



**Paragonimiasis and Tuberculosis - Diagnostic Confusion:
 A Review of the Literature**

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SUMMARY

Paragonimiasis and tuberculosis are overlapping public health issues in many countries in the world. The geographical distribution of tuberculosis is global and affects about 1.7 billion persons. In contrast, paragonimiasis is generally accorded little significance on the global health agenda although at least 20 million persons are currently estimated to be infected. These are both pulmonary diseases with similar clinical manifestations, especially haemoptysis. The radiological signs of both diseases are not pathognomonic.

Diagnosis of pulmonary paragonimiasis is confirmed when Paragonimus eggs are detected in the sputum, stool, bronchoscopic washing, biopsy specimens or pleural effusion. Exclusion of tuberculosis is of equal importance and based on the absence of acid fast bacilli in three consecutive sputum smears or, if available, culture for Mycobacteria tuberculosis.

In the major endemic areas of paragonimiasis in Asia (China, Korea, Laos, Philippines, Thailand) Latin America (Ecuador and Peru) and Africa (Cameroon and Nigeria) tuberculosis should always be excluded in suspect cases by three consecutive acid fast sputum examinations.

* * *

1. Introduction

Paragonimiasis and tuberculosis are overlapping public health issues in many countries in the world. Tuberculosis is a dramatic current public health problem due to years of neglect, its long association with poverty and more recently, with AIDS (acquired immunodeficiency syndrome) and drug resistance. In contrast, paragonimiasis is generally accorded little significance on the global health agenda although at least 20 million persons are currently estimated to be infected. Its focal geographical distribution is closely related to cultural habits of different ethnic groups who eat raw crabs and crayfish. Increased reporting of this disease

in Europe and the Americas has been attributed to changes in migration patterns, refugee movements and tourism. In contrast to the focal distribution of paragonimiasis, the geographical distribution of tuberculosis is global and affects about 1.7 billion persons.

The literature on the overlap between paragonimiasis and tuberculosis is reviewed herein and guidelines are suggested to ensure adequate public health policies and correct diagnosis in areas where both diseases may coexist.

2. Paragonimiasis

2.1 Historical

The genus Paragonimus, family Troglotrematidae, is the cause of paragonimiasis - also known as lung fluke disease, pulmonary distomiasis, endemic haemoptysis and parasitic haemoptysis^(1,2).

In 1828, Natterer observed Paragonimus rudis in the lungs of a giant otter- Lustra brasiliensis in Brazil. The same flukes were also described

by Diesing in 1850, and initially under the name Distomum rude. The type specimens of these flukes were redescribed by Braun in 1901 as Paragonimus rudis. Paragonimus rudis has not been found again, thus it is regarded as a "nomen nudum"^(68, 127).

In 1878 Kerbert⁽⁶²⁾ observed adult flukes in the lungs of a tiger and classified it as a new species Distoma westermani. Subsequently, the eggs of Paragonimus westermani were found in sputum from man independently in Japan by Baelz and in Formosa by Manson in 1880. Manson had been previously informed by Ringer that the adult fluke was observed in the lung of a patient at autopsy in 1879 and after comparative examination of the eggs taken from one of Ringer's adult specimens (courteously temporarily named Distoma ringeri by Manson) with those from his patient, he confirmed their association. Both Baelz⁽⁸⁾ and Manson⁽⁶⁴⁾ ascribed the etiology of human endemic haemoptysis in 1880 to this parasite. Since then, paragonimiasis has been known as a respiratory disease that was often confused with tuberculosis⁽¹³⁸⁾.

2.2 Life cycle

The life cycle of this parasite was elucidated by the experimental studies of Yokogawa in 1915⁽¹³⁹⁾ and of Nakagawa in 1916⁽⁷⁸⁾. Forty eight species/subspecies of Paragonimus have already been reported, and at least eleven different species are known to cause the disease in man^(113, 132). All species that infect people have similar life cycles, which require two intermediate hosts- a freshwater snail and a freshwater crab or crayfish^(34, 113). The most common route of infection occurs by the ingestion of raw or partially cooked freshwater crabs or crayfishes that contain the encysted stage of the parasite, the metacercariae.

After the ingestion of metacercariae by the definitive host, excystation occurs in the duodenum. The larvae penetrate through the intestinal wall into the abdominal cavity. The majority migrate through the peritoneal cavity, penetrate the diaphragm, and the lung surface and localize near the terminal alveoli or under the pleura⁽⁹⁵⁾, to mature to adulthood.

These flukes are hermaphroditic, so a single adult is able to produce fertilized eggs. The eggs are excreted either by expectoration in the sputum, or more commonly swallowed, and later excreted in the faeces.

Reaching freshwater, the eggs embryonate and usually hatch within 16-20 days. The swimming larvae, the miracidia, must enter a suitable snail which is the first intermediate host. There are 40 species of snails reported as the first intermediate hosts of Paragonimus. Within the snail, the development to the cercarial stage takes approximately 3 months. The cercariae emerge from the snail⁽⁸¹⁾ and become free-living organisms for a brief period, until their penetration into the second intermediate host, one of the various species of freshwater crabs and crayfish where they encyst and transform into metacercariae. 53 species of crustacea in 21 genera^(132, 142) have been reported to be second intermediate hosts of Paragonimus. Rats, wild boars, pigs and chickens are unusual paratenic (capable of transmitting larval stages of the adult parasite to another host) of Paragonimus westermani.

2.3 Clinical aspects

The clinical literature in pulmonary paragonimiasis is consistent, since the first observations of Baelz and Manson:

- a. Cough and haemoptysis are the most common symptoms^(12,25,93,128).
- b. Chronic pulmonary disease⁽¹³⁸⁾ is due to either flukes or the eggs in the pulmonary parenchyma with a surrounding fibrous tissue reaction⁽³⁴⁾.
- c. The pulmonary manifestations of paragonimiasis with or without fever and eosinophilia, frequently mimic tuberculosis clinically^(6,15,132).
- d. The severity of the clinical disease depends on the number of ingested metacercariae, age of onset and individual health status^(6,34,138).

The course of the disease may be divided into three stages, each of them being characterized by specific clinical and radiological findings⁽⁹³⁾:

Larval stage - Symptoms can persist from 3-12 months. Common features are blood-tinged sputum, cough, chest pain and abdominal pain

Adult worm stage - Cough and recurrent haemoptysis are the main features. This stage can last years.

Healing stage - After the death of the parasite, either spontaneously or following adequate chemotherapy, the symptoms disappear or become stable.

In most of the endemic areas of paragonimiasis, the majority of the infections are light or moderate and involve the lungs. In a small portion of infected persons, the disease is incapacitating⁽¹³⁸⁾. Pulmonary paragonimiasis is usually characterized by persistent cough, bloody sputum and nodular ring shadows in the lung by chest X-ray. However, atypical features such as massive pleural effusion without pulmonary infiltration have been described⁽⁸⁰⁾. This may be due to subpleural localization of the parasite or the early stage of infection. If a few metacercariae are ingested, a single worm may cause only pleural effusion without pulmonary infiltration.

Paragonimiasis can also involve other systems such as the central nervous system⁽⁹¹⁾, gastrointestinal tract, skeletal muscles and skin⁽⁷⁰⁾.

2.4 Diagnostic aspects

A high level of suspicion is necessary to diagnose paragonimiasis⁽¹⁰⁹⁾. Suggestive diagnostic features are the person's residence in a known endemic area, the long period of chronic cough, the relative well-being of most patients and the habit of eating raw or undercooked crabs or crayfish⁽¹⁰⁾.

2.4.1 Parasitological diagnosis

Diagnosis of pulmonary paragonimiasis is confirmed when eggs are detected in the sputum, stool, bronchoscopic washing, biopsy specimens or

pleural effusion^(30,108,137). Exclusion of tuberculosis is of equal importance^(15,35,81).

Rusty sputum is nearly pathognomonic of the disease, however, the observation of the ova is confirmatory and the most common diagnostic technique for paragonimiasis^(31,101,138). Nevertheless, eggs are not always present in the sputum of infected individuals.

The number of ova in the sputum is generally proportional to the severity of symptoms, as well as to the extent of radiological changes⁽²⁰⁾. Blood-streaked sputum generally has a higher density of eggs than purulent sputum without blood⁽¹⁰⁸⁾. The egg excretion rates in persons infected with Paragonimus have been reported to be low (28-39%) in several studies^(44,50,108). The detection of eggs in the sputum is infrequent when egg output is low during the first two months of Paragonimus infection, when only an ectopic lesion is present or during the chronic stage^(108,138). In these situations, repeated sputum examinations are necessary, especially in light infections or post treatment^(22,102,137). Up to seven sputum examinations have been recommended in suspected patients^(108,138), in order to ensure the highest rates of positive diagnosis in infected patients. Simple microscopy of a wet sputum smear can demonstrate the Paragonimus eggs^(35,73,83,108) or Papanicolaou stained smears of sputum at the time of haemoptysis when eggs are most commonly found.

Sadun and Buck⁽¹⁰¹⁾ observed that of 125 Korean patients with Paragonimus egg-positive sputum, eggs were first found by direct sputum smear in 103 (82.4%). If eggs were not found by direct sputum examination, all sputum produced during a 24 hour period was examined following alkaline sodium hypochlorite (antiformin) concentration and by this technique, 16 (12.8%) more cases were diagnosed. In 6 (4.8%) patients, eggs were found in empyema and pleural effusion. Among the 125 patients, eggs were found in one urine specimen and in one stool specimen as well as in the sputum.

Concentration of the sputum is possible in order to achieve a higher positive rate in diagnosing patients with pulmonary paragonimiasis⁽⁷³⁾. This is done by adding twice the volume of caustic soda (4% solution) to the sputum, mixing it for 20 minutes at a 37°C temperature, centrifuging the solution and observing the sediment with a light microscope.

Faecal concentration techniques are also useful in the diagnosis of paragonimiasis. Paragonimus eggs are frequently swallowed by the infected patient, especially children, and are often present in the faeces^(12,15,73,110,139). The highest rates of Paragonimus eggs in stool are in children below 10 years^(110,139). Concomitant sputum and faecal examinations improve the overall rate of detection of infection.

When ova are not found, other laboratory procedures can be used⁽³¹⁾. Sometimes, even more invasive procedures - such as bronchial washing, percutaneous lung aspiration, transthoracic fine-needle biopsy⁽⁵⁴⁾, bronchoscopy or even thoracotomy⁽¹²⁸⁾ - may be required to establish the correct diagnosis. Pleural fluid is characteristically sterile, contains a large number of eosinophils and, rarely, eggs can be found in the sediment^(10,108).

2.4.2 Laboratory findings

Eosinophilia suggests a parasitic infection⁽⁸¹⁾, and leucocytosis and eosinophilia are commonly observed in paragonimiasis^(48,50,108,110). However, in one series, Bercovitz⁽¹²⁾ noted that among 20 patients the blood count was normal. In contrast to Bercovitz's findings, Shim⁽¹⁰⁸⁾ reported that 66% of 76 patients had eosinophilia ($>500/\text{mm}^3$), and 30% had leucocytosis ($>10,000/\text{mm}^3$). Chang et al.⁽¹⁰⁾ reported that eosinophilia was commonly as much as 48% of the total leucocyte count. No quantitative correlation between eggs in the sputum and eosinophilia has been reported.

Eosinophilia is consistently present in the acute stage of the infection, when the flukes are alive and migrating, and the absolute count decreases in the chronic stage^(108,128). In 140 hospitalized patients in Korea⁽¹⁰¹⁾, the highest levels of leucocytosis were observed in patients with symptoms of less than six months duration and lower levels, but still above normal ranges, among those with symptoms of greater duration.

As in other helminthic infections, raised levels of serum IgE have been reported⁽⁴⁹⁾ and the levels of Paragonimus-specific IgE have been estimated by chromatography using immunoabsorbent column.

Blood sedimentation rates are elevated in pleural effusion or empyema and in those in whom paragonimiasis was associated with active pulmonary tuberculosis^(20,101,108).

Pleural fluid examination can assist in diagnosis when eggs are not found and is useful in distinguishing paragonimiasis from tuberculosis. A glucose value of less than 10 mg/dl, an LDH level greater than 1,000 IU/L, eosinophilia, a high protein value, and low pH are characteristic of paragonimiasis⁽⁹⁸⁾. The pleural fluid is usually described as an opaque exudate and occasionally grossly orange in colour. In one series, protein levels greater than 3mg/dl were observed in 36 (95%) out of 38 patients⁽¹⁰⁶⁾, while glucose levels were below 10 mg/dl in 30 (79%) patients. Lactate dehydrogenase (LDH) level was elevated over 1,000 IU/ml in 32 (84%) patients. Red blood cell counts in the pleural effusion were greater than 1,000/mm³ in 35 (92%) patients and total white blood cell count was over 1,000/mm³ in 37 (97%) patients.

2.4.3 Intradermal and serological tests

Immunological investigations such as intradermal and serological tests are valuable tools for differential diagnosis between paragonimiasis and tuberculosis, for epidemiological surveys and for follow-up studies after treatment^(14,101,138).

2.4.3.1 Intradermal tests

An intradermal test for paragonimiasis using a crude merthiolated saline extract of adult Paragonimus westermani (Veronal buffered saline [VBS] antigen) was standardized as a screening technique by M. Yokogawa in 1955⁽¹³⁷⁾. It was highly specific and sensitive in identifying active infection^(137,22). The intradermal sensitivity of another antigen, an acid-soluble protein fraction of Paragonimus westermani in 114 infected persons in Korea, was 100%⁽¹⁰¹⁾.

Intradermal reactivity can be detected within 2 weeks after

infection. Intradermal reactivity can persist from 6-24 months after complete disappearance of eggs from the sputum and stool due to treatment⁽¹¹⁰⁾. Yokogawa⁽¹³⁸⁾ and Razaque⁽⁹³⁾ have, however, stated that intradermal reactivity persists at least 5 years after cure and usually up to 20 years^(101,137). The degree of intradermal reaction may be related to the intensity of infection and/or number of metacercariae of Paragonimus westermani ingested.

Except for the possible cross-reaction with other trematodes, particularly Clonorchis sinensis⁽²²⁾, the intradermal test is a simple and reliable screening test for paragonimiasis infection. From our review, it appears that there is no cross-reactivity of intradermal Paragonimus antigens with tuberculosis or histoplasmosis^(102,101,138). Aside from one study in Korea⁽¹⁰¹⁾, suggesting that the specificity for active infections is 16-20%, no data on the overall specificity or predictive values have been reported.

2.4.3.2 Serological tests

The earliest serological test, complement fixation, for paragonimiasis was reported by M. Ando in 1917 (cited in¹³⁸) and correlated well with known infections. In general, positive serological tests for paragonimiasis correlate with active infection⁽¹²⁰⁾. Serological tests using purified antigens are now available and are of great value in the diagnosis of paragonimiasis, in the interpretation of positive intradermal reactions in epidemiologic studies⁽¹⁰²⁾, in follow-up studies after treatment⁽¹²⁰⁾ and particularly in the assessment of cure.

The complement fixation test, like other serological tests, is positive only in active infection,⁽²³⁾ Being sensitive and specific⁽¹³⁸⁾, the antibody levels return to normal usually within 6 to 12 months after treatment. The complement fixation test on cerebrospinal fluid was used to diagnose cerebral paragonimiasis for the first time in 1955⁽²²⁾.

The immunodiffusion test has been developed in 1970⁽¹²⁰⁾ and used for the same purposes. An immunoelectrophoresis test is also available which becomes negative between 3 to 24 months after successful treatment. The sensitivity and specificity of both these tests are equally satisfactory. However, they require one week before interpretation and a large quantity of antigen must be used.

Immunofluorescent IgG antibody and haemagglutination tests have also been used with satisfactory results, but their interpretation may be subjective⁽¹²⁰⁾. The titres of both tests decrease after effective treatment and the haemagglutination becomes negative between 1 to 18 months later and the indirect fluorescent antibody test between 2 to 24 months later.

Since 1976, a highly sensitive enzyme-linked immunosorbent assay (ELISA) for specific antibody has also been used for human paragonimiasis. This technique is simple, quick, sensitive and specific; the antibody levels become negative from 4 to 24 months after successful treatment. Low titre false positive reactions with cysticercosis, hydatidosis and tuberculosis have been described⁽¹⁴²⁾. Sera from persons with confirmed pulmonary tuberculosis was tested by ELISA and were nonreactive^(48,143), suggesting a high specificity. Antibody levels in cerebrospinal fluid can also be measured by ELISA when suspecting cerebral paragonimiasis. Also, parasite-specific IgE and IgG levels in pleural effusion can be measured by

ELISA⁽⁴³⁾.

Recently, latex agglutination test and Western immunoblot have also been evaluated as effective antibody tests, with promising results. In 1988, Kobayashi⁽⁶⁷⁾ compared the latex agglutination test with the complement fixation test, double diffusion test and ELISA for the serodiagnosis of paragonimiasis in Ecuador using P. westermani antigen and concluded that it was a useful serodiagnostic technique for paragonimiasis. The Western immunoblot was evaluated by Slemenda et al.⁽¹¹¹⁾. In that study, serum of 45 egg positive Southeast Asian and Korean refugees living in the United States were tested. The immunoblot sensitivity was 96% and specificity was 99% in this study. In addition, 20 sera from tuberculosis patients were tested and no reactivity with Paragonimus antigen was observed. It was therefore concluded that this is a rapid, accurate and sensitive serologic diagnostic test, needed sometimes where clinical symptoms of paragonimiasis is confused with other nonparasitic diseases, especially tuberculosis. Paragonimus - specific monoclonal antibodies have been isolated⁽¹¹⁶⁾ and allergens have been identified in pleural fluid from infected persons⁽⁴²⁾.

Thus, serological tests for Paragonimus infection are sensitive and specific and together with egg detection, are useful to support the diagnosis⁽¹⁰⁸⁾.

2.4.4 Radiology

The chest x-ray appearances of paragonimiasis and tuberculosis may be similar, but radiology is another valuable differential diagnostic tool^(101,129). However, neither pathognomonic^(12,15,35,50) nor abnormal⁽¹⁸⁾ x-ray findings may be observed in persons with repeatedly egg-positive sputum.

Ch'ien⁽¹⁹⁾ proposed four stages of development of the Paragonimus cysts based on x-ray findings and pathology in 61 patients in China: infiltrative, nodular, fibrotic and calcified. He noted the similarity and confusion between the radiological picture of the early stages of pulmonary tuberculosis and paragonimiasis, both manifesting a patchy infiltration of exudative pneumonitis.

Graumann and co-workers⁽³⁸⁾ correlated the radiological and clinical findings of 311 patients in Korea. Small lateral pleural shadows with bilateral involvement predominating were found in 64% of the patients. They noted that these pleural reactions were rarely observed in pulmonary tuberculosis. In 28% of this series, unilateral and bilateral pleural changes were found including thickening and exudation, similar to tuberculosis in some cases. Empyema was found in only 6%. In about 45% of the cases, central mediastinal or hilar changes were observed. They were present in all age groups, but mostly in children. About three quarters of this cohort had radiographic "cysts and nodules", the most typical findings, in agreement with other studies^(6,15,128).

In Nigeria, Ogakwu et al.⁽⁸⁵⁾ reported the radiological findings of 100 patients whose sputum examination confirmed the presence of Paragonimus eggs, but were negative for acid-fast bacilli. Out of 100 chest films, 21 were normal. The findings reported in this work indicate that apart from miliary shadows and extensive broncho-pneumonic lesions, practically all other appearances known in pulmonary tuberculosis can be encountered in pulmonary paragonimiasis. Therefore, radiological diagnosis of pulmonary tuberculosis is particularly hazardous where paragonimiasis also exists^(27,85).

Johnson & Johnson reported in 1983⁽⁵⁰⁾, a high frequency of pleural effusion (48%) in paragonimiasis in Indo-chinese refugees. Signs of mild pleural reaction were found in many patients (28,2%).

Razaque⁽⁵³⁾ conducted a study with 120 patients with pulmonary paragonimiasis in 1991 in Manipur, India. He classified the clinical and radiological manifestations into three stages: larval, adult worm and healing stages. All patients had ova in the sputum, stool or pleural fluid. The larval stage of the disease was observed in 77% of the patients. In this stage, chest radiographs showed pleural thickening or blunting of the costophrenic angle (53%), pleural effusion (9%) or ill-defined patchy consolidation (63%). Migratory pneumonitis was observed in 6% of the patients. In 15%, there were no abnormal findings in the chest radiographs, though the sputum was repeatedly positive for Paragonimus ova.

The findings of 18,3% of the patients were consistent with the presence of adult worms in the lungs. The characteristic radiological findings included well or moderately well defined nodular densities (13%) varying in size from 1-4 cm of diameter, cavities (11%) and small-ring shadows (7%).

In five patients (4,2%), there were linear opacities consistent with fibrotic changes. Intrapulmonary calcifications were present in 3% of the patients. The radiological appearance of bronchiectasis with frank haemoptysis was found in 3%. These changes are thought to represent the stage of recovery and healing. Of the 102 out of 120 patients with abnormal chest x-rays, the mid lung fields were affected in 61%, the lower zone in 29% and upper zone in 10%. The right side was affected in 48%, the left side in 33% and both lungs in 19%.

In general, the chest x-ray appearances of paragonimiasis are not pathognomonic^(44,45). Pulmonary infiltrates in paragonimiasis are usually poorly defined densities that change rapidly with time, while tuberculosis infiltrates are nodular lesions that change slowly. Cysts in paragonimiasis invariably have a smooth inner margin and a thin wall with a typical ring shadow. Sub-pleural linear opacities are common in paragonimiasis, especially in early stage, but are unusual in tuberculosis.

In radiographic imaging, patchy air-space consolidation with or without cysts, ring shadows, sub-pleural linear opacities, and bilateral pleural effusions are the typical findings. CT may be a useful diagnostic tool, providing more specific information about the cysts and worm migration tracks^(44,45).

Repeated sputum and stool examinations are essential in all suspected cases and a positive finding of ova, unlikely to be confused with other parasites except Fasciola in the faeces, is the only sure proof of the existence of the disease. The differential diagnosis of pulmonary paragonimiasis from other conditions involving the lungs is difficult without the aid of a microscopic examination of the sputum⁽¹²⁾.

3. Tuberculosis

3.1 Historical

Tuberculosis is a bacterial disease caused mainly by Mycobacterium tuberculosis and Mycobacterium bovis⁽¹¹⁾. As an ancient disease⁽⁷⁷⁾, it was

present in Egypt from as early as 3700 BC, and infects today 1.7 billion people worldwide, or one-third of the world's population⁽⁶⁸⁾. Tuberculosis was recognized by some as contagious since the Renaissance, and the term "tubercle" was first used in the 17th century to describe the nodules formed in the lungs as consequence of the disease. In 1865 it proved to be transmissible but only in 1934 was air-borne transmission via droplet nuclei proved conclusively⁽¹²³⁾. The isolation of M. tuberculosis in 1882 by Robert Koch was nearly concurrent with the discovery of human paragonimiasis. It's accurate diagnosis was made possible by the development of an acid-fast stain in 1885 and facilitated by the clinical introduction of X-rays in 1895.

3.2 Infection

M. tuberculosis is the main cause of human tuberculosis and virtually all new infections are acquired via airborne transmission^(11,63,77,114,121). Overall, approximately 10% of infected persons will develop clinical tuberculosis sometime during their lives⁽¹¹⁾.

Infection, in contrast to disease, usually involves the process of a self-limited localized pneumonia, frequently with no symptoms and followed 2 to 10 weeks later by sensitization to the tuberculin antigen and development of a tubercle at the site of localization⁽⁶⁹⁾. Infection is often found on screening and follow-up of household contacts of a known diseased case⁽¹¹⁾.

The interval between the stage of infection and disease is highly variable. Progression to disease is highest during the two first years after infection and especially among close contacts of sputum-smear positive patients.

3.3 Clinical aspects

When infection takes place initially, the disease may be designated "primary tuberculosis". In these cases, the lower respiratory tract (lung alveoli) is usually the first and only organ involved.

Disease occurring in those previously infected with virulent tubercle bacilli may be called "secondary tuberculosis" or "post-primary tuberculosis"⁽¹¹⁴⁾. Secondary tuberculosis may develop from an endogenous exacerbation of an old infection or may result from reinfection from an infectious source.

If the risk of tuberculous infection is high, primary tuberculosis occurs mostly among children. If the risk is low, it occurs at a low rate, in addition, among young adults. The risk of tuberculous infection can be studied directly, by use of the tuberculin test.

The development of clinical disease is related to age, infective dose, concomitant disease and the degree of immunosuppression such as that due to HIV^(92,121). In societies with high prevalence, the risk of developing bacillary pulmonary tuberculosis resulting from tuberculous infection is greater for persons not previously infected than for those infected previously with virulent tubercle bacilli, since previous infection provides some protection⁽¹¹⁴⁾.

Cough is the most obvious clinical feature of pulmonary

tuberculosis^(11,119). It progresses slowly, becoming more frequent with the production of mucoid or mucopurulent sputum. Haemoptysis may occur. Chest pain or dyspnea can occur, and are usually associated with extensive parenchymal involvement or massive pleural effusion⁽¹¹⁾.

3.4 Diagnosis and case-finding

A sputum-smear examination by light microscopy following staining with the Ziehl-Neelsen method is the principal means by which diagnosis of tuberculous disease is established in developing countries^(11,114). It is easy and quick and provides the physician with a preliminary confirmation of the diagnosis. Also, because it gives a quantitative estimation of the number of bacilli being excreted, the smear is of vital clinical and epidemiologic importance in assessing the patient's infectiousness⁽¹¹⁾. Smear positivity is strongly related to infectiousness. Various studies have indicated that 50 to 80% of patients with pulmonary tuberculosis will have positive sputum smears.

The physical examination of the individual with infection or disease can be unremarkable⁽⁶³⁾, unless pulmonary consolidation or pleural effusion are present.

The following investigations may be useful when resources are available. However effective tuberculosis control programmes can be established without them.

Standard postero-anterior radiographs of the chest should be obtained when resources permit and a lateral view is sometimes useful. The initial infection in the lung usually appears radiographically as a parenchymal infiltration sometimes accompanied by ipsilateral lymph node enlargement⁽¹¹⁾.

Tuberculosis may produce almost any form of pulmonary radiographic abnormality. The most common sites of involvement are the apical and posterior segments of the upper lobes and the superior segments of the lower lobes^(11,63). However, lesions may appear in any segment and nodular infiltrates of varying sizes are perhaps the most common. Lesions may be dense and homogenous, with lobar, segmental or sub-segmental distribution. Cavitation is common, except in AIDS or HIV infected patients. Other findings include atelectasis and fibrotic scarring with retraction of the hilus, and deviation of the trachea⁽¹¹⁾.

Haematogenous tuberculosis is characteristically diffuse, finely nodular (2-5mm), with uniformly distributed lesions on the chest X-ray. This appearance is called "miliary tuberculosis". Pleural effusion, unilateral or, rarely, bilateral, can be the only radiographic abnormality. Very rarely, patients may present with normal radiographs⁽¹¹⁾, especially if HIV infected.

Serological tests are nonspecific. Normochromic normocytic anaemia can occur, as well as leucopenia, or leukaemoid reaction, and in most cases an elevated erythrocyte sedimentation rate. Pleural fluid may reveal an exudative effusion with elevated protein, lymphocytosis, low glucose, low Ph, and elevated fluid/serum LDH ratio⁽⁶³⁾. Eosinophilia is not a feature of tuberculosis.

Special imaging techniques such as computed tomography (CT scan) and

nuclear magnetic resonance (NMR) imaging may be of particular value in defining nodules, cavities, cysts, calcifications, bronchial contours, and vascular details in the lung parenchyma.

Fibreoptic bronchoscopy is usually not necessary to diagnose tuberculosis, but the procedure has been used to localize sites of significant bleeding in both treated and untreated cases. When haemoptysis is massive, rigid bronchoscopy in the operating room may be preferable. When bronchoscopy is done, specimens obtained such as bronchial aspirates or brush smears should be collected for staining and culture of M. tuberculosis. Pleural biopsy can be done by the closed technique or, if necessary by an open surgical technique⁽⁶³⁾.

There are no specific changes in pulmonary function related to tuberculosis. When there is extensive parenchymal involvement, the vital capacity and other lung volumes are decreased⁽¹⁰⁾.

The most definitive diagnostic test for tuberculosis is the isolation of the M. tuberculosis by culture. Although the growth of the bacillus in culture usually takes from 3 to 8 weeks^(10,59), several new technologies have been introduced lately, including the BACTEC system (radiometric technology); genetic probes; immunoassay of mycobacterial antigens; serologic methods and chemical detection of biological compounds⁽¹¹⁾.

The tuberculin skin test has been the traditional method of demonstrating infection with M. tuberculosis. The Mantoux test (intracutaneous administration of tuberculin) should be used in preference to other techniques such as multipuncture tests. Although a significant Mantoux test (> 10mm of induration) strongly suggests tuberculous infection, a nonsignificant reaction should not rule out tuberculous infection, as false-negative tests may occur^(11,63). Cross reactivity of the tuberculin skin test in persons with paragonimiasis has not been reported.

3.5 Epidemiological tools

In the epidemiological study of the disease, the main methods utilized for this purpose are the tuberculin test, chest X-ray and bacteriological examination of sputum for tubercle bacilli.

3.5.1 Tuberculin test

In countries where BCG vaccination has been obligatory at birth for more than 10 years, the level of tuberculin sensitivity in young children provides no guide to the risk of infection, because sensitivity following natural infection cannot be separated from sensitivity following BCG vaccination⁽¹¹⁴⁾.

3.5.2 Chest X-ray

Several pulmonary diseases can mimic tuberculosis in its radiologic appearance and especially paragonimiasis⁽⁶⁵⁾. In general, X-ray evidence of clinically active tuberculosis is very unreliable, thus diagnosis of tuberculosis should not be solely based on chest X-ray findings, but on sputum smear for AFB, or sputum culture, if facilities are available.

3.5.3 Sputum Examination

Microscopic sputum examination and sputum culture to demonstrate the presence of the tubercle bacilli are the definitive means for diagnosis of pulmonary tuberculosis. Direct smear examination is essential in epidemiological studies. Classification of patients into smear-positive and smear-negative groups enables the study of the transmission of tubercle bacillus from host to host and their treatment outcome⁽¹¹⁴⁾.

3.6 Chemotherapy and chemoprophylaxis

A major step in treatment of tuberculosis was the demonstration of the effectiveness of intermittent chemotherapy regimens and later, the introduction of short-course regimens. By 1972, the conventional duration of the treatment was reduced to half, without lowering the therapeutic efficacy^(114,119), resulting in one of the most cost effective health interventions available in developing countries.

4. Epidemiology of Paragonimiasis

About 22 million people around the world are estimated to be infected by Paragonimus⁽¹³²⁾. Since its mode of infection is closely related to alimentary and cultural habits, the incidence of paragonimiasis in different countries varies greatly. Besides its generally focal distribution, paragonimiasis is more commonly found in mountainous areas⁽¹³¹⁾.

The term "paragonimiasis" embraces a range of clinical syndromes resulting from a number of causative agents⁽¹³¹⁾. Forty-eight species/subspecies of Paragonimus have been reported, some of which may not be valid. There are now 9 species causing human paragonimiasis around the world^(2,3,6,132):

- Paragonimus westermani- The most common causative species, causing the disease in many Asian countries.
- P. skrjabini- endemic in mountainous areas of China.
- P. miyazakii- endemic in Japan.
- P. philippinensis- in the Philippines.
- P. heterotremus- in South China, Thailand and Laos.
- P. kellicotti- in North America.
- P. africanus- Endemic in Nigeria and Cameroon.
- P. uterobilateralis- West and South Africa.
- P. mexicanus- Central and South America (synonym- P. peruvianus and P. ecuadoriensis).

There is no consensus on the etiological role of two other species:

- P. caliensis- Colombia, Panama and Peru
- P. hueitungensis- in China.

4.1 Korea

Paragonimiasis due to P. westermani has been recognized as an important endemic diseases in Korea⁽¹⁰⁶⁾. In a national sample survey of 1926, the sputum egg-positive rate was 7.9% (24,907 of 353,729 persons examined)⁽¹⁰⁶⁾. An intradermal test using purified adult antigens of P. westermani has been used in epidemiological surveys since the 1950's. In a national survey of 1959 the overall prevalence was estimated to be about 13%⁽¹³²⁾. In another survey in the same year, Walton and Chyu reported 1,229 (12.6%) positive skin reactions among 9,771 persons tested. In over 100

cities and counties between 1965-1967, 17,505 (7.5%) persons were intradermal positive out of 237,465 persons tested.

About 6 million people in 4 provinces (Cheju Do, Cholla-nan Do, Chollapuk Do and Kangwon Do or 25% of South Korean territory), are currently at risk of paragonimiasis due to P. westermani^(108,132). However only about 1000 persons harbour active infections⁽¹³²⁾.

4.2 China

Although more than 20 species and subspecies have been reported from China, four species are of medical importance, as follows:

P. westermani- The most important species, has been reported from 17 provinces^(17,132).

Pagumogonimus skrjabini (synonym: Paragonimus szechuanensis)- Since 1959 it is recognized as the second important species⁽¹⁸⁾, primarily causing cutaneous paragonimiasis in man⁽¹³²⁾. It has been found to exist in most provinces south of the Yellow River⁽¹⁷⁾.

P. heterotremus (synonym: P. tuanshanensis).

P. hueitungensis.

The first case of human paragonimiasis was reported from Taiwan as early as 1880 (Manson) (as cited in¹⁸) and before 1949, only 3 species were reported to infect man in China⁽¹⁴²⁾. Human paragonimiasis has now been reported from 21 out of 30 provinces, excluding Taiwan. Infected crabs and crayfish (second intermediate hosts) have been found in 422 counties and the population at risk in these areas is estimated to be about 185 million people⁽¹³²⁾. Based on intradermal testing, it is currently estimated that 20 million people are infected with Paragonimus in the in the following provinces: Hunnan, Liaoning, Jilin, Heilongjiang, Sichuan, Yunnan, Shanxi, Zhejiang, Jiangsu, Henan, Hubei, Hebei, Shaanxi, Gansu, Anhui, Guizhou, Guangxi, Guangdong, Hainan, Jiangxi and Fujian^(79,113,142).

Paragonimiasis remains an uncontrolled public health threat in most areas, particularly in mountainous areas where the accessibility to diagnosis and treatment is poor⁽¹³²⁾ and inspite of various control programmes that have been carried out in endemic areas⁽¹³⁵⁾.

4.3 Philippines

Paragonimiasis was first reported to be endemic in the country in 1907 by Musgrave. The human disease is caused in the Philippines by 2 species:

P. westermani- most important, present in all endemic areas of the country.

P. philippinensis- described as a new species by Miyazaki in 1978, present in Jaro.

Selected surveys to determine the prevalence rates of paragonimiasis have been done⁽¹⁶⁾. In 1973-1975 in three municipalities in Leyte, Cabrera et al. found 22 (0.57%) infected persons of 3866 persons examined by sputum examination. In 1974, using both sputum and stool examination, 21 persons (12,5%) out of 168 examined were found positive for Paragonimus eggs. In a 1977-1978 survey of 9 municipalities of Sorsogon province, 13 sputum egg positive persons (0.15%) were found among 8779 persons examined⁽¹⁶⁾.

The Sorsogon region of the island of Luzon, and the Leyte are

considered the main endemic areas. Based upon place of origin of individual cases, other areas, including Mindanao, have also been considered endemic, although no surveys have been reported⁽⁶⁹⁾. It is known that since the World War II, migrants have moved to Mindanao from Leyte and Sorsogon, and may be responsible for the introduction of paragonimiasis⁽⁶⁹⁾. Individual cases of paragonimiasis in man has also been reported from: Batanes, Manila, Cavite, Camarines Sur and Norte, Albay, Samar, Mindoro, Cebu and Negros⁽¹⁶⁾.

4.4 Lao People's Democratic Republic

Paragonimiasis has been recognized in Laos for many years. In 1967, Pathammavong reported 14 sputum samples to be positive for Paragonimus eggs out of 1939 examined for tubercle bacilli (cited in ¹¹²). P. heterotremus was the only species identified in 20 positive stool specimens from infected patients treated in Vientiane hospitals⁽³⁷⁾. In 1970 at post mortem examination Miyazaki and Fontan (cited in ¹¹²), confirmed that the infection was due to P. heterotremus^(37,112). In the laboratory records of 5 medical institutions between 1968-1972, Soh⁽¹¹²⁾ found reports of 151 egg-positive sputum. Furthermore, intradermal testing with P. westermani antigen was positive in 151 (9.8%) of 1531 randomly tested individuals. Most of the positive reactors were among those 25 years or older. This study identified 15 endemic foci in the provinces of Savannakhet, Vientiane, Xieng Khouang, Phong Sali, Sedone, Luang Prabang and Houa Phan⁽¹¹²⁾.

4.5 Thailand

The first case of human paragonimiasis in the country was reported in 1928 by Prommas in Petchaboon province in the northern part of the country⁽¹¹⁷⁾. Two other reports of this disease were made in 1957, in Saraburi province, Central Thailand. In 1959, Vajrasthira et al. reported the results of sputum surveys in Viharn-daeng district, confirming that was an endemic area⁽¹²³⁾.

In the districts of Muang and Pakplee of Nakorn-nayok, five species of Paragonimus were reported to be present⁽¹²³⁾. Sirisumpun postulated in 1963 (cited in ¹¹⁷) that paragonimiasis might have been introduced into the latter endemic area, Nakorn-nayok province, by Japanese troops during the World War II.

At the present, there are at least six species that have been reported in Thailand, but only two of them have been found to affect man^(117,123):

- P. westermani- the species involved in most of the human cases.
- P. heterotremus.

Between 1965-1970, Vajrasthira et al., reported that the prevalence of the infection in the mountainous villages was 3.64% (50 out of 1373) by sputum examination, and 0.2% (5 out of 2335) by stool examination⁽¹²³⁾.

Human paragonimiasis is prevalent in central, northern and northeastern regions. There are two endemic areas in the central region and a small focal area in Chiang Rai. Sporadic cases have been reported throughout the north and mostly from mountainous villages. One of the first reports of expectoration of mature adult worms, probably P. heterotremus, originated from this area⁽¹²⁶⁾. Other recently identified endemic areas were in Phitsanulok province (personal communication, C.

Khamboonruang, 1991), and in Mae Hong Son province⁽³²⁾.

4.6 Peru

Paragonimiasis was first described in Peru in 1910, by Alberto Barton (who also described bartonellosis) in Caballao. Between 1910-1980, 310 cases of paragonimiasis were reported in the country. Most of them were from the region of the Condebamba Valley, in the Cajabamba province, Department of Cajamarca⁽⁴⁰⁾. In 1979 in the Condebamba Valley, 1,800 residents had intradermal skin tests of whom 146 were positive of which 46 were positive by complement fixation test⁽⁴⁰⁾.

Until 1967, the positive cases of paragonimiasis were classified as due to P. westermani, which led some investigators to believe that this parasite was introduced to Peru by Chinese and Japanese immigrants in the 19th century.

Four Paragonimus species have been reported in Peru, being only one of them an etiological agent of human paragonimiasis.

P. peruvianus- until described in 1960 by Miyazaki, it was thought to be P. westermani. This species has a broad geographical distribution in the northern Peru and it was also reported in Ecuador, Panama and Costa Rica. Most of the Peruvian cases of paragonimiasis are thought to be due to P. peruvianus⁽⁴⁰⁾.

P. caliensis- described in 1972 by Miyazaki.

Not reported to infect man.

P. inca- described in 1975 by Miyazaki.

Not reported to infect man.

P. amazonicus- Not reported to infect man.

P. peruvianus, P. inca and P. ecuadoriensis are considered synonyms for P. mexicanus⁽⁶⁾.

Infected crabs are present in 5 out of the 23 departments of the country: Cajamarca, Huanuco, Amazonas, Junin, and Ucayali. In the main endemic area of Cajamarca, serological surveys indicate that 9.6% or about 27,000 persons are infected in the rural areas where people eat raw crabs⁽⁶⁷⁾.

4.7 Ecuador

Human paragonimiasis was described in this country for the first time in 1921, by Heinert^(6,7,73). From 1921 to 1969, 511 cases were reported in Ecuador: Esmeraldas, Pichincha, Los Rios, Canar, Azuay, Morona-Santiago, and Zamora-Chinche provinces^(7,73). From 1972 to 1976, 316 cases were reported in the following provinces of the country: El Oro (19 cases), Los Rios (16 cases), Pichincha (74 cases), and Manabi (206 cases)⁽⁴⁾. In 1980, as cited in⁽⁹⁾, Urrutia reported that in the northeast region of the country there were more than 2,000 registered cases of human paragonimiasis. In 1982, Yokogawa et al. identified three new endemic areas: Casacay, Caluma and Zapallo.

Since 1980, extensive epidemiological investigations have been conducted in the country, showing the presence of infected crabs in 15 of the 22 provinces of Ecuador, particularly in the Amazon Region, representing more than 70% of the total national territory⁽¹³²⁾.

The species causing the disease in man is P. ecuadoriensis (synonym - P. mexicanus), described as a new species in 1979, by Voelker and Arzube, as cited in⁽⁶⁾. In 1982, it was confirmed by Yokogawa et al., following their studies in Ecuador, that P. ecuadoriensis is synonymous to P. mexicanus (first described in 1968 by Miyazaki, as cited in⁽⁶⁾).

The population currently at risk is approximately 21% of the total population of the country. 24.3% of the population at risk are seroreactive and 12.3% of this same population are egg positive, yielding an estimate of at least 250,000 persons infected (2.6% of the total population)⁽¹³²⁾. In 1992, 252 cases of pulmonary paragonimiasis were diagnosed in routine sputum screening for tuberculosis conducted by the Ministry of Public Health⁽¹²⁸⁾.

4.8 Cameroon

Paragonimiasis in Cameroon was first described in 1932 by Libert in the Bakossi Region^(81,94). The main species causing the disease in man are: P. africanus- described by Voelker and Vogel in 1965, it is the most common species infecting man in the country⁽⁹⁴⁾.

P. uterobilateralis- described at the same time as P. africanus and by the same authors. Also present in Cameroon, but not so important.

Four foci are recognized: Mount Kupe, Mbam, Nyong, and Ntem⁽⁹⁴⁾. All these foci are located in the rainforest within the distribution area of the intermediate host of Paragonimus. Recently, an endemic area has been reported in the Lower Mundani area⁽¹⁰⁴⁾.

In 1952 in Lower Bakossi, Kumba division, Zahra⁽¹⁴⁰⁾ used a history of cough or haemoptysis combined with observation of clubbed fingers among 3002 persons in 4 villages to identify 1102 persons whose sputum was examined. Of these, 101 were egg-positive for paragonimiasis. This high prevalence of approximately 4% was considered an underestimate of the actual prevalence of paragonimiasis in this region. At the same time the prevalence of pulmonary tuberculosis was 1.5% in the same population⁽¹⁴⁰⁾.

Thirty years later, in three villages situated in the Lower Bakossi area, southwestern region of Cameroon, the prevalence of paragonimiasis among 900 persons was 5.6%⁽⁸⁰⁾, similar to that observed by Zahra⁽¹⁴⁰⁾. Eating raw and undercooked crabs and/or crayfish is still a current habit. According to Zahra⁽¹⁴⁰⁾, it is believed among the Bakossi people that crabs are a valuable aid to fertility. In the Cameroon, the epidemiology of paragonimiasis is limited by habits of eating raw crabs among specific ethnic groups⁽¹³²⁾.

4.9 Nigeria

Paragonimiasis in Nigeria was first described in 1943 by Yarwood and Elmes⁽⁸²⁾. Until 1970, only 5 cases of pulmonary paragonimiasis had been reported from this country.

As a result of the lack of food and increased crab consumption during the Nigerian Civil War (1967-1970), paragonimiasis was observed, particularly in young persons, in eastern Nigeria by Nwokolo⁽⁸³⁾. Subsequently, it was reported to the east of the Niger River⁽⁸⁴⁾. The main endemic focus was in Okigwi, in the Central State⁽⁸³⁾. In 1977, the main

endemic area was considered to be in the Upper Imo River basin⁽¹⁰⁰⁾. In 1987, Paragonimus infection was also reported in Lagos⁽¹⁾ and the Igwun Basin⁽¹²²⁾.

In Nigeria, the dominant Paragonimus species is P. uterobilateralis⁽¹⁰⁰⁾. In 1974, Nwokolo conducted an epidemiological survey, examining 501 patients in Eastern Nigeria⁽⁸⁴⁾. The study involved endemic foci mapping, examination of intermediate hosts and skin test examination. According to this study, intradermal Paragonimus skin tests were positive in 10% of 169 school children and 5% of 61 healthy women in the Okigwi area. The prevalence is estimated to be 5-10% in inhabitants under 40 years of age in the endemic areas⁽⁸⁴⁾.

4.10 Other countries

Japan has been an important endemic area. However few human infections due to P. miyazakii have been reported in recent years and spontaneous remission has been rarely noted in some patients⁽⁵³⁾. Human infection has been reported in Japan through eating raw wild boar meat⁽⁷¹⁾.

In the Americas, paragonimiasis have been described in most of the countries⁽⁶⁾. In Brazil, all four reported cases of human paragonimiasis were in Japanese immigrants (Prata, A. Personal communication, 1992). No indigenous cases have been described in Brazil until the present. In Mexico, human paragonimiasis due to P. mexicanus has been described^(61,103). In the United States, two autochthonous cases were described in 1984, in Missouri⁽⁹⁰⁾ and in Georgia⁽⁶⁵⁾ due to P. kellicotti. The first case of autochthonous human paragonimiasis was described in Venezuela in 1985⁽²⁾. In a subsequent field investigation⁽³⁾, 130 persons were examined in communities in mountainous areas of the easternmost range of the Coastal Cordillera. All stool and sputum examinations were negative, however 17 individuals had a positive skin-test reaction, 4 individuals had positive serological tests.

Human paragonimiasis was first reported in Manipur State (in the northeast of India) only in 1982. It is not known if it was recently introduced nor if the bordering areas of Myanmar are endemic. Subsequently, Singh et al⁽¹¹⁰⁾ reported 39 cases of human paragonimiasis due to P. westermani in Manipur in 1986. Males aged 11-30 years comprised two-thirds of the cases. The potential geographical distribution of paragonimiasis in India remains to be determined.

Between Feb. - April 1990, the first five cases of human paragonimiasis due to P. africanus have been detected in Equatorial Guinea, following the examination of stools of 1,242 persons. One case with Paragonimus ova in the sputum was detected among 28 samples remitted by the National Tuberculosis Project⁽¹⁰⁹⁾. This report emphasizes the importance of further studies in the country to assess the epidemiological characteristics of this parasitic infection in the country.

Among other African countries, in Liberia, the first 4 cases to be diagnosed in the country were reported in 1982⁽⁹⁹⁾. The same occurred in Guinea, with the description of one case in the same year⁽⁹⁹⁾. In 1981, 3 cases of pulmonary human paragonimiasis were described in Gabon⁽⁹⁸⁾. All of these cases were caused by P. uterobilateralis.

5. Epidemiology of Tuberculosis

No evidence was found in this literature review to support a hypothesis that paragonimiasis predisposed to tuberculosis. Tuberculosis has been reported to occur concomitantly with paragonimiasis^(4,12,23,66,101), but at no greater rate than in the general population. It is noteworthy that many countries which are endemic for paragonimiasis are among those with the highest incidence rates of tuberculosis, thus supporting the need for improved surveillance and case definition.

The rates of notification of active tuberculosis cited below are generally underestimates due to the poor health service coverage.

5.1 Region of Africa

The Regional total case notification (per 100,000 population) in 1992 was 76.5. Estimates for the subSaharan African region, however are at least 222 per 100 000 population. In the African countries where paragonimiasis is endemic, notification rates were:

Cameroon- 49.7 in 1991
Nigeria- 12.7 in 1992

5.2 Region of the Americas

The Regional total case notification in 1992 was 26.6. In the American countries where paragonimiasis is endemic, notification rates were:

Ecuador- 63.7 in 1991
Peru- 234.1 in 1992

5.3 South East Asian Region

This Region reported the highest number of cases in the 1984-1986 period (average 1,339,896). The Regional total case notification was 37.72 per 100,000 persons in 1992, but the true rate approximates about 240 per 100 000 persons. In one reporting country where paragonimiasis is endemic, the incidence rates were:

Thailand- 38.36 in 1992

5.4 Western Pacific Region

The Regional total case notification in 1992 was 65.0 per 100 000. Many countries in this Region are endemic for paragonimiasis, the notification rates of for tuberculosis in these countries were:

China- 32.1 in 1991
Laos-45.0 in 1991 and 6.5 in 1992
Philippines- 324.9 in 1991
Republic of Korea- 108.8 in 1992

6. Misdiagnosing paragonimiasis and tuberculosis

Blood-tinged sputum can be associated with a variety of diseases. Paragonimiasis may be confused with any of these, as has been reported with lupus erythematosus⁽⁵⁹⁾.

6.1 Confusion in diagnosis

In endemic areas, in persons with an atypical history of pulmonary tuberculosis or in suspected cases when sputum is smear negative for tubercle bacilli, the possibility of paragonimiasis should always be considered⁽¹²⁸⁾.

6.1.1 Clinical symptoms

Not only pulmonary paragonimiasis but also cases with intestinal, peritoneal, spinal or central nervous system involvement can be mistaken for tuberculosis, being particularly frequent in paragonimus meningitis^(22,23,86).

6.1.2 Laboratory findings

Misdiagnosis can occur between pulmonary paragonimiasis and pulmonary tuberculosis. Since the main diagnostic tool is still the examination of the sputum^(10,12,35,73,82,101,108,129), the observation of a large number of eosinophils and/or Charcot-Leyden crystals in the sputum should raise the suspicion of a Paragonimus infection^(81,108).

Since Paragonimus ova are destroyed by Ziehl-Neelsen stain for detecting acid-fast bacilli, and knowing that tuberculosis is also prevalent in endemic areas for paragonimiasis, separate sputum examinations are strongly recommended^(10,108). If that is not possible, sputum should first be examined for the presence of Paragonimus eggs and later for acid-fast bacilli by the Ziehl-Neelsen method⁽¹⁰¹⁾. A small amount of sputum directly under the microscope is enough to observe the typical yellowish-brown, operculate ova of the Paragonimus eggs. They are easily recognized even under low power for they are over ten times bigger than red-blood cells^(61,73,84). Paragonimus eggs have been observed in sputum digested prior to culture for Mycobacteria⁽²⁹⁾.

6.1.3 Radiological findings

More than 50 years ago in China, Wang⁽¹²⁹⁾ concluded that the chest x-ray appearance alone cannot differentiate paragonimiasis from pulmonary tuberculosis. This diagnostic confusion was noted by other authors⁽¹⁹⁾ and is confirmed by our review.

6.1.4 Invasive biopsy

If Paragonimus infection has not been considered as the initial diagnosis of pulmonary disease, numerous instances when bronchoscopy with biopsy was performed and its diagnosis confirmed without sputum examination^(13,54,80,86,106,107).

6.2 Outcome of confusion

6.2.1 Corticosteroid or antibiotic treatment

Misdiagnosis of acute paragonimiasis has resulted in treatment for assumed eosinophilic pneumonia with corticosteroids^(85,80) or assumed bacterial pneumonia^(15,38,117) with antibiotics. The lack of clinical response, continued coughing or haemoptysis, prompted further investigations and the final diagnosis of paragonimiasis.

6.2.2 Antituberculosis treatment

Besides confirmation of the diagnosis of paragonimiasis, it is necessary to ensure the exclusion of a tuberculosis infection. Since the incidence of tuberculosis is high in countries where paragonimiasis is also endemic, patients with pulmonary symptoms were treated for presumed tuberculosis, even though tubercle bacilli have not been demonstrated in the sputum^(20,31,35,38,49,50,67,72,73,85,93,107,110,117).

6.2.3 Surgical intervention

In some cases, surgical intervention with pulmonary resection has been carried out and the diagnosis of paragonimiasis was determined on examination of the excised specimens^(2,28,103,117).

6.3 Epidemiological confounding

Understanding the epidemiology of paragonimiasis will alert the public health authorities and clinicians to the possibility of confusing the diagnosis with tuberculosis. More detailed information on the prevalence of paragonimiasis will determine the probability of the frequency of misdiagnosis and hence, misclassification in epidemiological statistics. It should be recognized by public health education programmes that most people of endemic areas do not recognize paragonimiasis as a disease which is distinct from tuberculosis, since both are usually highly prevalent⁽⁶⁰⁾.

6.3.1 Role of socio-cultural habits

Cultural habits of eating raw crustaceans are the main epidemiological determinants in the distribution of Paragonimus infection⁽¹³¹⁾. Geographical differences in prevalence and severity of paragonimiasis can be traced to differences in these habits^(34,108).

The age and sex distribution of infection is closely related to the local patterns of eating raw crustaceans. While in most Eastern Asian countries, paragonimiasis is prevalent in 30-40 year old adults⁽¹⁰¹⁾, in the southern Lower Bakossi area of Cameroon⁽¹⁴⁰⁾, the highest prevalence occurred in girls about the age of puberty and adolescence due to a popular belief among the Bakossi people, that crabs are a valuable aid to fertility. It was a local practice for men to eat tadpoles and the women and children to eat crabs⁽¹⁴⁰⁾. A more recent study in this same region in 1982 by Kum et al.⁽⁶⁰⁾ reported the same age distribution, but the relative rarity of infection over 20 years of age. However, ingestion of crabs as an aid to fertility was no longer a habit and only 4% of the surveyed population considered that eating crabs aided fertility.

The absence of human paragonimiasis can be explained in many countries by the routine cooking of raw crabs and crayfishes by boiling⁽⁹⁰⁾. A general public health measure is to avoid eating raw or partially cooked crabs or crayfish⁽⁶⁾.

In the Andean countries, eating raw crabs mixed with lemon juice, is called locally "ceviche". This is the main route of infection in Peru⁽⁴⁰⁾. In Ecuador, the infection is acquired more frequently by children while eating raw crabs and crayfish or with lemon juice⁽⁵⁵⁾. Adults in Ecuador rarely ingest these crustaceans, except in certain regions where crabs are

abundant and an easy food source in the rice plantations during the rainy season. In these cases, they are eaten either raw or quickly roasted inadequately over fire⁽⁵⁵⁾.

In Korea, the habit of eating raw or partially cooked crabs and crayfish has been reported since the beginning of this century⁽⁴¹⁾. Throughout the country's endemic areas, the most important method of human infection is the habit of eating crabs immersed in soy-sauce ("Ke-jang"). Raw crayfish are not usually eaten by Koreans^(75,108). However in rural areas of the country, measles was treated by a traditional medicine of raw crayfish juice derived from mashed and strained raw crayfish⁽³¹⁾. This traditional practice is disappearing, with a concomitant reduction of childhood paragonimiasis in Korea.

In China, various dishes are prepared with these crustaceans. The recipes include crabs in brine, soya sauce or alcohol (also known as "drunken crabs"). The majority of the metacercariae still remain alive in the "drunken crabs", even when they are immersed in alcohol for up to 5 days⁽³³⁾. In southwest China, crab-jam and raw crab meat and sauce are commonly eaten, and in northeast China the disease is usually acquired by eating raw crayfish and crayfish curd containing live metacercariae among ethnic Korean populations⁽¹⁴²⁾.

The consumption of raw crabs is a long-standing custom in the Lao People's Democratic Republic. The soft tissues of the crabs are mixed with vinegar, local sauce or some other flavouring according to taste. The metacercariae can survive at least 24 hours when marinated in these preparations. While cooking crabs to make crab-juice, hands and utensils may be mechanically contaminated with metacercaria⁽¹¹²⁾.

In the Philippines, especially in the Sorsogon province, raw freshwater mountain crabs are prepared as a delicacy called "kinigang". Metacercariae may even get on the hands of the cook during the preparation of the crab juice^(16,69). Children often eat inadequately cooked crabs (roasted live into the fire). Other local dishes are sometimes prepared with raw or inadequately cooked crabs⁽¹⁶⁾.

6.3.2 Epidemiologic overlay today

Tuberculosis is a major public health problem in all countries where paragonimiasis is endemic, that is in the Americas, Africa, Southeast Asia and the Western Pacific. As early as 1906, the first case of paragonimiasis in Vietnam was at first mistaken for tuberculosis⁽⁷⁴⁾ and the first case of paragonimiasis in Africa in 1920 was initially treated as tuberculosis⁽⁶⁸⁾. In Venezuela, the first autochthonous case of human paragonimiasis was described in 1985, and the patient initially had a diagnosis of pulmonary tuberculosis⁽²⁾.

Epidemiological overlap between paragonimiasis and tuberculosis has been frequently described in many regions^(60,69,142), however clinicians and public health authorities have not fully recognized the consequences of misdiagnosis. Coexistence of paragonimiasis and tuberculosis in the same person has been described, although this condition is not common^(4,6,12).

Bercovitz⁽¹²⁾ concluded in Korea in 1937, that pulmonary paragonimiasis did not predispose to tuberculosis. In that series, 190 tuberculosis positive sputa and 108 Paragonimus positive sputum occurred among 1,108

sputa examined. 14 patients were found to be infected by both.

Zahra reported the overlapping endemicity of paragonimiasis and tuberculosis in the Lower Bakossi area in Cameroon in 1952. Based on a single sputum specimen, pulmonary tuberculosis was diagnosed in 38 of 3002 persons (1.26%) and 5 (0.16%) had both paragonimiasis and tuberculosis. 96 (3.29%) persons were infected only with paragonimiasis. In the same area 30 years later, Kum⁽⁶⁰⁾ surveyed 4 villages in the lower Bakossi area in Cameroon: among 1,102 sputum examinations, paragonimiasis prevalence was 4%, pulmonary tuberculosis prevalence was 1.3% and 0.22% had both paragonimiasis and tuberculosis.

In 1960, Sadun and Buck noted in Korea⁽¹⁰¹⁾ that due to the high prevalence of both diseases, pulmonary paragonimiasis was frequently misdiagnosed as tuberculosis. The intradermal test with Paragonimus antigen was helpful in the differential diagnosis of patients in whom pulmonary tuberculosis and/or paragonimiasis were suspected. The important social and economic impact of mistaken diagnoses was noted⁽¹⁰¹⁾.

In Nigeria^(82,108) the diagnosis of paragonimiasis was repeatedly delayed due to the confusion with pulmonary tuberculosis.

Singh et al. ⁽¹¹⁰⁾ in Manipur, India in 1986 reported that the lack of awareness of paragonimiasis and the similarity of clinical and radiological features in pulmonary paragonimiasis and pulmonary tuberculosis may have accounted for the misdiagnosis and treatment of 23 cases out of 39 (58.9%) as pulmonary tuberculosis, although none of them were found to have tubercle bacilli in sputum examination.

In China, paragonimiasis and tuberculosis are both endemic in many provinces of the country⁽⁷⁶⁾ as evidenced by the number of case-reports of misdiagnosis. In 1957, Xue et al. reported that in 100 cases of paragonimiasis, 43 were once diagnosed as pulmonary tuberculosis, and 2 as tuberculous pleuritis, with an overall misdiagnosis rate of 45%⁽¹³⁵⁾. In 1958, among 200 patients Chang et al.⁽²⁰⁾, reported that most of them were treated previously for pulmonary tuberculosis. Six of 200 patients were sputum smear positive for tubercle bacilli. In 1980, among 188 cases of paragonimiasis Huang et al.⁽³⁹⁾ reported that 23 and 2 out of 60 pulmonary paragonimiasis cases were previously diagnosed as pulmonary tuberculosis and tuberculous pleuritis respectively; 2 and 24 out of 30 pleural paragonimiasis cases were misdiagnosed as pulmonary tuberculosis and tuberculous pleuritis respectively. In total, the rate of misdiagnosis as tuberculosis in 90 cases was 56.6% (51 out of 90)⁽³⁹⁾. Still in China, in 1986, Lu described 54 cases of misdiagnosis among 170 paragonimiasis patients⁽⁸²⁾. Among these, 17 (10%) cases were misdiagnosed as pulmonary tuberculosis or tuberculous pleuritis.

Tourism and the refugee movements will have epidemiological consequences regarding paragonimiasis infection and its misdiagnosis with tuberculosis. In the early 1980's, the Swiss-Thai tuberculosis team in the Baan Vinai refugee camp near the Mekong river in northeast Thailand observed that paragonimiasis was a significant cause of misdiagnosis of tuberculosis among Hmong refugees from Laos (Prof. D. Bunnag, personal communication, 1994). Moreover, since 1970, tens of thousands of refugees have migrated from Southeast Asia to the United States and at least 3 million Americans have been in Southeast Asia in the last 25 years⁽⁹⁾. In the United States, paragonimiasis has been reported in Asian immigrants and

refugees^(16,24,26,47,60,67,118,136) and often confused with tuberculosis by the primary physicians.

7. Conclusions

7.1 Diagnostic guidelines

If tuberculosis is suspected in areas where Paragonimus infection is prevalent, paragonimiasis should be excluded by parasitological examination of the sputum before proceeding to further examinations. The sputum examination should be performed using a centrifugation concentration technique with 10% potassium hydroxide in equal amount to the sputum volume.

Conversely, particularly in endemic areas where the suspicion of paragonimus is high, tuberculosis should always be excluded by three direct sputum smears, and if available, culture of a concentrated sputum specimen.

7.2 Guidelines on public health policies

In endemic areas of paragonimiasis, pulmonary or meningeal involvement is commonly confused with pulmonary tuberculosis or tuberculous meningitis respectively. The cost of mistaken diagnosis is high and correct diagnosis will avoid high cost diagnostic procedures or unnecessary treatment. Tuberculosis laboratories should have the capacity and their staff the necessary training to undertake examination of Paragonimus in the sputum.

This review confirms that there is a significant overlap between the diagnostic algorithms, the clinical presentations and the distribution of both paragonimiasis and tuberculosis. The future challenge will be to achieve collaborative research between those in various professional fields, including anthropology, parasitology, bacteriology, and epidemiology to define the geographic extent of paragonimiasis and to reduce probability of misdiagnosis through increased public and public health awareness.

Acknowledgments

The authors wish to thank Ms. Josie Mercado for typing this manuscript.

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