HISTOPLASMOSIS

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MAY 18, 1995

In soil the microbe is a filamentous fungus which is easily fragmented into an air pollutant when these microfoci are bulldozed or otherwise upheaved. This situation persists in an age of continuous construction/demolition activities involving massive movement of soils.

Campbell, 1980

Contamination of the entire school building with courtyard air occurred via the school's forced air ventilation system with intakes in the courtyard.

Brodsky et al., 1973

Unusual presentations of histoplasmosis may occur even in patients who are not immunocompromised.

Lydiatt et al., 1993

The diagnosis of histoplasmosis begins with thinking of it.

Goodwin et al., 1981

Should I be worked up for histo? Southwestern patient, 1995

History.

In 1905, Samuel Darling performed an autopsy on a patient in Panama with disseminated histoplasmosis. He thought that the organism which he found in histocytes was a plasmodial species. It appeared to be surrounded by a capsule which was recognized later as an artifact of fixation. He termed the organism *Histoplasma capsulatum* from his observations of this case. During the next year, Darling autopsied two other patients with disseminated histoplasmosis. All three of the patients were non-Panamanians who were working in Panama excavating and constructing the Panama Canal. It was 45 years before another case of disseminated histoplasmosis was autopsied in Panama (75). When the organism was cultured, it was determined that *Histoplasma capsulatum,* in actuality, was a dimorphic fungus.

Using an extract of the mycelial phase of the organism, Christie and Peterson established that skin test positively to histoplasmin correlated with the presence of pulmonary calcifications in tuberculin skin test negative individuals in the central and eastern U.S. (14). In contrast to the Ghon complex of in tuberculosis, the calcific lesions found in persons with positive histoplasmin skin tests tended to be multiple. Hilar and mediastinal lymph nodes often were calcified and the extent of calcification was greater than that seen in tuberculin positive, histoplasmin negative individuals. Histoplasmin skin test positive persons sometimes had characteristic discrete multiple button-like foci of calcium deposits in lymph nodes. This pattern of calcification is known as "popcorn" or "mulberry" calcification. In a series of studies, Edwards and Palmer found first that student nurses and later Navy recruits who were life-long residents of a single county were more likely to have positive histoplasmin skin tests if they came from regions along the Ohio and Mississippi river valleys (24, 25, 58). From the results of their studies, they were able to map the geographic distribution of persons with histoplasma infections. Chester Emmons was the first person to isolate the organism from soil (28). Michael Furcolow isolated the organism in air samples and helped to describe chronic cavitary pulmonary histoplasmosis (83).

Ajello and Zeidberg recognized the association of the fungus with environmental sites contaminated with bird excrement (1). Wheat and his colleagues described a series of epidemics in Indianapolis in which an estimated 200,000 people were infected. They added to the list of clinical manifestations that could be caused by this organism (70, 97). Wheat described a polysaccharide antigen that could be found in body fluids, particularly of patients with disseminated disease (92).

Microbiology and Pathogenesis.

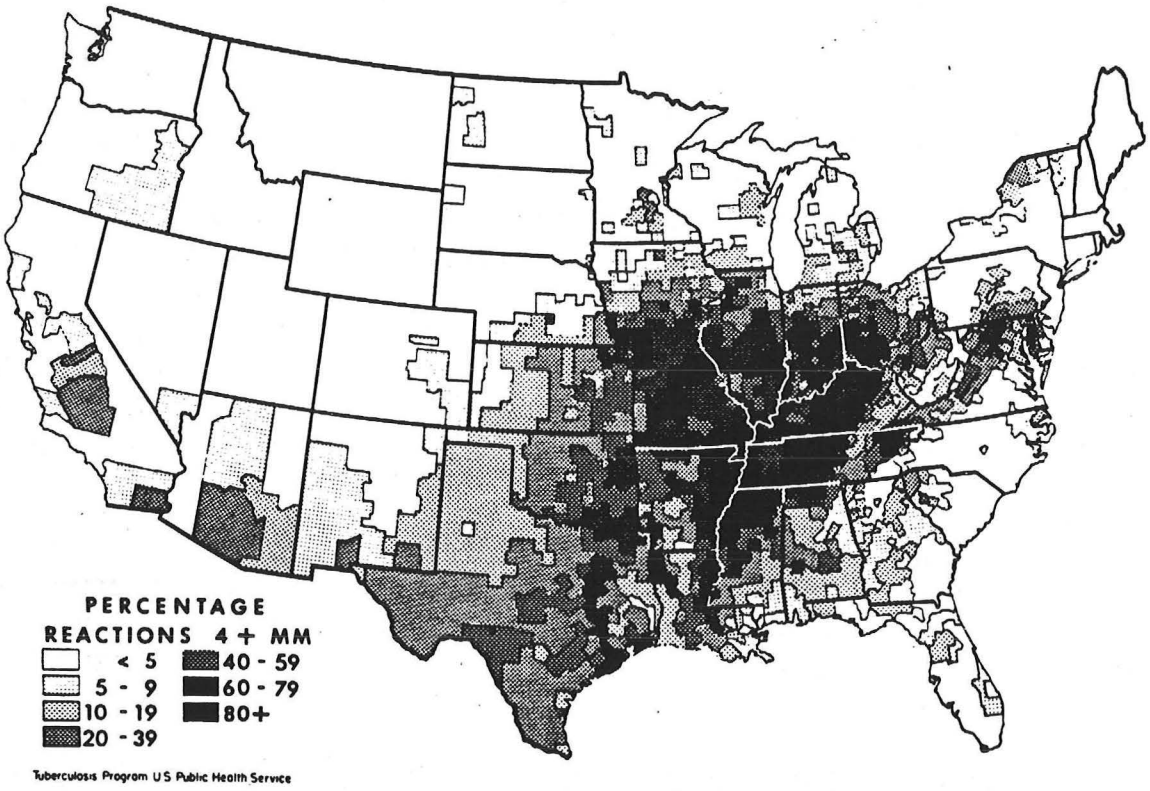
Histoplasma capsulatum is a dimorphic fungus. In soil it grows as a hyphal form with microconidia and macroconidia. The microconidia are 2-5 microns in diameter and are considered the infectious form of the organism. The macroconidia are 8-14 microns in diameter and have tuberculated protrusions, or knobs on their surfaces. The presence of the tuberculated macroconidia is characteristic of the morphology of the histoplasma mycelial phase. Once inhaled and at 37°C, the organism changes to a yeast phase where division occurs by budding. Macrophages are recruited to the alveolus and ingest the yeasts (40, 53). The organisms replicate within the macrophages. An area of pneumonitis results with subsequent expansion. Yeast forms, both free and within macrophages are transported back to hilar and mediastinal lymph nodes. Blood stream invasion then occurs. After 10 - 14 days in non-immune persons, cell-mediated immunity mechanisms become activated and the macrophages begin to destroy the organisms. Granuloma formation follows and the progress of the pneumonitis ceases. With further development of delayed hypersensitivity, caseation can occur in the center of the granuloma. A fibrous capsule is laid down around the area of granuloma formation and eventually calcification occurs either in the center of the granuloma or around its periphery.

In contrast to tuberculosis, where there may be but a single organism inhaled leading to a Ghon complex, exposure to dust may result in the inhalation of multiple histoplasma organisms and the formation of multiple complexes. In histoplasmosis, immunity confers protection but the protection is incomplete. Reinfection can occur and may be common (30, 61, 82). With reinfection, the incubation period is shorter and the disease course is milder. If massive re-exposure to spores occurs, there may be involvement of many lung areas and the subsequent development of miliary calcifications. *Mycobacterium tuberculosis* is a more virulent organism that *H. capsulatum.* Fewer organisms are necessary to induce infection, disease results more commonly after infection and reactivation of disease occurs in HIV/AIDS at a higher CD4 count than with histoplasmosis. In tuberculosis, miliary involvement of the lung results from hematogenous infection whereas in histoplasmosis, miliary lung disease most often is caused by the inhalation of multiple spores. In tuberculosis, reinfection is uncommon but reactivation occurs frequently with the usual development of posterapical cavitary disease.

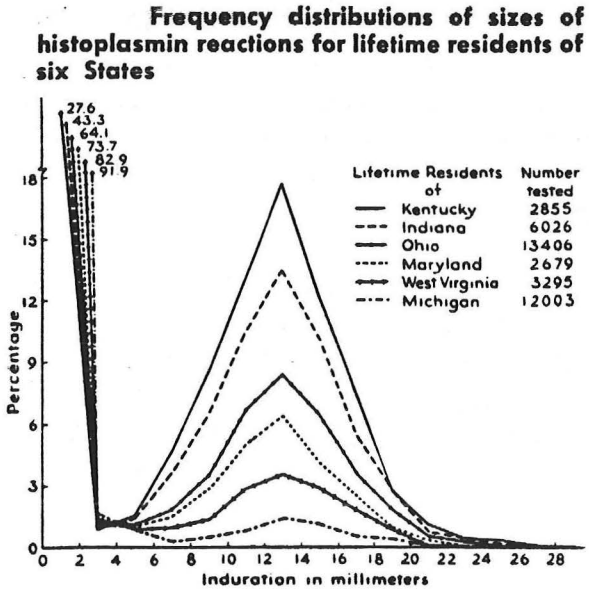
In contrast, chronic cavitary pulmonary histoplasmosis most likely represents the results of repeated infections in older men with chronic obstructive lung disease and an anatomically abnormal substrate (33, 100). Massive exposure to the organism, the extremes of age, and immunosuppression may lead to disseminated histoplasmosis. Women tend not to develop disseminated disease. More commonly than men, they may develop arthritis, erythema nodosum and erythema multiforme (46, 51, 63, 73). These arthritic complaints may occur after acute pulmonary disease or they may be no apparent acute pulmonary disease before the occurrence of arthritis.

Epidemiology.

Histoplasma capsulatum is found throughout the world, in Europe, Asia, Africa, and the Western hemisphere (11, 17, 57, 60). It is highly prevalent in Panama but its major focus is in the Central United States along the course of the Ohio and Mississippi river basins (Figure 1, 2) (24, 25).



Endemic distribution of histoplasmosis in the United States as based on histoplasmin skin test results in military recruits. (From Ed vard LB, et al: Am Rev Dis 99 (Suppl):1, 1969. Reprinted by permission.)



From: Edwards PQ, Palmer CE. *Nationwide histoplasmin sensitivity and histoplasmal infection.* Public Health Rep 1963;78:241-59.

The fungus lives in soil enriched by bird manure; it also lives and grows within the manure. Even after removal of the manure, the fungus can remain viable in soil samples for tens of years. The best concept of the epidemiology of histoplasmosis is that there is not a uniform distribution of the fungus in soil but there are "point sources" or "microfoci", which represent focal accumulations of the organism (9, 21). These microfoci occur in areas in which there have been roosts of birds or bats. Chicken coops represent a common point source.

Epidemiologically, the most dangerous event occurs in dry weather when the soil and manure has dried and when microfoci are disturbed by an activity that takes place promoting the production of dust and aerosols of infective microspores (6, 13, 18, 19, 35, 45, 62, 66, 82, 84). When the soil is wet and there is no disturbance of the microfocus by an active process, human infection appears relatively unlikely. The aerosols that are produced have the capacity to be transmitted over long distances but can be concentrated and directed to cause infections in humans by air conditioning systems. Activities implicated in outbreaks of acute pulmonary histoplasmosis with 10 or more clinical cases in the United States have been compiled and include shovelling pigeon droppings, chopping rotten wood, digging for treasure, digging for angleworms, shovelling coal and dirt, digging sewer lines, tossing a bag of soil around a class, raking leaves, bulldozing a bird roost, clearing and sawing rotten trees, digging, raking leaves, sweeping dirt, throwing dirt at bats, shovelling pigeon droppings, and sawing rotten trees (35). The construction of a tennis center in Indianapolis followed by the construction of a natatorium two years later resulted in two epidemics and an estimated 200,000 human infections in that city (70, 87, 97). Spelunking in caves which harbor bats also is associated with human infection (12).

In most instances, it seems likely that an active process of disruption of the microfocus has to occur. Simply being close to a point source has not resulted in numbers of cases being generated in the majority of instances reviewed in the literature. However, it should be noted that in one cave associated epidemic of histoplasmosis where bats were involved, mice were left outside the cave in cages and became ill without any disruptive activity occurring in the cave itself. In an epidemic of acute pulmonary histoplasmosis in campers who were adjacent to a known point source of *Histoplasma capsulatum,* it was thought that the campers most probably moved into the microfocus disturbing the soil during the course of the outbreak (35).

The point source or microfocus can usually be defined. Recommendations have been made to destroy the focus but this has been difficult since 3% formalin, an agent that has been shown to destroy histoplasma spores, cannot presently be used because of its potential carcinogenicity in humans (9). After exposure to an aerosol, persons of both sexes and every race develop acute disease with equal frequency. With massive exposure, clinical case attack rates may approximate or exceed 50% of those exposed.

In usual instances, however, clinical case attack rates are usually 1.0% or 1 in 100 persons infected (Table 1) (87).

Clinical Manifestations of Histoplasmosis

INFECTIOUS MANIFESTATIONS	HEAVY INOCULUM (%)	LIGHT INOCULUM (%)
Asymptomatic	50	99
Self-limited	50	1
Pulmonary (80% of symptomatic)		
Arthritis-erythema nodosum (10%)		
Pericarditis (10%)		
Mediastinal granuloma (unknown)		
Disseminated	Unknown	0.05
Chronic pulmonary	Unknown	0.05
Inflammatory or fibrotic manifestations	Unknown	0.02
Fibrosing mediastinitis		
Sarcoid-like		
Constrictive pericarditis		
Broncholithiasis		

Permission granted from W.B. Saunders Company. Wheat LJ. *Histoplasma capsulatum.* Chapter 286. Table 286-2 page 1907.

Incubation periods for the disease may be best explained by inoculum size and the occurrence of reinfection. They extend from 3 - 20 days and tend to be bimodal with an early peak occurring at 8 days, representing massive exposure in people who have been infected previously. A second peak at 14 - 15 days, represents the development of disease after the inhalation of smaller inocula in non-immune persons (Figure 3) (33).

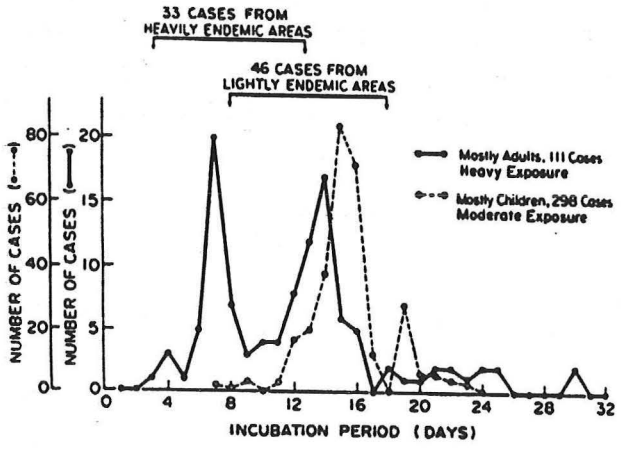


Figure 3: Reproduced by permission of the publisher, Williams & Wilkins, via the Copyright Clearance Center, Inc. Goodwin RA et al. *Histoplasmosis in normal hosts.* Medicine 1981;60:231-66.

Many epidemics have occurred in small towns or rural areas. The Indianapolis epidemics focus attention to the fact that disruption of microfoci can lead to large numbers of cases in urban areas. Since spores can be transmitted by wind currents over long distances, sporadic infections can occur. Without association with an outbreak, the point source may never be recognized.

Clinical Manifestations.

Case 1.

During a skin test survey in December 1994, this 45 year old white woman had a histoplasmin skin test which showed 31 mm of induration. In January 1995, a CXR done on persons with large skin test sizes showed a nodule 4 x 5 mm in size at the left lung base. There also was a fullness in the AP window and prominence of the left hilum, thought to be secondary to underlying adenopathy. A CT scan of the chest showed multiple pulmonary nodules less than 1 cm in diameter involving the mid-lung zone on the right and upper and lower lung zones on the left. In retrospect, in August of 1994, she had the onset of a dry cough, a mid-sternal sensation of pressure, decreased energy, dyspnea, fatiguability and arthralgias in her feet, ankles and knees. Since November, she had 3 discrete episodes of vertigo. She was placed on ketoconazole in February and gradually began to feel better with an increase in energy and a lessening of her cough. The vertiginous episodes disappeared. Before the skin test in December, she had attributed her symptoms to "getting older."

Case 2.

This 27 year old white man was in good health until February, 1994 when he developed fever, chills, night sweats, a dry cough and right pleuritic chest pain. After 5 weeks of symptoms, he sought medical attention. On March 15, he was afebrile and on exam had a 1 cm left posterior cervical lymph node. A CXR showed a left hilar mass which was confirmed by CT scan. A tuberculin skin test showed no reaction and sputum AFB stains and cultures were negative. He continued to have a dry cough and not to feel well. On April 21, he developed erythema nodosum over his lower extremities which was confirmed by biopsy. By the end of May, the patient's pulmonary and skin symptoms had resolved. A repeat tuberculin skin test showed no reaction. The following serological results were obtained:

	3/23/94	4/21/94	6/22/94
Histoplasma yeast CF	1:16	1:64	1:64
Histoplasma mycelial CF	<1:8	1:64	1:16

A urine histoplasma polysaccharide antigen (HPA) test on May 13 was negative. A CXR on December 1, 1994 showed no change.

Case 3.

This 38 year old white man ran 10 miles per day. On July 15, 1994, he noted the onset of fever, night sweats, headache, chest tightness, pleuritic chest pain, malaise and was unable to run. On August 1, he was seen at the Aston Center where he complained of fever, chills, headache and chest "heaviness." Physical examination showed splenomegaly. A CXR showed a RUL 1 cm nodule. A tuberculin skin test was negative. On August 16, a CT scan of the chest showed two 1 cm RUL nodules, diffuse mediastinal lymphadenopathy (1-2 cm in size) and an enlarged spleen. His symptoms began to abate at about this time.

Serological studies revealed the following:

	10/18/94	12/20/94
Histoplasma yeast CF	1:128	1:128
Histoplasma mycelial CF	1:32	1:64
Immunodiffusion		H&M bands +

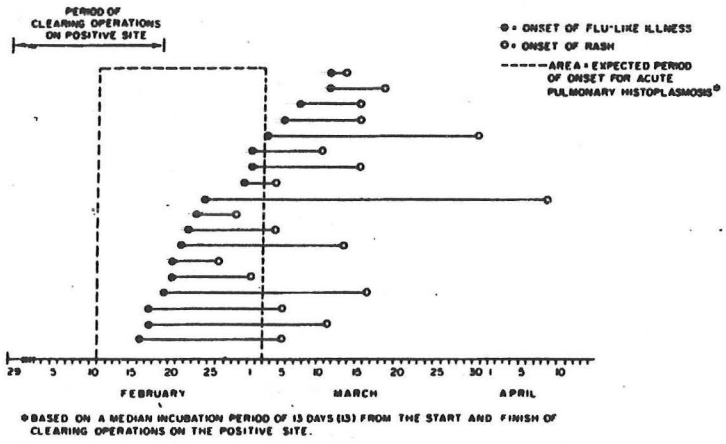
Case 4.

This 35 year old woman was in good health until September, 1994 when she noted the onset of malaise and a dry cough. She later developed dyspnea which prevented her from working out at a local Health and Fitness Club. In December, she noticed dysphagia with solid food sticking just above the sternal notch. A CT scan of the neck revealed paratracheal lymphadenopathy which narrowed and displaced the esophagus laterally. A CT scan of the chest showed a parenchymal infiltrate and paratracheal lymphadenopathy extended to the carina. A histoplasma yeast CF antibody titer was 1:64. There was no detectable antibody to the mycelial phase. She was started on itraconazole 100 mg BID. Ten days after beginning the medication, she was less dyspneic and had less difficulty swallowing. In retrospect, she remembered walking from the parking lot to the rear entrance of K building past a construction site. She noted that it had been quite dusty there during August and September, 1994.

In acute pulmonary histoplasmosis, the clinical illness consists of the relatively sudden onset of fever associated with headache, myalgias, and a dry non-productive cough (2, 7, 33, 43, 97).

Patients often complain of dyspnea and chest pain. The chest pain is of two types: (1) a substernal sensation of heaviness which is usually exacerbated by breathing and sometimes by swallowing, and (2) pleuritic chest pain which can be present without a pleural effusion. The substernal pain supposedly emanates from enlargement of mediastinal lymph nodes. Hoarseness may occur during the acute illness and connotes vocal cord involvement (67). Difficulty in swallowing may occur and is associated with tracheoesophageal lymphadenopathy. Although some persons only have a transient influenza-like illness with fever, muscle aches, and headache, more severe cases may last for several months with the patients reporting cough, chest pain, malaise and asthenia during that entire period. Weight loss is common.

Erythema multiforme, erythema nodosum, and arthritis may complicate the illness, being particularly common in women. The arthritis and skin manifestations either occur after the pulmonary syndrome or without pulmonary symptoms (Figure 4) (46, 51, 63, 73).



Period from Onset of Acute Pulmonary Histoplasmosis to Onset of Rash in 18 Cases of Erythema Multiforme and Nodosum.

Figure 4: Reproduced by permission of the publisher, Williams & Wilkins, via the Copyright Clearance Center, Inc. Medeiros AA, Marty SD, Tosh FE, Chin TDY. *Erythema nodosum and erythema multiforme as clinical manifestation of histoplasmosis in a community outbreak.* N Engl J Med 1966; 274:415-20.

Epidemics of erythema nodosum have been reported and represent primary infections. They are more likely to occur in areas in which reinfection histoplasmosis is uncommon. Sometimes the inoculum of spores is of sufficient a magnitude that patients develop acute miliary pulmonary disease with severe dyspnea requiring hospitalization and oxygen therapy. Organisms multiply locally producing areas of pneumonitis and associated

mediastinal lymph node involvement. Hematogenous dissemination occurs and metastatic complications can be produced. The variety of metastatic complications have been most completely studied during the Indianapolis epidemics in which it was estimated that over 200,000 people were infected. Esophageal ulcers, parotitis, adrenal insufficiency, chorioretinitis, intestinal lymphangiectasia, and epididymitis were reported (97). When lymph nodes abut on the pericardium, they may rupture into that structure producing acute pericarditis. The clinical manifestations are similar to that of acute pericarditis from other causes but hemorrhagic pericardial effusions may be common. It is unusual to isolate the organism from the pericardial fluid although this has been accomplished on occasion. Constrictive pericarditis may follow episodes of acute pericarditis and require pericardiectomy (99, 102). Endocarditis is a rare complication (101).

Acute ocular histoplasmosis involves the choroid and retina. The pathologic lesion most probably is similar to the pulmonary nodule. If it involves the macula, visual difficulties can be induced. Ocular histoplasmosis is a rare manifestation of acute disease but its pathogenesis is probably similar to the chorioretinitis that has been described in the disseminated form of the disease particularly as it complicates the course of AIDS (42, 77). Acute ocular histoplasmosis and disseminated histoplasmosis involving the eye almost certainly have a different pathogenesis than the presumed ocular histoplasmosis syndrome (POHS) in which visual difficulties usually occur 10-30 years after the inciting infection and in which the presence of organisms may be difficult if not impossible to demonstrate. The POHS will be considered in greater detail later.

Case 5.

A 47 year old white man presented in August, 1989 with a six-week history of difficulty in reading with the left eye. He was seen by his optometrist, who measured his best corrected visual acuity at 20/15 OD and 20/25 OS. The optometrist noticed "a peculiar macular reflex," and the patient was referred for retinal evaluation. At the time of his retinal evaluation, the past ocular history was unremarkable, except for mild myopic astigmatism. A review of the patient's medical history was unremarkable, except for a mild upper respiratory tract infection three weeks prior to onset of his symptoms. His vision had remained stable at 20/15 OD and at 20/25 OD with best correction OS. Peripheral visual fields exams were within normal limits; the Amsler grid in the left eye showed minimal central metamorphopsia. External ocular examination, anterior segments, pupillary reactions and tonometry were with normal limits. The right retinal exam was unremarkable; the left eye showed a deep chorioretinal yellowish lesion with no overlying vitreous cells. A fluorescein angiogram revealed the foveal lesion to be hypofluorescent, followed by mild staining in the late stages of the angiogram. A systemic medical evaluation revealed no significant abnormality.

The patient's symptoms and lesion changed minimally over the next six months, and the vision stayed stable at 20/30. In May, 1990, the patient noted further metamorphopsia, and the vision had deteriorated to 20/80. The right eye was unaffected. Examination of the left fundus revealed an enlargement of the lesion to approximately one disc diameter in size with a central pigmented spot. Once again, no subretinal fluid was noted, and the

lesion was localized to the outer retina. The patient was seen by eminent retina specialists around the country, but no specific diagnosis could be obtained.

The patient received a three-week course of 100 mg oral prednisone per day without any significant change in the ocular lesion or in his symptoms. Just before starting steroid therapy, a histoplasma antibody test was obtained. Prior negative tests included an ANA, RF, tuberculin skin test, antibody levels for toxoplasma, syphilis, Lyme disease, blastomycosis, and coccidioidomycosis. When the histoplasma CF antibody titer returned, the patient noted that he had saved a serum sample at the onset of illness that and stored it at -20°C.

The patient was started on fluconazole 400 mg per day in June, 1990 and the oral prednisone was rapidly tapered. After two months, the fluconazole was decreased to 200 mg per day and this dosage was continued for another four months. Soon after the onset of fluconazole antifungal therapy, the patient noticed an improvement in his visual acuity, and his vision had returned to 20/20 by December, 1990. Over the course of the last four years, the patient has been asymptomatic and has retained visual acuity of 20/15 in his left eye. His most recent exam showed a well-healed flat atrophic retinal scar just inferior to the fovea.

After the acute infection, manifestations of histoplasmosis occur which seem best related to immune reactions and excessive fibrosis. Sarcoidlike manifestations can occur (93). Another reaction has been termed the mediastinal granuloma. During the course of acute pulmonary histoplasmosis, lymph nodes in the mediastinum become involved, coalesce and become enveloped in a fibrous capsule (47, 48). The mediastinal granuloma with its fibrous capsule has a mass effect that can obstruct major structures within the mediastinum, including the superior vena cava (SVC) and the esophagus. The mediastinal granuloma has been treated successfully with azole therapy. In fibrosing mediastinitis, there is a central core of caseous necrosis containing a few viable organisms with a fibrous capsule that becomes thickened and surrounds mediastinal structures (34). In contrast to the mediastinal granuloma, the primary pathologic process in fibrosing mediastinitis is the excessive proliferation of fibrous tissue. This fibrous tissue encircles and obstructs major structures like the superior vena cava, the pulmonary arteries, the pulmonary veins and bronchi. Progressive disease may occur and the patient may be incapacitated by the SVC syndrome, pulmonary arterial obstruction, pulmonary venous involvement producing a physiological situation similar to mitral stenosis or bronchial narrowing with impairment of breathing and the subsequent development of bronchiectasis. In advanced fibrosing mediastinitis, medical therapy is not sufficient to reverse the unrelenting fibrosis and is not recommended. In early cases of fibrosing mediastinitis, there may be a situation where there may be relatively many organisms with chronic inflammation and only beginning fibrosis. In these cases, azole therapy with or without steroid administration may benefit the patient.

Case 6.

This 25 year old athletic white woman developed dyspnea on exertion in June, 1989. One month later she noted edema of her face and hands, relieved by diuretic therapy. Later that month, she noted easy fatigue and arthralgias most prominent in her shoulders, elbows and knees. Her appetite decreased and she lost 15 - 20 pounds. She noted lightheadedness and syncope with exercise, tying her shoes or rising from a squatting position. Her residence was in Tyler, Texas.

A CXR showed calcified mediastinal lymph nodes and a calcified RUL nodule; calcified splenic granulomas were also noted. The EKG was normal. An echocardiogram showed a bicuspid aortic valve but no valvular dysfunction. A cardiac catheterization and endocardial biopsy were normal. A CT scan of the chest showed a calcified mass in the right paratracheal area and RUL calcifications. An MRI of the chest showed a mediastinal mass causing marked narrowing of the superior vena cava. A venogram confirmed the obstruction of the superior vena cava.

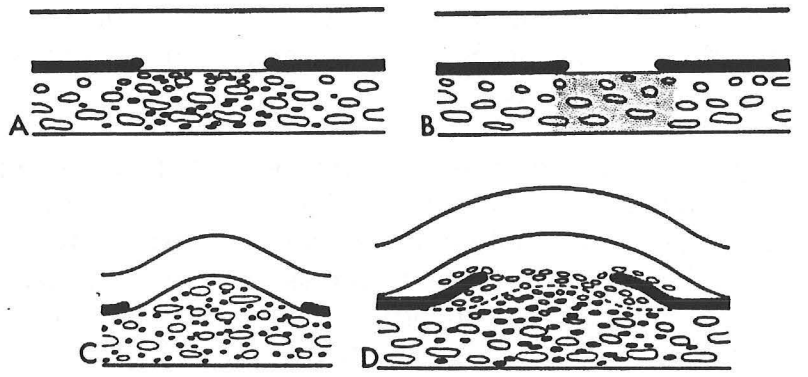
Thoracic surgery in July, 1990 showed encasement of the superior vena cava in an inflammatory calcified mass of lymph nodes. The SVC was narrowed over 2 - 3 cm in length beginning 2 cm above the right atrial junction and extending to the take-off of the innominate vein. The inflammatory mass was dissected from the SVC and its diameter was increased by insertion of a pericardial patch. In September, 1990 she was asymptomatic. In December, she had mild symptoms of SVC obstruction, particularly with exercise. Venography demonstrated a patent SVC with mild narrowing below the level of the innominate vein and no pressure gradient across this area.

In March, 1991, she had a recurrence of her symptoms including swelling of her hands and face and syncope after lifting an object. Venography showed partial obstruction of the SVC by extrinsic compression by a large adjacent lymph node. No gradient was noted. There was no significant change from the venogram performed in December. She was treated with 400 mg. fluconazole a day for 6 months and a 3 month course of prednisone. Repeat venograms in June and September of 1991 showed less obstruction of the SVC. The minimum diameter of the SVC had increased from 5 to 7 mm. In October, 1993, the minimum diameter of the SVC was 10 mm. The surface area of the most constricted part of the SVC had increased from 19.6 mm^2 (December, March, 1991) to 38.5 mm^2 (June, 1991) to 78.5 mm^2 (October, 1993). In December, 1990, a histoplasma yeast CF antibody titer was 1:16. In September, 1993, the titer was <1:8. In November, 1993, an echocardiogram and an MRI of the chest were normal. When contacted in April, 1995, she stated that her problems had essentially disappeared and that she had returned to work and complained only of fatigue at the end of a 12 hour work shift.

In the presumed ocular histoplasmosis syndrome (POHS), most patients have had their primary episode of histoplasmosis 10-30 years previously (20, 29, 38, 39, 49, 56, 64, 68, 69, 71, 86). The syndrome usually occurs in areas heavily endemic for histoplasmosis;

it also has been reported in non-endemic regions and these cases may represent infection with a different organism. In fully developed POHS, skin tests are usually positive although they are not presently performed because they may exacerbate the ocular problem. Serological studies for evidence of histoplasmosis are generally negative although occasionally they may be positive (51, 78). The diagnosis is established by symptoms, the ophthalmological examination, the exclusion of other diagnostic entities and by considering the regions of the U.S. where the patient had lived.

Patients with POHS have punched out chorioretinal holes, the so-called "histo spots", peripapillary scarring and burned out macular scars. With activity of the disease process, the macular scar enlarges due to edema or hemorrhage (Figure 5) (69).



Choroiditis in an old scar (A) may either subside (B) or progress by developing into an elevated lesion (C) or by developing a break in Bruch's membrane allow a neovascular net to grow under the pigment epithelium and/or under the sensory retina and result in detachment of one or both of them (D).

Retinal detachment may occur. Neovascular membrane formation may occur with the membrane having its origin in the choroid and extending between Bruch's membrane and the pigmented retinal epithelial layer. It can also extend between the pigmented retinal epithelial area and the rest of the retina. The neovascular membrane may originate in the macula or may extend into the macula from an adjacent retinal scar. Macular vision is impaired. The mechanism of activation of the macular scar is not known. Since organisms are difficult to find in this syndrome and serological tests are usually negative, antifungal therapy is not recommended. There have been, however, case reports in which amphotericin B has been tried with some success (32). These latter patients had elevated complement fixation test antibody titers and they may have represented instances of the earlier part of the syndrome in which organisms were present in the lesions. In the usual

case of POHS, therapy involves corticosteroid administration, laser treatment and the surgical removal of the neovascular membrane (4, 31, 80).

Most retinologists consider the POHS as a late manifestation of "burnt out" ocular histoplasmosis. The mechanism of activation of the macular scar is not known but widely thought to be immunological in nature (Table 2) (69).

Attributes and Risk Factors Related to Development of Maculopathy in POHS

Primary Infection with *H. capsulatum*	1. Heavier inoculum	No disseminated choroidal lesions	Attributes–risk factors: age 20–50, white race, male > female
		Disseminated choroidal lesions	→ Maculopathy
or other unknown agents	2. More virulent organisms 3. Chance		Histo spots in macula or around disc; pulmonary calcification; hyperreactive cellular immune system

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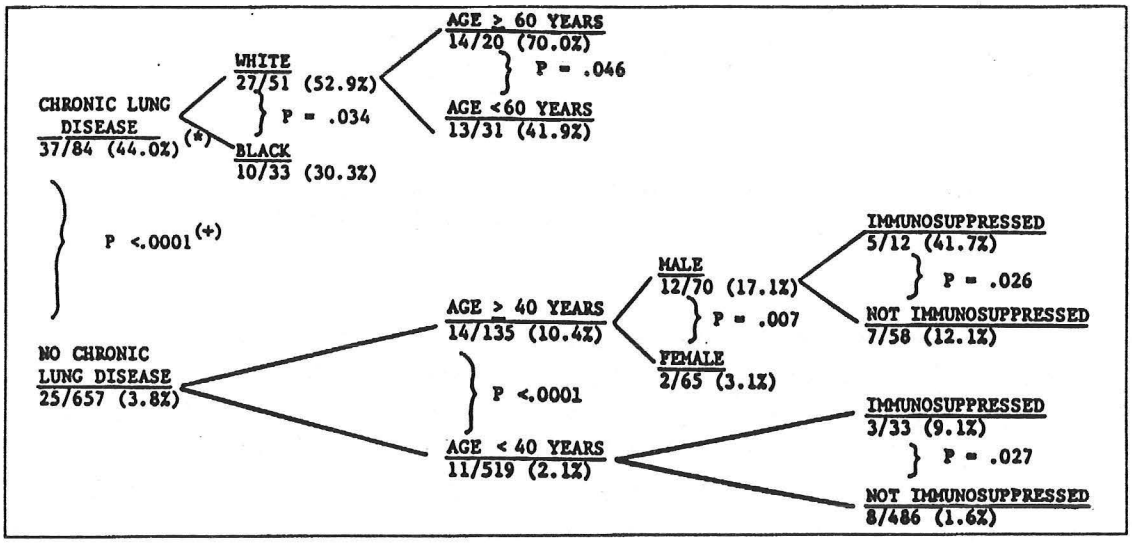
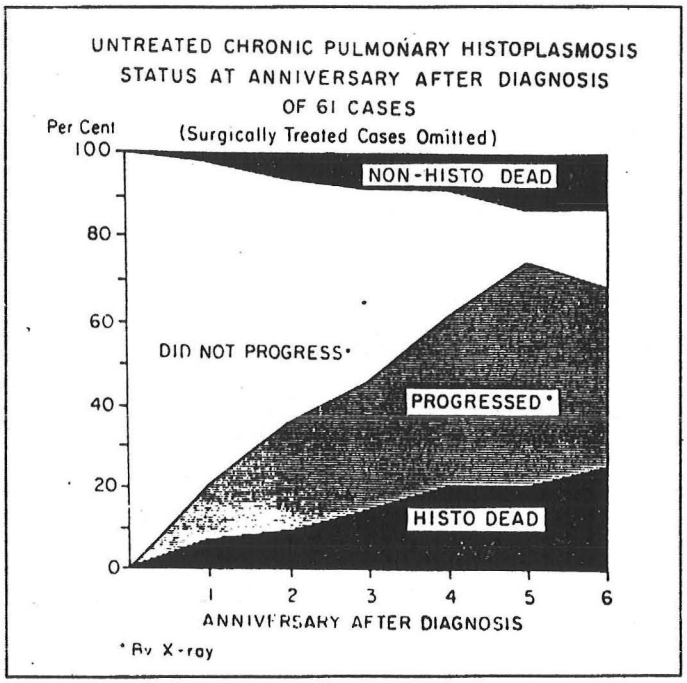
The POHS must be distinguished from acute ocular histoplasmosis or ocular involvement in disseminated disease in which organisms can be demonstrated easily and which may respond to antifungal therapy with either amphotericin B, itraconazole, or fluconazole.

Chronic cavitary pulmonary histoplasmosis occurs most commonly in middle to older aged white men who have been heavy cigarette smokers and who have underlying chronic obstructive lung disease (Figure 6) (65, 83, 100).



Reproduced by permission of the publisher, Williams & Wilkins, via the Copyright Clearance Center, Inc. *Cavitary histoplasmin occurring during two large urban outbreaks. Analysis of clinical, epidemiologic, roentgenographic, and laboratory features.* Wheat LJ, et al. Medicine 1984; 63:201-9.

To account for the age distribution, it has been thought to be a manifestation of reinfection. A minority of patients are immunologically suppressed. Typically, the process begins as an interstitial pneumonitis in an area of bullous emphysema. The apical region of the lung is usually involved, particularly the posterior apical segment. Replication of the organism occurs with release of antigen accompanied by delayed hypersensitivity reactions in a segment of lung with pre-existing disease. Ischemic necrosis related to vessel involvement may also contribute to cavity formation. Chronic cavitary pulmonary histoplasmosis may not be associated with new mediastinal lymphadenopathy. Two types of cavities are produced, a thin-walled and a thick-wall cavity. Thick-walled cavities progress and destroy more lung tissue (Figure 7) (83).



The clinical manifestations exactly simulate reactivation tuberculosis. Bronchoscopy or lung biopsy may be necessary to make the diagnosis. Once the diagnosis of chronic cavitary pulmonary histoplasmosis is made, the patient should receive a course approximating 2500 mg. of amphotericin B. This may be accomplished by amphotericin B alone or the combination of amphotericin B and itraconazole or itraconazole alone for a 6 month period. Hemoptysis may complicate the disease and resection of diseased lung may sometimes be necessary.

Case 7.

This 44 year old white man developed fever, a productive cough and left pleuritic chest pain in May, 1993. He was first seen at Parkland Memorial Hospital in June where a CXR showed RUL bullous disease and a LUL infiltrate with cavity formation. He smoked 2 packs cigarettes a day, had lost 20 pounds and complained of hemoptysis. He had a negative tuberculin skin test with positive controls. He was placed on anti-tuberculous chemotherapy and bronchoscoped. Cultures were negative for *M. tuberculosis* and fungi. In September, 1993, the infiltrate had spread to the RUL and a RUL lobectomy was performed. Biopsy shoed cavitary histoplasmosis. He was placed on itraconazole for 6 months. In June, 1994, he had an episode of hemoptysis, was bronchoscoped and was admitted to the hospital for a resulting pneumothorax. CXR showed LUL scarring and residual cavitary disease.

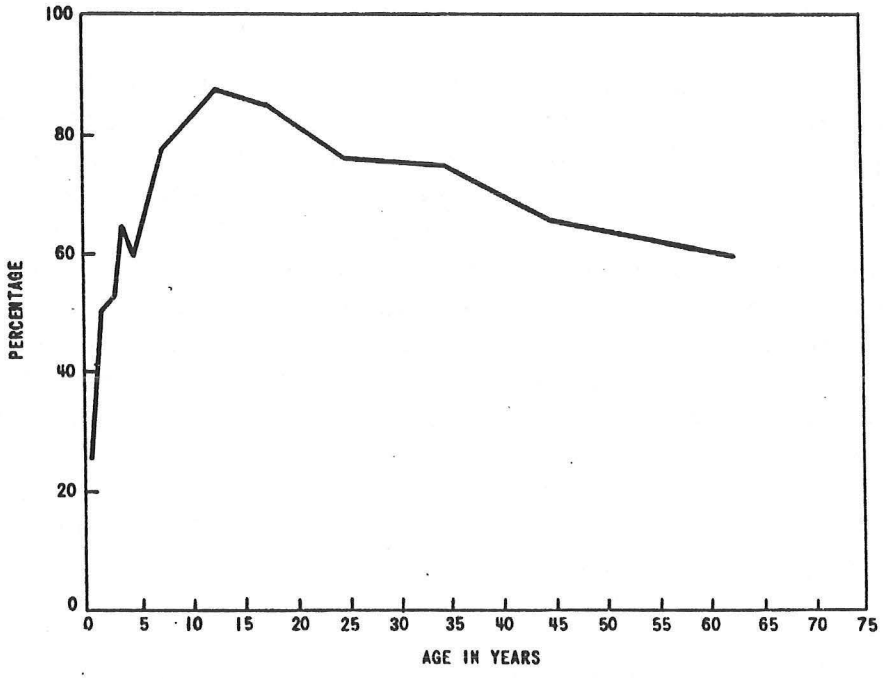
In immunocompromised patients, histoplasmosis can result in disseminated disease. Disseminated histoplasmosis is usually seen in HIV infections when the CD4 count is below 100 CD4 cells per mm^3 (50, 54). The disseminated form of the disease may be seen in other immunocompromised patients including infants and elderly persons. With a large inoculum, immunologically normal persons may be affected. Disseminated histoplasmosis usually implies the involvement of multiple organ systems (23, 72, 76, 88, 89, 98). It may result from primary infection or reactivation of a quiescent infection. Patients usually are febrile, have associated wasting, and an enlarged liver and spleen. They may have a skin rash (10, 26). Pulmonary infiltrates are common; there may be a diffuse reticulonodular infiltrate but often the lesions are not characteristic and cannot be distinguished from pneumonia caused by other organisms (16, 54). When the liver is involved, they may have the picture of granulomatous hepatitis, i.e., a disproportionately elevated alkaline phosphatase and only a slight to moderate AST or ALT elevation. Adrenal involvement can lead to adrenal masses and adrenal insufficiency (44). Gastrointestinal tract involvement is manifested by oral ulcers, small bowel and colonic ulcers, gastrointestinal tract perforation, and constricting "apple core" lesions of the colon simulating adenocarcinoma (3, 15, 37). Retroperitoneal lymphadenopathy may be present as well as mesenteric lymphadenopathy. Patients can present with small bowel obstruction. When the kidneys are affected, ureteral obstruction may occur, and the testicle and epididymis may be involved in an inflammatory mass (59, 79). Frequently there is bone marrow involvement with the development of anemia, leukopenia and thrombocytopenia. Patients may develop central nervous system disease manifested by granulomatous meningitis or they may actually have mass lesions in brain with central cavitation. Although seen only in a minority of patients, a characteristic presentation of disseminated histoplasmosis in AIDS is hepatosplenomegaly, pancytopenia, fever, and disseminated intravascular coagulation. A microangiopathic hemolytic anemia is present as well as a prolonged prothrombin time, decreased platelets, elevated partial thromboplastin time, decreased fibrinogen and an increased level of d-dimers (54, 98).

Diagnosis.

The histoplasmin skin test involves use of a standardized extract of a mycelial phase culture. The antigen (0.1 ml) is placed on the volar surface of the forearm and read as mm of induration at 48 hours. A positive test has ≥ 5 mm of induration. It should be used only for epidemiological purposes since it may remain positive for long periods and in sensitized persons may elevate the mycelial and less commonly the yeast phase complement fixation test titer or result in a positive M band in an immunodiffusion test (8, 36, 41, 85).

The skin test size can wane and become negative with age (Figure 8) (103).

—Percentage of Persons Positive to Histoplasmin by Age, Williamson County, Tennessee, August, 1945–July, 1950

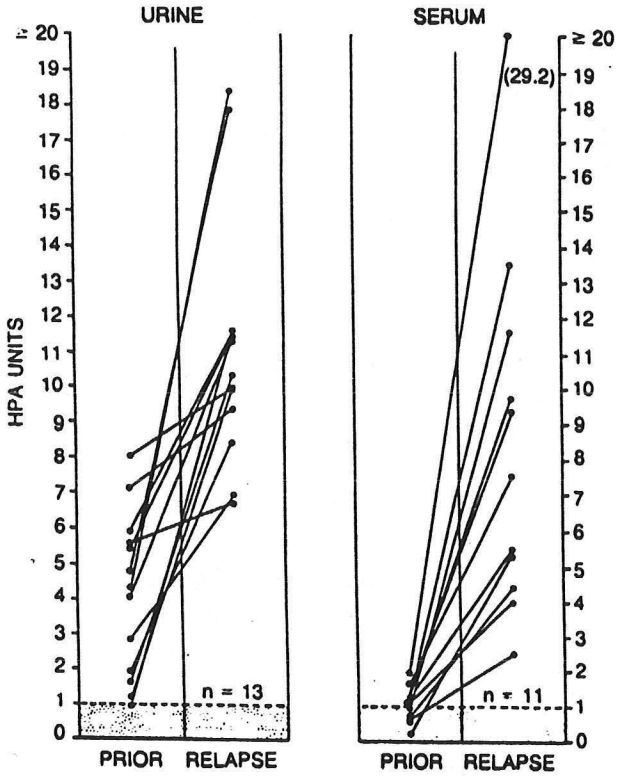


Zeidberg LD, Dillion A, Gass RS. *Some factors in the epidemiology of histoplasmin sensitivity in Williamson County, Tennessee.* Am J Publ Health 1951;41:80-9.

The most widely utilized serological test is the complement fixation test with yeast and mycelial phase antigens. A four-fold rise or fall in titer is diagnostic of acute disease; a complement fixation test titer of 1:32 in a single specimen is considered presumptive evidence of infection.

With the immunodiffusion test, the presence of both M and H bands is quite specific for recent disease. The presence of a single H band is more specific than that of an M band as evidence of acute disease if only one band is present. A new test ascertaining the presence of histoplasma polysaccharide antigen (HPA) in serum, urine, and other body fluids like cerebrospinal fluid or pleural fluid has been developed. Its presence in urine is a sensitive test for the presence of disease. The test is based upon radioimmunoassay technology. The presence of antigen can be used to diagnose disease but it can also

be utilized to follow patients and determine whether they are responding to therapy or whether they are having a relapse of disease (Figure 9) (90, 91, 96).



***Histoplasma capsulatum* variety *capsulatum* polysaccharide antigen levels in cases of relapse.**

Reproduced with permission from Wheat LJ et al. *Histoplasmosis relapse in patients with AIDS: Detection using Histoplasma capsulatum variety capsulatum antigen levels.* Ann Intern Med 1991;115:936-41.

Although formerly available only in a single laboratory, a number of other subspecialty laboratories are also beginning to perform the assay for HPA. The antigen is a polysaccharide that has an estimated molecular weight less than 10,000.

Laboratory techniques like the ELISA test and the Western blot have been used to diagnose infection with *Histoplasma capsulatum* (81). These tests appear to be sensitive and specific and in time may displace some of the other tests. The Western blot tests for five protein antigens. Infected persons most commonly have reactions with three of the higher molecular weight antigens. One should to be aware of the competence of the laboratory in ordering serological tests to determine the presence of infection.

The diagnosis of disseminated histoplasmosis usually depends upon demonstration of the organism or the polysaccharide antigen in body fluids, like blood, urine, or cerebrospinal fluid. Isolator tube blood cultures are oftentimes positive. Bronchoalveolar specimens may yield the organism. Cultures of the cerebrospinal fluid may be positive. Bone marrow cultures may also be positive for the organism. The organism may be seen in the peripheral blood or in buffy coat preparations. Elevated levels of histoplasma polysaccharide antigen (HPA) may be elevated in urine, serum, pleural fluid, or cerebrospinal fluid. HPA levels can be utilized to diagnose and follow the course of disease. A decreasing HPA urine level correlates with a positive therapeutic response with relapses showing increasing levels. The serological study of patients with disseminated histoplasmosis may not be rewarding because of their level of immunosuppression so that antibody formation to the organism may be diminished.

Therapy.

Effective drugs against *Histoplasma capsulatum* include amphotericin B (AMB), itraconazole, fluconazole, and ketoconazole (52, 55, 74, 94). The gold standard of therapy is amphotericin B. The azole with the best antimicrobial effect is itraconazole. The agent that penetrates best into the cerebrospinal fluid and the eye is fluconazole. Some isolates of *H. capsulatum,* however, may be resistant or relatively resistant to fluconazole. Ketoconazole is also an effective agent but its use has been superseded by itraconazole in the treatment of severe systemic disease. Although amphotericin B remains the cornerstone of therapy, its course does not have to be as prolonged as previously because of the availability of the azoles.

Most acute disease does not have to be treated but patients that have severe symptoms like esophageal obstruction can be treated with a course of itraconazole or ketoconazole with relief of their symptomatology. Patients with acute ocular histoplasmosis can be treated with fluconazole. Patients with symptoms due to a mediastinal granuloma have been reported to be have been cured by the administration of fluconazole. Chronic cavitary pulmonary histoplasmosis can be treated with 2500 mg of amphotericin or six months of itraconazole at 200 mg twice a day (95). The therapy of disseminated histoplasmosis in AIDS when the patient is acutely ill, with a high fever, central nervous system involvement or DIC involves the administration of amphotericin B. One gram of AMB should be administered over a four to twelve week period of time. AIDS patients will then require life-long maintenance therapy with itraconazole at 200 mg twice a day. In AIDS patients with less severe disease, induction can be initiated with itraconazole 200 mg three times a day for three days followed by 200 mg twice a day for their lifetime. In patients with lesser degrees of immunosuppression than AIDS, therapy can be initiated with amphotericin B given for 500 to 1500 mg followed by a course of itraconazole or ketoconazole to finish six months of therapy. In immunologically normal persons with disseminated histoplasmosis, therapy can be accomplished with 2500 mg of amphotericin

as a total dose or with a six month course of itraconazole at 200 mg twice a day. Ketoconazole at 200 mg twice a day has also been used successfully.

Important drug administration issues with itraconazole and ketoconazole include the fact that they need to be given when the pH of the stomach is acid so that absorption can occur. The use of rifampin, rifabutin, phenytoin, and to a lesser extent isoniazid may lower itraconazole levels (22). Concomitant administration of itraconazole or ketoconazole with one of the newer non-sedating antihistaminic agents (terfenadine, astemizole, loratadine), will raise the serum level of the antihistaminic agent. This can result in prolongation of the QT interval and ventricular tachycardia.

The Campus Experience with Histoplasmosis.

In 1989, the first case of histoplasmosis on the medical school campus occurred in a person who worked in the 5th floor of the L building. There have now been a total of 15 cases; five occurring from 1989 through November 1993 and ten cases occurring from the first of January 1994 through September 1994 (Table 3).

Case Number	Room Number	Onset	Syndrome	Laboratory Confirmation
1.	L5	8/89	Acute ocular histoplasmosis	4-fold drop in CF Ab titer
2.	L5	8/92	Fever, lung nodule	Pathology +
3.	K5	11/92	Fever, lung nodule	Pathology +
4.	Physical Plant	6/93	Fever, lung nodule	Pathology +
5.	H4*	11/93	Coin lesion	Granuloma on pathology CF Ab titer (yeast) 1:16
6.	J6	1/94	Pleural effusion	Culture +
7.	L5	3/94	Fever, lung nodule, hilar adenopathy, erythema nodosum	4-fold rise in CF Ab titer
8.	Grounds	3/94	Fever, hoarseness, vocal cord lesions, dry cough	CF Ab (yeast) 1:8, M band on immunodiffusion, 23 mm skin test, clinical response to ketoconazole
9.	L5	4/94	Fever, lung nodules	CF Ab (yeast) 1:32
10.	Y8	5/94	Tracheoesophageal lymphadenopathy	Pathology +
11.	K2	7/94	Mediastinal lymphadenopathy	CF Ab titer (yeast) 1:64, (mycelial) 1:8
12.	K5	7/94	Fever, lung nodule	CF Ab titer (yeast) 1:128, (mycelial) 1:32
13.	Grounds	7/94	Lung nodules, lymphadenopathy	CF Ab (yeast) 1:256
14.	L5	8/94	Lung nodules, mediastinal lymphadenopathy	Histo skin test 31 mm
15.	K2	9/94	Mediastinal lymphadenopathy, esophageal obstruction	CF Ab (yeast) 1:64

All these cases of histoplasmosis on the campus have been laboratory documented. Five cases occurred on L5, two on K5, two on K2, two in grounds keepers, one on H4, one on J6, one on Y8, and one in a physical plant employee who was an avid jogger. Of the cases, five had the diagnosis established by thoracotomy. In August 1994, when there were four documented and two suspicious cases, discussions were held concerning the best way to proceed to investigate the cases. With the occurrence of another documented case, it was decided to perform a skin test survey to define better the epidemiology of histoplasmosis on the campus. The skin test antigen was from a single lot of an extract from a mycelial phase culture (Parke-Davis). In December 1994, the skin test survey was done. 640 persons were picked by random assignment from the G, K, and L buildings and X and V, two off-campus buildings. Skin tests were placed and results obtained on 404 of those 640 persons. Skin tests were also applied on 16 of 17 grounds keepers. Persons not having a skin test applied and read were more likely to be from the off-campus buildings (X and V) but otherwise there were no significant differences between these persons in the sample and those who had had skin tests applied. G building was included because it was a potential intermediate building. It had had no cases but was on campus adjacent to K building. Using a skin test size ≥ 5 mm of induration, 94% of grounds keepers, 49% of persons in K and L buildings and 28% of persons in X and V buildings were positive (Table 4).

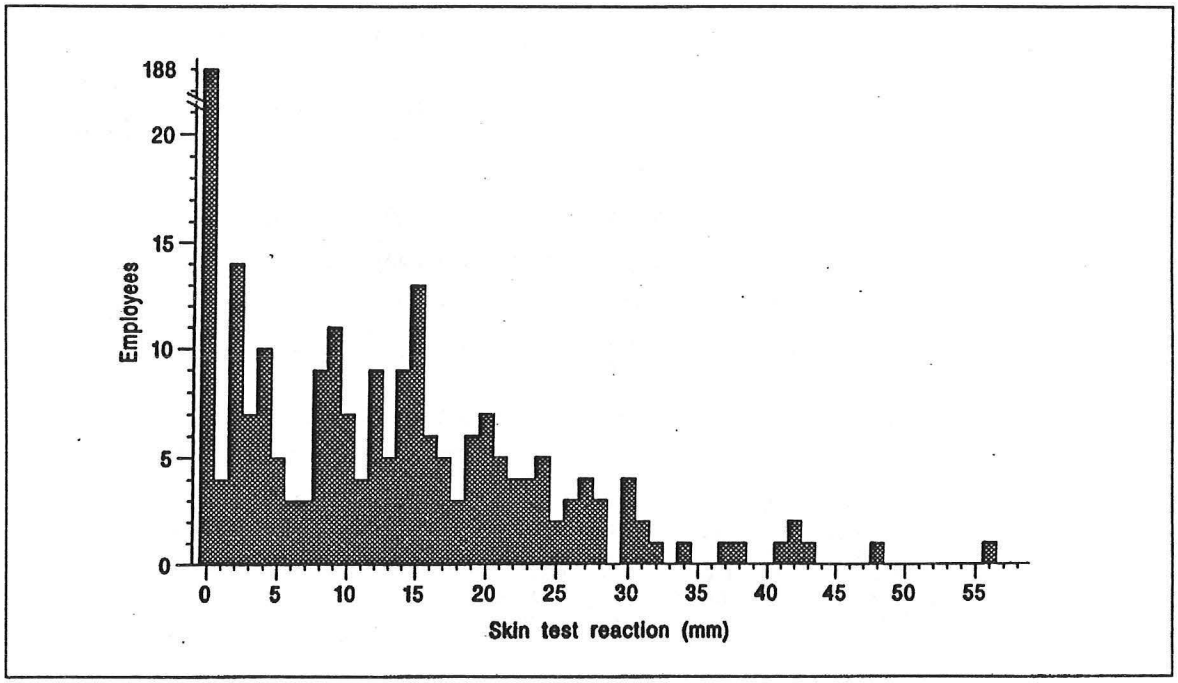
Rates of positive skin tests (≥5 mm) by building.

Building	Subjects	Positive skin test N (%)	RR (95% CI)
X and V	136	38 (28)	1.0
G	69	28 (41)	1.5 (1.0-2.1)
K and L	199	98 (49)	1.8 (1.3-2.4)¶
Grounds workers	16†	15 (94)	3.4 (2.5-4.5)¶
X	66	17 (26)	1.0
V	70	21 (30)	1.2 (0.7-2.0)
G	69	28 (41)	1.6 (1.0-2.6)‡
K	96	39 (41)	1.6 (1.0-2.5)‡
L	103	59 (57)	2.2 (1.4-3.4)§
Grounds workers	16†	15 (94)	3.6 (2.4-5.6)¶

*Includes skin test reactions with ≥1 mm of induration.
†One grounds keeper was anergic (failed to react to controls).
‡Difference from X building, p<.05.
§Difference from X building, p<.0001.
‖Difference from X and V buildings, p<.001
¶Difference from X and V buildings, p<.0001

The differences between the grounds keepers, the K and L buildings vs. the X and V buildings were significant ($p<.0001$). Mean skin test sizes were markedly different between grounds keepers (24.8 mm ± 2)(Mean ± 1 SEM), persons in K and L buildings (17.1 mm ± 1.0), and persons in X and V buildings (11.2mm ± 1.3). The differences in skin test sizes between grounds keepers and persons in the X and V buildings was significant ($p < .0001$) as was the difference in sizes between persons in the K and L buildings and the X and V buildings ($p< .001$). As expected, persons in the G building had an intermediate skin test prevalence and skin test sizes.

Although a skin test size of 5 mm or greater is the commonly excepted definition of a positive test, in this study an analysis of skin test sizes showed that persons having skin tests sizes less than 12 mm in duration could largely be explained for years of residence in states with known high endemic levels of histoplasmosis (Figure 9).



For the purposes of performing a multivariate analysis, persons with skin test sizes equal to ≥ 12 mm induration were counted as being positive. The same conclusions as summarized above were drawn from the results. Grounds keepers and persons working in the K and L buildings had the highest percentage of positive skin tests and the positive skin tests were significantly larger than persons working in buildings off campus. The multivariate analysis revealed other risk factors independent of being a grounds keeper and working in K and L buildings, viz., jogging, basketball playing and bird watching on campus.

The multivariate analysis excluded parking location and tennis playing as independent variables. Risks of developing a skin test size ≥ 12 mm tended to vary by year for each location on campus (Table 5).

Rates of positive skin test (≥12 mm) and average size of skin test reactions by building.

Building	Subjects	Positive skin test N (%)	RR (95% CI)	Mean size (mm) of skin test reactions (SEM)*
X and V	136	20 (15)	1.0	11.2 (1.3)
G	69	20 (29)	2.0 (1.1-3.4)‡	13.5 (1.7)
K and L	199	80 (40)	2.7 (1.7-4.2)¶	17.1 (1.0)‖
Grounds workers	16†	15 (81)	6.4 (4.2-9.7)§	24.2 (2.1)§
X	66	10 (15)	1.0	9.6 (1.4)
V	70	10 (14)	0.9 (0.4-2.1)	12.7 (2.1)
G	69	20 (29)	1.9 (1.0-3.8)†	13.4 (1.7)
K	96	31 (32)	2.1 (1.1-4.0)†	16.1 (1.6)†
L	103	49 (48)	3.1 (1.7-5.8)§	18.6 (1.2)§
Grounds workers	16†	15 (81)	6.2 (3.4-11.1)§	24.8 (2.1)§

*Includes skin test reactions with ≥1 mm of induration.
†One grounds keeper was anergic (failed to react to control antigens).
‡Difference from X building, p<.05.
§Difference from X building, p<.0001.
‖Difference from X and V buildings, p<.001
¶Difference from X and V buildings, p<.0001

The data derived from the analysis of cases and the skin test survey indicate that histoplasmosis is now being and has been transmitted on campus from at least 1989 through 1994. The data seem most consistent with a series of point source outbreaks occurring at different locations on campus and at different years. Grounds keepers must be being infected and reinfected probably at different places on campus. Since L5 had the next highest number of cases (5), and the highest percent of persons with positive skin tests (62%), these persons were probably intensely exposed to a point source, perhaps at

multiple times. Such a point source may have been the construction of the bridge between the north and south campuses and then the construction of the connector between L building and the bridge. The construction involved excavating the prior site of a large black bird roost. Excavation of the site may have generated aerosols of spores that were concentrated and distributed by the air treatment system for the building. The air intake vents for L building are immediately above L5. The air is not recirculated in either K or L buildings and large quantities of air intake are necessitated each day. These construction sites do not explain the case occurring before 1992 or the newest K2 cases. Both recent K2 cases recall walking past a construction site near K2 during the summer and being exposed to dust.

The bird sanctuary remains a concern. Two cases in grounds keepers occurred in 1994 after working in the sanctuary. In January 1994, grounds keepers entered the sanctuary to clear sections of the woods. In July 1994, a bird die-off occurred in which about 50 birds died due to salmonellosis, proven at autopsy at Texas A&M University. Grounds keepers collected the birds for autopsy. Although entry into the bird sanctuary probably generated at least two clinical cases, the multifocality of the other cases, their uneven distribution over time and the fact that the bird sanctuary usually remains undisturbed argues against the sanctuary as being the single continuing point source of the outbreak. Further continuing serological study of the grounds keepers and of persons in L5 is planned to detect instances of asymptomatic infection. Environmental samples need to be collected and cultured so that we can have an independent assessment of the problem. Building and construction sites will need to be prepared before and during excavation by keeping ground surfaces wet. Air intake filters will need to be maintained rigorously and tested in a regular fashion. Persons working on the campus need to be aware that histoplasmosis may be a recurring problem. Physicians need to know its clinical manifestations and the necessity to document the cases so that surveillance can establish whether infection is being controlled. If cases continue to occur, they must be investigated further to ascertain their epidemiology. Further control efforts should be directed by the occurrence of cases and their epidemiology.

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