KULLIYYAH OF MEDICINE & HEALTH SCIENCES
(Facilitator's copy)

Course	Medical Parasitology
Semester/Year	3/ 2
Topic	Liver & Lung Trematodes
Date	
Time	
Student's Name/ ID	
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Overview

This is the Self-Learning Package (SLP) for Medical Parasitology (MP). The exercise will help students to understand the biology, diagnosis, treatment and prevention and control measures for liver and lung trematodes (flukes).

Liver and lung fluke infections as well as other food-borne trematodiases are underappreciated emerging diseases. Although being important public health problems in some of the most heavily affected areas, they should be carefully observed in regions previously considered as nonendemic. Furthermore, they are also of growing importance for travel clinics in Europe and North America. However, accurate diagnosis and general neglect of these parasitic worm infections still pose problems.
The complex life cycle of these fluke infections and the epidemiology is strongly influenced by social-ecological systems factors. Human and animal infections can result in severe morbidity and, in rarer cases, even death. At present, safe and efficacious drugs against liver and lung fluke infections are available, but there is a pressing need to develop new trematocidal drugs to reduce the dependence on praziquantel and triclabendazole and provide additional options in case of emerging resistance.

Epidemiology

he epidemiology of liver and lung fluke infections, as well as other trematode and nematode infections, is governed by social-ecological contexts. Nutrition-related behavior (ie, consumption of undercooked aquatic products such as freshwater fish, crabs, and water plants) and distribution networks of aquatic foodstuffs that are contaminated with metacercariae play important roles in liver and lung fluke infections. The key risk factor for infection is the consumption of raw, undercooked, or pickled fish, crabs, and other aquatic products that are contaminated with the infectious stages of the parasites (ie, metacercariae).

In Southeast Asia and the Americas, aquatic food dishes are often rooted in local traditions with high ethnic, cultural, and nutritional values. For example, culinary dishes that cause lung fluke infection in the people of the Republic of Korea include raw crab meat spiced with soy sauce (kejang). Liver fluke infections in the People's Republic of China (P.R. China) have been linked to the consumption of raw grass carp dishes and in Thailand and Lao People's Democratic Republic (Lao PDR) to the consumption of freshly prepared uncooked or fermented fish (lab pla, koi pla, pla som, and pla ra). In Peru, alfalfa juice is consumed as a popular herbal medicine, but this habit has also been identified as a risk factor for *Faciola hepatica* infection. Food-borne trematodiases, in general, and liver and lung fluke infections, in particular, are rarely found in Africa, mainly explained by the tradition of cooking fish and other foodstuffs completely.
Although eating habits are deeply rooted in local traditions and thus difficult to influence, the social-ecological systems in many endemic regions have changed over the past decades, which, in turn, also modified the epidemiologic patterns of food-borne trematodiases. For instance, in Asia, the changing demographic and economic situation and modified agricultural production systems and ecosystems, sometimes coupled with disease control and education efforts, resulted in a remarkable shift in the prevalence of paragonimiasis. Children living in poor rural setting who catch and eat raw crustaceans while playing or helping their parents in the fields are still at high risk for infection. However, an increasing number of better off, middle-aged, and usually male city dwellers enjoying delicacies such as freshwater crabs or undercooked meat of wild boars (Sus scrofa leucomystax), which may act as paratenic host for *Paragonimus westermani*, are at risk of infection during their participation at parties, festivals, and recreational visits to the countryside. Similarly, Fu¨ rst et al foreign travelers tasting typical local delicacies during their journeys have been repeatedly diagnosed with liver and lung fluke infections after their return to their nonendemic home countries.

Life Cycle and Transmission

Fasciola spp. infect a broad range of animals and accidentally also humans. Domesticated farm animals (eg, sheep and cattle) are most commonly affected by fascioliasis and act as main mammalian end hosts. However, *Fasciola* spp. can develop in a variety of wild animals (eg, deer, llamas, kangaroos, rabbits, beavers, and rats), which shows the remarkable capability of the parasite to adapt to new hosts. Infections with *Opisthorchis viverrini* and *Clonorchis sinensis* have been reported in pigs, rats, cats, and dogs but mainly occur in humans. Definitive hosts of infections with *Paragonimus* spp. are humans, felids, canids, and small mammals.
In Fig. 2, the life cycle of the liver flukes *C. sinensis* and *F. hepatica* and the lung fluke *P. westermani* are depicted, with detailed accounts provided elsewhere. In brief, adult flukes produce eggs, which are released in the feces (liver flukes) or sputum (lung flukes) (see Fig. 2, A). Large numbers of fertilized eggs are typically released into the environment, so that transmission to new hosts is likely to occur. For example, an adult *F. hepatica* fluke is able to produce as many as 20,000 eggs per day.105 However, egg production is density-dependent, and hence varies according to worm burden. *F. hepatica* eggs are oval with a large size from 130 to 145 mm in length and 70 to 90 mm in width. *P. westermani* eggs range from 80 to 120 mm in length and 45 to 70 mm in width. For comparison, eggs of *C. sinensis* are much smaller and measure only 25 to 35 mm in length and 15 to 17 mm in width.104 Embryonated F hepatica and *P. westermani* eggs release free-swimming miracidia (see Fig. 2, B), which invade the molluscan first intermediate hosts, species of *Lymnaea truncatula* (synonym Galba truncatula) (F hepatica), and Thiaridae and Pleuroceridae *(Paragonimus* spp.) (see Fig. 2, C). *C. sinensis* and *Opisthorchis* spp. eggs are typically ingested by *Bithynia* spp. or *Parafossarulus*. spp snails and miracidia are released directly in the gastrointestinal tract of

the snail. The miracidia multiply asexually within the snail and develop during several weeks into sporocyst, rediae, and cercariae (see Fig. 2, D). For instance, a snail infected with a single *F. hepatica* miracidium is able to produce around 4000 free-swimming cercariae. Released cercariae either encyst on aquatic vegetation, such as watercress (*F. hepatica*), or invade and encyst into the tissues of fish (*C. sinensis*) or shellfish (*Paragonimus.* Spp.) (see Fig. 2, E). Humans and other definitive hosts become infected by ingesting metacercariae through consumption of insufficiently cooked aquatic products or when drinking contaminated water (see Fig. 2, F). After ingestion of the metacercariae, a juvenile worm is released, which migrates to the target organ, matures, and, after reaching sexual maturity, produces eggs (Fig. 3).

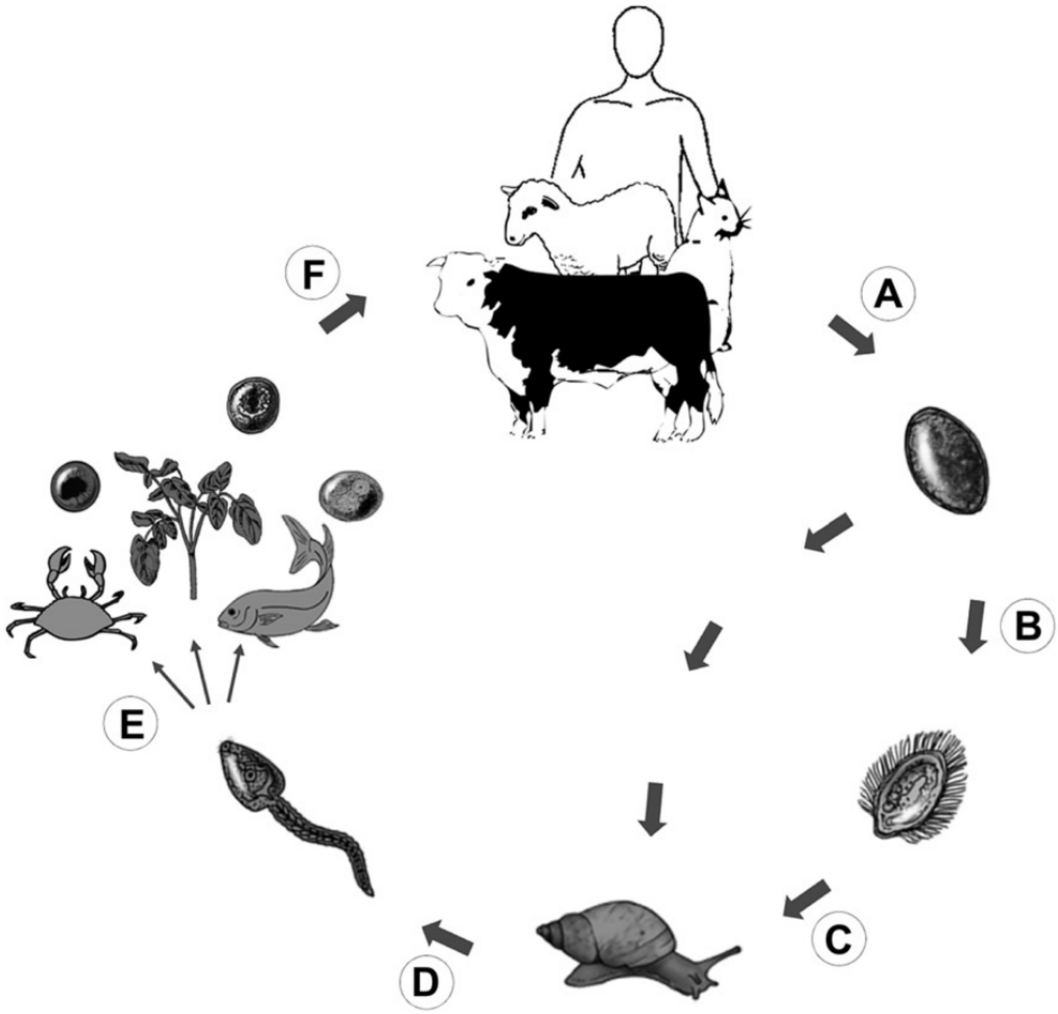

Fig. 2. Life cycle of major liver and lung flukes. (*Adapted from* Keiser J, Utzinger J. Food-borne trematodiases. Clin Microbiol Rev 2009;22:466–83.)

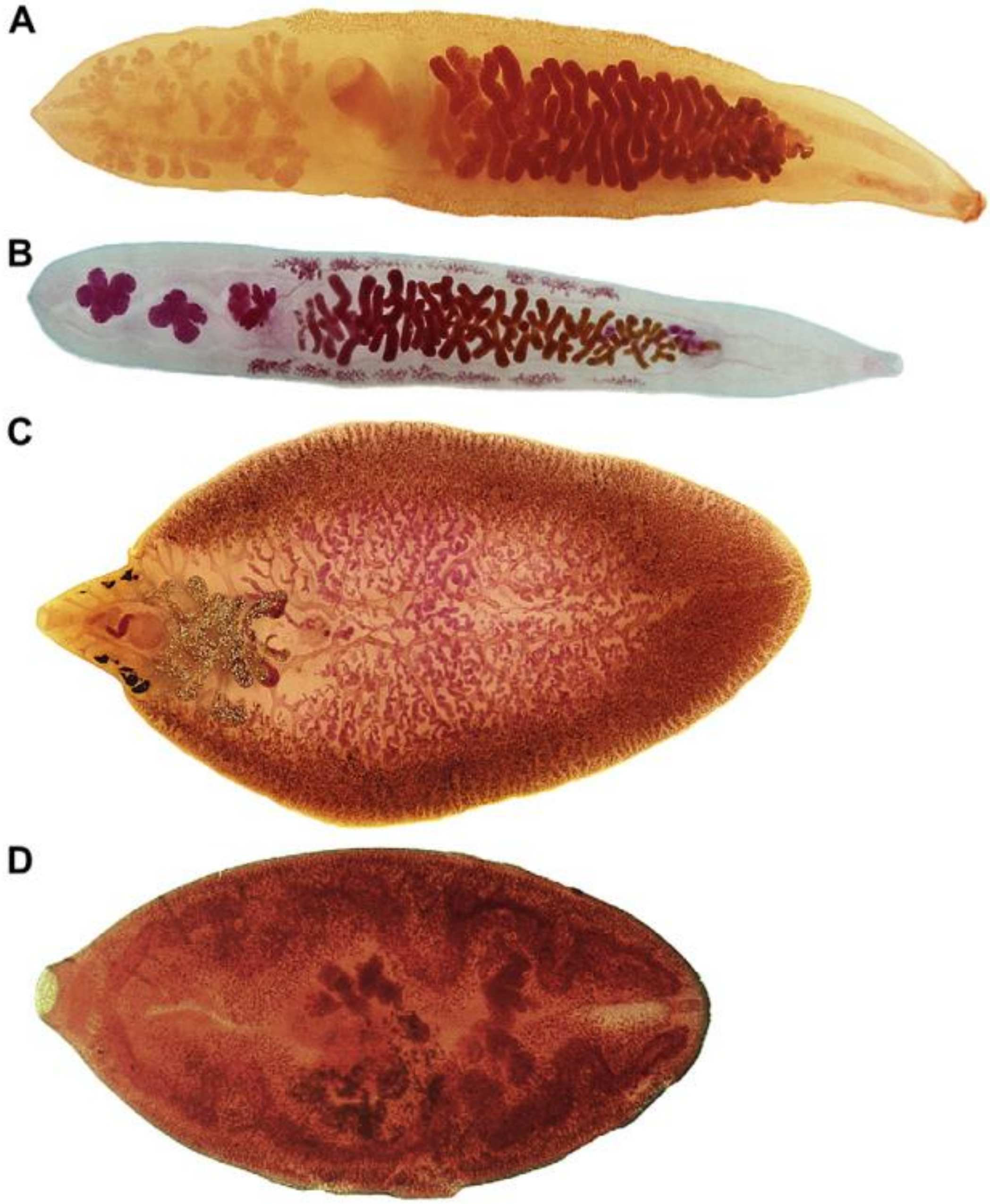

Fig. 3. Photos of major adult liver and lung flukes. (*A*) *Clonorchis sinensis*, (*B*) *Opisthorchis viverrini*, (*C*) *Fasciola hepatica*, and (*D*) *Paragonimus westermani*.

Clinical Signs and Symptoms

Chronic food-borne trematodiases are mainly asymptomatic. Regarding chronic clonorchiasis and opisthorchiasis, only few specific signs and symptoms occur, with the exception of an increased frequency of palpable liver, as revealed by community-based studies on physical examination. Hematological and liver function tests are generally unremarkable, regardless of infection intensity. However, ultrasound examinations show high frequencies of left lobe liver and gallbladder enlargement, sludge and stones in the gallbladder, and poor hepatobiliary function also in asymptomatic cases. Patients with symptomatic clonorchiasis and opisthorchiasis often present with pain in the right upper quadrant, weakness, lassitude, loss of appetite, diarrhea, indigestion, weight loss, ascites, and odema. A particular feature of O felineus infection, not often reported for other liver fluke infections, is acute opisthorchiasis, which is characterized by hepatosplenomegaly and tenderness, high levels of

eosinophilia (up to 40%), and chills and fever. Acute opisthorchiasis occurs early in infection and may be associated with primary exposure to a large dose of metacercaria. Clonorchis and Opisthorchis infection can lead to obstructive jaundice, cholangitis, cholecystitis, intra-abdominal mass, and, particularly in case of clonorchiasis, gallbladder or intrahepatic stones. The most severe complication of Asian liver fluke infection is cholangiocarcinoma.
Human infections with *Fasciola* spp. may proceed symptomatic or asymptomatic. Symptoms usually occur 2 months after the ingestion of metacercariae and 1 to 2 months before the onset of egg excretion. At the beginning of an infection, an acute phase may be caused by migration of the young developing fluke through the intestinal wall and the hepatic parenchyma before finally reaching the bile ducts. Manifestations of this acute phase include upper abdominal pain, prolonged fever, hepatomegaly, mild eosinophilia (early infection) or hypereosinophilia (mid or late acute infection), and multiple hypodense lesions seen on computed tomography (CT) scan. In contrast, ultrasound examinations are mainly unremarkable. Other symptoms included nausea, vomiting, anorexia, weight loss, lymphadenopathies, arthralgias, and cutaneous manifestations. Rarely, *Fasciola* spp. causes ectopic infections in the intestinal wall, lungs, pancreas, eye, brain, stomach wall, pharyngeal mucosa, skin, and other locations.
The chronic phase of human fascioliasis begins after approximately 6 months, may last several years (>10 years), and is asymptomatic in about half of the cases. In symptomatic cases, symptoms are more discrete and reflect intermittent biliary obstruction and inflammation caused by the adult fluke within the bile ducts. Manifestations comprise upper abdominal pain, intermittent jaundice, intrahepatic cystic abscesses with prolonged fever, eosinophilic cholecystitis, and extrahepatic cholestasis with increased levels of liver enzymes, mainly alanine aminotransferase, aspartate aminotransferase, total bilirubin, and g-glutamyl transpeptidase (GGT). In *Fasciola*-endemic areas, an increased level of GGT or alkaline phosphatase is a strong indicator of fascioliasis. In severe cases, ascites with blood and severe anemia may ensue. Because these signs and symptoms do not differentiate cholangitis and cholecystitis from other causes, the infection often goes unnoticed until worms are observed at surgery, after laparoscopic cholecystectomy, or during endoscopic retrograde cholangiopancreatography. Gastrointestinal symptoms may persist even after treatment in about 2–4% of patients. Eosinophilia may be absent in half of the chronic patients, so a normal eosinophil count does not rule out infection.

Clinical manifestations of lung fluke infections show a wide spectrum. In fact, about 20% of patients with paragonimiasis were asymptomatic and identified accidentally by chest radiographic examination during routine health checks. In pulmonary paragonimiasis, the common clinical symptom in the acute and subacute stage of infection is a chronic cough with rusty brown, blood-streaked, gelatinous, pneumonialike sputum caused by the worms wandering in the pleural cavity. Furthermore, paragonimiasis cases may suffer from pleural effusion, pneumothorax, empyema from secondary bacterial infection, and, particularly in case of heavy physical exertion, hemoptysis. Leukocytosis is not prominent and eosinophilia (up to 20–25%) is characteristic in the acute and subacute phase of an infection but may return to normal in the chronic phase. Pleurisy has also been described in infection with *P. miyazakii*, *P. westermani*, and *P. heterotremus*. Because of the similarity of the clinical manifestations, pulmonary paragonimiasis is frequently misdiagnosed as bronchial asthma, chronic bronchitis, bronchiectasis, and pulmonary tuberculosis.
As the liver flukes *Fasciola* spp., the lung flukes *Paragonimus* spp. may also occur in ectopic locations. Patients with extrapulmonary paragonimiasis may present with varying clinical manifestations depending on the exact location of the parasite in the human body. Cutaneous involvement is not uncommon and seen as painless, movable subcutaneous swellings most frequently on the abdomen or anterior chest wall. Immature

worms are frequently found in surgically resected tissues. The subcutaneous manifestation has been reported in infections with *P. skrjabini*, *P. miyazakii*, *P. westermani*, and *P. heterotremus*. *Paragonimus* worms may also migrate into the central nervous system, thereby causing serious conditions and in rare cases even death. The acute phase of central nervous system involvement can be seen as eosinophilic meningoencephalomyelitis. In chronic cases, the disease is characterized by convulsions, often associated with hemiplegia, and/or visual impairment with insidious onset.

Diagnosis

If inhabitants, migrants, or returning travelers from endemic areas present with any combination of the aforementioned, often diffuse clinical manifestations and particularly when they confirm the ingestion of undercooked aquatic food, liver and lung fluke infections should be listed as important differential diagnosis. Various techniques are available for the diagnosis of liver and lung fluke infections and associated disease, such as imaging techniques, detection of parasitic elements under a microscope, and immunologic and molecular methods. However, these techniques differ considerably with regard to their diagnostic accuracy. Imaging techniques, such as ultrasonography or CT, for instance, are used to examine organ damage caused by chronic trematode infection and to monitor evolution and prognosis after treatment. Sensitivity and specificity are frequently insufficient for accurate disease diagnosis.

The most widely used diagnostic approach is based on the direct detection of trematode eggs in biological samples, such as feces or bile aspirates for *C. sinensis*, *Fasciola* spp., and *O. viverrini*, or sputum for Paragonimus spp. Frequently used copromicroscopic techniques include the Kato-Katz method, or sedimentation, flotation, or an ether-concentration method of fixed stool samples. A strength of these methods is that the infection intensity as expressed by the number of parasite eggs per gram of feces can be determined, which allows quantifying treatment outcomes in terms of not only cure rate but also egg reduction rate. However, the sensitivity of these direct diagnostic tests, in particular for low-intensity infections, is frequently insufficient. Hence, multiple stool sampling or the combination of different diagnostic tests should be considered to enhance diagnostic accuracy. Promising results have been obtained with a new multivalent flotation method (FLOTAC), which allows considerably larger amounts of feces to be examined than the Kato-Katz or the McMaster techniques. Indeed, a single FLOTAC showed a considerably higher sensitivity than multiple Kato-Katz thick smears, McMaster, or sedimentation slides, including *F. hepatica* diagnosis.

Treatment

Praziquantel is the only drug available for the treatment of infections with *C. sinensis* and *O. viverrini*. It is also efficacious against infections with *Paragonimus* spp. Albendazole also shows activity against Asian liver flukes when given over a period of several days and at multiple doses. Triclabendazole is an alternative drug used for treating patients infected with *Paragonimus* spp. and standard treatment of patients infected with *Fasciola* spp.

Prevention

Chemotherapy is the current mainstay for morbidity control due to liver and lung fluke infections. However, control programs should be holistically designed and consider the root behavioral, ecological, and social causes of food-borne trematodiases.[1] Truly integrated strategies include setting-specific combinations of control measures, such as information, communication, and education (ICE) campaigns, improved sanitation, and control of intermediate, reservoir and paratenic hosts. The main aim of ICE campaigns is to change human behavior and particularly the dissuasion of people from eating raw or insufficiently cooked aquatic food. Travelers should be alerted that consumption of these food products poses a risk for infection. Improved food processing and food inspections further decrease the risk for human infections. Improved sanitation not only lowers the risk for humans to ingest parasite metacercariae but also helps to avoid that fertilized parasite eggs reach the environment where suitable intermediate hosts proliferate. Considering the wide range of animal intermediate, reservoir, paratenic, and definitive hosts, integrated approaches are the only way to ultimately interrupt disease transmission. Because the aquatic and livestock production sector is also negatively affected by liver and lung fluke infections, these sectors would greatly benefit from the aforementioned interventions.

Topic Learning Outcomes (TLOs)

Students should be able to:

1. Discuss the life-cycle and epidemiology of liver & lung flukes
2. Discuss the pathogenesis of liver & lung flukes
3. Discuss the clinical manifestations and diagnosis of liver & lung flukes
4. Discuss the treatment and prevention of liver & lung flukes

References:

1. Franklin A.N. & Harold W. (1998). **Basic and Clinical Parasitology** (6th Edition) New York Prentice Hall.
2. Viqar, Z., & Loh, A.K. (1996) **Handbook of Medical Parasitology** (3rd Edition).
3. Fürst T, Duthaler U, Sripa B, Utzinger J, Keiser J. **Trematode infections: liver and lung flukes.** Infect Dis Clin North Am. 2012 Jun;26(2):399-419. doi: 10.1016/j.idc.2012.03.008.

Using the references provided and other possible resource materials in the library, answer the following questions.

1. Discuss (compare) life cycle of liver and lung flukes

2. Discuss epidemiology of liver and lung flukes

Faciola hepatica	***Clonorchis sinensis***	***Opisthorchis* spp.**	***Paragonimus westermani***

3. Discuss the pathogenesis of *Faciola hepatica* infection.

4. Discuss the pathogenesis of *Clonorchis sinensis* infection.

5. Discuss the pathogenesis of *Opisthorchis* spp. infection.

6. Discuss the pathogenesis of *Paragonimus westermani* infection.

7. Discuss the clinical manifestations of liver and lung flukes.

Faciola hepatica	***Clonorchis sinensis***	***Opisthorchis* spp.**	***Paragonimus westermani***

8. Discuss the diagnosis of liver and lung flukes.

Faciola hepatica	***Clonorchis sinensis***	***Opisthorchis* spp.**	***Paragonimus westermani***

9. Discuss the treatment of liver and lung flukes.

Faciola hepatica	***Clonorchis sinensis***	***Opisthorchis* spp.**	***Paragonimus westermani***

10. Discuss the prevention of liver and lung flukes.

Faciola hepatica	***Clonorchis sinensis***	***Opisthorchis* spp.**	***Paragonimus westermani***