Histoplasma, Coccidioides, Aspergillus, Other Systemic Fungal Pathogens And *Paragonimus westermani*

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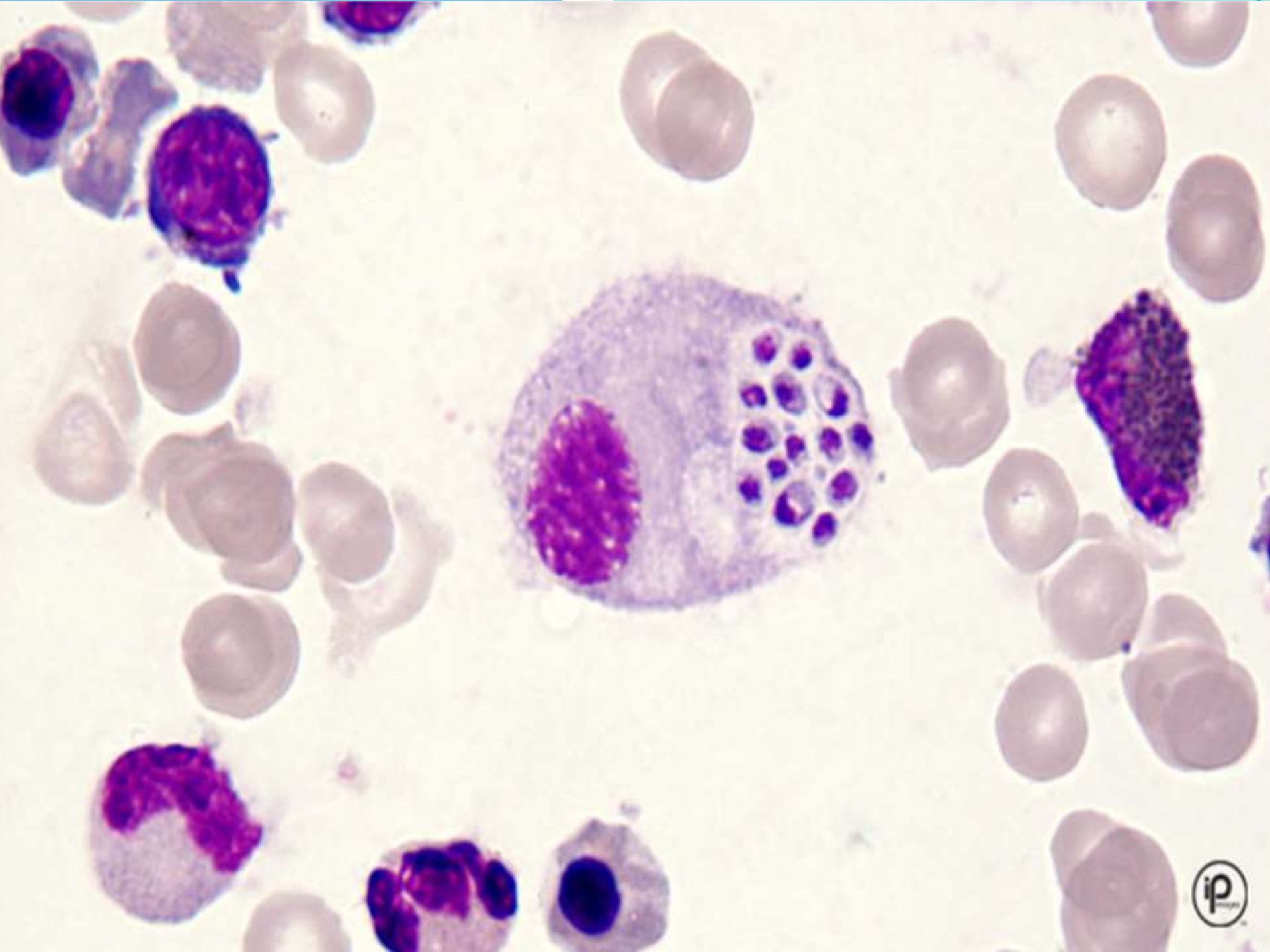
Histoplasma capsulatum

- *Histoplasma capsulatum* is a **dimorphic fungus** that grows in the yeast phase in tissue and in cultures incubated at 37° C. The **mold phase** grows in cultures incubated at 22 to 25° C and as a saprophyte in soil. The yeast forms are small for fungi (2 to 4 µm) and reproduce by budding (blastoconidia). The mycelia are septate and produce **microconidia** and macroconidia.
- Growth is obtained on blood agar, chocolate agar, and Sabouraud's agar, but may take many weeks.



DIMORPHISM

- The morphologic and physiologic events associated with conversion from the mold to the yeast phase of *H. capsulatum* have been extensively studied. They are understandably complex given the dramatic change of milieu encountered by the fungus when its mold conidia float from their soil habitat to the pulmonary alveoli. Conversion to the yeast phase is then triggered by the host temperature (37°C) and possibly by other aspects of the new environment. In vitro studies show that the earliest events in this shift from the mold to yeast form involve induction of the heat shock response *and uncoupling of oxidative phosphorylation.*
- Dimorphism in fungi is reversible, a feature that distinguishes it from developmental processes such as embryogenesis seen in higher eukaryotes.

HISTOPLASMOSIS

- Histoplasmosis is limited to the endemic area, where the vast majority of cases are asymptomatic or show only a fever and cough. If affected individuals are seen by a physician, a pulmonary infiltrate and hilar adenopathy may or may not be evident on a radiograph. Progressive cases show extension in the lung or enlargement of lymph nodes, liver, and spleen.

EPIDEMIOLOGY

- *H. capsulatum* grows in soil under humid climatic conditions, particularly soil containing bird or bat droppings. Inhalation of the mold microconidia, which are small enough (2 to 5 μm) to reach the terminal bronchioles and alveoli, is believed to be the mode of infection. The organism has a worldwide distribution but is particularly prevalent in certain temperate, subtropical, and tropical zones.
- The infection is not transmitted from person to person. Disease is more common in men but there are no racial or ethnic differences in susceptibility.

PATHOGENESIS

- The hallmark of histoplasmosis is infection of the lymph nodes, spleen, bone marrow, and other elements of the reticuloendothelial system with intracellular growth in phagocytic macrophages. The initial infection is pulmonary, through inhalation of infectious conidia, which convert to the yeast form in the host. They attach to CD18 integrin receptors and are readily phagocytosed by macrophages and PMNs. Inside phagocytes, they continue to multiply in the cytoplasm, surviving the combined effects of the oxidative burst and phagolysosomal fusion.
- With continued growth, there is lymphatic spread and development of a primary lesion similar to that seen in tuberculosis.
- Pathologically, granulomatous inflammation with necrosis is prominent in pulmonary lesions, but *H. capsulatum* may be difficult to detect, even with special fungal stains.

IMMUNITY

- Infection with *H. capsulatum* is associated with the development of cell-mediated immunity, as demonstrated by a positive delayed hypersensitivity skin test to a mycelial antigen called **histoplasmin**.
- Infection is believed to confer long-lasting immunity, the most important component of which is CD4+ T lymphocyte mediated.

HISTOPLASMOSIS

CLINICAL ASPECTS

MANIFESTATIONS

- Most cases of *H. capsulatum* infection are asymptomatic or show only fever and cough for a few days or weeks.
- Mediastinal lymphadenopathy and slight pulmonary infiltrates may be seen on x-rays.
- The histoplasmin skin test becomes positive after about 3 weeks.
- More severe cases may have chills, malaise, chest pain, and more extensive infiltrates, which usually resolve nonetheless. A residual nodule may continue to enlarge over a period of years, causing a differential diagnostic problem with pulmonary neoplasms. Progressive pulmonary disease occurs in a form similar to that of pulmonary tuberculosis, including the development of cavities, with sputum production, night sweats, and weight loss. The course is chronic and relapsing, lasting many months to years.
- Disseminated histoplasmosis generally appears as a febrile illness with enlargement of reticuloendothelial organs.

DIAGNOSIS

- In most forms of pulmonary histoplasmosis, the diagnostic yield of direct examinations or culture of sputum is low.
- In disseminated disease, blood culture or biopsy samples of a reticuloendothelial organ are the most likely to contain Histoplasma.
- Bone marrow culture has the highest yield.
- Because of their small size, the yeast cells are difficult to see in potassium hydroxide (KOH) preparations, and their morphology is not sufficiently distinctive to be diagnostic.
- Selective fungal stains such as methenamine silver demonstrate the organism but may not differentiate it from other yeasts. Hematoxylin and eosin (H& E)-stained tissue or Wright-stained bone marrow often demonstrates the organisms in their intracellular location in macrophages.

TREATMENT

- Primary infections and localized lung lesions usually resolve without treatment.
- Amphotericin B remains the treatment of choice, but its toxicity limits its use to cases of extensive disease such as progressive pulmonary and disseminated histoplasmosis.
- Itraconazole and ketoconazole have been effective for treatment and for suppression in AIDS patients with histoplasmosis. In some cases amphotericin B treatment may be followed with a course of itraconazole.

Coccidioides immitis

- *Coccidioides immitis* is also a dimorphic fungus, but instead of a yeast phase, a large (12 to 100µm), distinctive, round-walled **spherule** is produced in the invasive tissue form. This structure is unique among the pathogenic fungi.
- In alkaline soils and in culture, *C. immitis* grows only as a mold regardless of temperature. Growth becomes visible in 2 to 5 days. The hyphae are septate and produce thick-walled, barrel-shaped **arthroconidia** which are the infectious unit in nature and highly infectious when they develop in the laboratory.


Endospores
Spherules

C O C C I D I O I D O M Y C O S I S

- Acute primary infection with *C. immitis* is either asymptomatic or presents as a complex called valley fever by residents of the endemic areas. Valley fever includes fever, malaise, dry cough, joint pains, and sometimes a rash. There are few physical or radiologic findings, but the illness persists for weeks. Disseminated disease involves lesions in the bones, joints, skin, and a progressive chronic meningitis.

EPIDEMIOLOGY

- Coccidioidomycosis is the most geographically restricted of the systemic mycoses, because *C. immitis* grows only in the alkaline soil.
- Coccidioidomycosis is not transmissible from person to person.
- It is geographically restricted to Sonoran desert.
- High proportion of locals have been infected.
- Arthroconidia can be spread by dust storms.
- Rainfall pattern influences attack rate.

PATHOGENESIS

- Inhaled arthroconidia are small enough (2 to 6 µm) to bypass the defenses of the upper tracheobronchial tree and lodge in the terminal bronchioles.
- Human monocytes can ingest and kill some arthroconidia on initial exposure, although the outer portion of the wall of the arthroconidium has antiphagocytic properties, which persist in the early stages of spherule development.

IMMUNITY

- Lifelong immunity to coccidioidomycosis clearly develops in the vast majority of those who become infected. This immunity is associated with strong polymorphonuclear leukocyte and T lymphocyte-mediated responses to coccidioidal antigens. In most cases, a mixed inflammatory response is associated with early resolution of the infection and development of a positive delayed hypersensitivity skin test.
- Progressive disease is associated with weak or absent cellular immunity and skin test anergy. In most infected persons the infection is controlled after mild or inapparent illness. The disease progresses if cell-mediated immunity and consequent macrophage activation do not develop. Such immune deficits may be a result of disease (AIDS) or immunosuppressive therapy but may occur in persons with no other known cellular immune compromise.
- Humoral mechanisms are not known to play any role in immunity.

COCCIDIOIDOMYCOSIS

CLINICALASPECTS

MANIFESTATIONS

- More than one half of those infected with *C. immitis* suffer no symptoms, or the disease is so mild that it cannot be recalled when skin test conversion is discovered. Others develop malaise, cough, chest pain, fever, and arthralgia 1 to 3 weeks after infection. This disease, which lasts 2 to 6 weeks, is known as valley fever by the local populations in the United States. Objective findings are few.
- The chest x-ray is usually clear or shows only hilar adenopathy.
- Erythema nodosum may develop midway through the course, particularly in women. In most cases, resolution is spontaneous but only after considerable discomfort and loss of productivity.
- Disseminated disease is more common in men; in dark-skinned races, particularly Filipinos; and in AIDS patients and other immunosuppressed persons. Evidence of extrapulmonary infection almost always appears in the first year after infection.
- If untreated, the disease is slowly progressive and fatal.

DIAGNOSIS

- With enough persistence, direct examinations are usually rewarding. The thick-walled spherules are so large and characteristic that they are difficult to miss in a KOH preparation or biopsy section. Skin and visceral lesions are most likely to demonstrate spherules; CSF is least likely.
- Culture of *C. immitis* from sputum, visceral lesions, or skin lesions is not difficult.
- Skin and serologic tests are particularly useful in diagnosis and management of coccidioidomycosis. The coccidioidin skin test usually becomes positive 1 to 4 weeks after the onset of symptoms of primary infection and remains so for life.

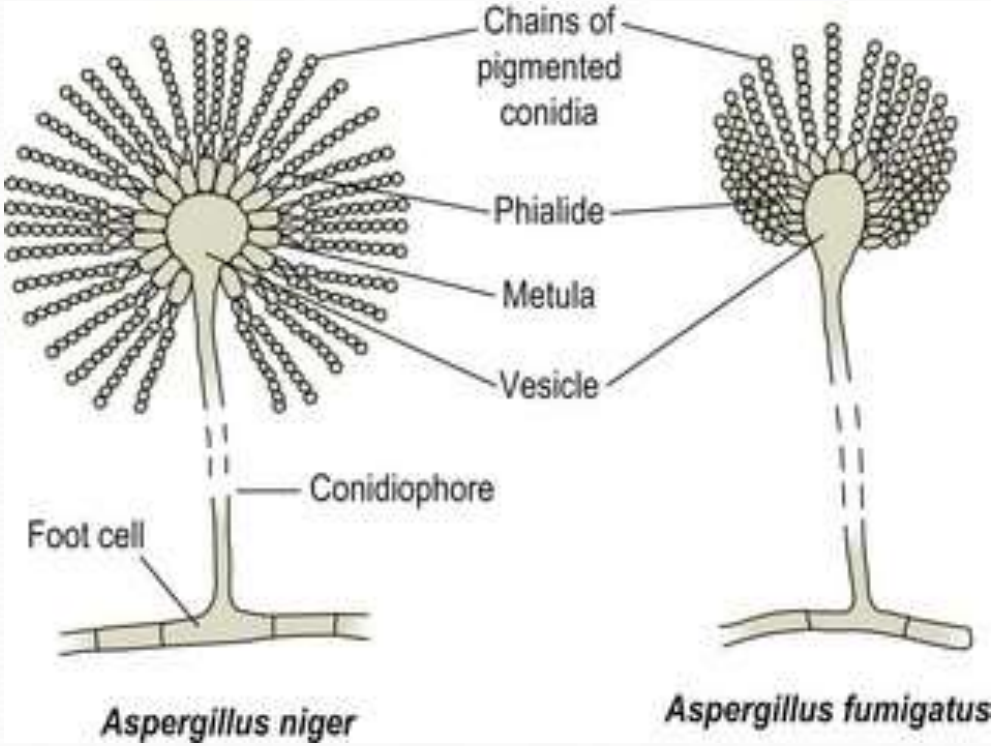
TREATMENT

- Primary coccidioidomycosis is self-limiting, and no antifungal therapy is indicated. Progressive pulmonary disease and disseminated disease require the use of antifungal agents, usually amphotericin B.
- Ketoconazole has proved effective, but relapses are common. Fluconazole and itraconazole are also active against *C. immitis*. With the exception of fluconazole, none of these agents have significant penetration into the CNS. Amphotericin B is commonly given directly into the CSF for the treatment of *C. immitis* meningitis.

ASPERGILLUS

MYCOLOGY

- *Aspergillus* species are rapidly growing molds with branching **septate hyphae** and characteristic arrangement of conidia on the conidiophore. Fluffy colonies appear in 1 to 2 days and, by 5 days, may cover an entire plate with pigmented growth. Species are defined on the basis of differences in the structure of the *conidiophore* and the arrangement of the **conidia**. The most frequent in human infections are *Aspergillus fumigatus* and *Aspergillus flavus*, but others, such as *Aspergillus niger*, may be involved.


Chains of pigmented conidia
Phialide
Metula
Vesicle
Conidiophore
Foot cell
Aspergillus niger
Aspergillus fumigatus

ASPERGILLOSIS

- Invasive aspergillosis is distinguished by its setting in immunocompromised individuals and its rapid progression to death. The typical patient is one with leukemia or under immunosuppression for a bone marrow transplant. The appearance of fever and a dry cough may be the only signs until pulmonary infiltrates are demonstrated radiologically. Until Aspergillus hyphae are demonstrated, almost any of the causes of pneumonia could be responsible.

EPIDEMIOLOGY

- *Aspergillus* species are widely distributed in nature and found throughout the world. They seem to adapt to a wide range of environmental conditions, and the heat-resistant conidia provide a good mechanism for dispersal. Like bacteria spores, the conida survive well in the environment and their inhalation is the mode of infection.
- Hospital air and air ducts have received attention as sources of nosocomial *Aspergillus* isolates. Occasionally, construction, remodelling, or other kinds of major environmental disruption have been associated with increased frequency of *Aspergillus* contamination, colonization, or infection.

PATHOGENESIS

- *Aspergillus* conidia are small enough to readily reach the alveoli when inhaled, but disease is rare in those without compromised defenses. Factors that aid the fungus in the initial stages are not known, but the ability of proteins on the surface of the conidia to bind fibrinogen and laminin probably contribute to adherence. Production of extracellular elastase, proteinases, and phospholipases has been associated with the more virulent species.
- The appearance of antibodies to these enzymes during and following invasive aspergillosis argues for their importance, but the pathogenic role of these enzymes remains to be demonstrated. Most species produce **aflatoxins** and other toxic secondary metabolites but their role in infection is also unknown.

IMMUNITY

- Macrophages, particularly pulmonary macrophages, are the first line of defense against inhaled *Aspergillus* conidia phagocytosing and killing them by nonoxidative mechanisms. For the conidia that survive and germinate, PMNs become the primary defense. They are able to attach to the growing hyphae, generate an oxidative burst, and secrete reactive oxygen intermediates.
- Little is known of adaptive immunity in humans. Antibodies are formed but their protective value is unknown. Although AIDS patients do develop *Aspergillus* infections, the association with T-cell deficiencies is not strong enough to draw conclusions about their importance.

ASPERGILLOSIS

CLINICAL ASPECTS

MANIFESTATIONS

- *Aspergillus* can cause clinical allergies or occasional invasive infection. In both cases, the lung is the organ primarily involved. Allergic aspergillosis, which can be a mechanism of exacerbation in patients with asthma, is characterized by transient pulmonary infiltrates, eosinophilia, and a rise in *Aspergillus*-specific antibodies. These conditions follow direct inhalation of fungal elements or, more commonly, colonization of the respiratory tract. Areas of the bronchopulmonary tree with poor drainage because of underlying disease or anatomic abnormalities may serve as a site for growth of organisms and continuous seeding with antigen.

- Invasive aspergillosis occurs in the settings of pre-existing pulmonary disease (bronchiectasis, chronic bronchitis, asthma, tuberculosis) or immunosuppression. Colonization with *Aspergillus* can lead to invasion into the tissue by branching septate hyphae.
- In patients who already have a chronic pulmonary disease, mycelial masses can form a radiologically visible fungus ball (aspergilloma) within a pre-existing cavity.
- An acute pneumonia may occur in severely immunocompromised patients, particularly those with phagocyte defects or depressed neutrophil counts due to immunosuppressive drugs. Multifocal pulmonary infiltrates expanding to consolidation are present with high fever. The prognosis is grave and dissemination to other organs common, which is not the case in immunocompetent hosts.

DIAGNOSIS

- *Aspergillus* is relatively easy to isolate and identify. Its rapidly spreading mold growth. The diagnostic problem is distinguishing contamination and colonization with *Aspergillus* from invasive disease.
- The diagnosis cannot be made for certain without the use of lung aspiration, biopsy, or bronchoalveolar lavage. With material directly from the lesion, the presence of large, branching, septate hyphae and a positive culture are diagnostic.
- Serologic methods have been developed to demonstrate *Aspergillus* antibodies. Although these tests may be helpful in suggesting allergic aspergillosis, they have little value in invasive disease because anti-*Aspergillus* antibody is common in healthy persons.

TREATMENT AND PREVENTION

- Amphotericin B and itraconazole are the recommended antimicrobics for invasive aspergillosis. Neither can be considered particularly effective, because the mortality rate of invasive disease approaches 100%.
- In cases with pulmonary structural abnormalities and fungus balls, chemotherapy has little effect. Surgical removal of localized lesion is sometimes helpful, even in the brain. Construction of rooms with filtered air has been attempted to reduce exposure to environmental conidia.

PARAGONIMUS SPECIES

- Several *Paragonimus* species may infect humans. *P. westermani*, which is widely distributed in East Asia, is the species most frequently involved. The short, plump (10 by 5 mm), reddish-brown adults are characteristically found encapsulated in the pulmonary parenchyma of their definitive host. Here they deposit operculate, golden-brown eggs, which are distinguished from similar structures by their size (50 by 90 µm) and prominent periopercular shoulder.
- When the capsule erodes into a bronchiole, the eggs are coughed up and spat out or swallowed and passed in the stool. If they reach fresh water, they embryonate several weeks before the ciliated miracidia emerge through the open opercula.

- After invasion of an appropriate snail host, 3 to 5 months pass before cercariae are released. These larval forms invade the gills, musculature, and viscera of certain crayfish or freshwater crabs; over 6 to 8 weeks, the larval forms transform into metacercariae. When the raw or undercooked flesh of the second intermediate host is ingested by humans, the metacercariae encyst in the duodenum and burrow through the gut wall into the peritoneal cavity. The majority continue their migration through the diaphragm and reach maturity in the lungs 5 to 6 weeks later.
- Immature ectopic adults in the striated muscles of the pig may infect humans after ingestion of undercooked pork.

PARAGONIMIASIS
(LUNG FLUKEINFECTION)

EPIDEMIOLOGY

- Although most of the human infections are concentrated in the Far East, paragonimiasis has recently been described in India, Africa, Latin America, eastern Canada and the USA.
- Approximately 1% of recent Indochinese immigrants to the United States are found to be infected with *P. westermani*.
- Human disease occurs when food shortages or local customs expose individuals to infected crabs. When these crustaceans are prepared for cooking, juice containing metacercariae may be left behind on the working surface and contaminate other foods subsequently prepared in the same area.

Paragonimus westermani

Egg

Adult

PARAGONIMIASIS

CLINICAL ASPECTS

MANIFESTATIONS

- The presence of the adult worms in the lung elicits an eosinophilic inflammatory reaction and, eventually, the formation of a 1 to 2 cm fibrous capsule that surrounds and encloses one or more parasites.
- With the onset of oviposition, the capsule swells and erodes into a bronchiole, resulting in expectoration of the brownish eggs, blood, and an inflammatory exudate. Secondary bacterial infection of the evacuated cysts is common, producing a clinical picture of chronic bronchitis or bronchiectasis. When cysts rupture into the pleural cavity, chest pain and effusion can result.

DIAGNOSIS

- Eggs are usually absent from the sputum during the first 3 months of overt infection; however, repeated examinations eventually demonstrate them in more than 75% of infected patients. When a pleural effusion is present, it should be checked for eggs. Stool examination is frequently helpful, particularly in children who swallow their expectorated sputum.
- A diagnosis in these cases, however, often depends on the detection of circulating antibodies. Their presence usually correlates well with acute disease and disappears with successful therapy.

TREATMENT AND PREVENTION

- The disease responds well to praziquantel or bithionol therapy.
- Control requires adequate cooking of shellfish before ingestion.