child died from the infection from whom about 14,000 worms were recovered at autopsy [6]. Freshwater snails, *Parafossarulus manchouricus*, *Bithynia leachi*, and *Lymnaea stagnalis* shed the cercariae [48]. Freshwater fish, such as *Carassius* sp., *Zacco platypus*, *Zacco teminckii*, and *Pseudorasbora parva*, harbor the metacercariae, which are encysted only on the gills [6,73]. Mammals, including rats, cats, dogs, foxes, fowls, and wild boars are the reservoir hosts [12,71,74].

Echinoparyphium recurvatum (von Linstow, 1873) Lühe, 1909

(syn. *Echinoparyphium koidzumii* Tsuchimochi, 1924)

This echinostome was first found in various avian species, and now also recognized as a parasite of mammals [6,12,75,76]. The first human infection was identified in Taiwan in 1929 and in Indonesia in 1948 [12]. It is characterized by having a relatively small body, a head collar armed with 45 collar spines arranged in 2 alternating rows and 4-5 end group spines on each side, a large ventral sucker, and a short uterus with only a few eggs [73,75]. It has been suggested that *E. recurvatum* complex consists of at least 3 species, including 2 other similar species, i.e., *E. pseudorecurvatum* and *E. mordwilkoi* [77]. The planorbid snails, including *Physa alexandrina*, *Physa fontinalis*, *Planorbis planorbis*, *Lymnaea pervia*, *Lymnaea peregra*, *Valvata piscinalis*, and *Radix auricularia coreana* shed the cercariae [78-80], and the metacercariae encyst in tadpoles and frogs of *Rana temporaria* and also in snails, *P. planorbis*, *Lymnaea* sp. [6], *R. auricularia coreana* [80], and *Lymnaea stagnalis* [81]. House rats [75], wild rats (*Arvicanthis niloticus*) [82], and species of birds are natural definitive hosts [48]. Human infections have been recorded in Taiwan, Indonesia, and Egypt [6,12].

Echinostoma angustitestis Wang, 1977

This echinostome was first described from dogs experimentally infected with metacercariae isolated from the freshwater fish in 1977 in China [6]. It has a head collar armed with a total of 41 collar spines arranged in 2 alternating rows [83]. Only 2 human infections were reported in Fujian, China, who complained of dizziness, abdominal pain, and diarrhea [83]. There is no available information on its life history.

Echinostoma cinetorchis Ando & Ozaki, 1923

This echinostome was first discovered in rats in Japan [84], and then in a dog in Taiwan [85,86], rats in the Republic of Korea [87,88]. This fluke also exists in China [89]. Human infection cases were first reported in Japan [90,91] and then in the Republic of Korea [92-94]. Its head collar is equipped with total 37-38 spines and abnormal location and/or disappearance of one or both testes is a characteristic feature [2]. The freshwater snails *Hippeutis cantori* [95] and *Segmentina hemisphaerula* [96] shed the cercariae and also harbor the metacercariae [95]. Other freshwater snails, including *Radix auricularia coreana, Physa acuta, Cipangopaludina* sp., and *Cipangopaludina chinensis malleata*, were proved to be the second intermediate hosts [97,98]. Tadpoles of *Rana nigromaculata, Rana rugosa*, and *Rana japonica* [99], and freshwater fish, especially the loach *Misgurnus anguillicaudatus* [100,101], were proven to harbor the metacercariae. Rats [62,84, 87,88] and dogs [102] serve as the natural definitive hosts. Rats and mice are good experimental animals [103].

Echinostoma echinatum (Zeder, 1803) Rudolphi, 1809

(syn. *Echinostoma lindoense* Sandground & Bonne, 1940; *Echinostoma barbosai* Jeyarasasingam et al., 1972)

This echinostome was originally described from the intestine of mammals in Germany in 1803 [104]. It has 37 collar spines arranged in 2 alternating rows [5]. This species closely resembles *Echinostoma revolutum*, and thus was once synonymized with *E. revolutum* by Diez in 1909 [104]. However, various authors acknowledge its distinctiveness [104-107]. In the meantime, *Echinostoma barbosai* Jeyarasasingam et al., 1972 and *Echinostoma lindoense* Sandground and Bonne, 1940 were synonymized with *E. echinatum* [105,108]. High prevalences (24-96%) of human infections with this echinostome were reported in 3 villages of Celebes, Indonesia, under the name of *E. lindoense* in 1940 [109]. Now this species is known to be distributed widely in Europe, Asia, and South America; natural definitive hosts can be birds and mammals [108]. Freshwater snails, including *Lymnaea, Planorbarius, Planorbis, Anisus, Gyraulus, Biomphalaria*, and *Viviparus*, shed the cercariae [108]. Mussels, *Corbicula lindoensis, Corbicula sucplanta*, and *Idiopoma javanica*, contain the metacercariae [12]. *Biomphalaria glabrata* snail is another second intermediate host in Brazil [110]. Experimental definitive hosts include rats, mice, ducks, and pigeons [12,73].

Echinostoma hortense Asada, 1926

This echinostome was originally described from rats in Japan [111]. After then, it has been reported from rats in Korea [2,62, 87,88,112] and China [113]. Its head collar is armed with 27-28 collar spines arranged in 2 alteranative rows [2]. A characteristic morphology includes a laterally deviated location of the ovary [2]. A new combination, *Isthmiophora hortensis*, was proposed for this species [114]. However, *E. hortense* should be retained until a definite conclusion could be drawn. Freshwater snails, including *Lymnaea pervia* and *Radix auricularia coreana*, shed the cercariae [2,115]. The loaches, *Misgurnus anguillicaudatus* and *Misgurnus mizolepis*, and other freshwater fish, including *Odontobutis obscura interrupta, Moroco oxycephalus, Coreoperca kawamebari*, and *Squalidus coreanus* harbor the metacercariae [2,116-118]. In Liaoning province of China, 69.7% of the loach *M. anguillicaudatus* from a market was infected with this echinostome [6]. Natural definitive hosts include rats [62,87,88,112], dogs [102], and cats [35]. Mice, rats, and humans have been shown experimentally to be susceptible to this echinostome infection [119,120]. Human infections have been reported in Japan, Korea, and China [2,5,121,122]. In Liaoning province of China, 6 out of 10 hospitalized hepatitis patients who had eaten raw loach were found infected [123]. In the Republic of Korea, an endemicity of this echinostome infection, with 22.4% prevalence, was reported among residents of Cheongsong-gun [124]. In hospitals of the Republic of Korea, clinical cases are at times diagnosed by extracting worms through gastroduodenal endoscopy [125-129].

Echinostoma ilocanum (Garrison, 1908) Odhner, 1911

This echinostome was first found from 5 prisoners in Manila, Philippines, and 21 adult flukes were recovered from 1 patient after anthelmintic treatment in 1907 [130]. Its head collar is armed with 49-51 collar spines and it characteristically has 2 deeply lobed testes [73,131]. Freshwater snails, *Gyraulus* or *Hippeutis*, shed the cercariae [6]. Large snails, *Pila conica* (Philippines) and *Viviparus javanicus* (Java), harboring the metacercariae are the source of human infections [12]. Reservoir hosts include rats and dogs [12]. Human infections have been reported from Celebes, Java, Indonesia, China, Thailand, the Philippines, and India [6,130-133]. In northen Luzon, the Philippines, the prevalence among the Ilocano population was 11% on average (7-17% by age group) [130].

Echinostoma macrorchis Ando & Ozaki, 1923

This echinostome was originally described from rats, *Rattus rattus* and *Rattus norvegicus*, in Japan [84]. The head collar is armed with 43-47 (usually 45) spines arranged in 2 alterating rows [73]. Thirty-four adult specimens were recovered from a Japanese boy in 1927 [134]. Freshwater snails, *Segmentina nitiella* and *Planorbis compressus japonicus* shed the cercairae and also harbor the metacercariae [73]. Other snails, *Cipangopaludina malleata, Cipangopaludina japonica, S. nitiella, Viviparus malleatus,* and the frog *Rana* sp. also harbor the metacercariae [6]. A bird, *Capella gallinago gallinago,* is another natural definitive host in Japan [135].

Echinostoma revolutum (Froelich, 1802) Looss, 1899

(syn: *Echinoparyphium paraulum* Diez, 1909)

This echinostome is the oldest species recorded in the literature [5]. It was first found in 1798 from a naturally infeted wild duck *Anas boschas fereae* in Germany and reported in 1802 as *Fasciola revoluta* by Froelich [104]. Now this is the most well known echinostome species, and represents the so-called 37-collar-spined *E. revolutum* group [105]. Its geographical distribution is wide in Asia, Europe, Africa, Australia, New Zealand, and North and South America [6,104,108]. The head collar is armed with 37 spines arranged as 5-6-15-6-5, including 5 corner spines, 6 lateral spines in single rows, and 15 dorsal spines in a double row [136]. Freshwater snails, *Lymnaea* sp., *Physa* sp., *Paludina* sp., *Segmentina* sp., and *Heliosoma* sp. shed the cercariae [12]. Tadpoles, snails, or clam Corbicula producta harbor the metacercariae and act as the source of infection for definitive hosts [12]. In the Republic of Korea, this echinostome was reported from house rats and cats [35,75]. *Echinoparyphium paraulum,* a synonym of *E. revolutum* [12], was described from dogs in India [48] and ducks in Japan [73]. Human infection was first reported in Taiwan in 1929 [137], and the prevalence in Taiwan was once estimated to be 2.8-6.5% [6]. Human infections are also known in Yunnan and Guangdong provinces of China, Indonesia, Thailand, and Russia [12,73,138]. Ducks, gooses, and muskrats are natural definitive hosts [6,104,108].

Episthmium caninum (Verma, 1935) Yamaguti, 1958

This echinostome was originally described in dogs in Calcutta, India [139]. Other *Episthmium* species have been reported from birds [48]. *E. caninum* has 24 dorsally interrupted collar spines; 12 dorsal spines are arranged in a single row and 12 lateral and ventral spines are arranged in 2 alterating rows [139]. The genus *Episthmium* was suggested to be a synonym of *Echinochasmus* [140]. Several human cases have been reported from northeast Thailand [139,141], and freshwater fish was the source of infection [141].

Fasciolopsis buski (Landkester, 1857) Odhner, 1902

This fascioliid fluke, the largest fluke among those parasitizing the human host, was first discovered in 1857 in the duodenum of an Indian man who died in London [12,142]. It is now known to be a common intestinal parasite of man and pigs in China, Taiwan, Thailand, Vietnam, Laos, Cambodia, Bangladesh, India, Indonesia, and Malaysia [4,6,142,143]. The prevalence of human infection varied according to countries, 10% in Thailand [144], 25% in Taiwan [145], 57% in China [146], and 60% in India [147]. Freshwater snails, *Segmentina* sp., *Hippeutis* sp., and *Gyraulus* sp. shed the cercariae [4,6,142]. Aquatic plants, such as, water chestnut *Eliocharis tuberose,* water caltrop *Trapa natans,* water hyacinth *Eichhornia* sp., roots of the lotus, water bamboo *Zizania* sp., and other aquatic vegetations have the metacercariae on their body surface; metacercariae may float in the water [1,6,12]. The major mode of human infection is consumption of raw or improperly cooked aquatic plants, or peeling off the hull or skin of the plants by mouth before eating the raw nut [6]. Pigs are the main source of eggs and drainage of pig excreta in farms is an important factor for maintaining high endemicity [6].

Fischoederius elongatus (Poirier, 1883) Stiles & Goldberger, 1910

This paramphistome species is a parasite of ruminants first reported in 1883 [6]. It is infected by ingesting aquatic plants having the metacercariae [6]. Only 1 human infection was reported from Guandong, China in 1992 [6]. The patient complained of epigastric pain for several months [6].

Gastrodiscoides hominis (Lewis & McConnell, 1876) Leiper, 1913

This amphistome species was originally described from an Indian patient in 1876 [12]. Now it is known to be a common parasite of humans and pigs in India, Pakistan, Myanmar, Vietnam, the Philippines, Thailand, China, Kazakstan, Indian immigrants in Guyana, and the Volga Delta in Russia [12,142]. In human infections, worms attach to the cecum and ascending colon and may produce mucous diarrhea [12]. The planorbid freshwater snails, *Helicorbis coenosus* shed the cercariae [12], and the cercariae encyst on aquatic plants, or in tadpoles, frogs, and crayfish [6]. Pigs, mouse deers, field rats, and rhesus monkeys are reservoir hosts [6,12].

Gymnophalloides seoi Lee, Chai & Hong, 1993

This gymnophallid fluke was first discovered from a Korean woman suffering from acute pancreatitis and gastrointestinal discomforts in 1988 [148,149]. The home village of the patient was a southwestern coastal island named Aphaedo, Shinan-gun, which was subsequently found to be a highly endemic area [150]. To date, more than 25 villages on western and southern coastal islands [151-155] and 3 non-island coastal villages [156] were identified as endemic areas. A 17th century femal mummy found in Hadong, a southern costal area of Korea, has been found to be infected with *G. seoi*; thus, this species is thought to have been prevalent in Korea for longer than several hundred years [157]. This parasite has been known to be present only in the Republic of Korea. Morphological characters of the adult parasite include a small body with a large oral sucker and a small ventral sucker, 2 short ceca, 2 compact masses of vitellaria, and a unique ventral pit [148,149]. Cercariae have not been discovered and the first intermediate host is yet unknown [149,158]. However, the oysters *Crassostrea gigas* have been proved to harbor the metacercariae [159,160]. The Palearctic oystercatchers *Haematopus ostralegus* [161] and feral cats [162] have been shown to be natural definitive hosts. Wading birds, such as, the Kentish plover *Charadrius alexandrinus,* Mongolian plover *Charadrius mongolus,* and grey plover *Pluvialis squatarola,* were experimentally proved to be susceptible to infection with this fluke [163]. Laboratory animals, including gerbils, hamsters, cats, and several strains of mice, were also found susceptible to experimental infections [164]. The metacercariae could be successfully cultured in vitro into adults using NCTC 109 medium or minimum essential medium [165,166].

Haplorchis pumilio (Looss, 1886) Looss, 1899

(syn. *Monorchotrema taihokui* Chen, 1936)

This heterophyid species, characteristically having only 1 testis and 27-39 (av. 32) minute chitinous spines on its ventrogenital sac, was originally described from birds and mammals in Egypt in 1886 [48,167]. Later the same species was discovered in Taiwan and described using the name, *Monorchotrema taihokui*, by Nishigori in 1924 [168]. Adult worms are characterized by the presence of only 1 testis and a ventro-genital-sucker complex armed with gonotyl and chitinous spines [168]. An experimental human infection with this fluke was successful by Faust and Nishigori [169], but natural human infections have been known after a report of 12 cases in 1983 in Thailand [167]. Now this fluke is known to be distributed in the Philippines, Thailand, Laos, Vietnam, South China, Taiwan, Iraque, Malaysia, India, Sri Lanka, and Egypt [6,167,170-173]. The freshwater snail, *Melania reiniana* var. *hitachiens,* was found to shed the cercariae [169,170], and freshwater fish, belonging to the Cyprinidae, Siluridae, and Cobitidae, harbor the metacercariae [170, 173]. Dogs and cats serve as the natural definitive hosts [48].

Haplorchis taichui (Nishigori, 1924) Chen, 1936

(syn. *Monorchotrema taichui* Nishigori, 1924; *Monorchotrema microrchia* Katsuda, 1932; *Haplorchis microrchis* Yamaguti, 1958)

This heterophyid species, characteristically having only 1 testis and 14-20 (av. 15) large chitinous spines on its ventrogenital sac, was originally described from birds and mammals caught in Taiwan [168,169,174]. An experimental human infection with this fluke was successful by Faust and Nishigori [169], but natural human infections have been known after reports in the Philippines [175]. Now it is known to be distributed widely in Taiwan, the Philippines, Bangladesh, India, Sri Lanka, Palestine, Iraque, Egypt, Malaysia, Thailand, Laos, Vietnam, and South China [4,6,170-172,175-177]. Freshwater snails, *Melania obliquegranosa*, *Melania juncea*, or *Melanoides tuberculata*, serve as the first intermediate hosts [169,170]. Freshwater fish, including *Cyclocheilichthys repasson, Cyprinus auratus, Cyprinus carpio, Gambusia affinis, Hampala dispar, Labiobarbus leptocheila, Puntius binotatus, Puntius brevis, Puntius gonionotus, Puntius leicanthus, Puntius orphoides, Puntius palata, Pseudorasbora parva, Rhodeus ocellatus,* and *Zacco platypus* [170,173] and *Raiamas guttatus, Mystacoleucus marginatus,* and *Henichoryhnchus siamensis* [178] harbor the metacercariae. Dogs, cats, and birds are the natural definitive hosts [48].

Haplorchis vanissimus Africa, 1938

This heterophyid species was originally described from a naturally infected man in the Philippines [175]. Thereafter, this fluke was reported from pelicans and wild mammals in Australia [179]. Freshwater fish serve as the second intermediate host [6].

Haplorchis yokogawai (Katsuta, 1932) Chen, 1936

(syn. *Monorchotrema yokogawai* Katsuda, 1932)

This heterophyid species, characteristically having only 1 testis and numerous (uncountable) minute chitinous spines on its ventrogenital sac, was originally described from dogs and cats experimentally fed the mullet *Mugil cephalus* in Taiwan [180]. An experimental human infection with this fluke was successful by Katsuda [180], but natural human infections have been known after reports in the Philippines [175]. Now this fluke is known to occur in the Philippines, South China, Malaysia, Indonesia, Thailand, Laos, Vietnam, India, Australia, and Egypt as human or animal infections [6,170,172,176]. Freshwater snails, *Melanoides tuberculata* or *Stenomelania newcombi*, shed the cercariae [170]. Freshwater fish, including *Cyclocheilichthys armatus*, *Hampala dispar*, *Labiobarbus leptocheila*, *Misgurnus* sp., *Mugil* spp., *Onychostoma elongatum*, *Ophicephalus striatus*, and *Puntius* spp. harbor the metacercariae [170,173]. Dogs, cats, cattle, and other mammals are natural definitive hosts [48].

Heterophyes nocens Onji & Nishio, 1916

(syn. *Heterophyes katsuradai* Ozaki & Asada, 1926)

This heterophyid species, which characteristically has 50-62 chitinous spines on its gonotyl, was first reported from experimental dogs and cats fed the mullet *Mugil cephalus* in Japan [181]. It is now known to occur as human infections in Japan, China, and the Republic of Korea [182,183-187]. Brackish water snails, *Cerithidea cingulata* (= *Tympanotonus microptera*), shed the cercariae [4,40]. Brackish water fish, such as the mullet *Mugil cephalus* or goby *Acanthogobius flavimanus*, harbor the metacercariae [2,187]. Domestic or feral cats are naturally infected with this fluke [35,162,188]. In the Republic of Korea, prevalences ranging from 10% to 70% were detected among residents in southwestern coastal areas, including islands [2,189]. In Japan, human *H. nocens* infections were reported from Kochi, Chiba, Yamaguchi, Chugoku, Hiroshima, and Shizuoka Prefectures [190,191].

Heterophyopsis continua (Onji & Nishio, 1916) Yamaguti, 1958

(syn. *Heterophyes continuus* Onji & Nishio, 1916; *Heterophyes expectans* Africa & Garcia, 1935)

This heterophyid species, characteristically having an elongate body, a genital sucker located separately from the ventral sucker, and 2 obliquely tandem testes, was first described from experimental cats fed the mullet *Mugil cephalus* that harbored the metacercariae in Japan [2,181]. Unknowing this species, Africa and Garcia [192] described *Heterophyes expentans* as a new species from dogs, which later has been synonymized with *H. continua* [48]. Human infections were first mentioned in Japan, without details [193]. After 2 natural human infections were first discovered [101], 8 more human cases have been confirmed in the Republic of Korea [94,151,152,194]. The snail host is unknown. Brackish water fish, including the perch *Lateolabrax japonicas*, goby *Acanthogobius flavimanus*, and shad, *Clupanodon punctatus* [195,196], conger eel *Conger myriaster* [197], and sweetfish *Plecoglossus altivelis* [198] harbor the metacercariae. Cats [35, 188], ducks [181], and sea-gulls [8] are the natural definitive hosts. Cats [181], dogs [101,195] and domestic chicks [199,200] are experimental host in the laboratory.

Hypoderaeum conoideum (Block, 1872) Diez, 1909

This echinostome, having a small inconspicuous head collar with 47-53 (usually 49) collar spines arranged in 2 alternating rows, was discovered in 1872 from birds and now is known to be an intestinal fluke of the duck, goose, and fowl in Europe, Japan and Siberia [48,73]. Freshwater snails, *Planorbis corneus*, *Indoplanorbis exustus*, *Lymnaea stagnalis*, *Lymnaea limosa*, *Lymnaea ovata*, and *Lymnaea rubiginosa*, shed the cercariae, and snails and tadpoles are the second intermediate hosts [48,201]. *Lymnaea tumida* in Russia [202] and *Lymnaea peregra* and *Lymnaea corvus* in Spain [203] were experimentally proven to be potential first intermediate hosts. In Thailand, this echinostome was reported from humans and birds [201,204]. In an area of northeast Thailand, 55% of 254 residents were found infected with this echinostome [204].

Isthmiophora melis (Schrank, 1788) Lühe, 1909

(syn. *Euparyphium melis* Railliet, 1919, *Euparyphium jassyense* Leon & Ciurea, 1922)

This fluke, characteristically having 27 collar spines, 19 of which are arranged in uninterrupted double rows and 4 are corner spines on each side, was described from rodents and carnivores in Europe and North America [48,73]. Its taxonomic position was unstable, either placing it in *Euparyphium* [12] or *Echinostoma* [201]. However, recently it has been assigned to the genus *Isthmiophora* [114]. Human infection with *I. melis* was first confirmed by Leon in 1916 in a diarrheic patient in Rumania and then at autopsy of a Chinese patient [12]. Further human cases were reported in China and Taiwan [6]. The snail *Stagnicola emarginata angulata* is the first intermediate host in the region of Douglas Lake, Michigan, and tadpoles serve as the second intermediate host [12]. The sourse of human infections in China was presumed to be the loach, a kind of freshwater fish [6]. Domestic and wild animals are natural definitive hosts in Russia [205].

Metagonimus minutus Katsuta, 1932

This heterophyid species, characterized by smaller sized uterine eggs, was reported from experimental mice and cats fed mullets harboring the metacercariae in Taiwan [206]. This parasite is listed among the human-infecting intestinal trematodes [6,12], but no literature background is traceable [4].

Metagonimus miyatai Saito, Chai, Kim, Lee & Rim, 1997

This heterophyid fluke, having widely separated 2 testes with 1 testis located near the posterior end of the body, was first found in Japan by Miyata in 1941, but its taxonomic position was not established until it was reported as a new species in 1997 [207]. This fluke is morphologically different from *M. yokogawai* and *M. takahashii* in the position of the posterior testis (separated considerably from the anterior one), the distribution of vitelline follicles (never crossing over the posterior testis), and the intermediate size of eggs (28-32 μm) [207]. Human infections with this species were first reported in 1980 (under the name of *Metagonimus* sp.) from people along the Gum River, the Republic of Korea [208]. Subsequently, high prevalences were reported among people residing around the Daechong Reservoir and its upper reaches [209], the upper reaches of the Namhan River [210], the Hantaan River basin [211], and the western inland of Gangwon-do [212]. In Japan, small rivers of Shizuoka Prefecture, Japan, were found to be endemic areas of this fluke [213]. Freshwater snails, *Semisulcospira globus* [209], *Semisulcospira libertina,* or *Semisulcospira dolorosa* [214], are the first intermediate host. Freshwater fish, including the sweetfish, dace, common fat-minnow *Morocco steindachneri,* pale chub *Zacco platypus,* and dark chub *Zacco temmincki,* harbor the metacercariae [207]. Mice, rats, hamsters, and dogs are experimental definitive hosts [2,215]. Natural definitive hosts are unknown.

Metagonimus takahashii Suzuki, 1930

This heterophyid fluke, having slightly separated 2 testes and extensive distribution of vitellaria near the posterior end of the body, was first reported in Japan from mice and dogs fed freshwater fish other than the sweetfish [216]. This species has been found also in the Republic of Korea, particularly along small streams in various inland areas [2]. Morphologically, it differs from *M. yokogawai* in the position of the 2 testes, the distribution of vitelline follicles, and the egg size (*M. yokogawai*, 28-30 μm; *M. takahashii*, 32-36 μm) [2,4]. The Koga type of *Metagonimus* encysting in the dace *Tribolodon* spp. [217] is regarded as a synonym of *M. takahashii* [4,218]. The presence of this species in the Republic of Korea was first documented by recovery of adult flukes from experimental rabbits in 1960 [219]. With regard to human infections, adult flukes were first confirmed in 1993 in inhabitants of Umsong-gun, Chunchungnam-do, along the upper reaches of the Namhan River [4,210]. The inhabitants were mixed-infected with *M. miyatai,* with an egg positive rate of 9.7% for both species [210]. Freshwater snails, *Semisulcospira coreana* or *Koreanomelania nodifila* [220], may be first intermediate host. Freshwater fish, including the crussian carp *C. carassius* [219], carp *C. carpio* [217], dace *Tribolodon taczanowskii* [218], and perch *Lateolabrax japonicus* [221], harbor the metacercariae. Different strains of mice could be experimentally infected with fluke [215]. There are no reports on reservoir hosts.

Metagonimus yokogawai (Katsurada, 1912) Katsurada, 1912

This heterophyid species, morphologically characterized by closely adjacent 2 testes and moderate distribution of vitellaria, is the most common intestinal fluke infecting humans in the Far East [2,4]. This fluke was first found from humans and experimental dogs in Taiwan by S. Yokogawa in 1911 [40]. It was originally named as *Heterophyes yokogawai* Katsurada, 1912 and then changed into *Metagonimus yokogawai* in the same year [40]. Human infections were reported from Japan, Korea, Siberia, Israel, the Balkan states, and Spain [6]. In the Republic of Korea, almost all large and small streams in eastern and southern coastal areas are endemic foci of metagonimiasis [4,222,223]. The Sumjin, Tamjin, and Boseong Rivers, Geoje Island, and Osip Stream (Gangwon-do) were the highest endemic areas with 20-70% egg positive rates in the villagers [2,222,224,225]. The high prevalence of *M. yokogawai* along the Tamjin River basin is persisting, although the intensity of infection among the villagers has been reduced [226]. Human infections have also been found in Guangdong, Anhui, Hubei, and Zhejiang provinces of China and Taiwan [6,183]. In Japan, the prevalence rate became negligible after the 1970s, except in some areas surrounding the Hamana Lake [227]. In fish hosts, however, small rivers of Shizuoka prefecture were prevalent with *M. yokogawai* metacercariae [213]. In Russia, the endemic areas include the Amur and Ussuri valleys of Khabarovsk territory where the prevalence in ethnic minority groups was between 20% and 70% [6]. In the north of Sakhalin Island, the infection rate was 1.5% in Russians and 10% in ethnic minorities. Sporadic cases were also reported in Amur district and Primorye territory [6]. Freshwater snails, *Semisulcospira coreana* or *Semisulcospira libertine*, shed the cercariae [220]. The sweetfish *Plecoglossus altivelis* [2], the dace *Tribolodon* sp. [218], and the perch *Lateolabrax japonicus* [228] serve as second intermediate hosts. Dogs, rats, and cats are the natural definitive hosts [88,102,229]. Variable mouse strains were found more susceptible to *M. yokogawai* infection and less susceptible to *M. miyatai* and *M. takahashii* infections [215].

Neodiplostomum seoulense (Seo, Rim & Lee, 1964) Hong and Shoop, 1995

This neodiplostomum species was originally described from naturally infected house rats in the Republic of Korea [87]. It is morphological unique due to its bisegmented body, presence of a tribocytic organ, 2 butterfly-shaped testes, and a wide distribution of vitellaria in the anterior body to the level of the ventral sucker [230]. This parasite is now known to be distributed countrywide among rodents in the Republic of Korea, but predominantly in mountainous areas [4,230]. This fluke was reported to be present also in a northeastern part of China [231]. The first human case was found in 1982 in a young man suffering from acute abdominal pain and fever, who had a history of consuming improperly cooked snakes 7 days prior to admission to a hospital [232]. Since then, 26 more human cases were found among soldiers who had eaten raw snakes during their survival training [233-235]. Freshwater snails, *Hippeutis cantori* [236] and *Segmentina (Polypylis) hemisphaerula* [237] shed the cercariae. Tadpoles and frogs of *Rana* sp. are the second intermediate host [236], and the snake *Rhabdophis tigrina* is regarded as a paratenic host [230]. Mice, rats, and guinea pigs have been found to be susceptible laboratory hosts [230]. Rats, *Rattus norvegicus* [88, 236] and mice *Apodemus agrarius* [238] are the natural definitive hosts.

Phaneropsolus bonnei Lie Kian Joe, 1951

This lecithodendriid species, which characteristically has 8 vitelline follicles on each anterolateral side, was first described from a human autopsy in 1951 in Jakarka, Indonesia, and then found in monkeys in Malaysia and India in 1962 [239]. After then, this fluke was reported from 15 human autopsies in Udornthani Provincial Hospital, northeast Thailand [240,241]. Subsequently, high prevalences of this fluke infection were found in noreastern provinces of Thailand [14]. Also in Lao PDR, a total of 1,303 adult specimens were recovered from 27 people residing in Mekong riverside areas of Savannakhet, Khammouane, and Saravane Provinces [62,171,176]. The egg morphology is very similar to that of heterophyid fluke or *Opisthorchis viverrini* [242,243]. Metacercariae were discovered in naiads and adult dragon- and damselflies in Thailand [244]. Local people in northeast Thailand and Laos sometimes eat naiads of these insects [171,176,244].

Phaneropsolus spinicirrus Kaewkes et al., 1991

This lecithodendriid species was described as a new species from a human infection case in northeast Thailand [245]. No further information is available on this parasite.

Plagiorchis harinasutai Radomyos, Bunnag & Harinasuta, 1989

This plagiorchiid species was reported as a new species in 1989 based on worms recovered from 4 human cases [246]. No other information is available on this fluke.

Plagiorchis javensis Sandground, 1940

This plagiorchiid species was originally described from a human case in Indonesia [247]. Later 2 more cases were found in Indonesia [6]. Larval insects are presumed to be the source of infection, and birds and bats are reservoir hosts [6].

Plagiorchis muris (Tanabe, 1922) Shul'ts & Skvortsov, 1931

This plagiorchiid species, which has a laterally located ovary, 2 tandem testes, and extensive distribution of vitellaria from the posterior end to the level of the pharynx, was originally described in Japan based on worms recovered from mice experimentally infected with the metacercariae [248]. An experimental human infection was reported in the U.S. [249], Natural human infections have been reported in Japan [250] and the Republic of Korea [251]. Freshwater snails, *Lymnea pervia* in Japan [248] and *Stagnicola emarginata angulata* in the U.S. [249], shed the cercariae. Aquatic insects (mosquito larvae), insect naiads, fresh water snails, and fresh water fish [248-251] harbor the metacercariae. Rats are an experimental definitive host [251]. House rats in Japan [248], and rats [87,88], mice [252], and cats [35] in the Republic of Korea are the natural definitive hosts.

Plagiorchis philippinensis Sandground, 1940

This plagiorchiid fluke was first recovered at autopsy of a resident in Manila, Philippines by Africa and Garcia in 1937 [6, 247]. Infection was acquired by eating insect larvae [6]. Birds and rats are reservoir hosts [6].

Plagiorchis vespertilionis (Müller, 1780) Braun, 1900

This plagiorchiid species was originally described from the brown long-eared bat in Europe, and then found in many countries, including the Republic of Korea [253]. This fluke has been found infected in a human in the Republic of Korea [254]. The patient had habitually eaten raw flesh of snakehead mullet and gobies [254]; however, it is uncertain whether these fish took the role for a source of infection. Its snail host is *Lymnaea* *stagnalis,* and the second hosts reported include mosquito larvae, caddis-fly larvae, mayfly larvae, and dragonfly nymphs [255].

Procerovum calderoni (Africa and Garcia, 1935) Price, 1940

This heterophyid species was first reported from 5 dogs and a native Filipino [256]. Later, it was reported from China and Africa [201]. Brackish water snails, *Thiara riquetti,* shed the cercariae [257]. Freshwater fish, *Ophiocephalus striatus, Glossogobius giurus, Mollienesia latipinna, Mugil* sp., and *Creisson validus* harbor the metacercariae [6,257,258].

Procerovum varium Onji & Nishio, 1916

This heterophyid parasite was described from experimentally infected dogs with the metacercariae in the mullet *Mugil cephalus* in Japan [181]. Experimental human infections were reported successful [259], but there have been no reports on natural human infections. It is now known to be distributed in China, the Philippines, Australia, India [260], and the Republic of Korea [35]. Cats are the natural definitive shosts [35].

Prosthodendrium molenkampi Lie Kian Joe, 1951

This lecithodendriid species, which characteristically has 12-30 vitelline follicles on each anterolateral side, was first described from 2 human autopsies by Lie Kian Joe in 1951 in Jakarka, Indonesia [244]. After then, this fluke was found in 14 human autopsies in Udornthani Provincial Hospital, Thailand [241,244]. Later, high prevalences were reported in different areas of northeast Thailand [14]. In Lao PDR, a total of 8,899 adult specimens were recovered from 52 infected people residing along the Mekong riverside areas of Vientian Municipality, Savannakhet, Khammoune, and Saravane Provinces [62,171,176]. Metacercariae were discovered in naiads and adult dragon- and damselflies in Thailand [244]. Local people in northeast Thailand and Laos at times eat naiads of these insects [62,171,244].

Psilorchis hominis Kifune & Takao, 1973

This psilostomid fluke was described from a 48-year-old Japanese patient, who had a mixed infection with *E. macrorchis,* after anthelmintic medication [261]. No other information is available on this species.

Pygidiopsis summa Onji & Nishio, 1916

This heterophyid species, characterized by a small concave body, median location of the ventral sucker, unique morphology of the ventrogenital apparatus, and side-by-side location of the two testes [262], was first found in dogs fed brackish water fish infected with the metacercariae in Japan [181], and then reported from the Republic of Korea [2]. Human infections were reported by detection of eggs in the feces in 1929 [263] and of adult flukes in 1965 in Japan [182]. In the Republic of Korea, 8 human infections were discovered from a salt-farm village of Okku-gun, Chollabuk-do [184]. In 2 other coastal areas of the Republic of Korea, 18 and 5 heterophyid egg-positive people were found to be infected with this fluke [151,152]. It is now known to be distributed widely along the western and southern coastal islands of the Republic of Korea [188]. Brackish water snails, *Cerithidea* sp. or *Tympanotonus* sp., shed the cercariae [4]. Brackish water fish, including the mullet *Mugil cephalus* and goby *Acanthogobius flavimanus,* harbor the metacercariae [187,196, 264,265]. Domestic or feral cats are the natural definitive hosts [35,162,188].

Spelotrema brevicaeca (Africa & Garcia, 1935) Tubangui & Africa, 1939

This microphallid fluke was originally reported under the name *Heterophyes brevicaeca* from a human autopsy case [256], and then 11 cases in the Philippines [175]. Eggs of this fluke were found in the heart, brain, and spinal cord of the patients who died of acute cardiac dilatation [175,256]. Brackish water crabs, *Carcinus maenas*, and shrimps, *Macrobrachium* sp., harbor the metacercariae in the Philippines [12].

Stellantchasmus falcatus Onji & Nishio, 1916

This heterophyid species, characterized by the slightly deviated ventral sucker to the right side of the body and the presence of an elongated sac-like seminal vesicle on the opposite side of the ventral sucker [2], was first described from cats experimentally fed the mullet harboring the metacercariae in Japan [181]. First human infections [263] and successive cases [40,266] were reported in Japan. Thereafter, human infections have been reported in many Asian-Pacific countries; the Philippines, Hawaii, Japan, Palestine, Thailand, Vietnam, and the Republic of Korea [2,4,48,172,267,268]. Brackish water snails, *Stenomelania newcombi* or *Thiara granifera,* shed the cercariae [42,269]. The mullet [2,270] and half-beaked fish *Dermogenus pusillus* [271,272] harbor the metacercariae. Rats were the better experimental hosts than mice [273]. Cats are the natural definitive hosts [35,263].

Stellantchasmus formosanus Katsuta, 1931

This heterophyid species was originally described from experimentally infected cats, dogs and mice with the metacercariae encysted in the mullet *Mugil cephalus* in Taiwan [274]. An experimental human infection was reported in Taiwan [274]. No reports have been available on natural human infections.

Stellantchasmus pseudocirratus (Witenberg, 1929) Yamaguti, 1958

(syn. *Stellantchasmus amplicaecalis* Katsuta, 1932)

This heterophyid species was first described from naturally infected dogs and cats in Palestine [275], followed by cats, dogs, and mice fed mullet in Taiwan [276]. Human infections were reported in the Philippines and Hawaii [48,175]. The mullet, *Mugil* sp., is the second intermediate host [48,275].

Stictodora fuscata (Onji and Nishio, 1916) Yamaguti, 1958

This heterophyid species, morphologically characterized by the presence of a gonotyl, which is superimposed on the ventral sucker and armed with 12 chitinous spines, a prominent metraterm, and 2 testes located obliquely in the middle field of the body, was originally described from cats experimentally fed infected mullets in Japan [4,181]. The first human infection with this fluke, under the name *Stictodora* sp., was found in a young Korean man, who regularly ate raw mullets and gobies [277]. Subsequently, 13 additional human cases were detected in a seashore village in the southwestern coastal area [2,4]. The gobies, *Acanthogobius flavimanus*, are the second intermediate host [196,278]. Cats (*Felis catus*) were used as an experimental definitive host [196]. Feral cats were found naturally infected with this fluke [35].

Stictodora lari Yamaguti, 1939

This heterophyid fluke, morphologically characterized by a gonotyl armed with 70-80 min spines, was first found in the small intestine of the sea gull *Larus crassirostris* in Japan [8,279]. Its adult flukes were first detected in 6 Korean people who resided in 2 southern coastal villages [280]. Brackish water gastropods, *Velacumantus australis*, shed the cercariae in Australia [281]. A number of esturine fish, including the goby, *Acanthogobius flavimanus*, harbor the metacercariae [278,281]. Cats and dogs were used as experimental definitive hosts [278]. Feral cats are the natural definitive hosts [35].

MOLECULAR STUDIES

Echinostomes

There has been no full genome sequencing project for echinostomes, and only 474 DNA sequences are available in Genbank, as of January 2008 [282]. Most of these DNA data have been generated for phylogenetic and taxonomic studies. This low number of genome sequences in the database often makes it fail to identify the protein from peptides obtained from echinostomes [282]. *Echinostoma paraensei* is the most frequently studied species, and 358 of 474 reported sequences were obtained from the sporocosysts RNA of this species [283]. *E. revolutum* and *E. caproni* are the next frequently studied species. The rest of the deposited sequences mainly represent molecules used in taxonomic and phylogenetic studies, including ribosomal or mitochondrial DNA [282]. There have been no studies on microarrays or reverse genetics of echinostomes.

Most of the ribosomal molecules sequenced corresponded to the internal transcribed spacers (ITS1 and ITS2), and 5.8S, 18S, and 28S genes [282]. With respect to mitochondrial markers, those studied included NADH dehydrogenase subunit 1 (ND1) and the cytochrome oxidase 1 [282]. Morgan and Blair [284] used ITS1, ITS2, and 5.8S ribosomal DNA to study 8 echinostome species. They found that 5 ('*revolutum*' group) of the 8 species revealed distinguishable ITS data from the others, but within the '*revolutum*' group, thery found only low sequence divergence. Later, the same authors [285] reported that ND1 is a more suitable marker for species and strain detection of echinostomes within the group. However, new cDNA and genomic libraries are required for further echinostome genetic studies.

The study of echinostome proteins has been initiated in 1968 by Taft and Fried [286], who first showed an indirect evidence of the presence of cytochrome oxidase in *E. revolutum.* Subsequently, larval antigens of *E. lindoense* were obtained from the snail host, *Biomphalaria glabrata* [287]. The cytochrome c oxydase of *E. trivolvis* was successfully purified by Fujino et al. [288]. Since recently, studies on proteomics using 2-dimensional electrophoresis (2DE) have been performed. Using 2DE, various kinds of proteins, including actin, tropomyosin, and paramyosin, glycolytic enzymes, including endolase, glyceraldehydes 3P dehydrogenase (GAPDH), and aldolase, detoxifying enzymes, in particular, glutathion-S-transferase, and the stress-related protein, Hsp 70 have been identified from *E. friedi* [289]. The major limitation in proteomic studies on echinostomes is the lack of sufficient genomic data.

Fasciolopsis buski

Only a few molecular studies have been performed on *F. buski.* Two sequences corresponding to the 18S rRNA gene are deposited in Genbank [142]. Using this DNA sequence, fluke specimens vomited by a child was confirmed as *F. buski* [290]. Species-specific ITS sequences of ribosomal DNA were described, and the sequences of eggs and adults were identical in length and composition [291]. Phylogenetically, *F. buski* resembles closely the other members of the family Fasciolidae, including *Fasciola hepatica* and *F. gigantica* [291].

Gymnophalloides seoi

Few studies have been performed on the molecular biology, genetics, and proteomics of *G. seoi.* Crude extracts of *G. seoi* containing antigenic proteins were found to enhance the expression of Toll-like receptors 2 (TLR2) and 4 (TLR4) mRNAs on HT29 cells, a human intestinal cell line, cultured in vitro [292]. However, monoclonal antibodies against *G. seoi* 46 kDa antigen revealed no significant effects on the TLR2 and TLR4 mRNA expression on HT29 cells [292], therefore, the responsible antigenic proteins should be further clarified.

With reference to other gymnophallid species, 10 polymorphic microsatellite loci were isolated and characterized for a *Gymnophallus* species [293]. The loci included G1C10, G3A4, GYM6b, GYM8, GYM9, GYM11, GYM12, GYM14, GYM15, and GYM16, and in each locus, 3-23 alleles were detected in 24 metacercariae isolated from the bivalve host [293]. These results show that there are marked heterozygosities among the metacercariae of this gymnophallid species. Subsequently, 406 metacercariae of the same species isolated from 15 cockles were genotyped using 6 of the 10 microsatellite loci, and as many as 400 unique genotypes were identified [294]. The results supported the role of the second intermediate host as an accumulator of genetic diversity in the trematode life cycle [294].

Proteomics are poorly known in *G. seoi.* In 2 papers, cysteine proteinases were isolated from the metacercariae and adults, and functionally characterized [295,296].

Metagonimus and other heterophyids

A SDS-PAGE/immunoblot analysis of crude extracts of *M. yokogawai* metacercariae showed that out of 14 protein bands found, 11 positively reacted with infected human sera, and among them 66 kDa and 22 kDa proteins were the most specific antigens [297].

Three species of *Metagonimus*, i.e., *M. yokogawai, M. takahashii,* and *M. miyatai,* can be genetically differentiated using PCR-RFLP analysis, where ITS1 site of ribosomal RNA and mitochondrial cytochrome c oxidase I (mtCOI) gene were targeted [298-300]. Especially in mtCOI gene, restriction patterns with Rsa I and Alu I produced differentially fragmented banding patterns [298]. PCR-based random amplification of polymorphic DNA (RAPD) technique using random 10-mer oligonucleotide primers also showed distinguishable banding patterns between *M. yokogawai* and *M. miyatai* [299].

Studies on the number of chromosomes and karyotypes of the genus *Metagonimus* supported strong evidence of genetic differences between *M. yokogawai* and *M. miyatai* [301]. They showed that the number of bivalents in the first meiotic division of *M. takahashii* was 9 ($n = 9$) and the diploid number of *M. miyatai* and *M. yokogawai* were 18 ($2n = 18$) and 32 ($2n = 32$). In addition, chromosomes of *M. miyatai* consisted of 1 pair of metacentric, 7 pairs of submetacentric, and 1 pair of telocentric chromosomes, whereas those of *M. yokogawai* consisted of 2 pairs of metacentric, 11 pairs of submetacentric, and 3 pairs of subtelocentric chromosomes [301]. Similarly, simple sequence repeat anchored PCR using primers of 3′ or 5′ termini of the (CA)n repeats showed distinguishable banding patterns among the 3 species of *Metagonimus,* suggesting that they have different genotypes [302].

The sequence comparison of 28S ribosomal DNA and mtCOI of 3 *Metagonimus* species also supported *M. miyatai* as a separate species [303]. The length of the rDNA sequence in 28S D1 region of the 3 *Metagonimus* species was 248 bp and its G+C content was 52% [303]. The length of the mtCOI sequence averaged 400 bp with a G+C content ranged from 44% in *M. miyatai* and 46% in *M. takahashii* to 47% in *M. yokogawai* [303]. Nucleotide sequence differences between species were 23.0% (92/400 bp) between *M. miyatai* and *M. takahashii,* 16.2% (65/400 bp) between *M. miyatai* and *M. yokogawai,* 13.2% (53/400 bp) between *M. takahashii* and *M. yokogawai* [303]. *M. takahashii* and *M. yokogawai* are placed in the same clade supported by the sequence and phylogenetic tree analysis of 28S D1 rDNA and mtCOI gene by neighbor-joining and parsimony method; *M. miyatai* is placed in a different clade from 2 other *Metagonimus* species [303].

With regard to other heterophyid species, only a few studies have been performed on the molecular biology, genetics, and proteomics. Sequencing and aligning of the 18S (SSU) rDNA of 6 heterophyid species, including *H. taichui, H. pumilio, Centrocestus* sp., *Pygidiopsis genata, Phagicola longa,* and *Dexiogonimus* *ciureanus,* revealed interspecific variations [304]. However, due to high sequence similarities, it was necessary to perform PCR-RFLP of the entire 18S subunit to differentiate between *Haplorchis* and *Dexiogonimus* [304]. A high annealing temperature (HAT)-based random amplified polymorphic DNA (RAPD) technique has been developed to detect DNA of *H. taichui* and *S. falcatus* [305,306].

Neodiplostomum seoulense

Few studies have been done regarding the genetic characteristics of *N. seoulense.* Recently, in order to support data on phylogeny of 3 *Neodiplostomum* species distributing in the Republic of Korea, i.e., *N. seoulense* [230], *N. leei* [307], and *N. boryongense* [308], mitochondrial COI gene was analyzed, and positive results were obtained (to be published).

A cysteine protease, with the molecular weight of 54 kDa, was purified from the crude extract of *N. seoulense* adults, although its function was suggested to aid nutrient uptake, rather than host tissue lysis [309]. Two cystatin-binding cysteine proteinases were successfully purified from *N. seoulense,* and they were found useful for cystatin-capture ELISA of human *N. seoulense* infection [310]. Other proteases and unique proteins should be purified and characterized to better understand host-parasite relationships.

PATHOGENICITY

Echinostomes

The pathogenicity of echinostomes is complex and diverse dependin on a wide variety of parasite- and host-side factors [5,6,311]. Mechanical irritation by the flukes and allergic reactions due to their toxic metabolites constitute the 2 important elements responsible for the pathogenesis. In this respect, the intensity of infection, in terms of individual worm load, may be highly important in the pathogenicity and severity of the disease [5,73,105]. Fried et al. [312] compared the host pathologies between single and multiple infections with an animal echinostome, *E. caproni*, in hamsters. Certain species of echinostome seem to be more pathogenic to humans, since a fatal human case of *A. malayanum* (under the name *A. mehrai*) was reported in India, from whom several hundred worms were recovered at autopsy [5,313]. Bowel perforation due to *A. malayanum* (under the name *A. mehrai*) infetion was also reported in an Indian child [314].

In echinostome-infected rodent hosts, intestinal histopathology was studied in *E. revolutum* [315,316], *E. hortense* [2,317], *E. caproni* [311,318], and *E. trivolvis* infection [319]. Adult worms were located in the lumen of the upper small intestine of the rodents and pathological changes occurred chiefly near the attachment sites of the echinostomes [2,311]. The flukes were tightly pinching and sucking the mucosa with their oral suckers, and it seemed that the mucosal layer was eventually eaten by the flukes [5]. Villous atrophy, crypt hyperplasia, inflammation of the stroma, and decreased villus/crypt ratios were observed in the small intestine of experimentally infected animals [316,317]. In focal areas, massive destruction and detachment of the villi, at times complete loss of the mucosal integrity and ulcerations, were observed [2,316]. These features are similar to those observed in severe catarrhal enteritis [5]. In pigs naturally infected with *A. oraoni,* fatal diarrhea was developed, and autopsy revealed massive parasite infections with hemorrhagic and edematous mucosa of the jejunum and duodenum [27].

Fasciolopsis buski

The severity of the disease is markedly variable depending on parasite load [142]. Adult flukes can cause mechanical damage to the intestinal mucosa and extensive intestinal and duodenal erosions, ulceration, hemorrhages, abscess, and catarrhal inflammation may occur [1,320]. Absorption of toxic and allergic worm metabolites can cause ascites and facial, orbital, and generalized edema [142]. A case of heavy *F. buski* infection hat caused intestinal perforation has been reported [321].

Gymnophalloides seoi

The pathogenicity of *G. seoi* is not well understood partly because no suitable experimental host has been found. It was observed in mice, though they are not a good host, that *G. seoi* parasitizes the small intestine, chiefly the duodenum and jejunum, pinching and sucking the intestinal villi with their oral suckers [322]. The infected intestinal mucosa showed villous atrophy and crypt hyperplasia, with inflammatory reactions in the villous stroma and the crypt [4,322]. The histopathological changes were generally not so severe, and the mucosal integrity was restored around day 14-21 post-infection [322]. In immunocompetent mice, the worms did not invade the submucosal layer; however, in immunosuppressed mice, worms invaded the submucosa [322]. In a colon cancer patient who received anti-cancer chemotherapy, a *G. seoi* worm was found to have penetrated into the colonic lymphoid tissue [323]. Mechanical irritation and antigenic stimulation by the flukes are considered to be important in the pathogenicity [4,322].

The small intestine is presumed to be the normal habitat of *G. seoi* in the human host [4]. In experimental rodents this was evidenced [164,322]. However, acute pancreatitis was diagnosed in 1 patient [148], and diabetes mellitus was accompanied in 2 patients [324]. Therefore, *G. seoi* is suspected to invade the pancreatic duct in humans [4]. It is of note that other gymnophallids were found in the bursa Fabricii and gallbladder of shorebirds as well as in the intestine [48]. Experiments using larger animals, such as monkeys, seem to be necessary to verify this possibility [4]. *G. seoi* was found to be able to invade the submucosa of immunosuppressed mice [322]. Therefore, there is a possibility that the eggs may be transferred to remote organs to cause erratic parasitisms in immunocompromised hosts, as reported in heterophyid infections [175].

Metagonimus and other heterophyids

Intestinal histopathology was studied in *M. yokogawai* [325-327], *P. summa* [328], and *C. armatus* [329] using experimental animals, including mice, rats, cats, and dogs. Adult flukes of *M. yokogawai* were found to parasitize the middle part of the small intestines, and invade the crypt of Lieberkühn in the early stage of infection (by day 2-3 post-infection), and localize between villi in later stages [4,325-327].

In *M. yokogawai* infection, the major histopathological findings included villous atrophy and crypt hyperplasia, with variable degrees of inflammatory reactions [4,325]. The infected mucosa shows blunting and fusion of the villi, edema of the villus tips, congestion and inflammatory cell infiltrations in the villous stroma, and decreased villus/crypt height ratios [2,4]. Very similar intestinal histopathology was reported in a naturally infected human with *M. yokogawai* [330]. The location of worms was confined to the intestinal mucosa in immunocompetent hosts [327,331,332]; however, immunosuppression allowed a deeper invasion of the worms into the submucosa in mice [333]. Immunosuppression also enhanced the survival of worms and prolonged the life spans in the same mouse strain [333,334]. Decreased enzyme activities were observed in acute infections with *M. yokogawai* [335]. In dogs experimentally infected with *M. yokogawai*, it was suggested that watery content might be a result of a poor absorption of the intestinal secretions from the secretory crypt cells [336].

In *M. miyatai*-infected mice, similar intestinal histopathology was observed, although the degree of mucosal damage was less severe than in *M. yokogawai*-infected mice, as represented by stronger expression patterns of the proliferating cell nuclear antigen (PCNA) in the intestinal mucosa [337]. In *P. summa*-infected mice, similar features were also observed; the worms caused severe villous atrophy and crypt hyperplasia, with inflammation of the villous stroma [328]. In experimental *C. armatus* infection in rats, the worms caused mechanical irritation and mucosal inflammations in the small intestines from as early as 3 days after the infection [329].

With respect to the pathogenicity of heterophyid flukes, it should be noted that several species, namely *S. falcatus*, *Haplorchis* spp., and *Procerovum* spp., can cause erratic parasitism in man, which is often fatal [175]. The 3 most frequently affected sites were the heart valve, brain, and spinal cord, where eggs and adult flukes originating from the intestinal mucosa embolized in the blood vessels [175]. Eggs of *H. nocens* (under the name *H. heterophyes*) [338] were found encapsulated in the brain of patients with nerological symptoms. Such erratic parasitism may occur in immunocompromised patients [4]. In experimental mice, *M. yokogawai* worms were found to have invaded the submucosa of the small intestine when they were immunosuppressed [333].

Neodiplostomum seoulense

The normal habitat of this fluke is the duodenum in experimental rats and mice [230]. The major histopathological features of the affected mucosa include villous atrophy, crypt hyperplasia, mucosal inflammation, and bleeding [339]. The worms were found to entrap the host intestinal villi with their concave ventral curvature of the anterior body, piercing into the villous stroma with their tribocytic organ [339]. The affected villi undergo severe destruction with hemorrhages and inflammation, and finally the mucosa completely loses its integrity [339]. The histopathological changes due to *N. seoulense* are severer compared with those observed in other intestinal trematode infections including *Metagonimus*, *Pygidiopsis*, and *E. hortense* infections [4].

With respect to the pathogenicity of *N. seoulense*, the most striking feature is its high pathogenicity and even lethality to laboratory mice [340,341]. Almost all infected mice died by day 23 post-infection with 200 metacercariae per animal [341]. The infected mice revealed severely contracted intestines, strongly suggestive of an intestinal paralysis [341]. The fatality of the host animal varied according to genetic backgrounds of the mice [342]. Its tribocytic organ was suspected to be an important worm structure responsible for the host mucosal damage, because the tribocytic organ was shown to secrete alkaline phosphatases, which could lyse the host villi and help the mucosal invasion of worms [343]. The tribocytic organ was also shown to contain neutral mucopolysaccharides, and thus the organ is suggested to play a protective role against host digestive enzymes [343].

IMMUNITY

Echinostomes

Immunological studies have been extensively performed in animal infecting echinostome species, i.e., *E. caproni*, *E. trivolvis*, and *Echinostoma friedi* [311]. Among the human infecting echinostomes, *E. hortense* has been mostly frequently studied [5,344,345]. Rodent hosts are known to express various types of resistance to echinostome infections [311]. One of them is spontaneous expulsion of primary infected worms [311]. However, the dynamics of worm expulsion are different depending on different parasite species and host species and strain [311, 344,346]. The elimination of *E. trivolvis* from mice occurs within 2-4 weeks [347], whereas worms can survive for long periods of time in golden hamsters [348]. In hamsters, *E. friedi* survive for at least 12 weeks, whereas the infection is expelled at 3-4 weeks in rats [349]. *E. caproni* worms are expelled from rats in 6-8 weeks, but they produce chronic infections in hamsters and mice [350]. An example of different immune responses by host strain includes *E. hortense* infection in BALB/c and C3H/HeN mice; whereas BALB/c mice reject worms, C3H/HeN mice undergo a chronic infection [120].

It has been suggested that 2 types of effector cells, i.e., goblet cells [346,351] and mucosal mast cells [352], are mainly associated with the worm expulsion [5]. However, the role of mast cells remains controversial [311]. For example, mastocytosis was suppressed in athymic nude mice but the kinetics of worm expulsion in these mice was similar to that of the conventional mice [353]. With respect to goblet cells, chronic infections with *E. caproni* in mice were accompanied by reduced goblet cell numbers [315,346,347]. In *E. trivolvis*-infected mice, the goblet cell numbers increased coinciding with worm expulsion, and expulsion was delayed when mice were treated with dexamethasone [353-355]. Similar immunosuppression effects by dexamethasone were observed in golden hamsters infected with *E. caproni* and *E. trivolvis* [356]. In addition, mucins increased by a primary *Nippostrongylus brasiliensis* infection in the intestine of mice were suggested to be responsible for a rapid expulsion of a challenge infection with *E. caproni* or *E. trivolvis* [357]. However, a contradicting result was observed in the RAG-2-deficient mice, a strain of genetically lacking B- and T-lymphocytes, infected with *E. caproni*; goblet cell hyperplasia was marked in RAG-2-deficient mice but worms survived as they did in normal ICR mice [358].

Neutrophils and mononuclear inflammatory cells in the mesentery were suggested to be essential in determining the course of *E. caproni* infection in mice [359]. Some factors in mouse serum were also shown to induce retraction of collar spines in *E. trivolvis*, probably enhancing worm expulsion [360]. IgG, IgM, and IgA levels were elevated in serum and the small intestine of mice infected with *E. caproni* [361,362]. Antibodies in mouse serum covered the surface of *E. revolutum* in vitro, and worms obtained from immune mice were covered by antibodies [363]. Local immune responses seem to be more directly related with host resistance [5]. Whereas the serum level of IgG2a remained constant during the course of *E. caproni* infection, the intestinal IgG2a responses were related with worm expulsion [362]. Since IgG2a is an important element mediating T-helper-2 (Th2) immune reposnes of mice [364], the expulsion of echinostomes from the host intestine is suggested to be mediated by a Th2 immune response [362].

Th1 and Th2 cytokines profiles were studied in rodent hosts experimentally infected with *E. caproni* [365] or *E. hortense* [344, 345]. Mesenteric lymph node cells from *E. caproni*-infected mice, which are unable to expel worms in a short period of time, produced significantly higher levels of IFN-γ upon antigen stimulation in vitro during 3 wk after infection [365]. When these mice were injected with anti-IFN-γ monoclonal antibodies, the worm burden of *E. caproni* was significantly decreased [365]. It was thus suggested that in *E. caproni*-mouse model, Th1 responses mediated by IL-12, TNF-α, and IFN-γ are related to establishment of a chronic infection, whereas Th2 responses mediated by IL-4 and IL-5 lead to host protection and worm rejection [365,366]. Similarly, in *E. hortense* infection, BALB/c mice, a resistant mouse strain [344], exhibited stronger mRNA expressions of IL-4 and IL-5 in the spleen, than C3H/HeN mice, a susceptible strain which undergo a chronic infection [345]. Treatment of BALB/c mice with kitotifen, an anti-allergic drug, suppressed the mRNA levels of IL-4 and IL-5 and elevated the worm recoveries from this mouse strain [345].

Fasciolopsis buski

No information is available regarding immunity of the host agasint *F. buski* infection.

Gymnophalloides seoi

The susceptibility of mice to *G. seoi* infection is variable among different species, and even strains, of animals [164]. Among mouse strains, C3H/HeN mice were the most highly susceptible and the best for growth and development of the worms; although the worm recovery at days 7-21 post-infection was not sufficiently high [164,367]. However, when C3H/HeN mice were immunosuppressed by prednisolone injection, the survival and the recovery of the worms were greatly enhanced, and the enhancement was strongly correlated with the duration of immunosuppression [164,367]. Immunosuppression also enhanced the fecundity of the worms [164,367]. On the other hand, ICR and BALB/c mice are quite resistant against *G. seoi* infection [4]. ICR and BALB/c mice retain many worms by day 3 post-infection; however, most worms are expelled by day 7 post-infection [4,164]. It is of note that goblet cell proliferation was marked in the small intestines of infected mice, in particular, on the villous epithelia of the jejunum during days 3-7 post-infection [322]. The importance of goblet cells in worm expulsion was further suggested by only a small number of flukes retained in the intestines at days 7-14 post-infection [367,368]. This was supported by the minimal degree of goblet cell hyperplasia in immunocompromised mice, with many more flukes surviving in the intestine [367,368]. The goblet cell proliferation was shown to be highly dependent on CD4+ T-helper cells; however, both T-cell dependent and independent mechanisms seem to operate for expulsion of *G. seoi* worms from the mouse intestines [369].

Metagonimus and other heterophyids

Host protective mechanisms against *M. yokogawai* and other heterophyid flukes seem to be significant viewing from the fact that intestinal histopathology caused by these fluke infection is normalized around 3-4 wk after the infection [333]. One of the possible immune effectors includes intestinal intraepithelial lymphocytes (IEL) that increase remarkably along the villous epithelial layer of the infected rats and mainly consist of CD8+ cytotoxic T-cells [370]. Another effector cell is the lamina propria lymphocytes (LPL) that is chiefly consisted with IgA producing B-cells [370]. Mucosal mast cells were suggested as a thrid effector responsible for the worm expulsion from infected rats [371]. Goblet cells are a fourth effector for the expulsion of worms [2]. Immunogold studies have revealed that the antigenicity of *M. yokogawai* is originating from the syncytial tegument, tegumental cell cytoplasms, vitelline cells, and epithelial lamellae of the cecum [372,373].

Neodiplostomum seoulense

Host protective immunity and survival of worms in the host intestine is known to be variable depending on different strains of mice [374]. BALB/c mice revealed a significantly higher recovery of worms than C3H mice, based on 28 days observation after an experimental infection [374]. Proliferation of mast cells was suggested to be a significant local immune response due to the presence of worms [375]. Goblet cells were also shown to increase significantly following experimental infection in mice [374]. However, these cells were not directly related with worm expulsion from the host intestine [374]. Binding of histamine released from mast cells to its receptors on intestinal smooth muscles would be more important than the level of histamine alone, or mastocytosis [376]. Recently, mixed Th1 and Th2 type immune responses were shown to occur during the course of *N. seoulense* infections in BALB/c mice, and IFN-γ (a Th1 cytokine), IL-4 (a Th2 cytokine), IgG, IgA, and IgG2a were all increased in the spleen and the small intestine [364]. Macrophages were also found significantly increased, which were found to kill *N. seoulense* worms in vitro [364].

Parasite-specific IgG levels were increased significantly in sera of infected mice, and 7 antigens, including 26, 30, 35, 43, 54, 67, and 94 kDa, were the major antigenic proteins of *N. seoulense* [377]. Serum and mucosal tissue IgA were increased after an experimental infection in mice, but the increase was not directly related to the worm expulsion [378]. Immunogold studies revealed that the tribocytic organ, seminal vesicle, caeca, and vitelline follicles were the major origins of worm antigens [379].

CLINICAL MANIFESTATIONS

Echinostomes

Patients infected with echinostome species suffer from abdominal pain, diarrhea, tenesmus, easy fatiguability, loss of body weight, and urinary incontinence [1,2,73,380]. The severity of symptoms is generally stronger than those seen in other intestinal fluke infections, such as heterophyids [5]. In this respect, reports of patients with *E. hortense* infection is noteworthy who sufferred from severe epigastric discomfort and ulcerative lesions in the stomach or duodenum and diagnosed by recovery of worms at gastroduodenal endoscopy [125-129]. A patient admitted to a hospital because of epigastric pain and hematemesis revealed in gastroduodenoscopy an adult fluke attached at the lesion, which was removed by an endoscopic clipper [125]. Another patient suffered from epigastric discomfort for a year, and acute epigastric pain and diarrhea for 1 month, which was accompanied by acidic belching, dizziness, and weight loss of 2 kg [126]. The third patient complained of epigastric discomfort for several days [127], and the fourth patient suffered from upper abdominal pain and discomfort persisting for 2 wk [128]. The fifth patient had epigastric discomfort, indigestion, anorexia, dizziness, headache, nausea, and vomiting; these symtpoms became severer and she was hospitalized [129]. The clinical signs, including laboratory findings, in echinostomiasis are poorly known [5]. However, the levels of peripheral blood eosinophilia in *E. hortense* infection were dependent upon individual worm burdens; 11-24% (av. 17%) among the patients with more than 100 worms, 4-21% (av. 10%) among those with 51-100 worms, and 2-14% (av. 5%) among those with less than 50 worms [124]. Patients infected with *E. ilocanum* experienced intestinal colic and diarrhea [12]. Clinical symptoms in *E. cinetorchis*, *E. japonicus*, and *A. tyosenense* infections are not well known [5,7,56,92]. In 10 of 18 American tourists to Kenya and Tanzania who were echinostome egg positive in fecal examinations (adult flukes were not recovered), moderately severe abdominal cramps and loose or watery stools were encountered [381].

In gastroduodenal endoscopy, a moving, leaf-like *E. hortense* worm attached to an ulcerated mucosal layer of the distal part of the stomach was found [125]. The lesion was accompanied by a stage IIc or stage III early gastric cancer, and multiple ulcerations with bleeding were noted in the stomach and duodenum [125]. These ulcerations were suggested to be caused by the flukes [125]. Upper endoscopy of another patient revealed 2 *E. hortense* worms in the stomach; 1 worm was penetrating into the mucosa on the lesser curvature of the antrum; the other was attached to the mucosal surface of the greater curvature of the antrum [126]. The worm wiggled on stimulation and became tightly stretched during retrieval with a forcep [126]. Two more patients diagnosed at gastroduodenal endoscopy had 2 living wroms each in the duodenal bulb area, at times accompanied by mucosal erosions [127,128]. In another patient, from whom 2 living *E. hortense* flukes were recovered, the affected gastric mucosa revealed signs of chronic gastritis, and at the proximal part of the duodenum multiple cured ulcerative lesions were observed [129]. In Japan, 4 cases of *E. hortense* infection were reported by recovery of flukes by upper endoscopy [382].

Fasciolopsis buski

Clinial manifestations remarkedly vary from subclinical to fatal outcome [142]. In light infections, anemia, eosinophilia, headache, dizziness, gastric pain, and loose stools can occur [383]. In moderate and heavy infections, severe epigastric pain, abdominal pain, diarrhea, bowel obstruction, nausea, acute ileus, anasarcha, and marked eosinophilia and leucocytosis may occur [383]. Due to allergic reactions to toxic worm metabolites, people infected with *F. buski* may suffer from facial, orbital edema, and anasarca. In heavy infections, intestinal perforation may occur [321].

Gymnophalloides seoi

Variable degrees of gastrointestinal troubles and indigestion, together with fever, anorexia, weight loss, easy fatiguability, and weakness may occur in *G. seoi*-infected patients [149,150]. However, the degree of symptoms seems to be variable from individual patients [4]. A patient underwent acute pancreatitis and acute cholecystitis with episodes of epigastric discomforts, indigestion, and diarrhea [148]. Laboratory studies revealed elevated serum and urine amylase levels, increased serum alkaline phosphatase activity, and slight to moderate degrees of eosinophilia [148]. Five days after a treatment with praziquantel, epigastric pain and diarrhea completely disappeared, and serum and urine amylase levels returned to their normal levels [148]. Most other patients complained of only mild gastrointestinal troubles, such as indigestion [149,150]. However, it is noteworthy that 2 patients were accompanied by diabetes mellitus with high glucose levels [324]. Therefore, some relations between the *G. seoi* infection and diabetes were suspected [4]. In fact, some of the infected people living in a highly endemic area had symptoms, such as thirst, polydipsia, and polyuria [384], that may occur among diabetic patients.

Metagonimus and other heterophyids

Clinical symptoms due to *M. yokogawai* or other heterophyid infections are generally mild and transient unless heavily infected or immunocompromised [2,4]. In patients infected with *M. yokogawai*, the most frequent symptoms are mild to moderate degrees of abdominal pain, diarrhea, lethargy, anorexia, and weight loss [220,385]. The degree of clinical symptoms seems to be related to the individual worm burdens; heavier infection cases tend to suffer from more severe illness [4]. However, the severity of the symptoms may also be related to the susceptibility as well as acquired immunity of individual patient [4]. A visitor to an endemic area, for example, suffered from a severe illness after a primary infection [386], whereas long-term residents generally complained of milder symptoms than expected [385]. Even a man living in a highly endemic area from whom as many as 63,587 worms were recovered complained of only minor gastrointestinal troubles, i.e., indigestion and epigastric pain [385]. Clinical symptoms due to other heterophyid fluke infections are not much different from those seen in *M. yokogawai* infection [4,151,152,387].

Neodiplostomum seoulense

In patients infected with *N. seoulense*, acute abdominal pain, diarrhea, lethargy, fever, and weight loss may occur [4]. However, clinical symptoms due to *N. seoulense* infection are not well documented except in the first patient, who experienced severe abdominal pain that led to admission to an emergency room of a university hospital [4,388]. The severity of symptoms may be dependent upon the individual worm burdens, as well as acquired immunity of each individual [4]. Patients repeatedly infected may complain of milder symptoms than primary infected patients, because most of the soldiers infected during survival trainings were asymptomatic [233,234]. However, because *N. seoulense* was reported to be highly pathogenic and even lethal to mice [341], infected humans may also experience severe clinical course as seen in the first patient [388].

DIAGNOSIS

Echinostomes

Human echinostomiasis is diagnosed by recovery of eggs in fecal examinations [5]. Careful microscopic observations with measurements of the eggs can provide even specific diagnosis in known endemic areas of certain echinostome species [5]. However, recovery and identification of the adult flukes is strongly recommended, if a definite diagnosis is preferred [4,5]. The detectability of eggs in fecal examinations varies remarkably depending on different echinostome species [5]. The fecundity is considerably high in *E. hortense* [119] and *E. cinetorchis* [101], whereas it is very low in *E. japonicus* [60] and *A. tyosenense* [7]. The difference may be due to remarkably different numbers of intrauterine eggs and the different egg laying capacity of each echinostome species [4,5].

Fasciolopsis buski

Diagnosis is carried out by coprological examinations to detect eggs or occasionally by examination of expelled adult worms vomited or passed in the stool [142]. Serodiagnosis detecting serum antibodies may help the diagnosis [389].

Gymnophalloides seoi

The diagnosis can be made by detection of eggs in the feces; however, an expert is needed to identify the eggs [4,158]. The eggs are very small, only 0.020-0.025 mm in length, smaller than those of *Clonorchis sinensis*, *Metagonimus yokogawai*, or other heterophyids, and have a very thin and transparent shell [148-150]. The size of *G. seoi* eggs is similar to that of *P. summa* [2]. The problem is that the eggs may be overlooked or misdiagnosed as an air bubble or other artifacts in routine fecal examinations performed by formalin-ether sedimentation or cellophane thick smear techniques [149]. Another problem is a very low egg laying capacity of *G. seoi*, i.e., only 2-84 eggs per adult fluke in the human host [384], compared to other intestinal parasites [2]. It is assumed that unless more than 100 worms are present, less than 8,400 eggs would be discharged in a whole-day stool, and the eggs per gram of feces (EPG) would be only 42 (daily stool weight; 200 g) [4]. This value means the appearance of only 1-2 eggs on the whole field of a fecal smear made by the Kato-Katz technique (41.7 mg of feces/smear) [2,4].

Metagonimus and other heterophyids

When heterophyid eggs are detected in fecal examinations, it is expressed using the term ‘heterophyid fluke infection’, because the eggs of different heterophyid species closely resemble each other [4,390]. The diagnosis can be confirmed after the recovery of adult flukes following anthelmintic treatment and purgation [5]. The specific diagnosis only by eggs is difficult in areas of no known endemicity, as well as in areas with mixed heterophyid infections [4].

However, close observations and measurements of heterophyid eggs are useful for differential diagnosis [4,390]. For example, *M. yokogawai* eggs can be differentiated from other heterophyid eggs by their length of 26.9-31.6 μm, elliptical shape with length/width ratio of 1.5-2.1, clean shell surface, less prominent operculum, no shoulder rims, and dark yellow or brown color [390]. *M. takahashii* and *M. miyatai* eggs are similar to those of *M. yokogawai*, but larger; hence, the measurement of egg size is essential [4]. *H. nocens* eggs are similar to those of *M. yokogawai*, but the former is a little smaller and has slight attenuations at one or both ends [390]. *H. continua* eggs are broadly oval in shape, and difficult to differentiate from those of *M. yokogawai*

[390]. *P. summa* eggs are characteristically small and pyriform in shape [390]; they resemble the eggs of *Clonorchis sinensis,* a liver fluke, but lack muskmelon patterns on the shell surface, and shoulder rims around the operculum are inconspicuous [4]. Serological tests such as ELISA are helpful in false egg negative cases infected with *M. yokogawai* [386,391].

Eggs of *H. taichui, H. pumilio,* and *H. yokogawai* closely resemble each other, and need differentiation also from eggs of *Opisthorchis viverrini* and lecithodendriid flukes, i.e., *Phaneropsolus bonnei* and *Prosthodendrium molencampi* [4,243].

Neodiplostomum seoulense

The diagnosis of *N. seoulense* infection can be done by recovery of typical eggs in the feces [230]. The eggs are ellipsoid to elliptical, thin-shelled, with an inconspicuous operculum, and frequently asymmetrical [230]. They differ from the eggs of *E. hortense* or *E. cinetorchis,* in that they have a clean shell surface and, unlike the latter, they do not have abopercular wrinkles at the posterior end [4,5].

TREATMENT AND CONTROL

Echinostomes

Treatment of echinostome infections can be done using 10-20 mg/kg praziquantel in a single oral dose [5]. Albendazole may be effective [4]. For prevention and control, eating raw or improperly cooked fresh water fish and fresh or brackish water snails should be avoided [4,5].

Fasciolopsis buski

Tetrachlorethylene had been the drug of choice before introduction of praziquantel for treatment of fasciolopsiasis in 1983 [142]. Now praziquantel, at the dose of 15 mg/kg single dose, is prescribed even in severe fasciolopsiasis patients [142]. A new drug, triclabendazole, has been introduced showing a promising efficacy without side effects in pigs [142,392]. Two other new drugs, oxyclozanide and rafozanide, were nearly equally effective as triclabedazole in pigs [392].

Gymnophalloides seoi

For treatment of *G. seoi* infection in humans, praziquantel in a single oral dose of 10 mg/kg is prescribed [4,148,149]. Albendazole may also be effective against *G. seoi* infection, but this needs confirmation [4]. The best way to prevent *G. seoi* infection is the avoidance of consuming infected oysters, under raw or improperly cooked conditions [4]. As control measures, oyster irradiation [393] and repeated chemotherapy of the people in endemic areas [384] were tried with considerable success.

Metagonimus and other heterophyids

For all infections with heterophyid flukes, praziquantel is the drug of choice [4]. A single oral dose of 10-20 mg/kg praziquantel is satisfactory, with 95-100% cure rate for *M. yokogawai* infection [394,395]. Niclosamide was used in vitro to observe damage to *H. taichui* worms [396]. Irradiation of the sweetfish, *Plecoglossus altivelis,* by 200 Gy was highly effective in controlling infectivity of the *M. yokogawai* metacercariae [397]. The heterophyid fluke infections could be prevented by the avoidance of eating uncooked fresh water or brackish water fish [4].

Neodiplostomum seoulense

Praziquantel in a single oral dose of 10-20 mg/kg is a highly effective treatment for *N. seoulense* infection [4,230]. For prevention, ingestion of raw or improperly cooked flesh of snakes or frogs should be avoided [4].

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