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Intestinal Flukes

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Around the world, 40 to 50 million people are currently estimated to be infected with food-borne intestinal trematodes (Fried et al., 2004), including at least 18 million people infected by fish-borne trematodes (Chai et al., 2005a). However, this may be an underestimate of the total number of humans infected. The number of trematode species, currently known to be involved, is 70 (Yu and Mott, 1994; Chai and Lee, 2002). Morphologically they are diverse, belonging to the families Heterophyidae, Echinostomatidae, Plagiorchiidae, Lecithodendriidae, Neodiplostomidae, Nanophyetidae, Paramphistomatidae, Cathaemaciidae, Fasciolidae, Gastrodiscidae, Gymnophallidae, Microphallidae, Strigeidae, and Brachylaimidae (Yu and Mott, 1994; Chai and Lee, 2002; Fried et al., 2004). Life cyles and geographical distributions are also diverse and characteristic for each species. This chapter, briefly describes the characteristics of each species of intestinal fluke involved, in terms of the biology, epidemiology, host–parasite relationships, pathogenicity, clinical aspects, diagnosis, and treatment.

Brachylaimidae Joyeux and Foley, 1930

Species Infecting Humans

Brachylaima cribbi Butcher and Grove, 2001

The first human infection with this fluke was reported in South Australia (Butcher et al., 1998), and subsequently 10 adults and children in South Australia (Butcher et al., 2003) were reported as infected. Birds, reptiles, and mammals were found to be infected with this fluke (Butcher et al., 1998; Butcher and Grove, 2001, 2005). The first intermediate host is a helicid land snail, *Theba pisana,* and cercariae begin to emerge 8 weeks after exposure to the eggs (Butcher and Grove, 2001). Cercariae encyst in other species of helicid land snails, such as *Cernuella virgata*, which serve as the source of human infections (Butcher and Grove, 2005). Symptoms due to this fluke infection vary depending on the worm burden and include diarrhea, abdominal pain, low-grade fever, and fatigue (Butcher et al., 2003).

Cathaemaciidae Fuhrmann, 1928

Species Infecting Humans

Cathaemacia cabrerai Jueco and Monzon, 1984

The first human infection with this fluke was reported from a patient in the Philippines (Jueco and Monzon, 1984). No information is available on the life cycle and the source of infection.

Echinostomatidae Poche, 1926

Species Infecting Humans

Acanthoparyphium tyosenense Yamaguti, 1939 (Fig. 2.1)

This species was originally found in the small intestines of ducks *Melanitta fusca stejnegeri* and *M. nigra americana* caught in the Republic of Korea (Yamaguti, 1939a). It is characterized by 23 collar spines on the oral sucker, 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 (Chai et al., 2001b). Human infections were first identified in 10 patients residing in two coastal villages in Chollabuk-do Province (Chai et al., 2001b). The patients had consumed various species of brackish water mollusks caught in an estuary near their villages; two species of bivalves, *Mactra veneriformis* and *Solen grandis*, and a gastropod *Neverita bicolor* were found to have the metacercariae (Chai et al., 2001b). The first intermediate hosts include the marine megagastropods *Lunatia fortuni* and *Glassaulax didyma* (Kim et al., 2004). The adult flukes were confirmed after experimental infection of metacercariae in chicks (Chai et al., 2001b; Han et al., 2003) and sea gulls *Larus crassiostris* (Kim et al., 2004).

Artyfechinostomum malayanum (Leiper, 1911), Railliet, 1925
[syn. *Artyfechinostomum surfrartyfex* Lane, 1915, *Paryphostomum surfrartyfex* Bhalerao, 1931, *Artyfechinostomum mehrai* Faruqui, 1930]

This fluke (under the name *A. surfrartyfex*) was first found in an Assamese girl in India and then found in pigs in India (Beaver et al., 1984). The source of infection is a snail, *Digoniostoma pulchella*, and the dog and rat are other definitive hosts (Yu and Mott, 1994). The taxonomic position of this species, in relation to related genera and species, has been confusing (Yamaguti, 1958; Lie, 1963; Beaver et al., 1984). However, a review by Kostadinova et al. (2002) suggested *A. surfrartyfex* to be conspecific with *A. malayanum*, which precedes *A. surfrartyfex*. In the meantime, *Artyfechinostomum mehrai* was reported from human infections in India (Beaver et al., 1984), but synonymized with *A. surfrartyfex* (Ahluwalia, 1962).

FIGURE 2.1. *Acanthoparyphium tyosenense* adult from an experimentally infected chick necropsied at day 20 postinfection. This echinostome species has 23 collar spines. Acetocarmine stain. Scale bar = 0.5 mm.

Artyfechinostomum oraoni Bandyopadhyay et al., 1989

This species was reported from human infections in a tribal community in India (Bandyopadhyay et al., 1989). The freshwater snail, *Lymnaea* sp., was experimentally proven to be a first intermediate host (Maji et al., 1995). In naturally infected pigs, this parasite provoked fatal diarrhea (Bandyopadhyay et al., 1995).

Echinochasmus fujianensis Cheng et al., 1992

This is a species reported from humans, dogs, cats, pigs, and rats in Fujian Province, China (Cheng et al., 1992a). The prevalence among residents in five areas of southern Fujian Province was 3.2% (1.6–7.8%); two thirds of the infected people were 3 to 15 years of age. Its first intermediate host is *Bellamya aeruginosa* and the second intermediate hosts include *Pseudorasbora parva* and *Cyprinus carpio* (Yu and Mott, 1994).

Echinochasmus japonicus Tanabe, 1926

This species was first reported from experimental animals such as dogs, cats, rats, mice, and birds that have been fed the metacercariae encysted in fresh water fish in Japan (Tanabe, 1926). The characteristic features of the adult worm include a small, plump body, the presence of total 24 collar spines, which are interrupted dorsally, two large, tandem testes, and a very small number of eggs in the uterus (usually less than five) (Chai and Lee, 2002). This species is known to exist mainly in countries in the Far East (Chai and Lee, 2002). An experimental human infection was reported in Japan (Ujiie, 1936a); natural human infections have been found in China (Zhu et al., 1986), and the Republic of Korea (Seo et al., 1985b). The first intermediate host is a fresh water snail, *Parafossarulus manchouricus* (Lee et al., 1983; Choi et al., 2006). Eighteen species of fresh water fish have been found to be the second intermediate host, including *Pseudorasbora parva, Hypomesus olidus*, and *Gnathopogon strigatus* (Lee et al., Kim, 1984a; Chai et al., 1985b; Choi et al., 2006). Natural infections in avian species, such as ducks (Eom and Rim, 1984), and mammalian species, such as cats (Sohn and Chai, 2005) have been confirmed by the recovery of adult flukes.

Echinochasmus jiufoensis Yu and Mott, 1994

This species was reported from a 6-month-old girl who died from pneumonia and dehydration in Guangzhou, China (Liang and Ke, 1988). The life cycle and route of infection are unknown (Yu and Mott, 1994).

Echinochasmus liliputanus (Looss, 1896); Odhner, 1910

This species was originally described from cats and dogs in Egypt, Syria, and Palestine (Yamaguti, 1958). Later, human infections were first discovered in Anhui Province, China, in 1991, with the prevalence rate of 13.4% among 2426 examined people (Xiao et al., 1992). Higher infection rates were observed in age groups 3 to 15 years (22.7%) and 16 to 30 years (16.4%) than in others. In the same place, the infection rates in dogs and cats were 60% and 45%, respectively (Xiao et al., 1992). The freshwater snail *Parafossarulus striatulus* (Yu and Mott, 1994), and the freshwater fish *Pseudorasbora parva* (Yu and Mott, 1994) and goldfish (Xiao et al., 2005) were the first and second intermediate hosts, respectively. Interestingly, it was postulated that humans can be infected with this parasite through drinking untreated water containing the cercariae (Xiao et al., 2005). As a mechanism for human oral infections with cercariae, the phenomenon of cercarial encystment in the presence of human gastric juice was proposed (Xiao et al., 2005).

Echinochasmus perfoliatus (Ratz, 1908); Dietz, 1910

This is a common parasite of the small intestine of dogs and cats in Hungary, Italy, Rumania, Russia, Japan, China, and Taiwan (Yu and Mott, 1994; Shimalov and Shimalov, 2002), and of red foxes in Denmark (Saeed et al., 2006). The rat, dog, and wild boar are also found infected (Beaver et al., 1984). Human infections were reported from China (Guangdong, Fujian, Anhui, and Hubei Provinces), with the prevalence rate of 1.8% (34/1846), including a child who died from the infection; about 14,000 worms were found in the child at autopsy (Yu and Mott, 1994). Many species of freshwater fish such as *Carassius* sp. harbor the metacercariae, which are encysted only on the gills (Yu and Mott, 1994).

Echinoparyphium recurvatum von Linstow, 1873 [syn. *Echinoparyphium koidzumii* Tsuchimochi, 1924]

This is a common intestinal parasite of birds and mammals, including wild rats, in Egypt (Yu and Mott, 1994) and Poland (Betlejewska and Jorol, 2002). This parasite was also reported from house rats in the Republic of Korea (Lee et al., 1990c). Human infections were recorded in Taiwan, Indonesia, and Egypt (Beaver et al., 1984; Yu and Mott, 1994). The metacercariae encyst in tadpoles and frogs of *Rana temporaria* and also in snails, *Planorbis planorbis, Lymnaea* sp. (Yu and Mott, 1994), and *Lymnaea stagnalis* (Yurlova et al., 2006).

Echinostoma angustitestis Wang, 1977

The genus *Echinostoma* (Rudolphi, 1809) is characterized by an elongated body and presence of a head collar with dorsally uninterrupted crown of spines around the oral sucker (Yamaguti, 1958). More than 95 species are known (Yamaguti, 1958), and seven to eight species infect humans (Yu and Mott, 1994). *Echinostoma angustitestis* was first described in 1977 from dogs experimentally infected with metacercariae isolated from the freshwater fish (Yu and Mott, 1994). Two human infections were reported in Fujian, China (Cheng et al., 1992b).

Echinostoma cinetorchis Ando and Ozaki, 1923 (Fig. 2.2)

This species was first reported in house rats in Japan (Ando and Ozaki, 1923), and also in rats in the Republic of Korea (Seo et al., 1964, 1981a). Characteristic

FIGURE 2.2. An adult fluke of *Echinostoma cinetorchis* from an experimentally infected rat. As a characteristic feature in this species, both testes disappeared. Acetocarmine stain. Scale bar = 1 mm.

features include the abnormal location or disappearance of one, or both, of the two testes, and the presence of 37 or 38 collar spines around the oral sucker (Chai and Lee, 2002). Human infections were reported in Japan (Kawahara and Tamamoto, 1933), the Republic of Korea (Seo et al., 1980a; Ryang et al., 1986; Lee et al., 1988a). The fresh water snail *Hippeutis cantori* was experimentally confirmed as the first as well as the second intermediate host (Lee et al., 1990a). Other fresh water snails including *Radix auricularia coreanus, Physa acuta,* and *Cipangopaludina chinensis malleata* (Ahn et al., 1989; Chung and Jung, 2000), and fresh water fish, especially the loach *Misgurnus anguillicaudatus* (Seo et al., 1984c), were proven to harbor the metacercarial stage. House rats (Ando and Ozaki, 1923; Seo et al., 1964, 1981a) and dogs (Cho et al., 1981) were found to be natural definitive hosts. Laboratory rats and mice are highly susceptible to experimental infections (Lee et al., 1988c).

Echinostoma echinatum (Zeder, 1803)
[syn. *Echinostoma lindoense* Sandground and Bonne, 1940]

This parasite has 37 collar spines and resembles *Echinostoma revolutum. Echinostoma lindoense* has been synonymized with *E. echinatum* (Huffman and Fried, 1990; Fried and Graczyk, 2004). During 1937 and 1956, a high prevalence of 24% to 96% and heavy infections among people were known in Celebes, Indonesia, under the name of *E. lindoense* (Yu and Mott, 1994). The mode of human infection was eating raw or insufficiently cooked mussels *Corbicula lindoensis, Corbicula sucplanta*, and *Idiopoma javanica* (Beaver et al., 1984). This fluke was found in Brazil where *Biomphalaria glabrata* snail was the source of infection (Lie, 1968). Rats and mice are experimental definitive hosts (Beaver et al., 1984).

Echinostoma hortense Asada, 1926 (Fig. 2.3)

This parasite was first described from house rats in Japan (Asada, 1926), and then reported from Korea (Park, 1938; Seo et al., 1964, 1981a, 1983; Chai and Lee, 2002) and China (Fan and Sun, 1989). Human infections have been found in Japan, Korea, and China. In Japan, more than 20 human infections have been reported based on the recovery of the adult flukes (Miyamoto et al., 1983). In the Republic of Korea, an infection rate of 22.4% was reported among residents of Cheongsong-gun (Lee et al., 1988b). In a survey in Liaoning Province of northeast China, six of 10 hospitalized hepatitis patients who had eaten raw loach were found infected (Chen et al., 1993). Morphological characters include a laterally located ovary, and 27 to 28 collar spines around the oral sucker (Chai and Lee, 2002). The molluscan intermediate hosts are the fresh water snail, *Lymnaea pervia* and *Radix auricularia coreana* (Chai and Lee, 2002). The second intermediate hosts are the loaches, *Misgurnus anguillicaudatus* and *Misgurnus mizolepis*, and other fresh water fish, including *Odontobutis obscura interrupta, Moroco oxycephalus, Coreoperca kawamebari*, and *Squalidus coreanus* (Chai et al., 1985c; Ryang, 1990; Chai and Lee, 2002). In a survey in China, 69.7% of the loach *Misgurnus anguillicaudatus* from a market in Liaoning Province was

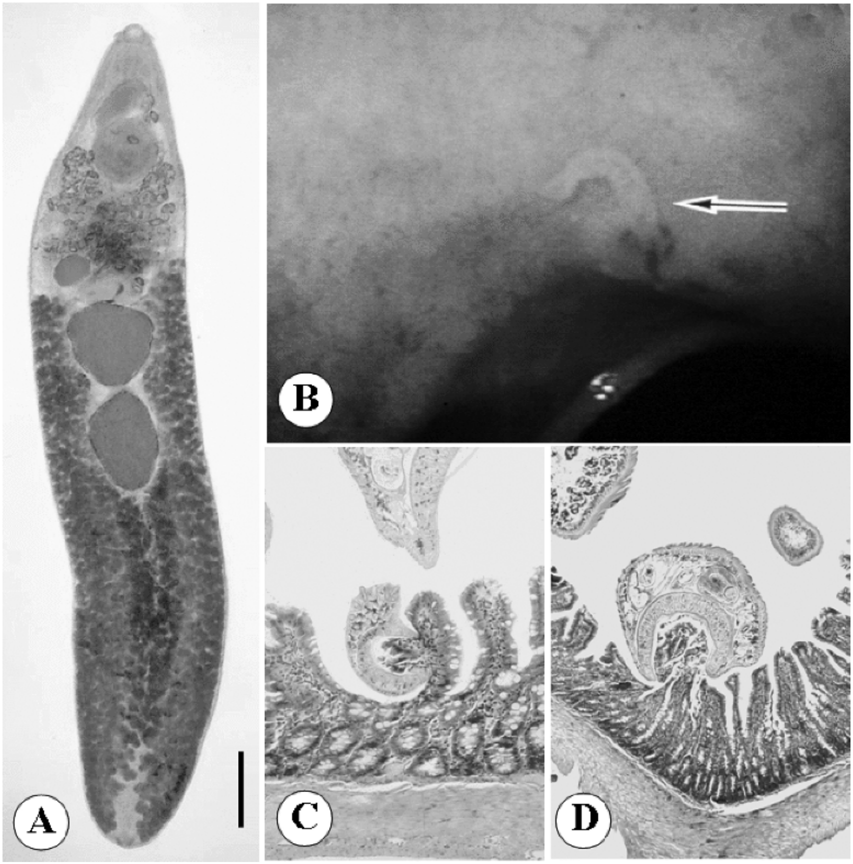

FIGURE 2.3. (A) An adult *Echinostoma hortense* worm recovered from an experimental rat. Aceto-carmine stain. Scale bar = 1 mm. (B) Gastroendoscopic view of an *E. hortense* worm attached to the ulcerated lesion of the stomach wall of a Korean patient. (From Chai et al., 1994c, with permission.) (C, D) Duodenal sections of experimental rats infected with *E. hortense*. Two worms are sucking the duodenal villi with their oral (C, ×100) and ventral suckers (D, ×100). Hematoxylin and eosin (H&E) stain. (From Lee et al., 1990b, with permission.)

infected (Yu and Mott, 1994). Rats (Park, 1938; Seo et al., 1964, 1981a), dogs (Cho et al., 1981), and cats (Sohn and Chai, 2005) have been found to be natural definitive hosts. Mice, rats, and humans have all been determined, experimentally, susceptible to *E. hortense* infection (Seo et al., 1985a; Lee et al., 2004a).

Echinostoma ilocanum (Garrison, 1908); Odhner, 1911

The eggs of this species were first found in the feces of a man in Manila, Philippines, in 1907, and later 21 adult flukes were recovered after anthelmintic treatment (Beaver et al., 1984). The Norway rat and the dog are reservoir hosts

(Beaver et al., 1984). Human infections were reported from Celebes, Java, Indonesia, China, Thailand, and India (Radomyos et al., 1982; Yu and Mott, 1994; Grover et al., 1998). The prevalence among the Ilocano population in northern Luzon, Philippines, was 5% on average (range 0–11%) (Cross and Bassaca-Sevilla, 1981). Characteristic morphological features include the presence of 49 to 51 collar spines and deeply lobed testes. The first intermediate hosts are *Gyraulus* or *Hippeutis* snails (Yu and Mott, 1994). The sources of human infections are the large snails *Pila conica* (Philippines) and *Viviparus javanicus* (Java) (Beaver et al., 1984). Infected humans may experience intestinal colic and diarrhea (Beaver et al., 1984).

Echinostoma macrorchis Ando and Ozaki, 1923

This parasite was first described from naturally infected rats in Japan (Ando and Ozaki, 1923). Subsequently, human infections were reported in Japan (Majima, 1927). Metacercarial cysts were found from snails *Cipangopaludina malleata, Cipangopaludina japonica, Segmentina nitiella, Viviparus malleatus*, and the frog *Rana* sp. (Yu and Mott, 1994).

Echinostoma malayanum Leiper, 1911

This fluke was first found in human infections in Singapore and Kuala Lumpur, Malaysia, in 1911, and then reported from Thailand, Indonesia, and India (Beaver et al., 1984; Maji et al., 1993; Radomyos et al., 1998; Yu and Mott, 1994). This fluke is now known to be distributed in the Philippines (Yu and Mott, 1994). The dog, rat, mouse, and hamster are experimental definitive hosts (Yu and Mott, 1994). The first intermediate host is a freshwater snail *Indoplanorbis exustus* and *Gyraulus convexiusculus* and the cercariae encyst in various species of snails, that is, *Pila scutata* and *Lymnaea (Bullastra) cumingiana* (Yu and Mott, 1994).

Echinostoma revolutum (Froelich, 1802); Looss, 1899 [syn. *Echinoparyphium paraulum* Diez, 1909]

This fluke is an intestinal fluke of the duck, goose, muskrat, and human in Asia, Europe, New Zealand, and Brazil (Yu and Mott, 1994; Fried and Graczyk, 2004). In Russia, domestic and wild animals were found to be infected with this fluke (Shimalov and Shimalov, 2002). The first human infection was reported from Taiwan in 1929, and the prevalence was estimated to be between 2.8% and 6.5% (Yu and Mott, 1994). This fluke was also reported from human infections in Yunnan and Guangdong Provinces, China, Indonesia, Thailand, and Russia (Beaver et al., 1984; Ashford and Crewe, 2002). This parasite was also reported from house rats and cats in the Republic of Korea (Lee et al., 1990c; Sohn and Chai, 2005). The snail host includes *Lymnaea* sp., *Physa* sp., *Paludina* sp., *Segmentina* sp., and *Heliosoma* sp. (Beaver et al., 1984). Cercariae penetrate into tadpoles, snails, or the clam *Corbicula producta*, which is the source of infection for definitive hosts (Beaver et al., 1984). *Echinoparyphium paraulum*, regarded as a synonym of *E. revolutum* (Beaver et al., 1984), was described from dogs in India (Yamaguti, 1958) and birds and a human in Russia (Ashford and Crewe, 2002).

Episthmium caninum (Verma, 1935); Yamaguti, 1958

This fluke was described from dogs in Calcutta, India (Yamaguti, 1958). Human cases were reported from northeast Thailand (Radomyos et al., 1985, 1991), and the source of infection was freshwater fish (Radomyos et al., 1991). The genus *Episthmium* was suggested to be tentatively retained as a synonym of *Echinochasmus* (Kostadinova and Gibson, 2001).

Himasthla muehlensi Vogel, 1933

Five adult worms were found from a German patient who lived in Colombia and traveled to New York City where he had eaten raw clams *Venus mercenaria* (Beaver et al., 1984). A species of marine operculate snail *Littorina littoria* serves as the first intermediate host and the bivalve mollusks *Mytilus* and *Mya* spp. as the host for metacercariae (Beaver et al., 1984). Birds are natural definitive hosts (Beaver et al., 1984).

Hypoderaeum conoideum (Block, 1872); Diez, 1909

This species was originally described from naturally infected birds in Europe, Japan and Siberia (Yamaguti, 1958). It is also a parasite of humans and birds in Thailand (Yokogawa et al., 1965a). In an area of northeast Thailand, 55% of 254 residents were found infected (Yokogawa et al., 1965a). The duck and fowl are reservoir hosts (Harinasuta et al., 1987). The first intermediate hosts are freshwater snails, *Planorbis corneus, Indoplanorbis exustus, Lymnaea stagnalis, Lymnaea limosa, Lymnaea ovata,* and *Lymnaea rubiginosa*, and snails and tadpoles are the second intermediate hosts (Yamaguti, 1958; Harinasuta et al., 1987).

Isthmiophora melis (Schrank, 1788); Lühe, 1909 [syn. *Euparyphium melis* Railliet, 1919, *Euparyphium jassyense* Leon and Ciurea, 1922]

This fluke has 27 collar spines, with four corner ones on each side, and was recovered from the diarrheic stools of a Romanian patient and at autopsy from a Chinese patient (Beaver et al., 1984). The taxonomic position of this parasite has been unstable, placing it into *Euparyphium* (Beaver et al., 1984) or *Echinostoma* (Harinasuta et al., 1987); however, it was later designated as a species of *Isthmiophora* (Fried, 2001; Kostadinova and Gibson, 2002). Human infections were also reported in Taiwan (Yu and Mott, 1994). Domestic and wild animals were found to be infected with this fluke in Russia (Shimalov and Shimalov, 2002). In the region of Douglas Lake, Michigan, the snail *Stagnicola emarginata angulata* is the first intermediate host and tadpoles serve as the second intermediate host (Beaver et al., 1984).

Psilorchis hominis Kifune and Takao, 1973

This fluke was described from a 48-year-old Japanese patient, who had a mixed infection with *E. macrorchis*, after anthelmintic medication (Kifune and Takao, 1973). The genus *Psilorchis* was assigned to the family Psilostomatidae (Ashford and Crewe, 2002). No other information is available on this species.

Pathogenicity and Host–Parasite Relationships of Echinostomes

The pathogenicity of echinostomes has not been well studied (Yu and Mott, 1994); however, it may be closely related to individual worm burdens (Rim, 1982). The intestinal histopathology was studied in a few species, including *E. revolutum* (Bindseil and Christensen, 1984; Huffman et al., 1986), *E. hortense* (Lee et al., 1990b; Chai and Lee, 2002) and *Echinostoma trivolvis* (Fujino et al, 1993). The worms were located in the lumen of the upper small intestine, and the pathological changes were observed chiefly in the mucosal layer (Chai and Lee, 2002). Villous atrophy, crypt hyperplasia, inflammation of the stroma, and decreased villus/crypt ratios were observed in the small intestine of experimentally infected animals (Huffman et al., 1986; Lee et al., 1990b) (Fig. 2.3). Compared with heterophyid infections, the mucosal damages were more severe, and in focal areas massive destruction and detachment of the villi and at times complete loss of the mucosal integrity and ulcerations were observed (Huffman et al., 1986; Chai and Lee, 2002). It was also reported that naturally infected pigs with *Artyfechinostomum oraoni* developed fatal diarrhea; at autopsy a massive infection with hemorrhagic and edematous mucosa of the jejunum and duodenum, extending up to the pyloric end of the stomach, was observed (Bandyopadhyay, 1995).

Spontaneous expulsion of worms from the small intestine of experimentally infected mice was observed in different species of echinostome infections; *E. trivolvis, E. hortense*, and *Echinostoma caproni* (Fujino et al., 1993; Kim et al., 2000; Brunet et al., 2000). Mucosal goblet cells (Fujino et al., 1993) and mucosal mast cells (Kim et al., 2000) were suggested to play important roles in the worm expulsion, although further studies are required to clarify the precise role of these cells. Roles of T-helper-1 (Th1) and Th2 cytokines were also suggested; injection of mice with anti–interferon-γ (anti–IFN-γ) monoclonal antibodies significantly lowered the worm burden, suggesting that host Th1 responses are related to establishment of a chronic infection (Brunet et al., 2000).

Clinical Symptoms, Diagnosis, and Treatment of Echinostomiases

Abdominal pain, diarrhea, and easy fatigability are the major symptoms due to echinostome infections (Rim, 1982; Chai and Lee, 2002; Fried et al., 2004). The symptoms are thought to be more severe than those seen in heterophyid infections, considering the more severe mucosal damages and even ulcerations of the mucosa seen in experimental rats infected with *E. hortense*, for instance (Lee et al., 1990b). A patient with an *E. hortense* infection complained of lower abdominal pain, diarrhea and tenesmus, easy fatigability, and urinary incontinence (Lee et al., 1986). Interesting to note are reports of patients with *E. hortense* infection suffering from severe epigastric discomfort and ulcerative lesions in the duodenum and diagnosed by discovery of worms at gastroduodenal endoscopy (Chai et al., 1994c; Lee and Hong, 2002; Cho et al., 2003; Chang et al., 2005). One of the patients was admitted to a hospital because of epigastric pain and hematemesis; through gastroduodenoscopy an adult fluke was seen attached at the lesion (Fig. 2.3) and it was removed by an endoscopic clipper; three more adult flukes were recovered from him after praziquantel treatment (Chai et al., 1994c). The levels of peripheral blood eosinophilia due to the *E. hortense* infection were dependent on individual worm burdens; 11% to 24% (average, 17%) among the patients with more than 100 worms, 4% to 21% (average, 10%) among those with 51 to 100 worms, and 2% to 14% (average, 5%) among those with less than 50 worms (Lee et al., 1988b). The clinical symptoms in *E. cinetorchis, E. japonicus*, and *A. tyosenense* infections are not well known (Seo et al., 1980a, 1985b; Chai et al., 2001b), but may be similar to those of *E. hortense* infection.

The diagnosis is based on recovery of echinostomatid eggs in the feces. Specific diagnosis can be made through careful observations and measurements of the eggs. However, a recovery and identification of the adult flukes is strongly recommended, if a definite diagnosis is preferred. The detectability of eggs in the feces is remarkably different among the species of echinostomes; it is high in *E. hortense* (Seo et al., 1985a) and *E. cinetorchis* (Seo et al., 1984c) infections, but very low in *E. japonicus* (Chai et al., 1985b) and *A. tyosenense* (Chai et al., 2001b) infections. The difference is greatly due to remarkably different numbers of the intrauterine eggs and the different egg-laying capacity of each species.

Echinostome infections can be treated successfully using praziquantel 10 to 20 mg/kg in a single oral dose (Seo et al., 1985a,b; Ryang et al., 1986; Lee et al., 1988a; Chai et al., 1994c, 2001b). Albendazole may also be effective. For prevention, eating raw or improperly cooked flesh of fresh water fish and fresh or brackish water snails should be avoided.

Fasciolidae Railliet, 1895

Three species of the family Fasciolidae (Railliet, 1895) are known to infect humans (Beaver et al., 1984; Mas-Coma et al., 2005). Two of them, *Fasciola hepatica* and *F. gigantica*, parasitize the liver of livestock animals, and accidentally infect humans. Only the remaining species, *Fasciolopsis buski*, is the species infecting the intestinal tract of animals and humans. Their cercariae encyst on the surface of aquatic plants, on debris, and also on the water surface (Fried et al., 2004).

Species Infecting Humans

Fasciolopsis buski (Landkester, 1857); Odhner, 1902 (Fig. 2.4)

This species was first discovered in the duodenum of an Indian man who died in London (Beaver et al., 1984). It is the largest fluke parasitizing humans (Kuntz and Lo, 1967; Mas-Coma et al., 2005), and a common intestinal parasite of humans and pigs in central and south China, Taiwan, Thailand, Vietnam, Laos, Cambodia, Bangladesh, India, Indonesia, and Malaysia (Yu and Mott, 1994;

FIGURE 2.4. An adult fluke of *Fasciolopsis buski* recovered from a patient. Acetocarmine stain. Scale bar = 5 mm.

Mas-Coma et al., 2005; Rohela et al., 2005). The prevalence in children varies according to countries, 10% in Thailand (Bunnag et al., 1983), 25% in Taiwan (Shyu et al., 1984), 57% in China (Lee, 1972) and 60% in India (Muttalib and Islam, 1975). Its first intermediate hosts are the freshwater snails *Segmentina* sp., *Hippeutis* sp., and *Gyraulus* sp. Metacercarial encystment occurs on the surface of edible aquatic plants, such as water chestnut *Eliocharis tuberose*, water caltrop *Trapa natans*, water hyacinth *Eichhornia* sp., roots of the lotus, water bamboo *Zizania* sp., other aquatic vegetation, or in the water (Beaver et al., 1984; Yu and Mott, 1994; Fried et al., 2004). People are infected through consuming raw or improperly cooked aquatic plants, or peeling off the hull or skin of the plants by mouth before eating the raw nut (Yu and Mott, 1994). The drainage of pig excreta in farms is an important factor for maintaining high endemicity (Yu and Mott, 1994).

Pathogenicity and Host–Parasite Relationships of Fasciolopsiasis

The disease can be fatal depending on worm burden (Bunnag et al., 1983; Mas-Coma et al., 2005). In light infections, anemia, eosinophilia, headache, dizziness, gastric pain, and loose stools can occur (Gilman et al., 1982). In moderate and heavy infections, severe epigastric and abdominal pain, diarrhea, bowel obstruction, nausea, acute ileus, anasarca, and marked eosinophilia and leukocytosis may occur (Gilman et al., 1982). Adult flukes damage the intestinal mucosa and cause extensive intestinal and duodenal erosions, ulceration, hemorrhages, abscess, and catarrhal inflammation (Marty and Andersen, 2000; Fried et al., 2004).

Symptoms, Diagnosis, and Treatment of Fasciolopsiasis

Absorption of toxic and allergic worm metabolites can cause ascites, general edema, and facial and orbital edema (Jaroonvesama et al., 1986). Diagnosis can be made by recovery of eggs in the feces. Praziquantel, in a single dose of 15 mg/kg, has been reported successful for treatment of fasciolopsiasis (Bunnag et al., 1983; Fried et al., 2004). Fasciolopsiasis is aggravated by socioeconomic factors, such as poverty, malnutrition, a lack of food inspection, poor sanitation, other helminthiases, and declining economic conditions (Yu and Mott, 1994).

Gastrodiscidae Stiles and Goldberger, 1910

Species Infecting Humans

Gastrodiscoides hominis (Lewis and McConnell, 1876); Leiper, 1913

This species was first found and described from the cecum of an Indian patient (Beaver et al., 1984). It has been known to be a common human parasite in India, Pakistan, Myanmar, Vietnam, the Philippines, Thailand, China, Kazakstan, Indian immigrants in Guyana, and the Volga Delta in Russia (Beaver et al., 1984; Mas-Coma et al., 2005). The pig is a common reservoir host, and the napu mouse deer, field rat, and rhesus monkey are local reservoir hosts (Beaver et al., 1984; Yu and Mott, 1994). The first intermediate host is the planorbid snail *Helicorbis coenosus* (Beaver et al., 1984) and cercariae encyst on aquatic plants, or in tadpoles, frogs, and crayfish (Yu and Mott, 1994). In human infections, the worms attach to the cecum and ascending colon and may produce a mucous diarrhea (Beaver et al., 1984).

Gymnophallidae Morozov, 1955

Species Infecting Humans

Gymnophalloides seoi Lee, Chai and Hong, 1993 (Fig. 2.5)

This fluke was first discovered in 1988 in a Korean woman suffering from acute pancreatitis and gastrointestinal discomforts (Lee et al., 1993b; Chai et al., 2003). Her home village in a southwestern coastal village (Aphaedo, Shinan-gun) was found to be a highly endemic area (Lee et al., 1994). Subsequently, 24 villages on western and southern coastal islands (Chai et al., 1997, 1998a, 2001c, Lee et al., 1996) and three nonisland coastal villages (Guk et al., 2006) were identified as endemic areas. This parasite has never been reported from other countries. The adult parasite is very small, and characterized by a large oral sucker, a small ventral sucker, short ceca, two compact masses of vitellaria, and a unique ventral pit (Lee et al., 1993). The first intermediate host is yet unknown (Lee and Chai, 2001; Chai et al., 2003), but the second intermediate host was confirmed to be the oyster *Crassostrea gigas* (Lee et al., 1995b; Sohn et al., 1998). Other than humans (Lee et al., 1993, 1994), the Palearctic oystercatcher *Haematopus ostralegus* (Ryang et al., 2000) has been shown to be a natural definitive host. Wading birds, such as the Kentish plover *Charadrius alexandrinus*, Mongolian plover *Charadrius mongolus*, and gray plover *Pluvialis squatarola*, were highly susceptible to experimental infection with this fluke (Ryang et al., 2001). Mammals, such as gerbils, hamsters, cats, and several strains of mice, were also found susceptible to experimental infections (Lee et al., 1997b). In vitro cultivation of the metacercariae into adults was successful using National Cancer Tissue Culture (NCTC) 109 medium (Kook et al., 1997).

Pathogenicity and Host–Parasite Relationships of Gymnophallids

In experimental mice, *G. seoi* parasitizes the small intestine, chiefly the duodenum and jejunum, pinching and sucking the intestinal villi with their large oral suckers (Chai et al., 2001a) (Fig. 2.5). Histopathologically, the infected

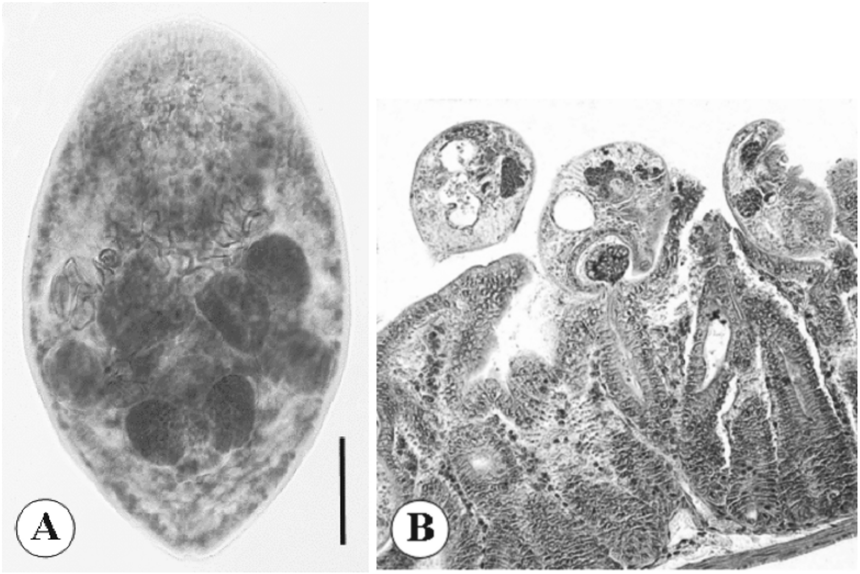

FIGURE 2.5. (A) *Gymnophalloides seoi* adult recovered from a patient. Acetocarmine stain. (B) Intestinal section of an experimentally infected mouse showing adult worms sucking the mucosal layer. H&E stain, ×200. Scale bar = 0.1 mm.

intestinal mucosa showed villous atrophy and crypt hyperplasia, with inflammatory reactions in the villous stroma and the crypt (Chai et al., 2001a). The histopathological changes were generally not so severe, and the mucosal integrity was restored around day 14 to 21 postinfection (Chai et al., 2001a). The worms did not invade the submucosal layer in immunocompetent hosts. However, in immunosuppressed hosts, worms were found to invade the submucosa (Chai et al., 2001a). It is of interest to note that, in a colon cancer patient who received anticancer chemotherapy, a *G. seoi* worm was found to have penetrated into the colonic lymphoid tissue (Seo et al., 2006). With regard to the mechanisms of the pathogenicity, mechanical irritation by the flukes was considered to be important (Chai et al., 2001a). Cysteine proteinases were isolated from the metacercariae and adults, and functionally characterized (Choi 1998a,b).

After experimental infections with metacercariae, Institute for Cancer Research (ICR) and BALB/c mice retained many worms by day 3 postinfection; however, most worms were expelled before day 7 postinfection (Lee et al., 1997). This had probably been caused by an innate immune response of the host. In this respect, it was 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 to 7 postinfection (Chai et al., 2001a). 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 to 14 postinfection (Chai et al., 1999; Seo et al., 2003). This was also suggested by the minimal degree of goblet cell hyperplasia in immunocompromised mice, with many more flukes surviving in the intestine (Chai et al., 1999; Seo et al., 2003). This is in good agreement with other workers studying other intestinal helminths, in which also goblet cells were found to be an important effector for the worm expulsion from the host, for example, *Nippostrongylus brasiliensis* (Nawa et al., 1994; Onah and Nawa, 2000) and *Echinostoma trivolvis* (Fujino et al., 1993).

The susceptibility of mice to an experimental infection with *G. seoi* was variable in different species of animals as well as different strains of mice (Lee et al., 1997). Among mouse strains, C3H/HeN mice were the most highly susceptible and the best for the growth and development of the worms, although the worm recovery at days 7 to 21 postinfection was not sufficiently high (Lee et al., 1997; Chai et al., 1999). It is likely that the difference in the susceptibility is caused by the genetic backgrounds of the host that regulate the immune responses of the host, including the mucosal goblet cell responses. In fact, when C3H/HeN mice were immunosuppressed by injection with prednisolone, the survival and the recovery of the worms were greatly enhanced (Lee et al., 1997; Chai et al., 1999), and the enhancement of the worm recovery had a strong correlation with the duration of the immunosuppression of mice. Immunosuppression of the C3H/HeN mice also enhanced the fecundity of the worms (Lee et al., 1997; Chai et al., 1999).

The habitat of *G. seoi* in the human host is presumed to be the small intestine, as seen in rodents (Lee et al., 1997; Chai et al., 2001a). However, the first patient suffered from acute pancreatitis (Lee et al., 1993), and two other patients were accompanied by diabetes mellitus (Lee et al., 1995a). It is thus suspected that *G. seoi* could infect the pancreatic duct in humans. In this respect, it is of note that other gymnophallids were found in the bursa Fabricii and gallbladder of shore birds as well as in the intestine (Yamaguti, 1975). However, the possibility of involvement of extraintestinal organs by *G. seoi* has not been experimentally proved; experiments using larger animals, such as monkeys, seem to be necessary to verify this possibility. Since *G. seoi* was able to invade the submucosa of immunosuppressed mice (Chai et al., 2001a), there is also a possibility that the eggs may be transferred to remote organs to cause erratic parasitisms in immunocompromised hosts, as reported in heterophyid infections (Africa et al., 1940).

Clinical Symptoms, Diagnosis, and Treatment of Gymnophalloidiasis

People infected with *G. seoi* complained of variable degrees of gastrointestinal troubles and indigestion (Lee et al., 1994; Chai et al., 2003). Fever, anorexia, weight loss, easy fatigability, and weakness may accompany the infection. However, the degree of symptoms seems to be variable among patients; the first patient underwent acute pancreatitis or acute cholecystitis, with episodes of epigastric discomforts, indigestion, and diarrhea (Lee et al., 1993), whereas other patients complained of only mild gastrointestinal troubles such as indigestion (Lee et al., 1994; Chai et al., 2003). In the first patient, laboratory studies revealed elevated serum and urine amylase levels, increased serum alkaline phosphatase activity, and slight to moderate degrees of eosinophilia (Lee et al., 1993). However, 5 days after treatment with praziquantel, epigastric pain and diarrhea completely disappeared, and serum and urine amylase levels returned to their normal levels (Lee et al., 1993). In the case of two patients, *G. seoi* infection was accompanied by diabetes mellitus (Lee et al., 1995a). Hence, some relations between the *G. seoi* infection and diabetes were suspected. It is of note that some of the infected patients in a highly endemic area in Aphaedo (Lee et al., 1994) complained of symptoms such as thirst, polydipsia, and polyuria (Chai et al., 2000a), that may occur among the patients with diabetes mellitus. Their blood and urine glucose levels, however, were within normal limits (Chai et al., 2000a).

In patients infected with *G. seoi*, the diagnosis can be made by detection of eggs in the feces; however, an expert is needed to identify the eggs (Lee and Chai, 2001). The eggs are very small, only 0.020 to 0.025 mm in length, smaller than those of *Clonorchis sinensis, Metagonimus yokogawai*, or other heterophyids, except for those of *P. summa*, and have a very thin and transparent shell (Lee et al., 1993, 1994). The problem is that the eggs are not readily detected in routine fecal examinations performed by formalin-ether sedimentation or cellophane thick smear techniques. They may be overlooked or misdiagnosed as an air bubble or other artifacts (Lee et al., 1993). Another problem is a very low egg-laying capacity of *G. seoi*, compared to other intestinal parasites (Chai et al., 2000a; Chai and Lee, 2002). The daily egg output was estimated to be only 2 to 84 eggs per adult fluke in the human host (Chai et al., 2000a). Unless more than 100 worms are present, less than 8400 eggs would be discharged in a whole-day stool; the eggs per gram of feces (epg) would be only 42 (daily stool weight; 200 g). This value means the appearance of only one to two eggs on the whole field of a fecal smear made by the Kato-Katz technique (41.7 mg of feces/smear) (Chai and Lee, 2002). When *G. seoi* (gymnophallid) eggs are detected in the feces, differential diagnosis is needed, because the egg morphology between different species of gymnophallids is similar to each other.

Praziquantel in a single oral dose of 10 mg/kg is highly effective for treatment of *G. seoi* infection in humans (Lee et al., 1993, 1994; Chai et al., 2000a). Albendazole may also be effective against *G. seoi* infection, but this needs confirmation. The best way to prevent *G. seoi* infection is the avoidance of consuming infected oysters, under raw or improperly cooked conditions. As control measures, oyster irradiation (Chai et al., 1996), and repeated chemotherapy of the people in endemic areas (Chai et al., 2000) were tried, with considerable success.

Heterophyidae Odhner, 1914

Species Infecting Humans

Apophallus donicus (Skrjabin and Lindtrop, 1919); Price, 1931

An experimental human infection with this species was successful in the U.S. (Niemi and Macy, 1974), and there were other reports of infection with this species in humans where fish are eaten raw (Schell, 1985). Heterophyid cercariae shed by the stream snail *Flumenicola virens* were found to encyst in hatchery-reared coho salmon, *Oncorhynchus kisutch* (Niemi and Macy, 1974). Many other kinds of fish, including blackside dace, suckers, squawfish, redside shiners, and rainbow trout, were found naturally infected with the metacercariae (Niemi and Macy, 1974). Reservoir hosts are dogs, cats, rats, foxes, and rabbits (Yamaguti, 1958).

Ascocotyle (Phagicola) longa Ransom, 1920

Flukes of *Ascocotyle* (Looss, 1899) [subgenus *Phagicola* Faust, 1920] are intestinal parasites of fish-eating birds or mammals in Europe, Asia, Africa, and the Americas (Yu and Mott, 1994). Human infections presumably with this species (described as a *Phagicola* sp.) were reported in Brazil (Chieffi et al., 1992). A dog was also found infected with this fluke (Chieffi et al., 1992). Freshwater fish are the second intermediate hosts (Chieffi et al., 1992). The taxonomic status of this species in relation to other related species was extensively studied (Scholz, 1999).

Centrocestus armatus (Tanabe, 1922b); Price, 1932

This fluke was first reported in dogs, cats, rabbits, rats, and mice experimentally fed on cyprinoid fish infected with the metacercariae (Tanabe, 1922b). Characteristic features of this species are the presence of 42 to 48 circumoral spines on the oral sucker, a small number of intrauterine eggs, the median location of the ovary, and the side-by-side location of the two testes. With regard to human infection, a successful experimental infection was reported in Japan (Tanabe, 1922b), and a case of natural human infection was reported in the Republic of Korea (Hong et al., 1988). The first intermediate host is the fresh water snail, *Semisulcospira* sp. (Takahashi, 1929b). The second intermediate hosts are fresh water fish, such as, *Zacco platypus, Zacco temminckii, Rhodeus ocellatus, Gobius similis, Pseudorasbora parva*, and *Pelteobagrus fulvidraco* (Lee et al., 1984a; Hong et al., 1989). The large egret *Egretta alba modesta* (Ryang et al., 1991) and the cat (Sohn and Chai, 2005) have been reported to be natural definitive hosts.

Centrocestus caninus (Leiper, 1913); Yamaguti, 1958 [syn. *Stephanopirumus longus* Onji and Nishio, 1916]

This fluke was first reported from dogs and foxes in Taiwan (Yamaguti, 1958), and two human infections in Thailand (Waikagul et al., 1997). The adult worm has 26 to 30 circumoral spines (Waikagul et al., 1997). Cercariae emerge from

Melanoides tuberculata and infect freshwater fish, such as *Cyprinus carpio, Hampala dispar, Puntius* sp., *Cyclocheilichthys* sp., and *Tilapia nilotica* (Wakagul et al., 1997). Adult worms were recovered from the posterior half of the small intestine of rats, 18 days after the infection (Waikagul et al., 1997).

Centrocestus cuspidatus (Looss, 1896), 1899

This species was described from a naturally infected dog in Egypt (Ransom, 1920). The adult worm has 36 circumoral spines (Ransom, 1920). Rats were experimentally infected after feeding them with the fish *Astatotilapia desfontainesi*, and adult worms were obtained in Tunis, Tunisia (Yamaguti, 1958). Human infections were reported in Egypt (Yu and Mott, 1994), although the literature background is uncertain.

Centrocestus formosanus (Nishigori, 1924); Price, 1932

This species was described from an experimental dog fed freshwater fish infected with the metacercariae and found also in a naturally infected fox (Nishigori, 1924). An experimental human infection was successful (Nishigori, 1924). The presence of natural human infections in Taiwan and Japan was mentioned by various authors (Ito, 1964; Premvati and Pande, 1974). The adult worm has 32 circumoral spines (Chen, 1942). This fluke is now known to be present in Taiwan, China, Japan, the Philippines, India, Hawaii, and Mexico (Chen, 1942; Martin, 1958; Yamaguti, 1975; Madhavi, 1986; Yu and Mott, 1994; Scholz and Salgado-Maldonado, 1999). Cercariae were found in the snail, *Stenomelania newcombi* (Martin, 1958).

Centrocestus kurokawai (Kurokawa, 1935); Yamaguti, 1958

This fluke was originally described from a naturally infected man in Hiroshima Prefecture, Japan (Kurokawa, 1935). The adult worm has 38 or 40 circumoral spines (Kurokawa, 1935). No information is available on the intermediate and reservoir hosts.

Cryptocotyle lingua (Creplin, 1825); Fischoeder, 1903

This species has been described from cats, dogs, rats, birds, and wild animals in Europe, North America, Russia, Denmark, and Japan (Yamaguti, 1958; Saeed et al., 2006). Human infection with this fluke was reported in Greenland (Yu and Mott, 1994). Cercariae develop in littorina snails, *Littorina littoria*, and encyst in the fish *Gobius ruthensparri* and *Labrus bergylta*; adults can be grown in gulls fed metacercarial cysts (Yamaguti, 1958).

Haplorchis pleurolophocerca (Sonsino, 1896); Yamaguti, 1958

The genus *Haplorchis* is characterized by the presence of only one testis and a ventrogenital-sucker complex armed with gonotyl and chitinous spines (Chen, 1936).

The genus consists of more than 20 species, and five of them, *Haplorchis pleurolophocerca, H. pumilio, H. taichui, H. vanissimus,* and *H. yokogawai* (one more species, *H. microrchis* is a synonym of *H. taichui*; Chen, 1936), are acknowledged as the species responsible for human infections (Yu and Mott, 1994). *H. pleurolophocerca* was described based on adults from cats in Egypt (Yamaguti, 1958). Cercariae were found in the snails, *Melania tuberculata* and *Cleopatra bulimoides* (Yamaguti, 1958). The fish *Gambusia affinis* is the second intermediate host (Yu and Mott, 1994). Human infections are known from Egypt (Yu and Mott, 1994).

Haplorchis pumilio (Looss, 1986), 1899

This species was originally described based on adult flukes obtained from birds and mammals in Egypt (Yamaguti, 1958). Later the same species was discovered in Taiwan and described under the name of *Monorchotrema taihokui* (Chen, 1936). It has also been found in the Philippines, Thailand, Laos, South China, Taiwan, and Egypt (Velasquez, 1982; Yu and Mott, 2002; Chai et al., 2005b). Human infections were reported in all of the above countries (Yu and Mott, 1994). The snail host is *Melania reiniana* var. *hitachiens* (Faust and Nishigori, 1926; Velasquez, 1982). The fish hosts are freshwater species belonging to the Cyprinidae, Siluridae, and Cobitidae, similar to *H. tachui* (Velasquez, 1982). Dogs and cats are the natural definitive hosts (Yamaguti, 1958).

Haplorchis taichui (Nishigori, 1924); Chen, 1936 (Fig. 2.6)
[syn. *Monorchotrema microrchia* Matsuda, 1932; *Haplorchis microrchis* Yamaguti, 1958]

This species was originally described from adult flukes in birds and mammals caught in the middle part of Taiwan (Faust and Nishigori, 1926; Ujiie, 1936b). It is also distributed widely in the Philippines, Bangladesh, India, Palestine, Egypt, Malaysia, Thailand, Laos, Vietnam, and South China (Velasquez, 1982; Yu and Mott, 1994; Chai et al., 2005b). Human infections are not uncommon in Thailand, Laos, the Philippines, and South China (Velasquez, 1982; Yu and Mott, 2002; Chai et al., 2005b; Belzario et al., 2005). The snail host is *Melania obliquegranosa, Melania juncea*, or *Melanoides tuberculata* (Faust and Nishigori, 1926; Velasquez, 1982). The fish hosts are mainly freshwater species, including *Cyprinus carpio, Cyprinus auratus, Zacco platypus, Pseudorasbora parva, Rhodeus ocellatus, Gambusia affinis, Puntius orphoides, Puntius leicanthus, Puntius gonionotus, Puntius binotatus*, and *Puntius palata* (Velasquez, 1982) and *Raiamas guttatus, Mystacoleucus marginatus*, and *Henichoryhnchus siamensis* (Kumchoo et al., 2005). Dogs, cats, and birds are the natural definitive hosts (Yamaguti, 1958).

Haplorchis vanissimus Africa, 1938

This species was originally described from adult flukes obtained in a naturally infected man in the Philippines (Africa et al., 1940). Later, this fluke was reported

FIGURE 2.6. An adult fluke of *Haplorchis taichui* from a human infection. Acetocarmine stain. Scale bar = 0.1 mm.

from pelicans and wild mammals in Australia (Pearson and Ow-Yang, 1982). The snail host is unknown. Freshwater fish are second intermediate hosts (Yu and Mott, 1994).

Haplorchis yokogawai (Katsuta, 1932); Chen, 1936

This species was originally described from adult flukes obtained in dogs and cats experimentally fed the metacercariae encysted in the mullet *Mugil cephalus* in Taiwan (Katsuta, 1932b). Later this fluke was reported in the Philippines, South China, Malaysia, Indonesia, Thailand, Laos, India, Australia, and Egypt (Velasquez, 1982;

Yu and Mott, 1994). Human infections were reported in most of the above countries (Yu and Mott, 1994; Chai et al., 2005b). The snail host is *Melanoides tuberculata* or *Stenomelania newcombi* (Velasquez, 1982). The fish hosts are freshwater species including *Mugil* spp., *Puntius* spp., *Misgurnus* sp., and *Ophicephalus striatus* (Velasquez, 1982). Dogs, cats, cattle, and other mammals are natural definitive hosts (Yamaguti, 1958).

Heterophyes dispar Looss, 1902

The genus *Heterophyes* is characterized by the median location of the ventral sucker and the presence of a genital sucker armed with gonotyl (Chai and Lee, 2002). The genus consists of about 10 species, and three of them, *Heterophyes dispar, H. heterophyes*, and *H. nocens* (syn. *H. katsuradai*), are the species responsible for human infections (Yu and Mott, 1994; Chai and Lee, 2002). *Heterophyes dispar* was first discovered in the intestines of dogs and cats in Egypt, and then from mammals including the fox and wolf in the northern Africa and eastern Mediterranean (Yu and Mott, 1994). Brackish water fish are second intermediate hosts (Taraschewski, 1984). Human infections were reported from two Korean men who returned from Saudi Arabia (Chai et al., 1986a) and from Thailand (Yu and Mott, 1994).

Heterophyes heterophyes (v. Siebold, 1852); Stiles and Hassall, 1900

This species was first discovered by Bilharz in 1851 at autopsy of an Egyptian in Cairo, and is now known to cause human infections along the Nile Delta of Egypt and Sudan (Yu and Mott, 1994; Fried et al., 2004; Chai et al., 2005a). It is also present in Greece, Iran, Turkey, Italy, and Tunisia (Himonas, 1964; Yu and Mott, 1994; Pica et al., 2003). In Asia, several foci have been reported (Yu and Mott, 1994); however, this parasite species might have been confused with *H. nocens* and should be verified. Imported human infections were reported in Japan (Kagei et al., 1980) and the Republic of Korea (Chai et al., 1986a; Chai and Lee, 2002), from people who returned from Egypt to Japan and from Saudi Arabia and Sudan to Korea. The snail host is *Pirenella conica* in Egypt (Taraschewski, 1984). Important second intermediate hosts are brackish water fishes including *Mugil cephalus, Tilapia nilotica, Aphanius fasciatus*, and *Acanthogobius* sp. Humans become infected by eating infected fish raw or inadequately cooked. A variety of mammals other than humans takes the role of the reservoir host, for example, dogs in India (Beaver et al., 1984; Harinasuta et al., 1987). In Egypt, human infections are prevalent among the inhabitants of the northern part of the Nile Delta, particularly around the Lakes Manzala, Borollos, and Edco where fishermen and domestic animals frequently consume fish (Yu and Mott, 1994). During 1987–1991, the prevalence of heterophyiasis in five governorates of the Nile Delta ranged between 0.01% and 1% (Yu and Mott, 1994). A review of 299 cases in Dakahlia Governorate indicated that the disease is common in both urban and rural localities owing to the habit of consuming salted or insufficiently baked fish (Sheir and Aboul-Enein, 1970). The mean prevalence of heterophyid infections in the villages of Khuzestan, Islamic Republic, was found to be 8% (range 2–24%) (Yu and Mott, 1994). In postmortem examination of carnivores in the same areas, 14.2% of jackals, 33.3% of foxes, and 2.5% of dogs were infected with heterophyid flukes including *H. heterophyes, M. yokogawai*, and *H. katsuradai* (a synonym of *H. nocens*) in order of frequency (Massoud et al., 1981). Metacercariae of *H. heterophyes* can survive up to 7 days in salted fish. The pathogenesis and intestinal pathology, clinical disease, diagnosis, chemotherapy, prevention, and control are the same as those for metagonimiasis.

Heterophyes nocens Onji and Nishio, 1916 (Fig. 2.7) [syn. *Heterophyes katsuradai* Ozaki and Asada, 1926]

This species was first reported in Japan from experimental dogs and cats fed the metacercariae encysted in the mullet *Mugil cephalus* (Onji and Nishio, 1916). It is now known to occur as human infections in Japan, China, and the Republic of Korea (Yokogawa et al., 1965b; Xu and Li, 1979; Seo et al., 1981b; Chai et al., 1984a, 1985a). In China, the species was described as *H. heterophyes* (Xu and Li, 1979), but is now presumed to be *H. nocens. H. nocens* is distinguished from *H. heterophyes* by the morphology of the genital sucker, especially the smaller number of rodlets on the gonotyl; 50 to 62 in *H. nocens* and 70 to 85 in *H. heterophyes* (Taraschewski, 1984; Chai and Lee, 2002). The first intermediate host is a brackish water snail *Cerithidea cingulata* (= *Tympanotonus microptera*). The second intermediate hosts are brackish water fish such as the mullet *Mugil cephalus* or goby *Acanthogobius flavimanus* (Chai and Lee, 2002). Domestic or feral cats were found naturally infected with this fluke (Eom et al., 1985; Sohn and Chai, 2005). In the Republic of Korea, the metacercariae were found in the mullet *Mugil cephalus* captured in three southern coastal areas (Seo et al., 1980b). Over 40% prevalences were detected in several southwestern coastal areas (Chai et al., 1994b, 1997; Chai and Lee, 2002). Individual worm burdens ranged from 1 to 1338, Average 263 per person (Chai et al., 1994a, 1997, 1998a). Many western and southern coastal islands were added to the list of endemic areas (Chai et al., 2004). In Japan, human *H. nocens* infections were reported from Kochi, Chiba, Yamaguchi, Chugoku, and Hiroshima Prefectures (Suzuki et al., 1982). Recently, two lakeside villages of Mikkabi-cho, north end of Hamana Lake, Shizuoka Prefecture, were added as new endemic areas, with prevalence rates of 7.5% and 10.5% (Kino et al., 2002).

Heterophyopsis continua (Onji and Nishio, 1916); Yamaguti, 1958

This species was first discovered from experimental cats fed the mullet *Mugil cephalus* that harbored the metacercariae in Japan (Onji and Nishio, 1916). *H. continua* differs from other heterophyid species in its elongate body, genital sucker located separately from the ventral sucker, and two obliquely tandem testes (Chai and Lee, 2002). The presence of human infections was first mentioned in Japan (Yamaguti, 1939b). Subsequently, in the Republic of Korea, two natural human infections were discovered (Seo et al., 1984a). Including these two

FIGURE 2.7. An adult specimen of *Heterophyes nocens* obtained from an experimentally infected rat. Acetocarmine stain. Scale bar = 0.1 mm.

cases, eight human cases in total have been confirmed by the recovery of adult flukes in the Republic of Korea (Chai et al., 1997, 1998a; Hong et al., 1996a). The first intermediate host is unknown. Metacercariae were found in the perch *Lateolabrax japonicus* and goby *Acanthogobius flavimanus* (Chun, 1960b). Other fish hosts include shad *Clupanodon punctatus* (Chun, 1960b; Sohn et al., 1994b), conger eel *Conger myriaster* (Kim et al., 1996), and sweetfish *Plecoglossus altivelis* (Cho and Kim, 1985). Domestic or feral cats (Eom et al., 1985; Sohn and Chai, 2005), ducks (Onji and Nishio, 1916), and sea gulls (Yamaguti, 1939a) were reported to be natural definitive hosts. Experimental definitive hosts include cats (Onji and Nishio, 1916), dogs (Chun, 1960b; Seo et al., 1984a), and domestic chicks (Hong et al., 1990a, 1991).

Metagonimus minutus Katsuta, 1932

Flukes of *Metagonimus* are characterized by the small body size, laterally deviated ventral sucker, and absence of the ventrogenital apparatus or genital sucker, which is present in other genera including *Heterophyes, Heterophyopsis, Haplorchis*, and *Stellantchasmus* (Yu and Mott, 1994; Chai and Lee, 2002). A total of seven species have been reported (Saito et al., 1997), and four of them, namely *M. yokogawai* (Korea, China, Taiwan, Japan, Indonesia, and Russia), *M. takahashii* (Korea and Japan), *M. minutus* (Taiwan), and *M. miyatai* (Korea and Japan), have been reported from human infections (Yu and Mott, 1994; Chai and Lee, 2002). *Metagonimus minutus*, characterized by small sized uterine eggs, was reported as adult flukes recovered from experimental mice and cats fed mullets infected with the metacercariae in Taiwan (Katsuta, 1932a). This parasite is listed among the human-infecting intestinal trematodes (Beaver et al., 1984; Yu and Mott, 1994), but no literature background is traceable.

Metagonimus miyatai Saito et al., 1997

This parasite was first found by I. Miyata, in 1941 in Japan, but its taxonomic significance was not established until 1997, when it was reported as a distinct species in Japan and Korea (Saito et al., 1997). The description was based on adult flukes collected from dogs and hamsters experimentally fed the metacercariae from sweetfish, dace, common fat-minnow *Morocco steindachneri*, pale chub *Zacco platypus*, dark chub *Zacco temmincki*, and also on specimens collected from naturally infected humans. 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) (Saito et al., 1997). This species is genetically distinct from *M. takahashii* and *M. yokogawai*, as shown by the polymerase chain reaction–based restriction fragment length polymorphism (PCR-RFLP) patterns (Yu et al., 1997a), karyotypes (Lee et al., 1999), simple sequence repeat (SSR)-PCR patterns (Yang et al., 2000), random amplification of polymorphic DNA patterns (Yu et al., 1997b), and 28S ribosomal DNA and cytochrome C oxydase subunit I patterns (Lee et al., 2004b). The snail intermediate hosts are *Semisulcospira globus* (Kim et al., 1987), *Semisulcospira libertina,* or

Semisulcospira dolorosa (Shimazu, 2002). Mice, rats, hamsters, and dogs are experimental definitive hosts (Chai and Lee, 2002; Guk et al., 2005). Reservoir hosts are unknown. In the Republic of Korea, the presence of this species was first reported in 1980 (under the name of *Metagonimus* sp.) from people along the Gum River, which is uninhabited by the sweetfish (Kim, 1980). A high prevalence of this fluke infection was reported among people residing around the Daechong Reservoir and its upper reaches (Kim et al., 1987), the upper reaches of the Namhan River (Chai et al., 1993a), the Hantaan River basin (Park et al., 1993), and the western inland of Gangwon-do (Ahn, 1993). A western tributary of the Nakdong River in Keochang-gun was also reported as a low-grade endemic area (erroneously under the name of *M. takahashii*) (Son et al., 1994). Small rivers of Shizuoka Prefecture, Japan, were found to be endemic areas of this fluke (Kino et al., 2006).

Metagonimus takahashii Suzuki, 1930

This fluke was first reported in Japan from mice and dogs fed metacercariae encysted in several species of fresh water fish other than the sweetfish (Suzuki, 1930), and is also distributed in Korea and Japan (Chai and Lee, 2002). It differs from *M. yokogawai* in the position of two testes (anterior testis separated from the posterior testis), the distribution of vitelline follicles (more abundant and crossing over the posteriormost end), and by the larger size of the eggs (*M. yokogawai*, 28–30 μm; *M. takahashii*, 32–36 μm) (Chai and Lee, 2002). The two species are genetically differentiated by the PCR-RFLP patterns, karyotypes, SSR anchored-PCR (SSR-PCR) patterns (Chai and Lee, 2002), and 28S ribosomal DNA and cytochrome C oxydase subunit I patterns (Lee et al., 2004b). The Koga type of *Metagonimus* encysting in the dace *Tribolodon* spp. (Saito, 1984) is regarded as a synonym of *M. takahashii* (Chai et al., 1991). The snail hosts involved may be *Semisulcospira coreana* or *Koreanomelania nodifila* (Cho et al., 1984), but this has to be confirmed. The fish hosts are the crussian carp *C. carassius* (Chun, 1960a), carp *C. carpio* (Saito, 1984), dace *Tribolodon taczanowskii* (Chai et al., 1991), and perch *Lateolabrax japonicus* (Kim et al., 2006). Numerous strains of mice could be experimentally infected with fluke (Guk et al., 2005). There are no reports on reservoir hosts. In the Republic of Korea, the presence of this species was documented based on adult flukes recovered from experimental rabbits in 1960 (Chun, 1960a). In humans, adult flukes were confirmed in 1993 from inhabitants of Umsong-gun, Chunchungnam-do, along the upper reaches of the Namhan River (Chai et al., 1993a). The inhabitants had mixed infections with *M. miyatai*, with an egg positive rate of 9.7% for both species (Chai et al., 1993a). People in the western inland of Gangwon-do were also found to be infected with the two species (Ahn, 1993). *M. takahashii* is distributed along small streams in various inland areas of the Republic of Korea (Chai and Lee, 2002).

Metagonimus yokogawai (Katsurada, 1912) (Fig. 2.8)

This parasite is probably the most common intestinal fluke infecting humans in the Far East (Chai and Lee, 2002). Human infections were reported also from the

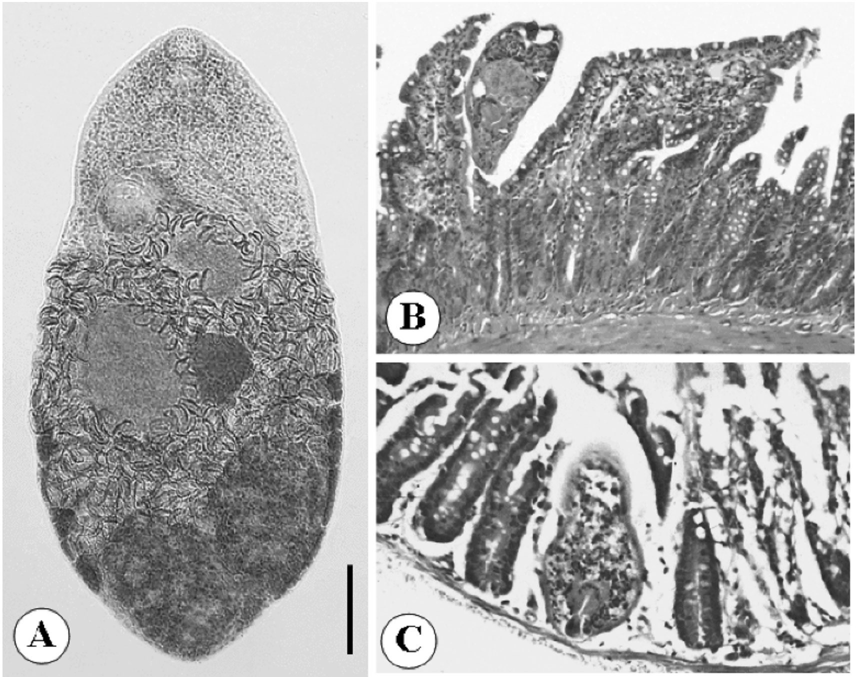

FIGURE 2.8. (A) *Metagonimus yokogawai* adult recovered from an experimentally infected rat. Acetocarmine stain. Scale bar = 0.1 mm. (B) Intestinal section of a rat experimentally infected with *M. yokogawai*, 4 weeks after infection. The mucosal pathology is characterized by villous atrophy and crypt hyperplasia. H&E stain, ×200. (C) An adolescent worm of *M. yokogawai*, which invaded beyond the submucosa and facing the muscular layer of the duodenum of an immunosuppressed mouse, day 5 postinfection. H&E stain, ×400. (From Chai et al., 1995a, with permission).

northern provinces of Siberia, Israel, the Balkan states, and Spain (Yu and Mott, 1994). The eggs of this species are confused with many other heterophyid species, thus the accuracy of the data on the prevalence of this infection is limited. The molluscan first intermediate host is the fresh water snail, *Semisulcospira coreana* or *Semisulcospira libertina* (Cho et al., 1984). The most important second intermediate host is the sweetfish *Plecoglossus altivelis* (Chai and Lee, 2002), but the dace *Tribolodon* sp. (Chai et al., 1991) and the perch *Lateolabrax japonicus* (Ahn, 1983) also serve as second intermediate hosts. Dogs, rats, and cats were reported as natural definitive hosts (Cho et al., 1981; Seo et al., 1981a; Huh et al., 1993), although their significance as the source of the human infection (i.e., as reservoir hosts) has not been established. Variable strains of mice were found to be susceptible to *M. yokogawai* infection but less susceptible to *M. miyatai* and *M. takahashii* infections (Guk et al., 2005). In the Republic of Korea, almost all the large and small streams in eastern and southern coastal areas are endemic foci of metagonimiasis (Seo et al., 1981d; Song et al., 1985). The Sumjin, Tamjin, and Boseong Rivers, Geoje Island, and Osip Stream (Gangwon-do) were the highest endemic areas with 20% to 70% egg positive rates in the villagers (Chai et al., 1977, 2000c; Seo et al., 1981d; Chai and Lee, 2002). The nationwide egg positive rate of people residing in river basins was once estimated at 4.8% (Seo et al., 1981d). Human infection has been recorded in Guangdong, Anhui, Hubei, and Zhejiang Provinces of China and Taiwan (Xu and Li, 1979). In Japan, the prevalence rate of *M. yokogawai* infection was low or negligible after the 1970s, except a few foci such as areas surrounding the Hamana Lake (Ito et al., 1991). However, small rivers of Shizuoka Prefecture still were prevalent with *M. yokogawai* in the fish intermediate hosts (Kino et al., 2006). In Russia, *M. yokogawai* is endemic in the Amur and Ussuri valleys of Khabarovsk territory where the prevalence in ethnic minority groups varies between 20% and 70% (Yu and Mott, 1994). 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 (Yu and Mott, 1994).

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

This species was reported from dogs and then two native people in the Philippines (Africa and Garcia, 1935). Later, it was reported from China and Africa (Harinasuta et al., 1987). Second intermediate hosts are the freshwater fish, *Ophiocephalus striatus, Glossogobius giurus, Mollienesia latipinna, Mugil* sp., and *Creisson validus* (Velasquez, 1973a,b; Yu and Mott, 1994). The first intermediate host is the brackish water snail, *Thiara riquetti* (Velasquez, 1973b).

Procerovum varium Onji and Nishio, 1916

This parasite was described from experimentally infected dogs with the metacercariae encysted in the mullet *Mugil cephalus* in Japan (Onji and Nishio, 1916). Experimental human infections were reported (Aokage, 1956), but there have been no reports of natural human infections. It is now known to be distributed in China, the Philippines, Australia, India (Umadevi and Madhavi, 2000), and Korea (Sohn and Chai, 2005). Natural infection of cats has been found (Sohn and Chai, 2005).

Pygidiopsis summa Onji and Nishio, 1916 (Fig. 2.9)

This species was first found in dogs fed brackish water fish infected with the metacercariae in Japan (Onji and Nishio, 1916). It is now known to be present in the Republic of Korea (Chai and Lee, 2002). Human infections were first reported in Japan by detection of eggs in feces in 1929 (Takahashi, 1929a), and adult flukes in human infections were identified in 1965 (Yokogawa et al., 1965b). The worms are 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 (Chai et al., 1986b). The metacercariae were detected in the gills and muscles of the mullet *Mugil cephalus* and goby *Acanthogobius flavimanus* (Chun, 1963; Seo et al., 1981c; Sohn et al., 1994b). Human infections in the Republic of Korea were first reported in eight residents of a seaside salt-farm village of

FIGURE 2.9. An adult worm of *Pygidiopsis summa* from an experimentally infected rat. Acetocarmine stain. Scale bar = 0.1 mm.

Okku-gun, Chollabuk-do, who habitually ate the raw flesh of the mullet (Seo et al., 1981b). In another coastal area of the Republic of Korea, 18 of 20 heterophyid egg–positive people were found to be infected with this fluke (Chai et al., 1997). Five infected people were detected in Buan-gun, Chollabuk-do (Chai et al., 1998a). It is now known to be distributed widely along the western and southern coastal islands (Chai et al., 2004). The first intermediate host in the Republic of Korea is the brackish water snail *Cerithidea* sp. or *Tympanotonus* sp. (personal observation). The natural infection of domestic or feral cats has also been reported (Eom et al., 1985; Sohn and Chai, 2005).

Stellantchasmus falcatus Onji and Nishio, 1916

This species was first reported from cats experimentally fed the mullet harboring the metacercariae, in Japan (Onji and Nishio, 1916). Morphological characteristics of this fluke include the ventral sucker, which is slightly deviated 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 (Chai and Lee, 2002). Human infections were reported first (Takahashi, 1929a) and then repeatedly reported in Japan (Ito, 1964; Kagei et al., 1964). Thereafter, human infections have been reported in various Asian-Pacific countries: the Philippines, Hawaii, Japan, Palestine, Thailand, and Korea (Yamaguti, 1958; Radomyos et al., 1990; Seo et al., 1984b; Chai and Lee, 2002). A successful life cycle study was performed in Hawaii; the first intermediate host was confirmed to be the brackish water snail *Stenomelania newcombi* or *Thiara granifera* (Martin, 1958; Noda, 1959), and the second intermediate host was shown to be the mullet (Chai and Sohn, 1988; Chai and Lee, 2002), and half-beaked fish *Dermogenus pusillus* (Wongsawad et al., 1998; Sripalwit et al., 2003). For experimental hosts, rats were better than mice (Saenphet et al., 2003). Natural infections in cats are known (Takahashi, 1929a; Sohn and Chai, 2005).

Stellantchasmus formosanus Katsuta, 1931

This parasite was described from experimentally infected cats, dogs, and mice with the metacercariae encysted in the mullet *Mugil cephalus* in Taiwan (Katsuta, 1931). An experimental human infection was reported in Taiwan (Katsuta, 1931), but there have been no reports of natural human infections.

Stellantchasmus pseudocirratus (Witenberg, 1929); Yamaguti, 1958 [syn. *Stellantchasmus amplicaecalis* Katsuta, 1932]

This parasite was described from naturally infected dogs and cats in Palestine (Witenberg, 1929) and cats, dogs, and mice fed mullet in Taiwan (Katsuta, 1932c). The mullet, *Mugil* sp., is the second intermediate host (Witenberg, 1929; Yamaguti, 1958). Human infections were reported in the Philippines and Hawaii (Africa et al., 1940; Yamaguti, 1958).

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

This species was originally described from cats experimentally fed on infected mullet in Japan (Onji and Nishio, 1916). The worm is morphologically characterized by the presence of a gonotyl, which is superimposed on the ventral sucker and armed with 12 chitinous spines, a metraterm, and two testes located obliquely in the middle field of the body. Human infection with this fluke (reported under the name of *Stictodora* sp.) was found in a young Korean man, who regularly ate raw mullets and gobies (Chai et al., 1988). Thirteen additional human cases were subsequently detected in a seashore village in the southwestern coastal area (Chai and Lee, 2002). The metacercariae were found in gobies, *Acanthogobius flavimanus*, collected from a market in Chollanam-do Province (Sohn et al., 1994a, 1994b). The domestic cat (*Felis catus*) has been used as an experimental definitive host (Sohn et al., 1994b). Feral cats were found naturally infected with this fluke (Sohn and Chai, 2005).

Stictodora lari Yamaguti, 1939

This fluke was first found in the small intestine of the sea gull *Larus crassirostris* in Japan (Yamaguti, 1939a). Morphological characters include a gonotyl armed with 70 to 80 minute spines (Chai et al., 1989a). Adult flukes were first recovered from six Korean people who resided in two southern coastal villages (Chai et al., 2002). The first intermediate host is the brackish water gastropod *Velacumantus australis* in Australia (Howell, 1973). The metacercariae of this fluke were found in a species of brackish water fish, that is, the goby *Acanthogobius flavimanus*, in the Republic of Korea (Chai et al., 1989a). Other fish hosts include a number of species of estuarine fish (Howell, 1973). In gobies, metacercariae were observed mainly in the head of the fish (Chai et al., 1989a). Cats and dogs were used as experimental definitive hosts (Chai et al., 1989a). Reservoir hosts include feral cats (Sohn and Chai, 2005).

Pathogenicity and Host–Parasite Relationships of Heterophyid Flukes

At the site of attachment in the host intestinal mucosa, *H. heterophyes* adults can cause mild inflammatory reactions, ulcers, irritation, and superficial necrosis of the mucosa (Yu and Mott, 1994; Fried et al., 2004). The intestinal histopathology was studied in *M. yokogawai* (Chai, 1979; Lee et al., 1981; Kang et al., 1983) (Fig. 2.8), *P. summa* (Seo et al., 1986), *H. heterophyes* (Marty and Andersen, 2000), and *C. armatus* (Hong et al., 1997) using experimental animals, including mice, rats, cats, and dogs. The adult flukes of *M. yokogawai* were found to parasitize the middle part of the small intestines; within the crypts of Lieberkühn in early stages of the infection (by day 2 to 3 postinfection), and between the villi in later stages (Chai, 1979; Lee et al., 1981; Kang et al., 1983).

The pathological features were characterized by villous atrophy and crypt hyperplasia, with variable degrees of inflammatory reactions. The infected mucosa showed 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 (Chai and Lee, 2002). In a naturally infected human with *M. yokogawai*, similar intestinal histopathology was reported (Chi et al., 1988). In immunocompetent animals, the location of worms was confined to the intestinal mucosa (Kang et al., 1983; Rho et al., 1984; Jang et al., 1985). However, immunosuppression of mice by prednisolone injection allowed a deeper invasion of the worms into the submucosa (Chai et al., 1995a) (Fig. 2.8). In addition, immunosuppression enhanced the survival of worms and prolonged their life spans in the same mouse strain (Chai et al., 1984b, 1995a). 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 (Yu et al., 1997c). Similar features were also observed in rats and mice experimentally infected with *P. summa*; the middle part of their small intestines was most frequently affected, and like *M. yokogawai*, the worms caused severe villous atrophy and crypt hyperplasia, with inflammation of the villous stroma (Seo et al., 1986). 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 (Hong et al., 1997).

Intestinal histopathology due to *M. yokogawai* infection was normalized at 3 to 4 weeks after the infection (Chai et al., 1995a). Hence, there may be host protective mechanisms against *M. yokogawai* and other heterophyid fluke infections. However, the immunophysiology and pathogenesis of the intestinal pathology and symptoms due to intestinal fluke infections have seldom been studied, in contrast to other intestinal helminth infections including nematode infections such as trichinosis (Castro, 1989). One of the possible immune effectors for the spontaneous recovery of the histopathology includes intestinal intraepithelial lymphocytes that increase remarkably along the villous epithelial layer of infected rats (Chai et al., 1994a). Mucosal mast cells were suggested as another effector responsible for the worm expulsion from infected rats (Chai et al., 1993b). Goblet cells were suggested to be a third effector for the expulsion of worms (Chai and Lee, 2002). However, intensive studies are required to understand the precise roles of mucosal mast cells and goblet cells in the host defense against heterophyid infections. Immunogold studies revealed that the antigenicity of *M. yokogawai* originated from the syncytial tegument, tegumental cell cytoplasms, vitelline cells, and epithelial lamellae of the cecum (Ahn et al., 1991; Rim et al., 1992). A sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE)/immunoblot analysis of crude extracts of the metacercariae showed that out of 14 protein bands found, 11 reacted with infected human sera, and among them 66-kd and 22-kd proteins were the specific antigens (Lee et al., 1993a).

In terms of pathogenicity of heterophyid flukes, it is of interest to note that several species, namely *S. falcatus, Haplorchis* spp., and *Procerovum* spp., can cause erratic parasitism in humans, which is often fatal (Africa et al., 1940). The most frequently affected sites of the erratic parasitism were the heart valve, brain, and spinal cord, where eggs and adult flukes originating from the intestinal mucosa embolized in the blood vessels (Africa et al., 1940). Eggs of *H. heterophyes* (Collomb et al., 1960) and probably of *H. nocens* (under the name *H. heterophyes*) (Zhang and Fan, 1990) were found encapsulated in the brain of patients with nerological symptoms. Presumably such erratic parasitism could occur in immunocompromised patients, rather than immunocompetent individuals. In this respect, it is worthwhile mentioning that *M. yokogawai* worms were found to have invaded the submucosa of the small intestine in the immunosuppressed mice (Chai et al., 1995a). Further studies are required to elucidate the pathogenesis of this erratic parasitism by heterophyid flukes.

Clinical Symptoms, Diagnosis, and Treatment of Heterophyidiases

Clinical symptoms due to intestinal heterophyid infections are generally mild and transient, unless patients are heavily infected (Chai and Lee, 2002) or immunocompromised. In patients with *M. yokogawai* infection, for example, the most frequent symptoms reported are mild to moderate degrees of abdominal pain, diarrhea, lethargy, anorexia, and weight loss (Cho et al., 1984; Seo et al., 1985c). Decreased enzyme activities were also observed in association with diarrhea and malabsorption, which are commonly encountered in acute infections with *M. yokogawai* (Hong et al., 1990b). From a biochemical study on the watery content in the small intestines of dogs experimentally infected with *M. yokogawai*, it was suggested that the watery content might be a result of a poor absorption of the intestinal secretions from the secretory crypt cells (Cho et al., 1985).

The degree of clinical symptoms seems to be related to the individual worm burdens; heavier infection cases tend to suffer from more severe illness. However, the severity of the symptoms may also be related to the susceptibility as well as the degree of acquired immunity of the individual patient. A new visitor to an endemic area, for example, suffered from a severe illness after a primary infection (Chai et al., 1989b). On the other hand, long-term residents in endemic areas generally complained of milder symptoms than those expected (Seo et al., 1985c). Even in the most heavily infected case in the Korean literature, a man who resided in a highly endemic area and harbored as many as 63,587 worms, complained of only minor gastrointestinal trouble—indigestion and epigastric pain (Seo et al., 1985c). Clinical symptoms due to other heterophyid fluke infections were not much different from those seen in *M. yokogawai* infection (Chai et al., 1994b, 1997, 1998a).

The diagnosis can be made by the recovery of heterophyid eggs in fecal examinations, and is expressed using the term *heterophyid fluke infection*, because the eggs of different heterophyid species closely resemble each other (Lee et al., 1984c). The confirmatory diagnosis should be carried out usually after the recovery of adult flukes following anthelmintic treatment and purgation. The specific diagnosis using only eggs is difficult in areas of no previously known endemicity, as well as in endemic areas with mixed heterophyid infections. Close observations and measurements of the heterophyid eggs in the feces are useful for differential diagnosis (Lee et al., 1984c). For example, the eggs of *M. yokogawai* can be differentiated from other heterophyid eggs by their length of 26.9 to 31.6 μm, elliptical shape with length/width ratio of 1.5 to 2.1, clean shell surface, less prominent operculum, no shoulder rims, and dark yellow or brown color (Lee et al., 1984c). The eggs of *M. takahashii* and *M. miyatai* have similar morphology to those of *M. yokogawai*, with the exception of the larger egg sizes of the two former species; hence, the measurement of egg size is essential. The eggs of *H. nocens* are similar to those of *M. yokogawai*, but the former is a little smaller and has slight attenuations at one or both ends (Lee et al., 1984c). The eggs of *H. continua* are broadly oval in shape, and difficult to differentiate from those of

M. yokogawai (Lee et al., 1984c). The eggs of *P. summa* are characteristically small and pyriform in shape (Lee et al., 1984c); they resemble the eggs of *Clonorchis sinensis*, a liver fluke, but lack musk-melon patterns on the shell surface, and shoulder rims around the operculum are inconspicuous. Similarly, eggs of *H. taichui, H. pumilio*, and *H. yokogawai*, closely resemble each other, and need differentiation from eggs of *Opisthorchis viverrini* and lecithodendriid flukes, including *Phaneropsolus bonnei* and *Prosthodendrium molenkampi* (Tesana et al., 1991). There could be false egg-negative cases among the light infection cases with *M. yokogawai*, for example, with less than 100 worms in an infected person. The number of eggs produced per day per worm for *M. yokogawai* was reported to be only 14 to 64 in the human host (Ahn, 1993), so the detectability of eggs in feces from such a case is negligible. Serological tests such as enzyme-linked immunosorbent assay (ELISA) are helpful in false egg-negative cases (Chai et al., 1989b; Cho et al., 1987).

Praziquantel is the drug of choice for all infections by heterophyids. A single oral dose of 10 to 20 mg/kg praziquantel is satisfactory, with a 95% to 100% cure rate for *M. yokogawai* infection (Rim et al., 1978; Lee et al., 1984b). Irradiation of the sweetfish, *Plecoglossus altivelis*, by 200 Gy was highly effective in controlling infectivity of the *M. yokogawai* metacercariae (Chai et al., 1995b). The heterophyid fluke infections could be prevented by the avoidance of eating uncooked fresh water or brackish water fish.

Lecithodendriidae Odhner, 1911

Species Infecting Humans

Phaneropsolus bonnei Lie Kian Joe, 1951 (Fig. 2.10)

This species was first reported from a single human autopsy in Jakarta, Indonesia, and after that from 15 human autopsies in Udornthani Provincial Hospital, Thailand (Manning et al., 1971). This fluke was also discovered in Malaysia and India (Manning et al., 1971). Later, high prevalences of this fluke infection were found in Thailand (Radomyos et al., 1998). In Laos, a total of 366 adult specimens were recovered from four people residing in Mekong riverside areas of Saravane Province (Chai et al., 2005b). Metacercariae were discovered in naiads and adult dragonflies and damselflies in Thailand (Manning and Lertprasert, 1973). Local people in northeast Thailand and Laos are known to eat naiads of these insects (Manning and Lertprasert, 1973; Chai et al., 2005b). The egg morphology is very similar to that of heterophyid fluke and of *Opisthorchis viverrini* (Kaewkes et al., 1991b; Tesana et al., 1991).

Phaneropsolus spinicirrus Kaewkes et al., 1991a

This species was reported from only one human infection in northeast Thailand (Kaewkes et al., 1991a). No further information on this parasite is available.

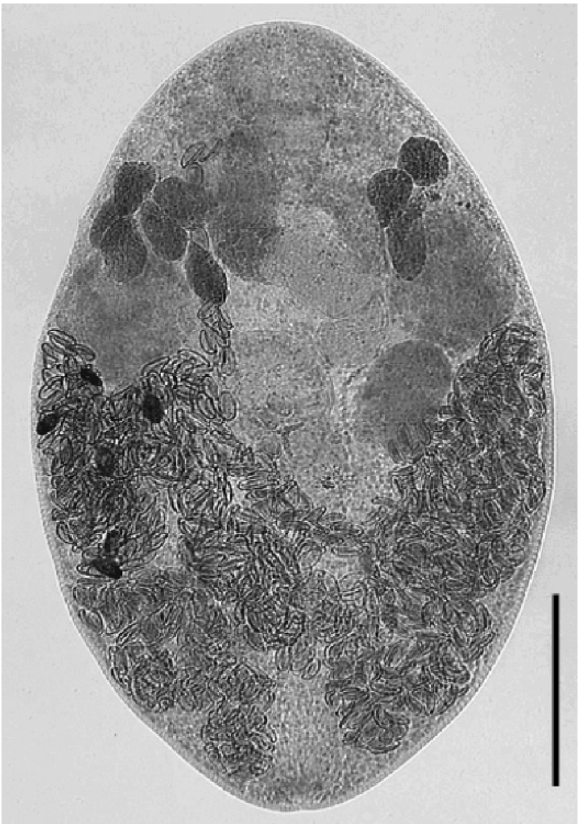

FIGURE 2.10. *Phaneropsolus bonnei* adult recovered from a human infection. Aceto-carmine stain. Scale bar = 0.1 mm.

Prosthodendrium molenkampi Lie Kian Joe, 1951 (Fig. 2.11)

This species was first reported from a single human autopsy at Jakarta, Indonesia, and then from 14 human autopsies in Udornthani Provincial Hospital, Thailand (Manning et al., 1971). Later, high prevalences were reported in Thailand (Radomyos et al., 1998). The prevalence for *P. molenkampi* was 19.4% among 681 small trematode egg–positive individuals (including *Opisthorchis viverrini*) treated with praziquantel and purged in northeast Thailand (Radomyos et al., 1998). In Laos, a total of 502 adult specimens were recovered from 14 infected people residing along the Mekong riverside areas of Vientian Minicipality and Saravane Province (Chai et al., 2005b). Metacercariae of *P. molenkampi* were discovered in naiads and adult dragonflies and damselflies in Thailand (Manning and Lertprasert, 1973). Local people in northeast Thailand and Laos are known to eat naiads of these insects (Manning and Lertprasert, 1973).

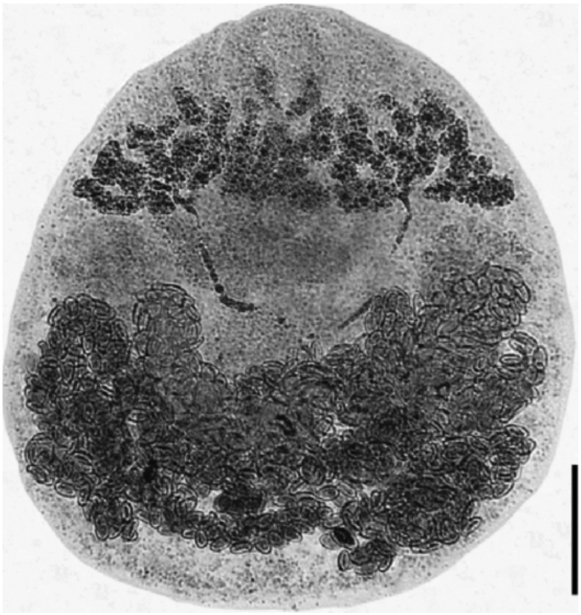

FIGURE 2.11. *Prosthodendrium molenkampi* adult recovered from a human infection. Acetocarmine stain. Scale bar = 0.1 mm.

Microphallidae Travassos, 1920

Species Infecting Humans

Spelotrema brevicaeca (Africa and Garcia, 1935); Tubangui and Africa, 1939

This fluke was originally reported under the name *Heterophyes brevicaeca* from human infections in the Philippines (Africa and Garcia, 1935). Fluke eggs were found in the heart, brain, and spinal cord of persons who died of acute cardiac dilatation (Africa and Garcia, 1935). The metacercariae were found in the crab *Carcinus maenas* and the shrimp *Macrobrachium* sp. in the Philippines (Beaver et al., 1984).

Nanophyetidae Dollfus, 1939

Species Infecting Humans

Nanophyetus salmincola Chapin, 1926, 1927 [syn. *Troglotrema salmincola* Witenberg, 1932]

This fluke infects the intestine of mammals including humans, dogs, cats, raccoons, and fox, and three species of birds in the Pacific coast of North America and Canada, and Eastern Siberia (Millemann and Knapp, 1970; Beaver et al., 1984; Chai et al., 2005a). It has a minute pyriform body, and is characterized by the presence of two large testes in the posterior half of the body. Its snail host is *Oxytrema silicula*, and second intermediate hosts are a wide variety of fish, including salmon, trout, and nonsalmonid fish (Millemann and Knapp, 1970; Yu and Mott, 1994). Nanophyetiasis is endemic in the far-eastern part of Russia including Amur and Ussuri valleys of Khabarovsk territory and north Sakhalin, where the average prevalence is 5% (Yu and Mott, 1994). In local ethnic minorities, the prevalence is higher, 20%, and reaches up to 60% in some localities. In the U.S., 20 human cases were reported after 1974 (Eastburn et al., 1987). People acquire the infection by ingestion of improperly cooked salmon or trout. Infected people may experience diarrhea, abdominal discomfort, and eosinophilia, but the symptoms are generally mild. In animals such as dogs, foxes, and coyotes, however, the fluke has been proven to be the vector of a rickettsia, *Neorickettsia helmintheca*, which causes a serious and often fatal systemic infection known as salmon poisoning. Salmon poisoning has not been reported in humans. A new species, *Nanophyetus schikhobalowi*, was described from natives of far-eastern Siberia by Skrjabin and Podjapolskaja (1931) (Yamaguti, 1958). However, it is regarded as a subspecies, *Nanophyetus salmincola schikhobalowi* (Milleman and Knapp, 1970). Its major difference from *Nanophyetus salmincola* is that *Nanophyetus salmincola schikhobalowi* is apparently not a vector for the rickettsial organism (Milleman and Knapp, 1970).

Neodiplostomidae Shoop, 1989

Species Infecting Humans

Fibricola cratera (Barker and Noll, 1915); Dubois, 1932

This species is a parasite of wild mammals in North America (Shoop, 1989). Frogs are the second intermediate hosts, and snakes are paratenic hosts (Shoop, 1989). An experimental human infection was proved to be successful with recovery of eggs in the feces; the worms lived longer than 3 years in the human (Shoop, 1989).

Neodiplostomum seoulense (Seo et al., 1964); Hong and Shoop, 1995 (Fig. 2.12)

This species was first reported from naturally infected house rats in the Republic of Korea (Seo et al., 1964) and then repeatedly reported from house rats (Seo et al., 1981a, 1988). This parasite is now known to be distributed countrywide in the Republic of Korea, but predominantly in mountainous areas (Seo, 1990). This species has never been reported in other countries (Chai and Lee, 2002), except in a northeastern part of China (Quan et al., 1995). Its characteristic morphology includes a bisegmented body; the tribocytic organ, which is for dissolving the host tissues; two butterfly-shaped testes; and a wide distribution of vitellaria in the anterior body to the level of the ventral sucker (Seo, 1990). The first human infection was found in 1982 in a young man suffering from acute abdominal pain

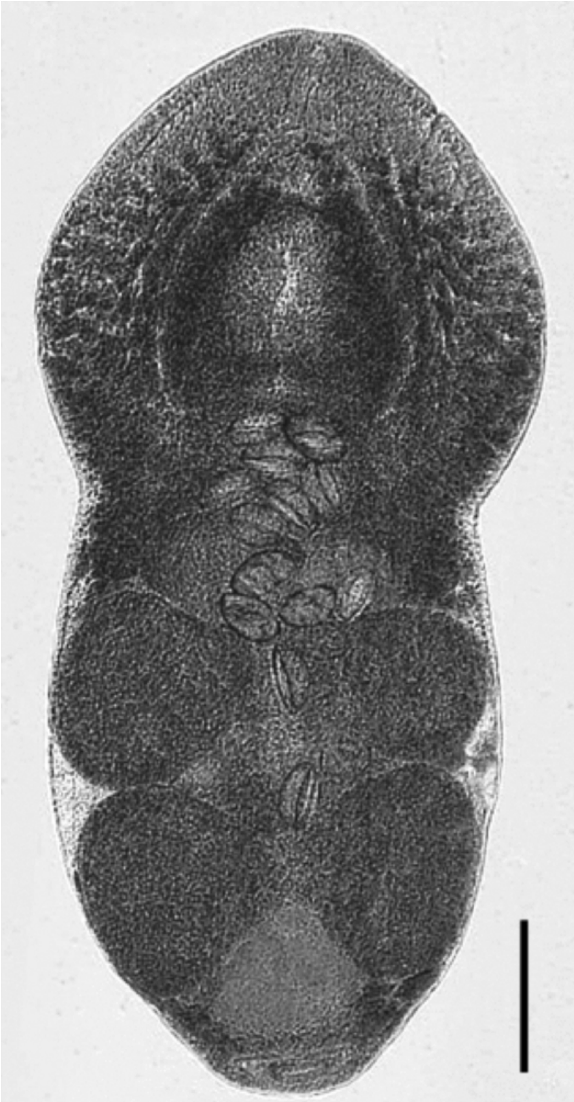

FIGURE 2.12. An adult fluke of *Neodiplostomum seoulense* recovered from an experimentally infected rat. Acetocarmine stain. Scale bar = 0.1 mm.

and fever (Seo et al., 1982). He had a history of consuming improperly cooked snakes 7 days prior to admission to a hospital (Seo et al., 1982). Subsequently, the grass snake *Rhabdophis* (= *Natrix*) *tigrina* was found carrying the metacercariae (Hong et al., 1982). Further, 25 human cases were found among soldiers who had eaten raw snakes during their survival training (Hong et al., 1984, 1986). Later, an egg-positive case was found in a soldier (Huh et al., 1994). Studies on the life cycle revealed that the first intermediate hosts are freshwater snails, *Hippeutis cantori* (Seo et al., 1988) and *Segmentina (Polypylis) hemisphaerula* (Chung et al., 1996); the second intermediate hosts are tadpoles and frogs of *Rana* sp. (Seo et al., 1988). The snake *Rhabdophis tigrina* is regarded as a paratenic host (Seo, 1990). Mice, rats, and guinea pigs have been found to be susceptible laboratory hosts (Seo, 1990).

Pathogenicity and Host–Parasite Relationships of Neodiplostomes

The duodenum is the most favored site of *N. seoulense* in experimental rodents (Seo, 1990). Villous atrophy, crypt hyperplasia, mucosal inflammation, and bleeding are the major histopathological features of the affected mucosa (Lee et al., 1985). The worms entrapped the host villi using their concave ventral curvature of the anterior body, with their tribocytic organs piercing into the villous stroma (Lee et al., 1985). The affected villi underwent severe destruction with hemorrhages, and finally the intestinal mucosa lost its integrity (Lee et al., 1985). The histopathological changes due to *N. seoulense* were more severe compared with those observed in other intestinal trematode infections including *Metagonimus* (Chai, 1979), *Pygidiopsis* (Seo et al., 1986), and *E. hortense* (Lee et al., 1990b) infections.

A unique feature in host–parasite relationships of *N. seoulense* infection is high pathogenicity and lethality to laboratory mice (Huh et al., 1988; Kook et al., 1998). A 100% fatality of experimentally infected mice was observed by day 23 postinfection, with 200 metacercariae per animal (Kook et al., 1998). The whole intestine of the infected mice was severely contracted, and the contraction was irreversible, which was strongly suggestive of an intestinal paralysis (Kook et al., 1998). The fatality of the host animal varied according to genetic backgrounds of the mice (Chai et al., 2000b). The tribocytic organ of *N. seoulense* was suspected to be an important body structure responsible for the host mucosal damage (Huh et al., 1990). In a histochemical study, it was shown that the tribocytic organ, which entrapped and pierced into the host villi, secreted alkaline phosphatases, which could lyse the host villi and help the mucosal invasion of worms (Huh et al., 1990). The secretory function of this organ was explained by demonstrating the presence of microvilli on the surface of the organ (Huh and Song, 1993). The tribocytic organ was shown to contain neutral mucopolysaccharides, and thus the organ is suggested to play a protective role against host digestive enzymes (Huh et al., 1990). 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 (Choi et al., 1999). Other proteases should be purified and their functions be elucidated to understand their roles in eliciting the pathogenicity to the host.

It is interesting to note that the survival of worms in the host intestine was variable depending on the strain of mice (Chai et al., 1998b). BALB/c mice revealed a consistently higher recovery of worms than C3H mice, based on 28 days' observation after an experimental infection. In experimental mice and rats, mucosal mast cells and goblet cells were shown to increase markedly (Chai et al., 1998b; Kho et al., 1990). Despite a suggestion that proliferation of these host cells is a result of local immune response due to the presence of worms (Kho et al., 1990), they may be more or less responsible for the different susceptibility of the different strains of mice. It was speculated that binding of histamine from mast cells to its receptor on intestinal smooth muscles would be more important than the level of histamine alone, or mastocytosis (Shin et al., 2003). Serum and mucosal tissue immunoglobulin A (IgA) were increased after an experimental infection in mice, but the increase was not directly related to the worm expulsion (Huh et al., 1995). Immunogold studies revealed that the tribocytic organ, seminal vesicle, ceca, and vitelline follicles were the major origins of worm antigens (Lee et al., 1997).

Clinical Symptoms, Diagnosis, and Treatment of Neodiplostomiases

In patients infected with *N. seoulense*, acute abdominal pain, diarrhea, lethargy, fever, and weight loss may occur. However, clinical symptoms and signs 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 (Seo et al., 1982). The severity of symptoms may be dependent on the individual worm burdens, as well as on the acquired immunity of each individual. Repeatedly infected patients may complain of milder symptoms than primarily infected patients, as seen in the asymptomatic soldiers infected during survival training (Hong et al., 1984, 1986).

Humans or animals infected with *N. seoulense* can be diagnosed by the recovery of typical eggs in the feces (Seo, 1990). The eggs are ellipsoid to elliptical, thin-shelled, with an inconspicuous operculum, and frequently asymmetrical (Seo, 1990). 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. Praziquantel in a single oral dose of 10 to 20 mg/kg is a highly effective treatment for *N. seoulense* infection (Hong et al., 1984, 1986). For prevention, ingestion of raw or improperly cooked flesh of snakes or frogs should be avoided.

Paramphistomatidae Fischoeder, 1901

Species Infecting Humans

Fischoederius elongatus (Poirier, 1883); Stiles and Goldberger, 1910

This species is a parasite of ruminants infected by ingesting aquatic plants having the metacercariae (Yu and Mott, 1994). The first human infection was reported from Guandong, China (Yu and Mott, 1994). The patient complained of epigastric pain for several months (Yu and Mott, 1994).

Watsonius watsoni (Conyngham, 1904); Stiles and Goldberger, 1910

This species, an aquatic plant-borne trematode, was discovered only once at the autopsy of a West African Negro who died of severe diarrhea (Beaver et al., 1984). Many worms were recovered from the intestine, some attached to the duodenal and jejunal wall, others free in the lumen of the colon (Beaver et al., 1984). Various species of primates are natural hosts of this parasite in eastern Asia and Africa (Beaver et al., 1984).

Plagiorchiidae Ward, 1917

Species Infecting Humans

Plagiorchis harinasutai Radomyos et al., 1989

Four humans infected with this fluke were discovered, and the worm was described as a new species (Radomyos et al., 1989). The life cycle is unknown.

Plagiorchis javensis Sandground, 1940

This species was reported from human infections on several occasions in Indonesia (Sandground, 1940). Larval insects are the source of infection, and birds and bats are reservoir hosts (Yu and Mott, 1994).

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

This species was described in Japan from worms recovered from the small intestines of mice experimentally infected with the metacercariae (Tanabe, 1922a). It has been found in house rats in Japan (Tanabe, 1922a), and rats (Seo et al., 1964, 1981a) and cats (Sohn and Chai, 2005) in the Republic of Korea. Its morphological characteristics include a laterally located ovary, two tandem testes, an extensive distribution of the vitellaria, and large eggs. Experimental human infection has been reported in the U.S. (McMullen, 1937), and natural ones in both Japan (Asada et al., 1962) and the Republic of Korea (Hong et al., 1996b). The molluscan intermediate host in Japan is the freshwater snail, *Lymnaea pervia* (Tanabe, 1922a), and *Stagnicola emarginata angulata* in the U.S. (McMullen, 1937). The snail host in the Republic of Korea is unknown. The second intermediate hosts include a wide range of animals such as aquatic insects (mosquito larvae), insect naiads, fresh water snails, and fresh water fish (Tanabe, 1922a, McMullen, 1937; Hong et al., 1996b; Hong et al., 1999). Albino rats are an experimental definitive host (Hong et al., 1999). The reservoir hosts are unknown.

Plagiorchis philippinensis Sandground, 1940

Adult flukes were recovered at the autopsy of a resident in Manila, the Philippines (Yamaguti, 1958; Yu and Mott, 1994). Infection was acquired by eating insect larvae. Birds and rats are reservoir hosts (Yu and Mott, 1994).

Strigeidae (Railliet, 1919)

Species Infecting Humans

Cotylurus Japonicus (Ishii, 1932)

The first human infection with this fluke was reported from a 13-year-old girl in Hunan Province, China (Chen and Cai, 1985). Ducks were found to be infected with this fluke (Yu and Mott, 1994). The first intermediate hosts are freshwater snails belonging to the genera *Stagnicola, Lymnaea, Physa*, and *Heligsoma*, and cercariae encyst in the same snail hosts to become specialized metacercariae known as tetracotyles (Fried et al., 2004). Infection may occur when birds or mammals ingest tetracotyles in infected snails (Fried et al., 2004).

Summary

A total of 70 species (14 families and 36 genera) of food-borne human intestinal flukes are known around the world. The largest family is the Heterophyidae, which constitutes 29 species in 12 genera (*Apophallus, Ascocotyle, Centrocestus, Cryptocotyle, Haplorchis, Heterophyes, Heterophyopsis, Metagonimus, Procerovum, Pygidiopsis, Stellantchasmus*, and *Stictodora*). The next is the Echinostomatidae, in which 22 species in 10 genera (*Artyfechinostomum, Acanthoparyphium, Echinochasmus, Echinoparyphium, Echinostoma, Episthmium, Euparyphium, Himasthla, Hypoderaeum,* and *Psilorchis*) are involved. The Lecithodendriidae includes three species in two genera (*Phaneropsolus* and *Prosthodendrium*), and the Paramphistomatidae two species in two genera (*Fischoederius* and *Watsonius*). For the other families, one to four species in one genus each is involved; Brachylaimidae (*Brachylaima*) (one species), Cathaemaciidae (*Cathaemacia*) (one species), Fasciolidae (*Fasciolopsis*) (one species), Gastrodiscidae (*Gastrodiscoides*) (one species), Gymnophallidae (*Gymnophalloides*) (one species), Microphallidae (*Spelotrema*) (one species), Nanophyetidae (*Nanophyetus*) (one species), Neodiplostomidae (*Neodiplostomum*) (two species), Plagiorchiidae (*Plagiorchis*) (four species), and Strigeidae (*Cotylurus*) (one species). Among these trematodes, heterophyids and echinostomes are the two major groups, in terms of the number of species involved, the number of people infected, and the distribution of endemic areas. 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 are various species of mammals or birds.The host–parasite relationships have been studied extensively in several species, including *Heterophyes heterophyes, Metagonimus yokogawai, Echinostoma hortense, Echinostoma trivolvis, Fasciolopsis buski, Neodiplostomum seoulense*, and *Gymnophalloides seoi*; however, more information is needed. The pathogenicity of each parasite species and host mucosal defense mechanisms are poorly understood. Clinical aspects of each parasite species need more clarification. Diagnosis of intestinal fluke infections can be done by fecal examination, but differential diagnosis is

difficult because of morphological similarity of eggs. Praziquantel is an effective anthelmintic for most of the intestinal flukes. Epidemiological surveys and detection of further human cases are required for a better understanding of the distribution and endemicity of each trematode species.

TABLE 2.1. Taxonomic classifications of food-borne intestinal flukes.

Family	Genus	Species
Brachylaimidae	*Brachylaima*	*B. cribbi*
Cathaemaciidae	*Cathaemacia*	*C. cabrerai*
Echinostomatidae	*Acanthoparyphium*	*A. tyosenense*
	Artyfechinostomum	*A. malayanum, A. oraoni*
	Echinochasmus	*E. fujianensis, E. japonicus, E. jiufoensis, E. liliputanus, E. perfoliatus*
	Echinoparyphium	*E. recurvatum*
	Echinostoma	*E. angustitestis, E. cinetorchis, E. echinatum, E. hortense, E. ilocanum, E. macrorchis, E. malayanum, E. revolutum*
	Episthmium	*E. caninum*
	Himasthla	*H. muehlensi*
	Hypoderaeum	*H. conoideum*
	Isthmiophora	*I. melis*
	Psilorchis	*P. hominis*
Fasciolidae	*Fasciolopsis*	*F. buski*
Gastrodiscidae	*Gastrodiscoides*	*G. hominis*
Gymnophallidae	*Gymnophalloides*	*G. seoi*
Heterophyidae	*Apophallus*	*A. donicus*
	Ascocotyle	*A. (Phagicola) longa*
	Centrocestus	*C. armatus, C. caninus, C. cuspidatus, C. formosanus, C. kurokawai*
	Cryptocotyle	*C. lingua*
	Haplorchis	*H. pleurolophocerca, H. pumilio, H. taichui, H. vanissimus, H. yokogawai*
	Heterophyes	*H. dispar, H. heterophyes, H. nocens*
	Heterophyopsis	*H. continua*
	Metagonimus	*M. minutus, M. miyatai, M. takahashii, M. yokogawai*
	Procerovum	*P. calderoni, P. varium*
	Pygidiopsis	*P. summa*
	Stellantchasmus	*S. falcatus, S. formosanus, S. pseudocirratus*
	Stictodora	*S. fuscata, S. lari*
Lecithodendriidae	*Phaneropsolus*	*P. bonnei, P. spinicirrus*
	Prosthodendrium	*P. molencampi*
Microphallidae	*Spelotrema*	*S. brevicaeca*

Nanophyetidae	*Nanophyetes*	*N. salmincola*
Neodiplostomidae	*Fibricola*	*F. cratera*
	Neodiplostomum	*N. seoulense*
Paramphistomatidae	*Fischoederius*	*F. elongatus*
	Watsonius	*W. watsoni*
Plagiorchiidae	*Plagiorchis*	*P. harinasutai, P. javensis, P. muris, P. philippinensis,*
Strigeidae	*Cotylurus*	*C. japonicus*

Table 2.2. Fish-borne intestinal flukes.

Parasite species	Source of human or animal infections
Apophallus donicus	Freshwater fiish, blackside dace, sucker, squawfish, redside shiner, rainbow trout, coho salmon
Ascocotyle (Phagicola) longa	Freshwater fish
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 cuspidatus	Freshwater fish, *Astatotilapia desfontainesi*
Centrocestus formosanus	Freshwater fish
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	Unknown
Echinochasmus liliputanus	Freshwater fish, *Pseudorasbora parva,* goldfish
Echinochasmus perfoliatus	Freshwater fish, *Carassius* sp.
Echinostoma angustitestis	Freshwater fish
Echinostoma cinetorchis	Freshwater fish, *Misgurnus anguillicaudatus*
Echinostoma hortense	Freshwater fish, *Misgurnus anguillicaudatus, Misgurnus mizolepis, Odontobutis obscura interrupta, Moroco oxycephalus, Coreoperca kawamebari, Squalidus coreanus*
Episthmium caninum	Freshwater fish
Haplorchis pleurolophocerca	Freshwater fish, *Gambusia affinis*
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, siamensis*
Henichoryhnchus	
Haplorchis vanissimus	Freshwater fish
Haplorchis yokogawai	Freshwater fish, *Mugil* spp., *Puntius* spp., *Misgurnus* sp., *Ophicephalus striatus*
Heterophyes dispar	Brackish water fish
Heterophyes heterophyes	Brackish water fish, *Mugil cephalus, Tilapia nilotica, Aphanius fasciatus, Acanthogobius* sp.
Heterophyes nocens	Brackish water fish, *Mugil* sp., *Acanthogobius* sp.
Heterophyopsis continua	Brackish water fish, *Acanthogobius* sp., *Lateolabrax* sp., *Clupadon punctatus*

(Continued)

TABLE 2.2. *(Continued)*

Parasite species	Source of human or animal infections
Metagonimus minutus	Mullet, *Mugil cephalus*
Metagonimus miyatai	Sweetfish, dace, common fat-minnow *Morocco steindachneri*, pale chub *Zacco platypus*, dark chub *Zacco temmincki*,
Metagonimus takahashii	Crussian carp *C. carassius*, carp *C. carpio*, dace *Tribolodon taczanowskii*, and perch *Lateolabrax japonicus*
Metagonimus yokogawai	Sweetfish *P. altivelis,* dace *Tribolodon* sp., perch *Lateolabrax japonicus*
Nanophyetes salmincola	Freshwater fish, salmon, trout, nonsalmonid fish
Plagiorchis muris	Freshwater fish, various species
Procerovum calderoni	Freshwater fish, *Ophiocephalus striatus, Glossogobius giurus*, *Mollienesia latipinna, Mugil* sp., and *Creisson validus*
Procerodum varium	Mullet *Mugil cephalus*
Pygidiopsis summa	Mullet *Mugil cephalus* and goby *Acanthogobius flavimanus*
Stellantchasmus falcatus	Mullet, half-beaked fish
Stellantchasmus formosanus	Mullet *Mugil cephalus*
Stellantchasmus pseudocirratus	Mullet *Mugil cephalus*
Stictodora fuscata	Goby *Acanthogobius flavimanus*
Stictodora lari	Goby *Acanthogobius flavimanus*, and other estuarine fish

TABLE 2.3. Snail-borne intestinal flukes.

Parasite species	Source of human or animal infections
Acanthoparyphium tyosenense	Bivalve, *Mactra veneriformis, Solen grandis,* gastropod, *Neverita bicolor*
Artyfechinostomum malayanum	Snail, *Digoniostoma pulchella*
Brachylaima cribbi	Helicid land snail, *Cernuella virgata*
Cotylurus japonicus	Freshwater snail, *Stagnicola, Lymnaea, Physa, Heligsoma* spp.
Echinoparyphium recurvatum	Freshwater snail, *Planorbis planorbis, Lymnaea* sp., *Lymnaea stagnalis*
Echinostoma cinetorchis	Freshwater snail, *Radix auricularia coreanus, Physa acuta, Cipangopaludina chinensis malleata*
Echinostoma echinatum	Mussel, *Corbicula lindoensis, Corbicula sucplanta, Idiopoma javanica,* freshwater snail, *Biomphalaria glabrata*
Echinostoma ilocanum	Large snail, *Pila conica, Viviparus javanicus*
Echinostoma macrorchis	Large snail, *Cipangopaludina malleata, Cipangopaludina japonica, Segmentina nitiella, Viviparus malleatus*
Echinostoma malayanum	Large snail, *Pila scutata, Lymnaea (Bullastra) cumingiana*
Echinostoma revolutum	Snail or clam, *Corbicula producta*,
Gymnophalloides seoi	Oyster, *Crassostrea gigas*
Himasthla muehlensi	Clams, *Venus mercenaria,* bivalve mollusk, *Mytilus, Mya* spp.
Hypoderaeum conoideum	Snail
Plagiorchis muris	Freshwater snail

TABLE 2.4. Amphibia, reptile, crustacean, insect, and aquatic plant-borne intestinal flukes.

Parasite species	Source of human or animal infections
Echinoparyphium recurvatum	Tadpole and frog of *Rana temporaria*
Echinostoma macrorchis	Frog of *Rana* sp.
Echinostoma revolutum	Tadpole
Fasciolopsis buski	Aquatic plant, including water caltrop, water cress, water chestnut, and water bamboo
Fibricola cratera	Snake, frog
Fischoederius elongates	Aquatic plant
Gastrodiscoides hominis	Tadpole, frog, crayfish, aquatic plant
Hypoderaeum conoideum	Tadpole
Isthmiophora melis	Tadpole
Neodiplostomum seoulense	Grass snake, *Rhabdophis tigrina*, Tadpole and frog of *Rana nigromaculata*
Phaneropsolus bonnie	Naiad of dragonfly, damselfly
Plagiorchis javensis	Larval insect
Plagiorchis muris	Larval insect, insect naiad
Plagiorchis philippinensis	Insect larva
Prosthodendrium molenkampi	Naiad of dragonfly, damselfly
Spelotrema brevicaeca	Crab *Carcinus maenas,* shrimp *Macrobrachium* sp.
Watsonius watsoni	Aquatic plant

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