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Update on the Human Broad Tapeworm (Genus *Diphyllobothrium*), Including Clinical Relevance

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INTRODUCTION

Tapeworms of the genus *Diphyllobothrium* Cobbold, 1858 (Cestoda: Diphyllobothriidea), commonly called "broad tapeworms" or "fish tapeworms," have been known as intestinal parasites of humans for a long time. Some of the milestones in the history of human diphyllobothriosis are summarized in Table 1.

Diphyllobothriosis Today: Decline or Recrudescence?

In the early 1970s, diphyllobothriosis was estimated to affect 9 million humans globally, with 5 million in Europe, 4 million in Asia, and the rest in America (164). More recent data indicate that 20 million people are infected worldwide (27,

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TABLE 1. Milestones in the history of diphyllobothriosis

Yr	Event	Reference(s)
10000–4000 BC	Earliest evidence of human infection (Peru)	137
4000 BC	Eggs of *Diphyllobothrium* in France and Germany	42, 62, 86
1592 AD	First recognizable description (T. Dunus in Locarno, Switzerland)	158
1747 AD	First recognition of the link between the parasite and fish by H. D. Spöring	127
1758 AD	The species named as *Taenia lata* by C. Linnaeus	90
1819 AD	First scientific description of *D. latum* (as *Bothriocephalus latus*)	24
End of the 19th century	Elucidation of transmission to humans through consumption of infected fish	23, 103, 123
1917 AD	Elucidation of the role of copepods as first intermediate hosts	68

105), but no recent estimation concerning the global prevalence of this parasitosis has been done.

Nevertheless, in the last years, some studies showed a decline of human diphyllobothriosis in several countries, particularly in North America (39, 40, 79), Asia (87, 174), and most of Europe (45; B. Wicht, R. Peduzzi, and J. Dupouy-Camet, unpublished data). The number of human cases in areas where the prevalence of diphyllobothriosis was highest, such as Finland and Alaska, has decreased considerably during the last decades (39, 40).

In contrast, diphyllobothriosis has shown a reemergence in some countries such as Russia (136), South Korea (87), Japan (66, 174), and South America (Brazil) (46, 47, 153). Several cases have also been recently reported from the regions where a disappearance of the disease had been expected, such as Alpine lakes in Switzerland, northern Italy, and eastern France (Haute-Savoie) (see "Europe" below).

Aims of the Review

Although the broad fish tapeworm has been recognized as a human parasite for a long time, many aspects of its biology and epidemiology, including the spectrum of hosts causing human infection, clinical relevance, and present distribution, still remain poorly known. The importance of the disease is empha-

sized by its current recrudescence in some regions of the most developed countries throughout the world. Therefore, an updated overview of the current state of knowledge is presented, with focus on epidemiology (infective sources) of the disease and its reliable diagnosis based on molecular methods. Another aim of the review is to map existing gaps in our understanding of different aspects of diphyllobothriosis to promote future research and attract the attention of public health authorities.

LIFE CYCLE

Egg and Coracidium

Eggs released into the stool are unembryonated and possess an operculum on the narrower end (Fig. 1). The first-stage larva (oncosphere) is covered with a ciliated outer envelope, thus forming a coracidium, which hatches in the water. The motile coracidium swims and attracts potential first intermediate hosts (158).

First Intermediate Host

Approximately 40 species of the genera *Acanthodiaptomus*, *Arctodiaptomus*, *Diaptomus*, *Eudiaptomus*, *Eurytemora*, and
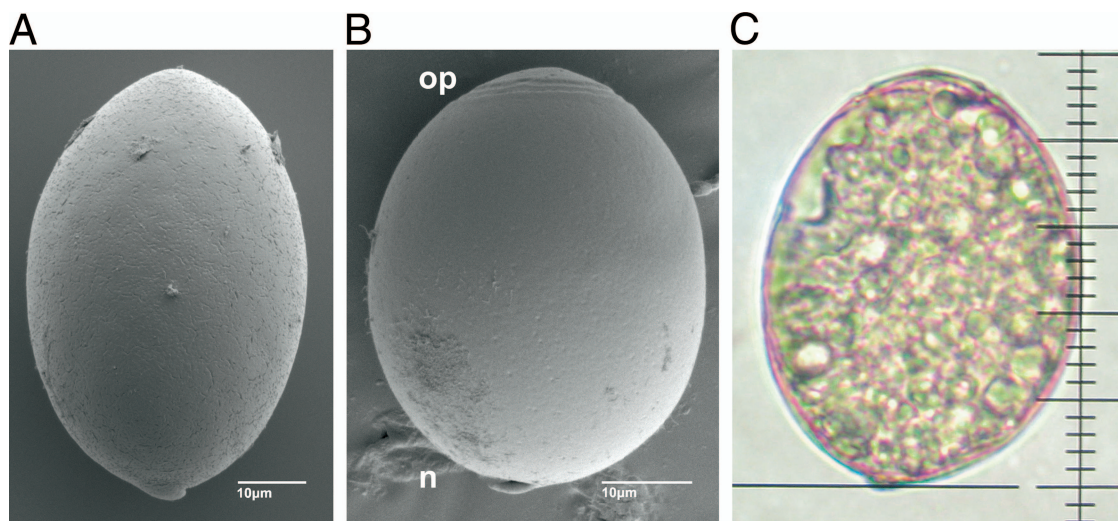

FIG. 1. (A) Egg of *D. latum* from a dog from Russia (scanning electron microscopy photomicrograph). (B) Egg of *D. pacificum* from a man from Lima, Peru (scanning electron microscopy photomicrograph). Abbreviations: op, operculum; n, abopercular knob. (C) Egg of *D. nihonkaiense* from a man from Geneva, Switzerland. One major unit of the ocular micrometer equals 10 μm.
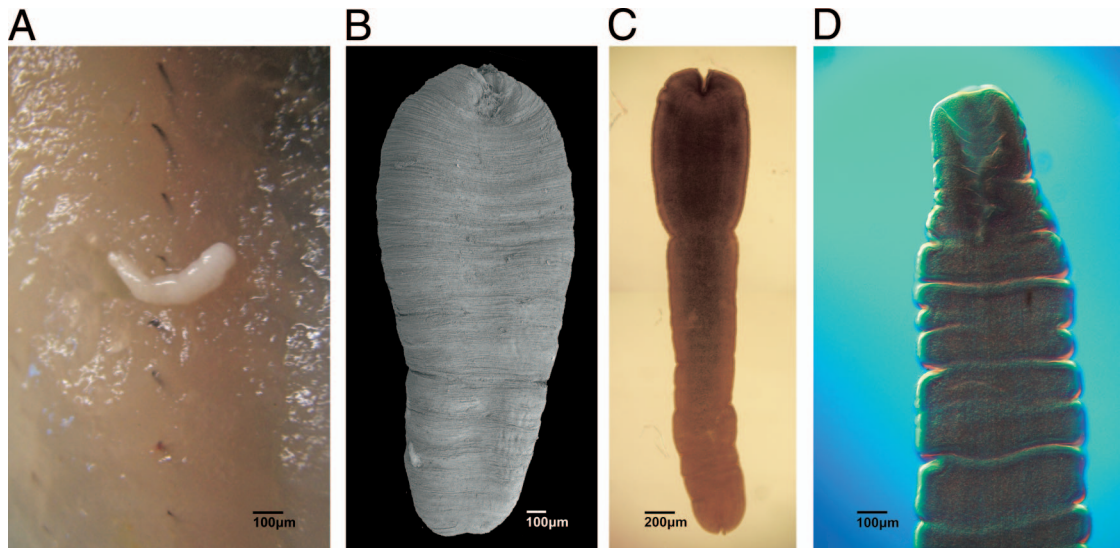
FIG. 2. (A) Plerocercoid of *D. latum* from pike from Como Lake, Italy (plerocercoid in fish musculature). (B) Plerocercoid of *D. latum* from pike from Como Lake, Italy (scanning electron microscopy photomicrograph). (C) Plerocercoid of *D. latum* from pike from Como Lake, Italy. (D) Plerocercoid of *D. dendriticum* from whitefish from Loch Lomond, United Kingdom.

Boeckella (Copepoda: Diaptomidae), *Cyclops*, and probably *Mesocyclops* (Copepoda: Cyclopidae) serve as the first intermediate hosts (48, 97, 157). The coracidium penetrates the intestinal wall of the copepod and develops into the procercoid, which lacks a differentiated anterior end with attachment organs (scolex) but possesses a posterior appendage (cercomer) that contains six embryonic hooks (28).

Second Intermediate Host

Second intermediate hosts include freshwater, anadromous, or marine fish. Through the ingestion of infected copepods, the procercoid enters their tissues and develops into the plerocercoid stage (28). The sites of development may differ according to the fish species, with the larvae being localized in almost any organ and frequently even free in the abdominal cavity. Plerocercoids usually lie unencapsulated in the host tissue (Fig. 2A), but they may be enclosed in connective tissue cysts (40). From the epidemiological point of view, the presence of larvae in muscles, liver, and gonads is of particular importance, but plerocercoids from viscera may migrate to the muscles after the death of the host. In addition, larvae of *Diphyllobothrium dendriticum*, normally encapsulated in the viscera, were also found unencapsulated in the musculature (29, 61).

Major groups of fish that may serve as source of human infection are briefly listed below.

Freshwater Nonsalmonid Fish

Most common intermediate hosts, especially of *D. latum*, are predatory fish such as perch (*Perca fluviatilis*), pike (*Esox lucius*) (Fig. 2A to C), and burbot (*Lota lota*) in Europe and pikeperch or walleye (*Sander canadensis* and *S. vitreus*) in North America (7). The recrudescence of human diphyllobothriosis in the Alpine region corresponds to heavy infection of perch with *D. latum* plerocercoids. For example, in Lake

Geneva, 4 to 10% of perch fillets examined between 2003 and 2005 contained *D. latum* plerocercoids (116). The infection rate of perch in Lake Maggiore reached up to 14% in 2005 and 2006 (167).

Salmonid Fish

Plerocercoids of *Diphyllobothrium* cestodes from salmonids have often been identified as being *D. latum*. However, this identification is questionable, especially in the case of whitefish (*Coregonus* spp.) (171). It is possible that many, if not most, records from salmoniform fish (salmon, trout, and whitefish, etc.) actually belonged to other species. Evidence inferred from molecular data is necessary to confirm previous identifications of plerocercoids from salmoniform fish as being *D. latum*. Pacific salmons such as cherry, pink, chum, and sockeye salmon (*Onchorhychus masou*, *O. gorbuscha*, *O. keta*, and *O. nerka*, respectively) harbor *Diphyllobothrium nihonkaiense* in the northern Pacific Ocean (16, 39, 40, 48, 56, 107, 172, 181).

Whitefish (Coregonidae) do not harbor plerocercoids of *D. latum*, but they are frequently infected with larvae of other *Diphyllobothrium* species, especially *D. dendriticum* (Fig. 2D) and *D. ditremum* (Creplin, 1825) (7, 171).

Brackish-Water and Marine Fish

There are very few reliable data on the occurrence of plerocercoids of *Diphyllobothrium* in brackish-water and marine fish (5, 152). In South Korea, five human cases of "*D. latum*" infection were attributed to the consumption of raw flesh of redlip mullet (*Liza haematocheila*) (33). Common snook (*Centropomus undecimalis*), a marine fish that can enter fresh waters (55), was eaten raw, together with Atlantic salmon (*Salmo salar*) in sushi and sashimi, by patients infected with human broad tapeworms during an outbreak in São Paulo, Brazil (146). Plerocercoids of *Diphylloboth-*
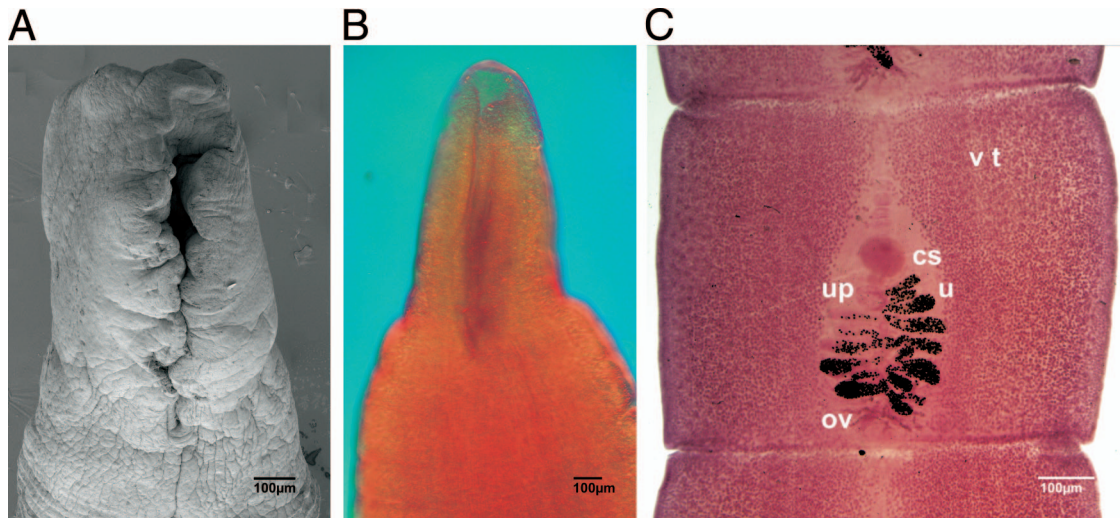
FIG. 3. (A) Scolex of *D. latum* from a dog from Russia (scanning electron microscopy photomicrograph). (B) Scolex of *D. nihonkaiense* from a brown bear from Kamchatka, Russia. (C) Segment of *D. pacificum* from a man from Lima, Peru. Abbreviations: cs, cirrus sac; ov, ovary; t, testes; u, uterus; up, uterine pore; v, vitellaria.

rium pacificum were found in a number of predatory fish (152), which are supposed to be paratenic rather than second intermediate hosts (M. Tantaleán, personal communication). Japanese anchovy or "shirasu" (*Engraulis japonica*) and Japanese sardine (*Sardinops melanostictus*) have been suspected to be the source of human infection with *Diplogonoporus* tapeworms (11, 80).

Definitive Host

Plerocercoids develop rapidly into adults in the definitive hosts' intestine, yielding their first eggs 2 to 6 weeks later (48, 158). Most *Diphyllobothrium* species are characterized by a relatively low specificity at the adult stage, which implies that humans may become infected with parasites normally maturing in carnivore mammals or even in fish-eating birds (25).

MORPHOLOGY AND SPECIES DIVERSITY

Basic Characteristics

Diphyllobothrium tapeworms are among the largest parasites of humans and may grow up to 2 to 15 m in length as adults in the intestine; the maximum length (up to 25 m) was reported for tapeworms with as many as 4,000 segments (158). The growth rate may be as high as 22 cm/day, or almost 1 cm/h (83). These parasites may live up to 20 years or longer; a patient with an infection more than 25 years old was reported by Dogiel (41).

Species of *Diphyllobothrium* are characterized by a scolex with a paired slit-like attachment groove (bothrium) on the dorsal and ventral surfaces, dividing it into two lips or leaves (6) (Fig. 3A and B). A proliferative zone (neck) is usually present posterior to the scolex. The remaining body (strobila) is composed of a high number of segments (proglottids [singular, proglottid]), each containing one set (or, rarely, two sets) of genital organs of both sexes (36) (Fig. 3C and 4A).

Testes are numerous and oval to spherical. The bilobed ovary (germarium) lies in the posterior one-third of each segment. The vitellarium is formed by numerous follicles distributed throughout the segments (Fig. 3C). The vagina and the cirrus sac containing the male copulatory organ, a muscular cirrus, open medially into a common genital atrium on the ventral surface, anterior and median to the uterine pore (82) (Fig. 4B). The uterus is tubular and extends far anterior to the ovary; its outer coils form a rosette that leads to the uterine pore (36). Eggs are operculate (Fig. 1), are unembryonated when laid, and measure 35 to 80 μm in length and 25 to 65 μm in width, depending on the species (36). In fact, there is a large overlap in size among many taxa; host species and intensity of infection may also influence egg size (8).

Taxonomy and Phylogenetic Relationships

Many species in the genus *Diphyllobothrium* have been described since Linnaeus proposed *Taenia lata* as the first representative of this group. The taxonomic composition of the genus has changed many times, as have opinions on the validities of individual species (36, 72, 149). Notwithstanding uncertain systematics of many taxa, it is unquestionable that besides *D. latum*, several other species are implicated in human infections in circumpolar regions and in the Pacific area. A total of 14 out of more than 50 *Diphyllobothrium* species, currently considered to be valid, have been reported from humans (14, 36, 72).

Phylogenetic relationships within the genus are not well known, because DNA sequences of only a few taxa, especially those infecting humans, are available (11, 150, 169). In most analyses, *D. pacificum* and/or *D. stemmacephalum* (type species of the genus) represent the most basal taxa of the genus (12, 22, 81, 150). *Diphyllobothrium nihonkaiense* is the basal taxon to the clade formed by *D. latum*, *D. dendriticum*, and *D. ditremum*, which also contains members of the genera *Ligula* and *Digramma*, the adults of which are parasites of fish-eating birds (44). Such a topology of the cladogram implies that the genus
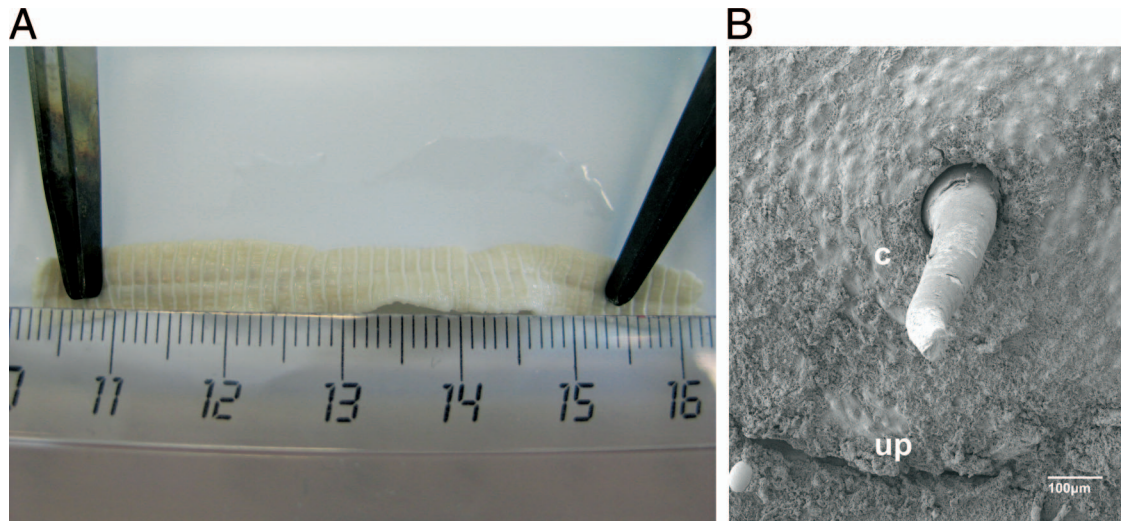
FIG. 4. (A) Strobila of *D. latum* from a man from canton Vaud, Switzerland. (B) Detail of the cirrus and uterine pore of *D. stemmacephalum* from an Atlantic white-sided dolphin from Massachusetts (scanning electron microscopy photomicrograph). Abbreviations: c, cirrus; up, uterine pore.

Diphyllobothrium represents a para- or polyphyletic assemblage of taxa that do not form a monophyletic group (12, 22, 169).

Molecular data also indicate that *Diplogonoporus balanopterae* (Lönnberg, 1891) [synonym, *Diplogonoporus grandis* (Blanchard, 1894)] is a species of *Diphyllobothrium* with doubled genitalia in a segment (11, 12). This human-infecting parasite is therefore included in our review.

Human-Infecting Species

Basic information on the species of *Diphyllobothrium* and *Diplogonoporus* reported for humans is presented in Tables 2, 3, and 4, including the most frequent synonyms to prevent confusions in reporting individual taxa (for an extensive list of syn-

onyms, see references 36 and 72). The species are divided on the basis of their life cycles, i.e., freshwater (the life cycle is completely realized in fresh water), anadromous (salmonids entering from the sea to freshwater), and marine (all the cycle takes place in the sea) (65). For each one, most pertinent papers are mentioned to facilitate the search for more data.

DISTRIBUTION OF HUMAN DISEASE

Diphyllobothriosis is known to occur widely in the world. Since this disease is generally considered to be a mild illness and is not systematically reportable, our understanding of its global distribution is somewhat fragmentary, based on a restricted number of surveys or clinical case reports. Human

TABLE 2. Freshwater species of *Diphyllobothrium*[a]

Species	Definitive host	Second intermediate host	Site of infection	Distribution	References
D. dalliae Rausch, 1956[b]	Dog, Arctic fox, occasionally humans	Alaska blackfish, dolly varden	Body cavity (free)	North America (Alaska)	132, 134
D. dendriticum (Nitzsch, 1824)[c]	Fish-eating birds, especially gulls (Laridae); mammals, including humans	Salmonid and coregonid fish (Salmoniformes)	Usually viscera (free)	Circumpolar (more northerly range than *D. latum*)	9, 30, 134, 158, 166
D. latum (Linnaeus, 1758)[d]	Humans (most suitable), terrestrial mammals	Mainly pike, perch, burbot, char; less frequently ruff, pikeperch, yellow perch	Musculature (free)	Europe, North America (Alaska, Great Lakes), Asia	27, 39, 134, 158

[a] Fish names are as follows: Alaska blackfish, *Dallia pectoralis*; burbot, *Lota lota*; char, *Salvelinus alpinus*; dolly varden, *Salvelinus malma*; perch, *Perca fluviatilis*; pike, *Esox lucius*; pikeperch, *Sander vitreum*; ruff, *Gymnocephalus cernuus*; yellow perch, *Perca flavescens*. Mammal names are as follows: Arctic fox, *Alopex lagopus*; dog, *Canis familiaris*.

[b] This species is a relatively common parasite of humans in western Alaska, where Alaska blackfish is frequently eaten raw or frozen by the Eskimos. Plerocercoids, but no human cases, were also recorded in eastern Siberia.

[c] It is probably the third most frequent causative agent of diphyllobothriosis in humans. The tapeworm is normally parasitic in birds and mammals but is quite frequently found in humans also. Plerocercoids are usually encysted on the viscera, but they were also found in the musculature (29, 39, 158). Synonyms are *Diphyllobothrium fissiceps* (Creplin, 1829); *D. cordiceps* (Leidy, 1872); *D. exile* (Linton, 1892); *Sparganum sebago* Ward, 1910; *D. minus* Cholodkovsky, 1916; *D. canadense* Cooper, 1921; *D. strictum* (Talysin, 1932); *D. obdoriense* Piotnikoff, 1933; *D. nenzi* Petrov, 1938; *D. laruei* Vergeer, 1942; *D. oblongatum* Thomas, 1946; *D. medium* Fahmy, 1954; *D. microcordiceps* Szidat et Soria, 1957; and *D. norvegicum* Vik, 1957.

[d] This is the most frequently found human-infecting species, but almost all cases reported as being caused by *D. latum* from Japan and South Korea, as well as many records from North America, may belong to other species, particularly *D. nihonkaiense* (see references 27, 72, 166, 169, 172, and 174). Records of *D. latum* from South America are questionable and should be confirmed using molecular markers. Synonyms are *Taenia lata* Linnaeus, 1758; *Diphyllobothrium americanum* Hall et Wigdor, 1918; *D. tungussicum* Podyapolskaya et Gnedina, 1932; and *D. skrjabini* Plotnikoff, 1933 (see reference 36 for other synonyms).

TABLE 3. Anadromous species of Diphyllobothrium[a]

Species	Definitive host	Second intermediate host	Site of infection	Distribution	References
D. alascense Rausch et Williamson, 1958[b]	Dog, occasionally humans	Burbot, boreal smelt	Lumen of stomach	North America (Alaska)	2, 65, 133–135
D. nihonkaiense Yamane et al., 1986[c]	Brown bear, humans	Pacific salmons, mainly cherry, pink, and chum salmon; Japanese huchen	Musculature (free or encysted)	Northern Pacific Ocean	4, 10, 12, 72, 169, 172, 174, 181
D. ursi Rausch, 1954[d]	Bears (Ursidae), occasionally humans	Unknown	Stomach (encysted on serous membrane)	North America (Alaska)	65, 131, 134

[a] Fish names are as follows: burbot, Lota lota; boreal smelt, Osmerus mordax; cherry salmon, Oncorhynchus masou; chum salmon, Oncorhynchus keta; Japanese huchen, Hucho perryi; red salmon, Oncorhynchus nerka; pink salmon, Oncorhynchus gorbuscha. Mammal names are as follows: brown bear, Ursus arctos; dog, Canis familiaris.

[b] Plerocercoids are small (0.7 to 1.5 mm long) and are located only in the gastric lumen of burbot; dogs are readily infected after consuming burbot.

[c] D. nihonkaiense Yamane, Kamo, Bylund et Wikgren, 1986. Kamo (73) proposed a reconsideration of the taxonomic status of tapeworms identified as being D. latum from patients in Japan. Yamane et al. (172) showed taxonomic differences between D. latum from Finland and that from Japan and proposed D. nihonkaiense as a new species. The validity of D. nihonkaiense was confirmed by biochemical (57, 59) and molecular (102, 169) differences from D. latum. Human cases had been limited to Japan, but the tapeworm has been recently reported from Canada (British Columbia) (169). Diphyllobothrium klebanovskii Kuratov et Posokhov, 1988, was isolated from the lower Amur River basin in the Russian Far East (72). Synonymy with D. nihonkaiense has been confirmed by molecular data (12).

[d] This species is a common parasite of bears but has also been found in humans. It is a large cestode (up to 11 m long) and differs from D. latum by a larger, more massive scolex. According to Rausch and Hilliard (134), D. ursi may be a junior synonym of D. gondo Yamaguti, 1942.

infections with Diphyllobothrium tapeworms are generally associated with cold waters, because most cases were reported from the Palaearctic region and some parts of North America. However, clinical cases from South America, especially from its Pacific coast, are also known.

Europe

Human diphyllobothriosis is still present in western Europe, but compared with data from previous studies (69, 85, 158), it has shown a marked decrease in the historical Baltic areas of

TABLE 4. Marine species of Diphyllobothrium and Diplogonoporus[a]

Species	Definitive host	Second host	Site of infection	Distribution	Description	Reference(s)
D. cameroni Rausch, 1969	Hawaiian monk seal, occasionally humans	Unknown	Unknown	Pacific Ocean	Human cases in Japan	74, 129
D. cordatum (Leuckart, 1863)	Arctic seals, walruses, occasionally dogs and humans	Unknown	Unknown	Circumpolar	One human case in Greenland	100
D. hians (Diesing, 1850)	Arctic seals, occasionally humans	Unknown	Unknown	Circumpolar	Two human cases in Japan	75
D. lanceolatum (Krabbe, 1865)	Hair seals, occasionally dogs and humans	Sardine cisco	Body cavity (free)	Circumpolar	One human case in Alaska	134
D. orcini Hatsushika et Shirouzu, 1990	Killer whale, occasionally humans	Unknown	Unknown	Pacific Ocean	Two human cases in Japan	64, 77
D. pacificum (Nybelin, 1931)[b]	Sea lions, eared seals; occasionally humans	Marine fish	Musculature	Pacific coast of South America, Japan	—[c]	15, 17, 18, 94, 144, 147, 148, 152, 155
D. scoticum (Rennie et Reid, 1912)	Leopard seal, southern sea lion, occasionally humans	Unknown	Unknown	Circumpolar	One human case in Japan but no scolex	58
D. stemmacephalum Cobbold, 1858[d]	Harbor porpoise, bottle-nosed dolphin; occasionally humans	Unknown	Unknown	Circumpolar		6, 72, 84, 88, 173
Diplogonoporus balaenopterae (Lönnberg, 1891)[e]	Whales, occasionally humans	Probably Japanese anchovy and sardine	Unknown	Circumpolar		11, 32, 49, 71, 72, 80, 130, 177

[a] Fish names are as follows: Japanese anchovy or "shirasu," Engraulis japonica; Japanese sardine, Sardinops melanostictus; sardine cisco, Coregonus sardinella. Marine fish include species of Ariidae, Carangidae, Coryphaenidae, Haemulidae, Merlucciidae, Ophidiidae, Sciaenidae, and Scombridae (152). Mammal names are as follows: bottle-nosed dolphin, Tursiops truncatus; dog, Canis familiaris; harbor porpoise dolphin, Phocoena phocoena; leopard seal, Hydrurga leptonyx; southern sea lion, Otaria byronia; whales, Balaenoptera and Megaptera.

[b] Synonyms are Adenocephalus pacificus Nybelin, 1931; A. septentrionalis Nybelin, 1931; Diphyllobothrium arctocephali Drummond, 1937; D. arctocephalinum Johnston, 1937; D. krotovi Delyamure, 1955; and D. atlanticum Delyamure et Parukhin, 1968.

[c] Most human cases are reported from Peru (but also from Argentina, Chile, Ecuador, and Japan), where humans become infected by eating a local dish called ceviche. The dish is made mainly from "suco" (Paralonchurus peruanus), "lorna" or "cachema" (Sciaena deliciosa), and "corvina" (Cilus gilberti). One patient in Chile was most probably infected after eating smoked "jurel" (Trachurus murphyi).

[d] Type species of the genus. Yamane et al. (173) proposed a new species, D. yonagoense, based on a single specimen found in humans. So far, 20 human cases from Japan and a single case from South Korea have been recognized as being caused by D. yonagoense infection, according to data described previously (72). Synonyms are Diphyllobothrium ponticum Delyamure, 1971, and D. yonagoense Yamane, Kamo, Yazaki, Fukumoto, et Maejima, 1981.

[e] More than 200 cases of human diplogonoporosis are known from Japan, whereas only two human cases have been reported outside Japan (South Korea and Spain). In addition, two other species of Diplogonoporus, namely, D. brauni Leon, 1907, and D. fukuokaensis Kamo et Miyazaki, 1970, have been reported from humans, but they may represent synonyms of D. balaenopterae.

endemicity (Estonia, Latvia, and Lithuania) as well as in Poland, Romania, Sweden, and Norway (Wicht et al., unpublished). In Finland, where the number of human cases was very high (159), human infections with *D. latum* showed a decrease until the 1980s, and the rate is currently about 20 cases/year (128; Wicht et al., unpublished).

Reports of diphyllobothriosis have increased in sub-Alpine areas around the great Swiss, Italian, and French lakes, where raw or undercooked perch (*Perca fluviatilis*) is consumed. More than 200 cases were documented in a survey from 1987 to 2002 (45), and 330 cases were documented from a survey conducted between 2002 and 2007 (Wicht et al., unpublished). An outbreak of diphyllobothriosis in Geneva has recently been reported by Jackson et al. (67). In some countries previously considered to be disease free (Austria, Czech Republic, Belgium, The Netherlands, and Spain), sporadic cases have been reported over the last 6 years, which were presumably linked to the consumption of raw imported fish (Wicht et al., unpublished).

Diphyllobothrium latum has been considered to be the principal species infecting humans in Europe, whereas *D. dendriticum* is present in northern Europe (45). Molecular analyses of samples isolated from clinical cases in Finland, France, and Switzerland indicate the presence of *D. nihonkaiense* locally acquired from imported salmons (124, 169, 179; Wicht et al., unpublished).

North America

The first case of *D. latum* in humans in North America was reported by Nickerson (115), in a child born in Minnesota. Subsequent investigations led to the conclusion that this species was introduced by immigrants from Scandinavian regions of endemicity (96, 163), but there is convincing evidence that infection with *D. latum* is primarily a worldwide zoonosis and that the tapeworm occurred in indigenous people and dogs in North America prior to its colonization (27, 39, 40). Until 1982, diphyllobothriosis was a reportable disease in the United States. The Centers for Disease Control and Prevention (CDC) estimated that about 125 to 200 cases occurred during the period of 1977 to 1981. Most cases occurred in the Great Lakes region, central Canada (Manitoba), and Alaska, although human infections elsewhere have been reported. However, there has been a drastic decline in reports of *D. latum* over the last 100 years (39, 40).

The following species of *Diphyllobothrium* were documented as adults from humans in North America: *D. latum*, *D. dendriticum*, *D. dalliae*, *D. lanceolatum*, *D. ursi*, *D. alascense* (133, 134), and, just recently, *D. nihonkaiense* (169).

South America

The first case of human diphyllobothriosis was documented in Argentina in 1911, in a young Russian immigrant who had just arrived in the country (34). The second case was reported as late as in 1950 from Chile (114) and was attributed to the infection of introduced rainbow trouts (*Oncorhynchus mykiss*) due to water contamination with tapeworm eggs shed by tourists and immigrants from North America.

Diphyllobothrium latum and *D. dendriticum* were supposed to have been brought to South America via European immi-

grants (148). South American diphyllobothriosis caused by *D. pacificum* is an ancient disease, because eggs of this species (morphologically diagnosed) were found in coprolites from 2000 to 3000 BC (138). *Diphyllobothrium pacificum* was first reported from humans in Peru (17), and multiple human cases were then documented in Peru and Chile.

Most human infections caused by *D. pacificum* and, allegedly, *D. latum* have been reported from Chile and Peru, with other cases in Argentina, Brazil, and Ecuador (17, 18, 39, 40, 54, 145–147), including recent outbreaks of diphyllobothriosis in Rio de Janeiro and São Paulo (46, 47, 153).

Asia

Diphyllobothriosis is frequently reported in Japan, especially along the coast of the Sea of Japan, averaging about 100 cases per year since the 1970s (120). In this country, as many as 11 species of human diphyllobothriid cestodes, including *Diplogonoporus grandis*, have been reported (39, 40, 72, 80). Recent taxonomic studies strongly suggest that the majority of human infections are due to *D. nihonkaiense* (39, 40, 172, 174). About 45 human cases of diphyllobothriosis and one case of diplogonoporiasis have also been reported from South Korea (32, 87, 88).

Infections by *Diphyllobothrium* are common in Russia, especially in the Far East, including the Amur River region, where *D. nihonkaiense* (reported as *D. klebanovskii*) is regarded as an important zoonotic species (76, 91, 106–108, 136). The parasite is widespread in all major river basins east of the Urals, including those of Lena, Kolyma, and Indigirka (151). The coastal areas of the Okhotsk Sea, where human prevalence ranges from 1.0 to 3.3% (91), are also endemic foci (12).

Rare clinical cases attributed to different species of *Diphyllobothrium* have been reported from the Middle East, Saudi Arabia, India, Indonesia, Malaysia, Mongolia, and Taiwan (1, 3, 31, 38, 51, 93, 99, 109, 121, 141, 142). However, some cases were probably imported from areas of endemicity such as Japan (3). In addition, species of *Spirometra* that cause sparganosis (105) may have been confused with *Diphyllobothrium* because the genus was synonymized by some authors (149).

Africa and Australia

There are no reliable recent reports on the occurrence of broad fish tapeworms in humans from Africa and Australia.

EPIDEMIOLOGY

Food Risk

Diphyllobothriosis is associated with the ancestral habit of eating raw or poorly cooked fish. This includes the consumption of raw salted or marinated fillets in Baltic or Scandinavian countries, "carpaccio" (very thin slices of raw fish, also called "carpaccio di persico" in northern Italy and "carpaccio d'omble chevalier"); "tartare maison," made with raw salmon; "poisson du lac façon nordique" in French-speaking areas of Europe; and "gefilte fish" (balls of finely chopped fish mixed with crumbs, eggs, and seasonings, cooked in a broth) in Jewish populations. In Latin America, lightly marinated fish known as "ceviche" (or "cebiche") (pieces of raw fish freshly marinated

in lemon and salt) is a common dish (17, 27). In Japan, "sushi" (bite-size pieces of cold cooked rice topped with fish, egg, or vegetables and wrapped in seaweed) and "sashimi" (slices of fresh raw fish) are traditional dishes served with soya sauce for dipping. Among the three major types of sushi, "nigiri," a piece of sliced raw fish fillet on a vinegared rice ball, is the commonest dish (112). Specialties such as sweetish "ayu" and cherry trout, "sakura mad," are still popular in Japan even though they can serve as sources of human infection (70). In developed countries, the popularization of restaurants serving uncooked fish is thought to be responsible for the increase of the number of human cases of fish-borne parasites.

Occupational risks are exemplified by the often high infection rates in fishermen who have the habit of eating roe and liver of their fresh catches and in women who taste foods under preparation that contain raw fish (39, 40). Salmons are probably the most common hosts that transmit diphyllobothriosis, although broad fish tapeworms may also be transmitted by whitefish, trout, pike, and other species (19, 39, 40) (Fig. 2A).

Epidemiological Monitoring

The recent increase of human cases in some regions accentuates the necessity to carry out epidemiological surveys in order to provide reliable data on the actual distribution of diphyllobothriosis within the population. As an example of such a campaign, epidemiological monitoring realized by one of the authors in Switzerland, a country where *D. latum* is considered to be the principal causative agent of diphyllobothriosis, is briefly described.

In the first part of the study, physicians, veterinarians, and medical laboratories were invited to collect samples of *Diphyllobothrium* diagnosed in their routine practice. After standard morphological identification, they were asked to preserve a part of fresh stool samples containing eggs, as well as tapeworm segments, in 96% ethanol for further investigations. When possible, a questionnaire reporting clinical data, type of fish eaten, and cooking habits was completed for each patient. In the successive phase, parasites were analyzed using molecular techniques. The partial nucleotide sequence of the cytochrome *c* oxidase subunit I (cox1 or COI) gene was obtained and compared with reference sequences available in GenBank. The survey allowed us to identify three cases caused by exotic species of *Diphyllobothrium* locally acquired from imported fish (166, 167). According to anamnestic data, the other patients were infected with *D. latum* acquired mainly from perch fished in local lakes.

At the same time, parasitological inspections of fish sold in restaurants, fisheries, and supermarkets in Ticino and Geneva put in evidence the presence of *D. latum* plerocercoids (identified with molecular methods) in 9.5% and 5% of fillets of perch originating from Switzerland, Poland, Estonia, and Russia (170).

Environmental Contamination and Reservoirs of the Parasite

The fecundity (reproductive potential) of *Diphyllobothrium* parasites is extremely high: one worm is estimated to produce up to 1 million eggs per day (158). This implies that the environment can be easily contaminated if basic hygienic or sanitary rules, such as using toilets and effective treatment of sewage waters, are not realized.

The problem of water contamination with tapeworms' eggs is improved by the ability of most *Diphyllobothrium* species to mature in nonhuman hosts. Because of their generally broad host specificity, their life cycles are maintained in nature independently from humans (39, 40). Therefore, dehelminthization of the human population does not necessarily eliminate the parasite from concerned areas. Sylvatic cycles involving bears, foxes, seals, gulls, and other fish-eating birds and mammals probably play a crucial role in water contamination (2, 39, 139, 154). The close contact between dogs, cats, and humans may represent a risk of transmitting zoonotic agents, but some surveys revealed a low infection rate of these hosts (48). For example, coprological examinations of 505 and 296 dogs from Switzerland and Finland, respectively, revealed the presence of *D. latum* in only 0.4% of dogs examined (125, 143).

The high vagility of animals serving as a reservoir of adult tapeworms may result in the dissemination of parasites to new geographical areas similarly to the import of fish intermediate hosts such as Pacific salmons, rainbow trout, or whitefish (167). Sporadic human carriers may also cause a heavy infection load of plerocercoids in fish populations, even in lakes of considerable size (39). Fish are fundamental reservoirs of *Diphyllobothrium* because plerocercoids may survive in their body from several months up to a few years (39, 40).

Well-established, new endemic foci of the disease often originate from population transfers from infected areas due to emigrations and war, etc. In such circumstances, people often retain their dietary habits, which is indispensable for the epidemiological cycle of the disease (39, 158).

DIAGNOSTICS

Importance of Specific Diagnostics

Since human diphyllobothriosis is in most cases mild or asymptomatic, and because patients can be easily treated with praziquantel, the general tendency of physicians and medical laboratories is to identify the parasite only to the genus level. From the clinical point of view, this attitude is, in principle, correct. Species identification in routine laboratories may actually be difficult because procedures involving molecular techniques require trained personnel. Nevertheless, some aspects concerning the importance of species identification deserve to be discussed.

The diagnosis of *Diphyllobothrium* species as well as the detection of their sources for human infection (through anamnestic data) are of great importance with respect to epidemiology. The identification of hosts and parasites at the species level would contribute to a better understanding of the present distribution of different taxa. In light of recent case reports, human infections with exotic (imported) species of *Diphyllobothrium* might be present in a number of countries, being actually underestimated. Imported parasites may also enhance the probability of the appearance of outbreaks even in countries with a high level of medical care (39, 67).

Morphology-Based Diagnostics

Diagnosis of human broad tapeworms is based largely on finding eggs of the typical ovoid shape with an operculum on a narrowed pole and a size of 35 to 80 by 25 to 65 μm or segments with medially situated genital pores (Fig. 1, 3C, and 4B). Morphology-based diagnoses are cheap and relatively easy but in most cases do not enable identification at the species level. Some taxa can be differentiated from one another only on the basis of the shape and size of the scolex, which is usually absent in clinical samples. In addition, after treatment, most samples are not suitable for morphological evaluation and identification because of the damage of tapeworm tissues.

Most cases of diphyllobothriosis are correctly diagnosed at least at the genus level, but there have been misidentifications with flukes (or trematodes [Digenea]), which may also possess operculate eggs of a similar size, or with segments of taenias (Taenia saginata or T. solium) that may have a similar shape (13, 105). Many samples are identified automatically as being D. latum, but D. nihonkaiense and other taxa may be misidentified (39, 87, 169).

Some species can be differentiated on the basis of the shape and size of the embryonic hooks of the oncosphere (95, 175). However, embryonated eggs are not present in fresh stool of definitive hosts, and embryonation requires several days in the water (158).

Morphological identification of plerocercoids in fish is often difficult (98), but a simple key is available for the three main species that are parasitic in the Holarctic fish, namely, D. latum, D. dendriticum, and D. ditremum (7). Plerocercoids differ from each other in the body surface (wrinkled or smooth), the length of microtriches, the retraction of the scolex, and the number of subtegumental longitudinal muscles (7, 9) (Fig. 2B to D). Identification of Diphyllobothrium plerocercoids in marine fish is more problematic (5, 156, 178), and molecular-based diagnostics will be necessary to confirm previous records, including those of D. nihonkaiense from marine fish in Peru (152).

Procercoids in copepods cannot be identified at the species level because of their morphological similarity.

Molecular Diagnosis

Molecular methods have been widely used in diagnoses because of their specificity and the possibility of evaluating a large number of samples in a short time. At present, they represent the most reliable tool to identify clinical samples of Diphyllobothrium at the species level. They can also be applied to determine different ontogenetic stages of parasites such as segments of adult tapeworms and their eggs as well as plerocercoids in fish to trace the origins of sources of human infections.

Restriction fragment length polymorphism with the endonucleases SmaI, HinfI, and HhaI used as species-specific markers enabled D. nihonkaiense and D. latum to be distinguished (102). The sequencing of nuclear and mitochondrial DNAs provided essential data for the identification and the phylogeny of Diphyllobothrium tapeworms. Phylogenetic trees based on sequences of ribosomal genes (18S rRNA and 28S rRNA) and ITS1-5.8S-ITS2 regions have been used to elucidate the rela-

tionships among some taxa (22, 92). However, these data are not useful for the routine discrimination of all Diphyllobothrium species (180). The characterization of the complete mitochondrial genomes of D. latum and D. nihonkaiense provided essential information as to the utility of coding and noncoding regions for the parasite's identification (78, 111, 122). In particular, the cox1 gene sequence appeared to be an appropriate target for species identification of human broad tapeworms mainly because of its higher mutation rate than that of nuclear genes (167, 169, 180).

Samples to be identified with molecular techniques (eggs, larval stages, and adult parasites) should be preserved in pure ethanol, whereas DNA extraction from native fecal samples should be performed immediately. Fixatives containing formalin, widely used for the storage of clinical samples, as well as denatured alcohol should be avoided because they damage DNA. It is possible, in some cases, to amplify short DNA regions from parasites already fixed in such solutions (20, 89).

When molecular analysis (PCR) is made directly from fecal samples, a preliminary concentration of eggs (formol-ether concentration), without the addition of formalin, is suggested to obtain sufficient amounts of DNA (140). Sonication (two to three times for 10 s each at medium intensity) allows the disruption of egg shells and release of their content. Larvae and adult specimens conserved in ethanol should be washed carefully with phosphate-buffered saline before genetic analysis.

DNA extraction can be made either with a commercial kit or with the classic phenol-chloroform method, which seems to yield larger amounts of DNA, especially from small-sized procercoid larvae (165). Eluting DNA in water, instead of in buffers, can be useful in cases of small amounts of DNA because it can be concentrated using a vacuum centrifuge (i.e., SpeedVac; Savant Instruments, Inc.).

The most appropriate targets for the identification of Diphyllobothrium at the species level are the cox1 (21, 166, 180), tRNA^{Pro}, tRNA^{Ile}, tRNA^{Lys}, NADH dehydrogenase subunit 3 (NADH3) (179), and cytochrome b (cob) (Wicht et al., unpublished) genes.

CLINICAL RELEVANCE

Adult tapeworms lie folded in loops of the small intestine of their vertebrate host. Attachment to the intestinal wall usually takes place at the level of the ileum and less commonly in the jejunum or other levels. Rarely, the worms attach in a bile duct (101). Despite the large size of most Diphyllobothrium species and, thus, their mechanical effect on the host, many infections with this parasite are reported to be asymptomatic (70, 101). In about one out of five infections, diarrhea, abdominal pain, or discomfort occurs; other symptoms of diphyllobothriosis may include fatigue, constipation, or pernicious anemia (60, 160) and, sometimes, headache and allergic reactions. Less commonly, massive infections may result in intestinal obstruction, and migrating segments can cause cholecystitis or cholangitis. Other symptoms including pain in the tongue at eating have been associated to diphyllobothriasis.

Prolonged or heavy D. latum infection may cause megaloblastic anemia due to a parasite-mediated dissociation of the vitamin B$_{12}$-intrinsic factor complex within the gut lumen,

TABLE 5. Treatment of diphyllobothriosis

Drug	Presentation	Dose	Description
Niclosamide	500-mg tablets	Adults and older children, 2 g, single oral dose; children under 6 yr old, 50 mg/kg, single oral dose	Hardly available in most countries
Praziquantel	600-mg tablets	5 to 10 mg/kg, single oral dose	Limited availability; it may rarely trigger seizures in individuals with silent cerebral cysticercosis

making B_{12} unavailable to the host (162). Approximately 80% of the B_{12} intake is absorbed by the worm, with a differential absorption rate of 100:1 in relation to the absorption by the host. About 40% of D. latum-infected individuals may show low B_{12} levels, but only 2% or less develop clinical anemia, which is hyperchromic and macrocytic and may be associated with low platelets or low white blood cell counts. Severity of the disease is known to be directly associated with worm burden and by-products produced by tapeworms (60). This deficiency may produce damage to the nervous system, including peripheral neuropathy or central nervous system degenerative lesions. Diphyllobothrium-associated pernicious anemia is rarely reported nowadays (43), and anemia is also rare or nonexistent in the small D. pacificum tapeworm. After successful treatment, B_{12} levels come back to normal ranges in a period of several months.

Although the symptoms are also generally mild, infection by D. nihonkaiense can have a substantial emotional impact on patients and their families, because segments are evacuated over a long period of time. An in-depth study of eight clinical cases has shown that severe clinical symptoms can lead to specialized consultations and expensive complementary analyses, resulting in an average cost of €400 for the management of a single diphyllobothriosis case (37).

Human Diphyllobothrium infection becomes patent (begins to pass eggs in stools) after approximately 15 to 45 days after ingestion of plerocercoid larvae. Typically, the presence of the tapeworm is noted because of the expulsion of chains of segments with the stools (Fig. 4A). The total length of D. latum usually ranges between 3 and 12 m (3,000 to 4,000 segments), and adult parasites may survive for decades in the human host.

CONTROL

The aim of preventive and control measures must be to break the life cycle of the parasite. Theoretically, any point of the life cycle can be attacked. In practice, measures should be focused on the following three principal points: (i) prevention of water contamination (see above), (ii) treatment of people harboring the parasite, and (iii) prevention of transmission of infective larvae from fish to humans.

Sewage treatment plants and the use of sanitary facilities represent the most effective sanitary measures to avoid water contamination (161). Treatment of infected patients and prevention of food risk are discussed in detail in the next section.

Treatment of Infected Persons

Adult tapeworms are easily treated with praziquantel (Table 5). A single oral dose of 25 mg/kg is highly effective against human D. latum infections (26, 63). A lower dose of 10 mg/kg

was effective against human infections with D. pacificum (63, 94) but showed a poor effect against D. latum in experimentally infected golden hamsters (26). Diphyllobothrium nihonkaiense seems to be more sensitive to praziquantel than D. latum and equally or more sensitive to praziquantel than D. pacificum.

Oral administration of a single dose of praziquantel at 5 to 10 mg/kg was reported to be effective and safe for D. nihonkaiense infections, but a single administration of a 25- to 50-mg/kg dose is usually applied (117–119). However, some studies revealed lower effectiveness of this medicament and a low proportion of tapeworms with a detached scolex (80).

Side effects of praziquantel are usually mild and do not require treatment, although they may be more frequent and serious in patients with a heavy worm burden. The following side effects, in order of severity, have been observed: malaise, headache, dizziness, abdominal discomfort with or without nausea, rise in temperature, and, rarely, urticaria (63). Such symptoms can, however, also occur with the infection itself.

Niclosamide (a single dose of 2 g in adults and 1 g in children older than 6 years) is an alternative antihelminthic drug effective for diphyllobothriosis. Side effects are infrequent because it is not absorbed from the gastrointestinal tract. The availability of niclosamide is, however, limited in many countries.

Intraduodenal gastrographin (used for contrast-enhanced intestinal radiographs) has been reported to be efficacious in the treatment of large cestodes including Taenia saginata, T. solium, D. nihonkaiense, D. yonagoense (D. stemmacephalum), and Diplogonoporus grandis (110). The first case of treatment by oral administration of gastrografin (181) resulted in finding the expelled strobila more than 6 m long with the scolex, which was morphologically identical to D. nihonkaiense. However, this method is not considered to be the best choice of therapy because the insertion of the duodenal tube is painful, the therapy is expensive, and fluoroscopic images are needed. On the other hand, the advantage of this method is the discharge of a complete, living worm with the scolex and thus one suitable for species identification (80).

Food Safety

The best prophylaxis is to avoid the consumption of raw, smoked, or pickled fish. Fish should be well cooked; alternatively, freezing for 24 to 48 h at −18°C also prevents the infection. The Fish and Fishery Products Hazards and Controls Guide recommends an internal temperature below −20°C for 7 days or −35°C for 15 h to kill the parasites (52). Based on currently available data, these recommendations may appear stringent because they were developed for parasites that are considered to be the most resistant to freezing (52).

On an individual basis, infections with Diphyllobothrium tapeworms can easily be prevented by eating well-cooked fish

or deep-frozen fish (at least −10°C for 24 h) or by placing the fish in a concentration of brine (12% NaCl) (126). Cooking fish at a temperature of 55°C kills plerocercoid larvae in 5 min (40), whereas freezing at −10°C kills them within 8 to 72 h, depending on the thickness of the fish flesh (53). Eguchi (48) observed that plerocercoids survived for 4 h but died after 12 h at −8°C; all plerocercoids died after 6 h at −10°C. Smoking of fish does not kill the parasite (19).

The U.S. Food and Drug Administration (FDA) suggested that fish intended for raw or semiraw (such as marinated dishes) consumption should be blast frozen to −35°C or below for 15 h or be regularly frozen to −20°C or below for 7 days. Similarly, according to the European Union Hazard Analysis and Critical Control Points, marine fish for raw consumption should be frozen at −20°C for more than 24 h. Salting of fish also results in reduced infectivity, but it may take several days or weeks depending on the size of the fish and the volumes of salt used.

To avoid new outbreaks of human diphyllobothriosis, salmon and other fish should not be eaten raw, at least not until it has been frozen under the conditions discussed above. Salmons are now transported worldwide only on ice, and this is the way fish helminths are usually introduced to new areas and may infect humans anywhere (167, 171, 180). It is therefore necessary to inform consumers about the risks linked to some culinary habits. Inspection of fish sold to the public should also help detect infected species and orientate public health measures, particularly by identifying infected species and areas of endemicity.

CONCLUSIONS AND PERSPECTIVES

Human diphyllobothriosis seems to be generally declining in many areas where it represented an actual medical problem several decades ago. However, this parasitic disease should not be regarded as neglected, because new foci and human infections with exotic species have recently appeared, even in countries with a high standard of medical care. The increasing popularity of eating uncooked or raw fish, uninspected import of Pacific salmon and other fish, as well as global climate changes represent factors that might lead to a rapid and massive recrudescence of diphyllobothriosis in the near future.

Certain projections indicate that the future worldwide demand for fish will increase substantially (50), which may result in more intensive exploitation of the marine environment for food (35). A higher demand for fish may also increase the risk of diphyllobothriosis by increasing the harvesting and the export of products from areas where this zoonotic disease is endemic. Higher risks for urban populations may also arise because of the incentive for exporters to ship fresh (nonfrozen) fish by air to gain a competitive edge in the market (35, 104, 113). Europe and Canada, both still areas where diphyllobothriosis is endemic, supply about one-third of the U.S. demand for seafood (35).

Seemingly unrelated environmental changes may also have unexpected effects on the epidemiology of this zoonosis. It has been suggested that the increase in human infections with *D. pacificum* in northern Chile during the period of 1975 to 2000 was related to the cyclic appearance of El Niño phenomena in the Eastern Pacific, which affected not only fish populations

but also the primary definitive host of this tapeworm, the sea lion (145).

The species-specific identification of clinical samples is not essential for the effective treatment of most human infections by *Diphyllobothrium*. However, it is important from an epidemiological perspective, because there is an urgent need to detect the most important sources of plerocercoids, in particular those of *D. pacificum* and other marine taxa transmitted by yet-unknown sea fish. Molecular methods have been proven to be a powerful tool for the specific identification of causative agents of human disease, but a fast, cheap, and simple molecular-based diagnostic method for the routine laboratory evaluation of clinical samples is still unavailable.

Treatment of human cases does not seem to represent a serious problem at present, unlike a generally low awareness of the infection risk when eating raw or undercooked fish. Better education of all population segments, such as consumers, health professionals, fishermen, and sellers, particularly in the regions under potential risk of infection, is necessary (153). A more rigorous sanitary inspection of fish products before they are transported throughout the globe should also be applied.

Many aspects of the biology, epidemiology, and control of the broad fish tapeworm are still poorly known and require intensive research. However, it is hoped that warning of the potential risk of reemergence of diphyllobothriosis due to changing eating habits, globalization of the food market, and climatic change will help in a more effective control of this parasitic disease on the global scale.

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