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Paiboon Sithithaworn, and Trevor N. Petney ESSENTIALS Liver flukes, otherwise known as trematodes, are leaf-like hermaph- roditic flatworms. In certain parts of the world, the hepatobiliary system of humans is commonly infected by flukes of the genera Clonorchis and Opisthorchis and occasionally by other species
(Table 8.11.2.1). People acquire liver fluke infection by the ingestion of viable metacercariae that are found in second intermediate hosts through raw or partially cooked food, predominately freshwater cyp- rinid fish. These infections are usually diagnosed by finding eggs in the faeces. Unfortunately, eggs of many of these species cannot be differentiated from each other, nor can they be distinguished reli- ably from the eggs of certain intestinal trematodes. In such cases, definitive diagnosis can only be made if adult worms are recovered from the stools after anthelmintic treatment, at surgery, or at autopsy; parasitological texts should be sought for diagnostic details. The dis- eases caused by liver flukes range from asymptomatic, mild disease to fatal bile duct cancer. Currently the drugs of choice for treatment of liver fluke infection are praziquantel and triclabendazole. The medically important liver flukes are the food-borne digenean trem- atodes of which, in recent times, two species have been acknow- ledged and listed as Group 1 carcinogens that cause bile duct/liver cancer, cholangiocarcinoma; namely Opisthorchis vivverini sensu lato (sl; a species complex) and Clonorchis sinensis, which are distributed throughout

Southeast Asia, China, and North Korea, and Opisthorchis felineus, which is distributed in Eastern Europe and Russia and has recently been implicated as causing cholangiocarcinoma. There are two larger trematodes of medical importance, Fasciola hepatica and Fasciola gigantica, which have worldwide distributions and have not been associated with cancer. These are more likely to present with abdominal pain or biliary symptoms and are usually acquired by in- gestion of aquatic plants, such as watercress, to which the infective metacercariae cling. Introduction The major human liver fluke diseases, which still remain neglected tropical diseases, are opisthorchiasis, clonorchiasis, and fascioliasis. They are transmitted by the fish/food-borne trematodes O. viverrini sl and C. sinensis found in continental Southeast Asia, China, and North Korea, and O. felinius, which is found in Eastern Europe and Russia. Currently 45 million people are estimated to be infected with liver flukes in Asia and Europe; 35 million are infected with C. sinen- sis, 10 million with O. viverrini sl and 1.2 million with O. felineus. It has been estimated that 67.3 million people are at risk of infection in Southeast Asia. It is important to note that the northeast of Thailand is the highest incidence world wide of cholangiocarcinoma (CCA) which is induced by O. viverrini sl, with an estimate of between 10 000 and 20 000 deaths caused by CCA each year, predominately among the poor in regions that are resource limited. Individuals with premalignant pathology, i.e. periductal fibrosis, are considered as a high-risk group for CCA. Alarmingly, it has been estimated that 700 million people world- wide are at risk of infection when the three species are considered. O. viverrini sl and C. sinensis have been classified as Group 1 car- cinogens. Moreover, O. felineus is also a significant human pathogen and recent evidence suggests that it may be carcinogenic in ani- mals and humans. The remaining liver flukes, Metorchis species and Dicrosidium, appear to be of medical importance only spor- adically. Importantly, the liver flukes and the diseases they cause, opisthorchiasis and clonorchiasis, as well as CCA, have received limited attention in a clinical/diagnostic context, perhaps due to Table 8.11.2.1 Liver flukes infecting humans Species Geographical distribution Source of infection Clonorchis sinensis Eastern Asia Freshwater fish Dicrocoelium dendriticum Widespread Ants accidentally ingested with food Eurytrema pancreaticum Eastern Asia Grasshoppers Fasciola gigantica Asia, Africa Vegetation, e.g. watercress Fasciola hepatica Widespread Vegetation, e.g. watercress Metorchis conjunctus Canada Freshwater fish Opisthorchis viverrini sl Southeast Asia Freshwater fish Opisthorchis felineus Europe, Asia Freshwater fish Opisthorchis guayaquilaris Ecuador Freshwater fish Opisthorchis noverca India Freshwater fish Opisthorchis lobatus Lao PDR Freshwater fish Acknowledgement: We wish to thank David I. Grove and other past authors of this chapter for the significant contributions to the Oxford Textbook of Medicine.

 their extremely complex life cycles and because they are considered to be a ‘tropical’ local problem. It has been estimated that 17 million people are infected with the two larger human liver flukes, Fasciola hepatica and Fasciola gigan- tica. In a worldwide context including Europe, Africa, the Americas, and Oceania, 91 million people are estimated to be at risk of infec- tion. Fascioliasis, the disease caused by these liver flukes results in serious acute and chronic morbidity. F hepatica and F. gigantica commonly infect domestic ruminants and wildlife. They also infect humans who represent accidental definitive hosts and usually are infected by eating aquatic fresh water plants from areas in which the water is contaminated with the faeces from animals harbouring Fasciola. Liver flukes belong to the subclass Digenea. These have sexual re- production in definitive human and animal hosts and asexual repro- duction in their first intermediate snail hosts. They have complex life cycles involving one or more intermediate hosts and many morpho- logical stages (see next). To date, control of liver

flukes and treatment have been dependent on chemotherapy, with the drug of choice being praziquantel and the most successful drug for Fasciola being triclabendazole. During the past few years efforts have been made to improve sanitation systems and behaviour, and health promotion cam- paigns have been introduced to encourage the cooking of fish involved in the transmission of the opisthorchid liver flukes as important components of control to prevent reinfection. It is im- portant to appreciate that eating habits have cultural, social, and religious significance. As such, individual, village and community health perceptions of the detrimental effect and consequences of 'raw' or 'partially' cooked eating behaviour(s) are difficult to change. However, liver fluke control is a prerequisite for the reduc- tion of CCA. Opisthorchiasis and clonorchiasis Epidemiology Opisthorchis viverrini sl, O. felineus (opisthorchiasis) and Clonorchis sinensis (clonorchiasis) Opisthorchis viverrini sl, Clonorchis sinensis, and O. felineus, are still important public health problems in many endemic areas. For instance, of the estimated 35 million people infected with C. sin- ensis globally, an estimated 15 million people are in China alone. Prevalence and intensity of infection usually increase with age, with initial infections occurring in the early teens. There is a higher prevalence and intensity of infection in males than females. Even though praziquantel is widely available and massive control ef- forts have been made, these liver flukes are still common and are a significant public health problem in many endemic areas. In add- ition to causing hepatobiliary disease, O. viverrini sl and C. sinen- sis are major aetiological agents of bile duct cancer, CCA, which, as stated earlier, is a leading cause of death in northeast Thailand. These three liver fluke species have similar egg morphologies, life cycles and pathogenesis, and distinction between them is usually based on the adult worm morphology. With respect to O. felineus, it is prevalent in animals throughout Europe and it has also been re- ported in people from Italy, eastern Germany, Poland, Kazakhstan, Russia, and the Ukraine, with high prevalences and intensities being reported in Siberia. During the past few years, control efforts in northeast Thailand have resulted in a decreased prevalence of O. viverrini sl infection from 35% in 1981, to 24 to 30% in 1992 and 18.6% in 1994 and 15.7% in 2009. However, some studies examining adult worms post- treatment and viable metacercariae in fish suggested that estimates of prevalence of infection may be influenced by misdiagnosis of minute intestinal fluke infections. O. viverrini sl, and minute intes- tinal fluke infection are common in Lao PDR, having an extensive distribution and a particularly high prevalence of infection in people in the southern region. During the past few years there has been mounting evidence from independent genetic, molecular, biological, and morphological studies that show that O. viverrini is not a single species but that it is species complex containing cryptic and/or morphologically distinct species and defined genetic groups in specific wetlands in Thailand and Loa PDR. Whether the O. viverrini sl species/genetic groups correlate with levels of CCA incidence, infectivity levels in fish and snails, varying levels of pathogenicity, and so on remains to be determined. Dishes of freshwater cyprinid fish that are eaten raw or dishes that contain partially cooked or fermented fish are a well-established dietary tradition of people from Thailand, Lao PDR, Myanmar, Cambodia, and Vietnam. Raw cyprinid fish dishes may contain large numbers of metacercariae and are eaten occasionally, usually with the local alcoholic drink. Partially cooked fermented fish, which is eaten daily in many dishes, may also contain viable metacercariae and serve as a source of infection. Clonorchis sinensis remains prevalent and common in parts of Taiwan, Hong Kong, Vietnam, Macao, and China, even though it has largely been eliminated from Japan and significantly reduced in Korea. Human infection occurs in 24 provinces in China, predom- inately in the south (especially Guangdong and Guangsxi provinces) and the northeast (Henjian). Some Chinese people enjoy eating raw fish dipped in hot

rice porridge, which is a popular dish, and children catch and eat them during play, the latter resulting in an unusual age-related pattern of infection compared to the other two liver fluke species. Life cycle Adult liver flukes are found in the smaller intrahepatic bile ducts of definitive hosts, namely, people, cats, dogs, and other wild and domestic freshwater fish-eating mammals (Fig. 8.11.2.1). Eggs pass down the bile duct of the definitive hosts into faeces and are fully embryonated upon excretion. Those that end up in fresh water can be located and eaten by snails were they hatch into miracidia. Normally, less than 1–2% of snails are infected. Snails are the critical amplifying stage where the miracidia transform into sporocysts and rediae which multiply before becoming free-swimming cercariae. Numerous cercariae are released by snails which swim about until they contact, attach, penetrate, and encyst in susceptible species of second intermediate host, in this case fresh water cyprinid fish, where they form metacercariae, the infective stage. Studies have found a wide variation in metacercarial prevalence (up to 100%) and intensity between seasons and different wetlands, and between different species of fish. Metacercariae are infective to

8.11.2 Liver fluke infections 1553 humans and other mammals if consumed with raw or insufficiently cooked fish. Once eaten, the metacercariae excyst, migrate up the duodenum through the ampulla of Vater and the extrahepatic bil- iary system to the intrahepatic bile ducts, where they mature to adult flat worms (Fig. 8.11.2.2). This occurs in about 1 month and the adult worms can live for many years. For instance, adult worms of C. sinensis might live for up to 40 years. Pathology and pathogenesis In heavily infected cases, liver enlargement and dilated subcapsular bile ducts with thick fibrotic walls can be seen grossly, and microscop- ically. Bile duct pathology is characterized by desquamation of the epi- thelial cells of secondary and tertiary ducts and chronic inflammation with infiltration by lymphocytes, monocytes, eosinophils, and plasma cells. Occasionally, along the bile ducts granulomatous inflammation can be observed around the eggs. At an early stage of infection, epithe- lial hyperplasia may be observed. In severe cases, adenomatous hyper- plasia, and goblet cell metaplasia may occur. The most prominent and significant histological feature of chronic infection is periductal fibrosis, which corresponds to periportal echoes detected by ultrason- ography. There have also been reports of inflammation, necrosis, and atrophy of hepatic cells. Fluke-associated cholecystitis pathology in- volves fibrosis, infiltration of mast cells and eosinophils and mucosal hyperplasia of the gallbladder wall. Perforation of the gallbladder wall is not a common phenomenon in liver fluke infection. Adult worms Adult worms in humans, dog, and cat Cyprinid fish Second intermediate host In water and intermediate hosts Cercaria Redia Sporocyst Miracidium First intermediate host Adult in bile ducts Egg Fig. 8.11.2.1 Life cycle of O.viverrini sl. Fig. 8.11.2.2 Adult O. viverrini sl worms.

section 8 Infectious diseases 1554 and eggs have been found in the nidus of the gallbladder together with intrahepatic stones. (Figs. 8.11.2.3 and 8.11.2.4). Liver fluke mediated tissue damage may be caused by direct mechanical or chemical irritation and/or an immune-mediated re- sponse. The activities of the flukes contribute to biliary ulceration, which can be caused by injury due to the suckers of adult worms during feeding and migrating activities. Chemical irritation can occur via adult worm secretion and excretion of metabolic prod- ucts and wastes from the tegument and excretory openings into the bile, some of which are highly mitogenic to fibroblast, kidney, or biliary cell lines. The long-observed hyperplasia of biliary epi- thelial cells in opisthorchiasis might be caused by these products. Additionally, the fluke excretory-secretory products are known to be highly immunogenic. Marked inflammatory infiltration is as- sociated with excretory and secretory

antigens in the intrahepatic and extrahepatic bile ducts in animals experimentally infected with liver flukes. Direct cytotoxic and mutagenic effects and in- creased cell proliferation may be caused by nitric oxide and other reactive oxygen intermediates produced by inflammatory cells during infection. An increase of 8-nitroguanine (8-NO2-G) and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) is associated with liver fluke infection. This is further enhanced with repeated infection and/or by praziquantel treatment, and is considered to be mutagenic. Highly mutagenic conditions for the chronically pro- liferating bile duct epithelium and enhanced hepatic activation of carcinogens in fibrosis areas may be caused by the increased en- dogenous production of N-nitroso compounds. Independently, or in combination, these conditions provide an ideal environment for cancer development. Clinical features Most infections are asymptomatic and are diagnosed inciden- tally by examination for eggs in the faeces. Chronically infected people usually have few specific signs or symptoms, except for an increased frequency of a palpable liver. Biochemical and haem- atological features are unremarkable, even in people with heavy infections. On the other hand, ultrasonography reveals a high fre- quency of gallbladder enlargement, sludge, gallstones, and poor function in asymptomatic individuals. These are reversed within 10 months of praziquantel treatment if reinfection does not occur. In symptomatic cases of Opisthorchis and Clonorchis, infected in- dividuals generally experience pain in the right upper quadrant and have diarrhoea, loss of appetite, indigestion, and fullness. Severe cases may have general weakness, lassitude, weight loss, ascites, and oedema, while complications can include cholangitis, obstructive jaundice, intra-abdominal mass, cholecystitis and gallbladder or intrahepatic stones (the latter are particularly fre- quent in clonorchiasis). Enhanced susceptibility to CCA is the most important clinical manifestation of liver fluke infection (Fig. 8.11.2.5). In Thailand, case-control studies have shown a fivefold increased risk during infection at any intensity, while heavily infected individuals face a 15-fold risk, which is also reflected geographically. For instance, the population-adjusted frequency of CCA has been found to be six- and tenfold higher in females and males, respectively, in an en- demic province compared to a nonendemic area in Thailand. Even though such a large geographical association has not been reported for C. sinensis infection, accumulating evidence has shown that in- fection by C. sinensis is also strongly associated with CCA. An im-portant and not often reported point for O. felineus is that infection is acute and opisthorchiasis is associated with severe histopatho- logical changes. This is characterized by hepatosplenomegaly, ten- derness, up to 40% eosinophilia, chills, and fever, which occur early in infection and might be due to primary exposure to a large dose of metacercariae. Diagnosis Opisthorchis The traditional method used to diagnose liver fluke infection has been egg counts in faeces, usually using the Kato thick smear method, Stoll’s dilution, or the quantitative formalin ethyl acetate concentration techniques. Moderate to heavy infections are effect- ively detected by the three methods. Comparative studies in low- intensity areas, however, have shown that 70% of infections are detected with a single reading of the concentration and dilution techniques, while the sensitivity of 45% by the Kato technique was markedly lower. Results using Stoll’s dilution technique have shown Fig. 8.11.2.3 Egg of O. viverrini sl. Courtesy of AR Butcher. Fig. 8.11.2.4 Histological section of a gallstone showing masses of degenerate Clonorchis/Opisthorchis eggs.

 a close correlation between worm burden and egg count with an es- timated egg output of 53 per gram of faeces per worm. Egg counts using the Stoll’s technique are generally higher than those of the con- centration technique. Although molecular detection of egg DNA is possible with high specificity, the presence of polymerase chain re- action (PCR) inhibitors may interfere with the PCR method. The eggs of C. sinensis and the Opisthorchis species

cannot be dif- ferentiated. They are all yellow-brown, 25–35 µm long by 12–19 µm wide and have a seated operculum with a small knob at the other end. Furthermore, they are extremely difficult to differentiate from eggs of flukes in the family Heterophyidae (see intestinal trema- tode infections, Chapter 8.11.4), although the latter tend to have a smoother egg shell, a less prominent shoulder at the operculum and the knob may be absent. The diagnosis can only be confirmed by examination of adult flukes. To date, egg detection is commonly used in surveys and treatment programmes. Recently, however, several immunodiagnostic tests have been developed for Opisthorchis and Clonorchis infections. Since parasite-specific antibodies persist for a long after treatment and have potential cross-reactivity to other parasites, serological tests are not routinely used for diagnosis. Recent reports on parasite antigen detection in faeces, as well as urine, provide more sensitive diagnoses for opisthorchiasis and clonorchiasis. Particularly, urine antigen detection provides a considerable practical advantage over conventional faecal examination. Early disease detection: CASCAP—cholangiocarcinoma screening and care programme Recently there have been exciting developments in the early detec- tion of CCA of people at risk of O. viverrini infection, allowing for potentially curative surgery in early stage cancer and thus increasing the life span and quality of life of CCA patients. This has been achieved since the inception in 2014 of the Cholangiocarcinoma Screening and Care Program, CASCAP, at Khon Kaen University, northeast Thailand. CASCAP was developed and instigated because each year up to 20 000 cases of CCA are diagnosed in northeast Thailand. As most patients are first seen during the late stage of the disease, they have a five-year survival of less than 10%. For more than three decades control and prevention programmes have been aimed at primary prevention. These programmes have focused on health education aimed at reducing the consumption of raw, fermented, or partially cooked freshwater cyprinid fish that are likely to be infected with O. viverrini sl. Studies at CASCAP have shown that early detection can significantly increase 5-year survival. Before the inception of CASCAP 4 years ago, there were no strategies in place to increase the screening of the risk group or for early diagnosis of CCA. CASCAP represents a conceptual framework and extensive data base for health policy and strategies so that the opisthorchiasis and CCA problem can be administered and managed in a systematic and effective way. Management and treatment A single dose of praziquantel at 40 mg/kg body weight is an effective treatment against opisthorchiasis and clonorchiasis. It is the regimen used most commonly in large-scale treatment programmes. In China, however, higher doses of 120 mg/kg over 2 days have been reported to be necessary to cure heavy Clonorchis infections. Side effects, including dizziness, vomiting, and abdominal pain, occur frequently, but are transient and rarely severe. Most stop after elim- ination of the adult worms which also usually results in the reduc- tion of most abnormalities of the gallbladder. Results from animal models have shown a relatively high efficacy of artesunate and artemether treatment against C. sinensis compared to O. viverrini sl infection. Recently, high efficacy of tribendimidine has been re- ported where a single dose of 200 mg (age below 14 years) or 400 mg (age above 14 years) resulted in a 99% egg reduction rate, which was equivalent to praziquantel in individuals with opisthorchiasis. Mebendazole (30 mg/kg daily) or albendazole (400 mg twice daily) may be effective if given for several weeks. For O. felineus infections, hexachloroparaxylol (Chloxyle) has also been used extensively, but it may be less effective than praziquantel. For cholangiocarcinoma, surgery or biliary extraction at enteric retrograde cholangiopancreatography (ERCP) may be required in some patients with obstructive jaundice. To improve long-term survival outcome, focus should centre on radical surgical techniques and perioperative care to improve the R0 resection rate and to min- imize postoperative morbidity and mortality along with screening tools to detect early lymph node negative cases. Prevention Prevention of human liver fluke infection can be

facilitated by treatment (to reduce the excretion of eggs), early diagnosis (the de- velopment and introduction of new diagnostic techniques, in ultra- sonography, biomarkers, and so on), sanitation (to prevent eggs from reaching water sources) and health education (to modify people's perception of the health problems associated with the eating of raw (a) (b) (c) Fig. 8.11.2.5 Hilar cholangiocarcinoma: (a) Magnetic resonance cholangiopancreatography (MRCP) image of tumour (b) enteric retrograde cholangiopancreatography (ERCP) image of tumour (c) histological section showing cholangiocarcinoma. Courtesy of M. Silva.

section 8 Infectious diseases 1556 or partially cooked fish). Reduction of metacercarial contamination of fish in the freshwater aquaculture industry can be achieved by the application of Hazard Analysis Critical Control Point principles and procedures. Freezing, irradiation and chemical treatment have also been suggested as treatment of raw fish. Because snails have a wide- spread geographical distribution and are resistant to adverse condi- tions, it is not considered feasible to use molluscicides for control. To have a significant longstanding effect, health education should be designed and delivered in a culturally sensitive manner aimed at modifying behaviour, as well as providing understandable scientific- ally informed information. To date, the large-scale treatment efforts in endemic areas by public health ministries have had an impact on the intensity of all three infections. Fascioliasis Epidemiology: Fasciola hepatica and Fasciola gigantica (Fascioliasis) Eggs of Fasciola are excreted 3–4 months after eating water plants which contain infective metacercariae. The life cycle is completed within 4–6 months and moderate temperates, high humidity, and rainfall favour transmission. The most common infection of people with Fasciola is in villages and larger towns within rural areas, es- pecially sheep- and cattle-buffalo grazing areas. Infection levels are dependent on the frequency of people eating plants (mainly water- cress in Europe, morning glory in Asia) from water bodies contam- inated with animal faeces. In most endemic areas, human infection is relatively rare, even where prevalence among domestic/produc- tion animals is high. Where there have been outbreaks of F. hepatica in households and communities, they are often found to be asso- ciated with native, rather than cultivated, watercress. Of the high proportion of exposed people who become infected, some do not have symptoms, and infection may be the result of contaminated drinking water or cooking utensils. Infection by Fasciola infection is underestimated since eggs are often not detected by faecal examination. Results from community-based studies using improved diagnostic methods have detected areas with very high prevalence and intensity of infection in Bolivia, Peru, and Egypt. The frequent consumption of kjosco (raw water-plant salad) by children tending their grazing animals in the high altitudes of the Bolivian Altiplano region has resulted in heavy infections. Studies have also indicated that infection can occur by drinking water contaminated with floating metacercariae. Infection can also occur by ingesting metacercariae that are attached to the food or kitchen uten- sils which were washed with water contaminated with metacercariae. Life cycle Fascioliasis is due to infection with the sheep liver fluke Fasciola he- patica or with Fasciola gigantica. Adult F. hepatica flukes 20–30 mm by 8–13 mm in size live in the large bile ducts and produce eggs which are passed in the stools. The eggs require a period of 9–15 days for the miracidia to develop and hatch in water at 22–25°C. They can remain viable for up to 9 months if kept moist and cool. The miracidia penetrate the tissues of various species of amphibious snails of the family Lymnaeidae and develop over the following 4 to 5 weeks from sporocyst, rediae, and daughter rediae to cer- cariae. The cercariae emerge from the snails and encyst on a variety of aquatic vegetation to become infective metacercariae. Many mammal species are susceptible to infection; however, sheep and cattle are the most important. Usually people are infected by eating watercress or by drinking water

contaminated with metacercariae. Once eaten, the metacercariae excyst in the duodenum, penetrate the intestinal wall, and subsequently pass into the peritoneal cavity. They then invade the liver capsule and migrate through the hep- atic parenchyma to the bile ducts where they mature in about 3 to 4 months. These liver flukes have a life span of several years. F. gigan- tica is large, attaining a size of 25–75 mm × 12 mm wide. The eggs are difficult to distinguish from those of F. hepatica and the life cycles of the two parasites are similar. Pathology and pathogenesis Fascioliasis is a serious medical condition because of the large size of the liver flukes, which reflect their origin as a flat worm of livestock. They cause considerable mortality in sheep and cattle. They also cause human morbidity which is dependent on the number of liver flukes and the stage of infection. The acute phase of infection oc- curs during migration of the immature liver flukes through the liver. Liver fluke ingestion and destruction of parenchymal tissue, sub- sequent haemorrhage, parasite death, and inflammatory responses which are largely mediated by eosinophils cause severe pathology. Repair mechanisms can result in extensive fibrosis, increased pres- sure atrophy of the liver, and periportal fibrosis. The chronic phase occurs when liver flukes are present in the bile ducts and tends to be less severe. Progressive inflammation (including bile duct prolif- eration, dilatation and fibrosis) is predominantly caused by mech- anical obstruction of the ducts, inflammatory responses, and the activity of proline. The liver flukes excrete proline in large quan- tities which may facilitate movement through the narrow ducts. Anaemia may result from blood loss through bile duct lesions and death caused by haemorrhaging in the bile duct is not common but occurs more frequently in children. Some liver flukes can migrate out of the intestine. If they do not locate in the liver they can form ectopic lesions in many tissues, causing nodules, granulomas, or mi- gration tracts which are often misdiagnosed as malignant tumours or gastric ulcers. During the chronic infection phase of proliferation, dilatation, fibrosis and calcification of the bile ducts and sequelae of partial obstruction may occur. Granulomas and abscesses can form around eggs trapped in the parenchymal tissue. Dead flukes have been detected inside calcified areas of tissue. Eosinophils can infiltrate the gallbladder wall, which may be thickened and oedema- tous with perimuscular fibrosis. Clinical features Fascioliasis can be symptomatic or asymptomatic, with more than 50% of cases subclinical (asymptomatic). Human infection can be classified as acute or chronic based upon clinical and labora- tory findings. Clinical symptoms can include upper abdominal or right costal margin pain and fever. Constitutional symptoms in- clude, urticaria, itching, respiratory symptoms, headache, malaise, weight loss, and night sweats and can occur about 2 months after ingestion of metacercariae and 1–2 months prior to egg excretion. Hepatomegaly, splenomegaly, anaemia, and weakness are signs of the acute infection phase. Studies have revealed eosinophilia (>500/mm3) and leukocytosis (>10 000/mm3) in up to 80% of egg positive cases. For chronic infection beyond the latent phase, clinical symptoms are those of the complications of fascioliasis, for example,

8.11.2 Liver fluke infections 1557 ascending cholangitis, cholelithiasis, cholecystitis, pancreatitis, bil- iary cirrhosis, and hepatic fibrosis. Unlike the Opisthorchis species discussed in the previous sections, Fasciola species (fascioliasis) have not been associated with cancer. Typical fascioliasis is due to the mi- gration of immature worms through Glisson’s capsule and the liver parenchyma on their way to the bile ducts, where they mature and remain as adults (Fig. 8.11.2.6). In some circumstances immature worms reach ectopic destinations which lead to cutaneous or vis- ceral larva migrans, similar to strongyloidiasis and gnathostomiasis. Diagnosis Diagnosis of fascioliasis is usually by detection of eggs during faecal examination, by parasite-specific antibody detection in a variety of immunodiagnostic assays, by radiological methods and by lapar- otomy. To enable effective differential diagnosis and to investigate sources of outbreaks, the dietary history is very

useful. However, examination of faeces for eggs is limited as eggs are not excreted during the invasive stage of infection. This is when many people with severe symptoms present to medical facilities, and frequently eggs are undetectable during the chronic phase. It is uncertain whether the diagnostic techniques are not sensitive for very low egg out- puts in light infections (<100 eggs per gram) or if eggs are not being produced. It is very difficult to differentiate eggs from F. hepatica, F. gigantica, echinostomes, and Fasciolopsis. Additionally, to compli- cate matters, eggs may be passed after eating liver from infected ani- mals, which does not indicate infection. In cases such as these, any positive cases should be re-analysed if liver has been eaten recently. Many immunodiagnostic tests using every available technique have been used for diagnosis, from skin tests to antibody and antigen de- tection assays targeting the somatic and excretory/secretory antigens of adult worms. Most of these methods claim more than 90% sensi- tivity. Problems resulting from cross-reactivity with other trematode infections are avoided through the use of purified specific antigens, cystatin-treated plates or specific antibody subclasses. A Fasciola-specific serologic response develops within 2 to 4 weeks of infection, whereby confirmation of infection can be done 5 to 7 weeks before eggs appear in the faeces. In the chronic phase, positive serology can also be used to detect infection when egg release might be irregular or absent. A significant advantage of immunodiagnostic methods over para- sitological techniques is that they can detect early, prepatent infec- tions. They can also detect infection at chronic stages where there is irregular or no egg output. Unlike other parasitic infections, antibody levels decline rapidly after successful treatment. As a consequence, the assays are likely to detect only active infection and as such serology is likely to revert to negative within a year after successful treatment. Additionally, biochemical and blood cell microscopy techniques can also support diagnosis. Eosinophilia, leukocytosis, and elevated inflammatory markers are frequent in acute infections, whereas an- aemia and/or elevated serum hepatic transaminases, bilirubin, and al- kaline phosphatase are infrequently present during chronic infection. As presentations are not markedly different from hepatobiliary disease of other origin(s), clinical diagnosis can be difficult and fascioliasis might not be considered by clinicians in regions where human infections are uncommon. Studies have shown that lapar- otomy and radiological imaging by ultrasonography, endoscopic retrograde cholangiopancreatography and percutaneous cholangi- ography can be useful for diagnosis as they allow detection of the lesions of acute and chronic fascioliasis and at times eggs (by lapar- otomy) or worms in the hepatobiliary system. Management and treatment The regimen of choice against fascioliasis is a single dose of triclabendazole, 10 mg/kg body weight, as it is active against both immature and adult worms. It has a high cure rate and there are only temporary and mild adverse reactions following treatment. Even at relatively high doses praziquantel has been found to be ineffective against fascioliasis. Efficacy is frequently variable and difficult to as- sess, which arises from different sensitivities of adult and migrating worms, the size and thick tegument of Fasciola, damaged hepatic function and variation in clinical presentation. In the past, bithionol was most often used against fascioliasis with dosages varying form 30–50 mg/kg body weight per day ad- ministered in three divided doses on alternate days for 10–15 days dehydroementine at a dose of 1 mg/kg daily for 10 days, adminis- tered intramuscularly or subcutaneously, has been reported to be successful against acute infection, but moderate to severe side effects have been observed. Additionally, both drugs and multiple courses are often required for successful outcome. Some clinical trials have shown that nitazoxanide is effective; for instance, one study found that 97% of people were free of Fasciola eggs in faeces after 30 days of treatment. However, further studies are required to confirm these results. Depending on when people present, other drugs given be- fore the fasciolicide could be useful in recovery, for instance, pred- nisolone (5–10 mg/day) may alleviate toxaemia. Antibiotics are

frequently administered to treat acute cholangitis due to secondary bacterial infection. Previously, chloroquine was administered be- cause it rapidly relieved symptoms of acute disease but, unfortunately, it does not eradicate Fasciola species. Prevention The eventual control of Fasciola should aim at introducing a stra- tegic treatment or immunization programme for livestock and other
Fig. 8.11.2.6 Fasciola hepatica fluke retrieved by ERCP from bile duct. Courtesy of A. Bailey.

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