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Surgical aspects of pulmonary histoplasmosis

A series of 110 cases

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Histoplasmosis is of special interest to thoracic surgeons because it may appear in such a wide variety of clinical forms. Fourteen years' experience with 110 proved cases of surgically treated pulmonary histoplasmosis has been reviewed. Twenty-one of these patients manifested as 'coin-lesion' and underwent only wedge resection without amphotericin B therapy. A long-term follow-up of these patients indicates that these lesions are benign and need no additional therapy. Thirteen patients with pulmonary infiltration underwent surgery and three received post-operative amphotericin B therapy. Our largest group of surgically treated patients is of cavitary histoplasmosis. There were 76 patients in this group; 38 were managed with only surgical resection and the other 38 had surgical resection together with amphotericin B therapy. Operative indications, various forms of treatment, post-operative complications, and their results have been critically analysed. From this study we conclude that amphotericin B offers little protection against the immediate post-operative complications, but it reduces mortality and a recurrence of the disease, as judged from long-term follow-up.

Histoplasmosis is a specific fungus infection caused by the organism *Histoplasma capsulatum*. Darling (1906) described the first case in Panama and gave the name *Histoplasma capsulatum* to round and oval bodies found in the endothelial cells of the spleen, and thought it was a protozoan. DeMonbreun (1934) isolated the organism by culture and proved it to be a fungus. Cultural characteristics were described by Conant (1941). Christie and Peterson (1945) introduced the histoplasmin skin test, emphasized the importance of the disease, and provided evidence of the high incidence of histoplasmosis in certain areas of the Mississippi Valley. Since then, several reviews of pathogenesis (Vivian, Weed, McDonald, Clagett, and Hodgson, 1954; Straub and Schwartz, 1955), epidemiology (Manos, Ferebee, and Kerschbaum, 1956; Furcolow, 1960), clinical manifestations (Furcolow, 1956; Prior, Saslaw, and Cole, 1954), course, and prognosis (Furcolow, 1963; Rubin, Furcolow, Yates, and Brasher, 1959) have been reported. The Missouri State Sanatorium lies on the periphery of the endemic belt which includes the Mississippi and Ohio River Valley and runs along the Appalachian mountains. When patients presented findings similar to pulmonary tuberculosis and could not be proved, then chronic pulmonary histoplasmosis was suspected.

Resection of lung tissue has been carried out at this institution for various fungus infections of the lung, including actinomycosis, aspergillosis, mucormycosis, spirotrichosis, geotrichiosis, North American blastomycosis, monosporiosis, and histoplasmosis. However, this communication will be limited to a consideration of the role of excisional surgery, with or without amphotericin B therapy, in the management of chronic pulmonary histoplasmosis.

METHODS AND MATERIAL

From January 1955 to January 1969, 530 patients were diagnosed as having pulmonary histoplasmosis at the Missouri State Sanatorium. The case records of all these patients were reviewed and 110 who had surgery, with or without amphotericin B, were studied in detail. The criterion for inclusion in this study was the demonstration of *H. capsulatum* by positive culture and/or differential staining of sections. Table I summarizes the mode of diagnosis in this series.

CLINICAL FEATURES There were 77 men and 33 women, the ratio of male to female being 2·3 to 1.

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Their ages ranged from 16 to 75 years, with an average age of 46 years. Table II gives data for each decade of life; 107 of these patients were white and three were Negro. Sixty-six (60%) of these patients were farmers or had lived on a farm for many years.

TABLE I

MODE OF DIAGNOSIS

	No.
Positive sputum	11
Positive sputum for histopathological studies	31
Positive histopathological study	68
Total	110

TABLE II

AGE BY DECADES

Age Range	No. of Patients	Per Cent
10–20	4	4
20–30	16	14
30–40	22	20
40–50	25	23
50–60	30	27
60–70	10	9
70–80	3	3
Total	110	100

SYMPTOMS Fourteen of the 110 patients were asymptomatic. They were advised to enter hospital because of abnormal chest radiographs. The incidence of presenting symptoms in the remaining 96 patients is listed in Table III. The most frequent presenting symptoms were cough (75%), chest pain (45%), fever (42%), fatigue (38%), dyspnoea (32%), and haemoptysis (25%).

TABLE III

	No. of Patients	Per Cent
Asymptomatic	14	13
Symptomatic	96	87
Symptoms:		
Cough	82	75
Chest pain	49	45
Fever	46	42
Fatigue	43	38
Weight loss	42	38
Dyspnoea	35	32
Haemoptysis	27	25

As a diagnostic screen test, complement fixation and the histoplasmin skin test were performed in 99% of the patients reported here. Table IV summarizes the findings in all diagnostic tests. The histoplasmin skin test was positive in 81% of the patients. There were positive complement fixation tests in 62%, with titres ranging from 1 : 8 to as high as 1 : 256. Sputum culture yielded *H. capsulatum* in 35% of the patients, whereas histopathological studies, by differential staining using methenamine silver stain, demonstrated *H. capsulatum* in 90%. Table V summarizes the relationship of the histoplasmin skin test to complement fixation tests. P.P.D. (5 units) skin test was positive in 56%. Both P.P.D. and histoplasmin skin tests were positive in 45%. Sputum cultures for tubercle bacilli were positive in 17 out of 110 patients.

TABLE IV

SUMMARY OF FINDINGS IN ALL DIAGNOSTIC TESTS

P.P.D. (5 units)	Histoplasmin Skin Test	Complement Fixation	Sputum Culture	Histopathological Study
Positive 62 (56%)	89 (81%)	68 (62%)	39 (35%)	99 (90%)
Negative 48 (44%)	20 (18%)	40 (36%)	71 (65%)	11 (10%)
Not done	1 (1%)	2 (2%)	0	0

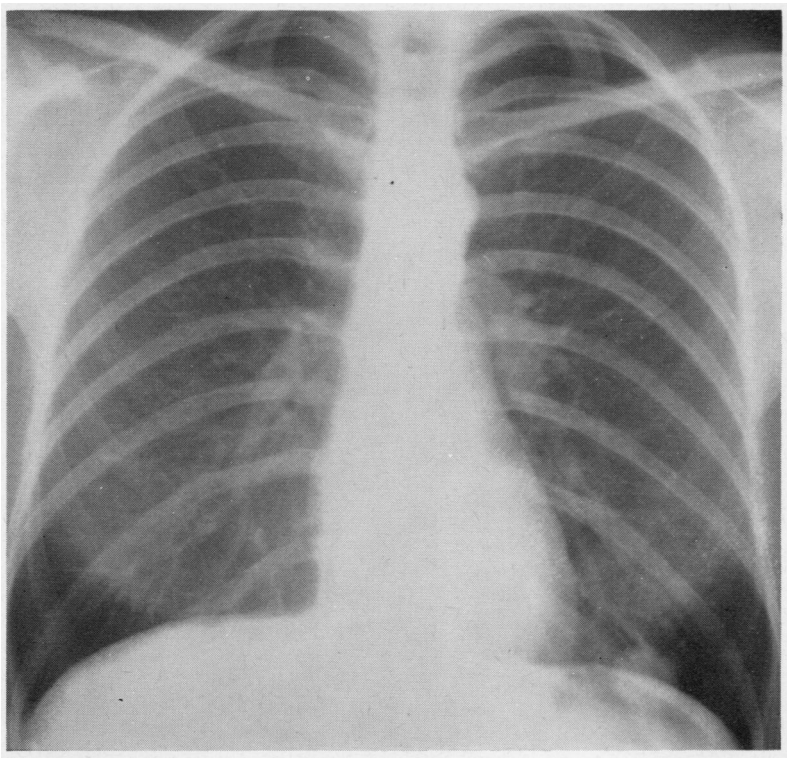
TABLE V

RELATIONSHIP OF SKIN TEST TO COMPLEMENT FIXATION TEST IN 110 PATIENTS

No.	Skin Test	Complement Fixation	Per Cent
57	+	+	52
32	+	–	29
11	–	+	10
8	–	–	7
1	–	0	1
1	0	0	1

CHEST RADIOGRAPHS A definitive diagnosis of pulmonary histoplasmosis was seldom made from the radiographs. Twenty-nine of the 110 patients had radiographic evidence of bilateral lung disease. The right lung was involved in 74 (67%) and the left lung in 64 (58%). Twenty-one (19%) of the patients presented with focal, solitary lesions (coin lesion) measuring 1–4 cm. in diameter. In many, focal histoplasmosis was suspected from radiographic evidence of the characteristic laminated or stippled calcification (Fig. 1a, b). A cavitary lesion was found in 76 (70%) and pulmonary infiltration in 13 (12%). One patient who had a typical middle lobe syndrome is included as pulmonary infiltration. Four patients had marked pleural effusion; and following aspiration, tomograms showed cavitary lung disease. Three other patients who had cavitary lung disease were admitted to the sanatorium because of empyema with bronchopleural fistula. One had marked pleural thickening. Thus radiographic evidence of coin lesion (Fig. 1), non-resolving pulmonary infiltration (Fig. 2), cavitary lesion (Fig. 3), middle lobe syndrome, pleural thickening, pleural effusion, and empyema with bronchopleural fistula (Fig. 4) exemplify the protean radiological pattern of this disease.

Table VI summarizes the findings of radiographic evidence of lobe involvement. Twenty-one coin lesions presented as solitary, focal, unilateral lesions. The right upper lobe was involved in 74% and the left upper lobe in 57% of the cavitary lesions. Pulmonary infiltrations were found in 12% of the patients.



(a)

(b)

FIG. 1. (*a*) *Chest radiograph showing 'coin lesion' in left lower lobe.* (b) *Enlargement of lesion showing characteristic laminated or stippled calcification.*

TABLE VI

SUMMARY OF RADIOGRAPHIC FINDINGS OF LOBE INVOLVEMENT

Type of Lesion	Total	Uni-lateral	Bi-lateral	Right			Left	
				UL	ML	LL	UL	LL
Coin lesion	21	21	0	5	—	2	4	10
Cavitary ..	76	52	24	56	16	12	43	7
Pulm. infiltration ..	13	8	5	6	3	4	6	4
Total	110	81	29	66	19	18	53	21

BRONCHOSCOPIC EXAMINATION Bronchoscopic examinations were performed on 53 of the 110 patients. They were negative in 46. In three patients, tumour was seen through the bronchoscope and biopsy showed squamous-cell carcinoma. Three patients had endobronchial disease proved by a positive smear, and sputum culture yielded *H. capsulatum*. In one patient, stenosis of the left upper lobe was visualized but smear and sputum culture were negative.

BRONCHOGRAM A bronchogram was performed in 11 patients. Five of the 11 had abnormal bronchograms. Four had evidence of bronchiectasis, and one showed stenosis of the right middle lobe.

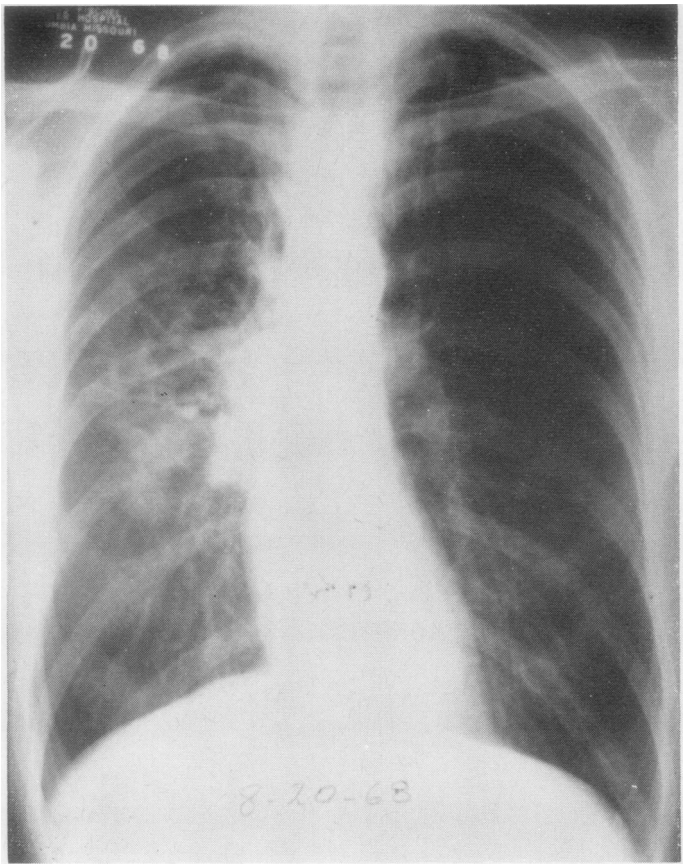


FIG. 2. *Chest radiograph* (20/8/68) *shows pulmonary infiltration in the right lung.*

PULMONARY FUNCTION TESTS Pulmonary function tests were performed in 100 of the 110 patients. Twenty-six of these had abnormal pulmonary function tests. Thirteen had obstruction impairment, six had restrictive impairment, and seven had mixed impairment.

ASSOCIATED CONDITIONS Forty-six (42%) of the 110 patients had other associated conditions along with pulmonary histoplasmosis. Active pulmonary tuberculosis was present in 20. The diagnosis was established by positive sputum in 17, and in three tubercle bacilli were cultured from resected specimens. Pulmonary emphysema was present in 11. Eight had associated bronchogenic carcinoma. Three had associated infection due to aspergillosis. Sputum culture and histopathological examination yielded *Aspergillus fumigatus* in all three cases. Other associated conditions, such as heart disease (3), diabetes (2), cirrhosis of liver (2), malignant lymphoma (1), fibrosarcoma of chest wall (1), hypertension (1), and peptic ulcer (1), were present in 11 patients.

THERAPY Forty-one of the 110 patients were treated with amphotericin B and surgery. We consider a total dose of 2 g. amphotericin B to be adequate for treatment of active histoplasmosis. Twenty-one patients with focal histoplasmosis had only wedge resection and received no amphotericin B therapy. Among the 76 patients who had cavitary disease, 38 had only surgery and the other 38 were treated with surgery together with amphotericin B. Twenty-nine of these patients received an adequate dose of amphotericin B. Detailed evaluation of these cases reveals that nine patients received pre-operative amphotericin B, 12 had post-operative amphotericin B, and 17 received pre- and post-operative amphotericin B. Three of 13 patients in the pulmonary infiltration group received post-operative amphotericin B therapy.

OPERATIONS One hundred and twenty-five operations were performed on 110 patients. Fourteen patients had more than one operative procedure, three for recurrence of disease in the opposite lung and 11 for the treatment of complications. One patient had three

operations. Among these 11 patients who required a second operation for the treatment of complications, 10 had thoracoplasty—four for persistent apical air space and six for bronchopleural fistula—and one patient had pleurectomy for empyema. Table VII

TABLE VII

TYPE OF PRIMARY OPERATION ON 110 PATIENTS WITH PULMONARY HISTOPLASMOSIS

Operation	Coin	Cavitary	Infiltration	Total
Wedge resection ..	21	0	0	21
Segmental resection	0	17	4	21
Lobectomy	0	38	3	41
Lobectomy and wedge	0	9	1	10
Pneumonectomy ..	0	8	2	10
Thoracoplasty ..	0	3	0	3
Lung biopsy ..	0	1	2	3
Pleurectomy ..	0	0	1	1
Total	21	76	13	110

summarizes the various primary operations performed on 110 patients for different types of pulmonary histoplasmosis. Twenty-one patients with coin lesion had wedge resections. Among the 76 patients with cavitary disease, 17 had segmental resections, 47 had lobectomies or lobectomy with wedge resections. Pneumonectomy was done on eight patients, three for associated carcinoma and five for destroyed lung due to extensive cavitary disease. Three patients presented as empyema with bronchopleural fistula associated with far-advanced cavitary disease and had thoracoplasty. A lung biopsy was done on one patient with cavitary disease because of inoperable carcinoma of the lung. Among the 13 patients with pulmonary infiltration, four had segmental resection, and four had lobectomy or lobectomy with wedge resection. Two patients in this group required pneumonectomy because of associated carcinoma of the lung, and in two patients with diffuse pulmonary infiltration lung biopsy was performed to establish the diagnosis. One patient had pleurectomy for recurrent pleural effusion and diffuse pleural thickening.

COMPLICATIONS Twenty (18%) of the 110 patients developed post-operative complications. Table VIII

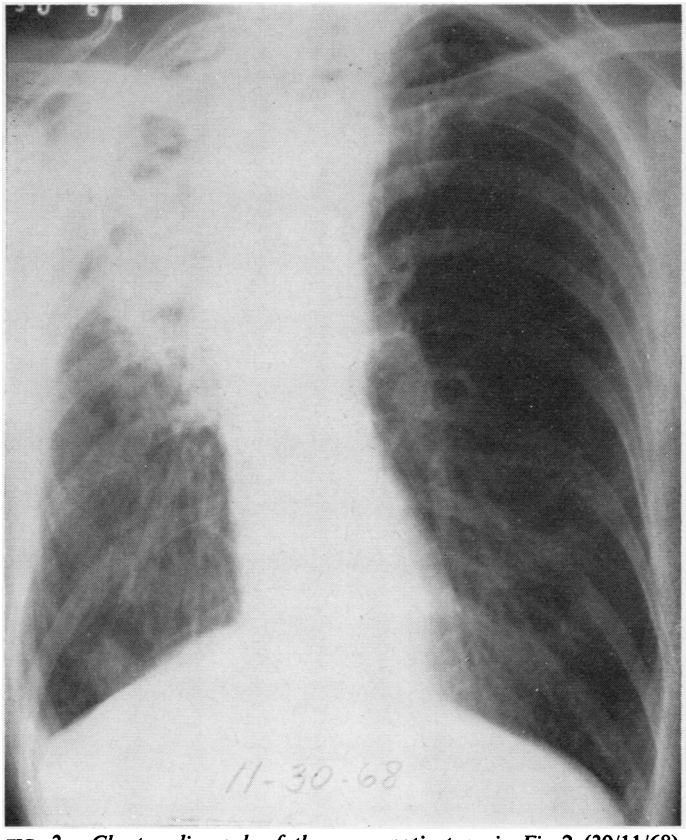


FIG. 3. *Chest radiograph of the same patient as in Fig.* 2 (30/11/68) *reveals marked progression with cavitation.*

TABLE VIII

TYPE OF COMPLICATION, TREATMENT, AND OUTCOME OF 110 PATIENTS TREATED WITH SURGERY FOR PULMONARY HISTOPLASMOSIS

Post-operative Complication	No.	Treatment	Outcome
Persistent apical air space	5	1 pneumoperitoneum 4 thoracoplasty	Improved Improved
Bronchopleural fistula ..	6	6 thoracoplasty	Improved
Empyema	1	Pleurectomy	Improved
Persistent pleural effusion	1	Tube drainage	Improved
Atelectasis	3	3 bronchoscopy and aspiration	Improved
Pericarditis and effusion	1	Conservative	Improved
Serum hepatitis ..	1	Conservative	Improved
Wound infection ..	2	2 secondary closure	Improved
Total	20		

summarizes the type of complication, its treatment, and outcome. There were five patients with persistent air space; four required tailoring post-resection thoracoplasty, and one had pneumoperitoneum. Six patients developed bronchopleural fistula and ultimately required post-resection thoracoplasty and improved. One patient developed empyema seven months following right pneumonectomy for carcinoma of lung associated with cavitary histoplasmosis. He was treated with pleurectomy and improved. One patient required tube drainage for persistent pleural effusion. Three patients developed post-operative atelectasis requiring bronchoscopy for re-expansion. Two had post-operative wound infection and were treated with secondary closure.

RESULTS

One hundred and four patients have been followed for a period ranging from six months to 13 years, with an average follow-up of 58 months. Six patients were lost to follow-up immediately, but at the time of discharge they had improved subjectively and objectively. Two patients died during the post-operative period. One patient had left pneumonectomy for destroyed lung due to extensive cavitary histoplasmosis and died 10 days following surgery due to respiratory failure. The other had right upper and middle lobectomy for

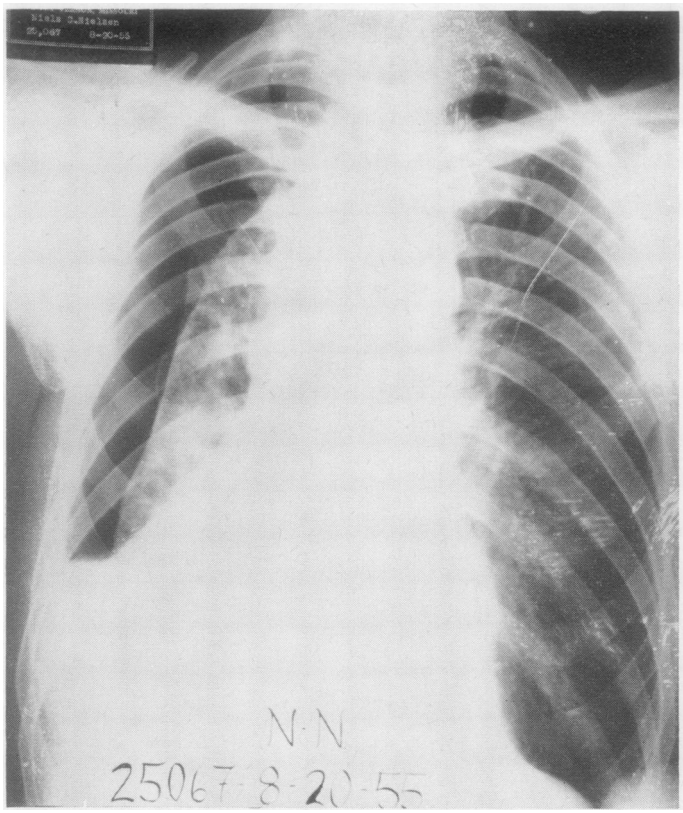


FIG. 4. *Chest radiograph shows 'destroyed lung' with empyema and bronchopleural fistula on the right.*

cavitary disease and died on the 15th post-operative day due to respiratory failure. In both these patients, pulmonary emphysema contributed to respiratory failure. Among the 16 late deaths, only five were due to progressive histoplasmosis. Seven patients died of bronchogenic carcinoma, two due to pneumonia and one to pulmonary emphysema. In one case the cause of death is not known.

DISCUSSION

First, a comment should be made on the high incidence (18%) of tuberculosis among these cases of proved chronic pulmonary histoplasmosis. It must be remembered that our patients admitted to the Missouri State Sanatorium represent a selected group in which tuberculosis was already proved or suspected. Thus the actual percentages of chronic pulmonary histoplasmosis cases with and without concomitant tuberculosis in the general population cannot be estimated from these data. The incidence of progressive pulmonary histoplasmosis appears to be high among the elderly, debilitated patient suffering from tuberculosis, emphysema, or bronchogenic carcinoma.

FOCAL HISTOPLASMOSIS (COIN LESION) Focal lesions of histoplasmosis are often indistinguishable from neoplasm, tuberculoma, coccidioidoma, and other granulomatous lesions in their gross, radiographic, and clinical manifestations and require surgical removal and histopathological examination of the excised tissue for differentiation. The majority of the patients in this group presented diagnostic problems, and the most frequent indication for surgery was to aid in the establishment of diagnosis.

Our experience with focal histoplasmosis parallels that of Puckett (1953) and Forsee, Puckett, and Hagman (1953), in that in no patient had *H. capsulatum* been cultured pre-operatively and the organism was cultured rarely after surgery. The diagnosis was established by demonstrating organisms resembling *H. capsulatum* in the pathological specimen. The course of these patients following surgery has been benign. There were no post-operative complications or recurrence of disease in this group treated with wedge resection only. They have been followed for a period of nine months to 13 years, with an average follow-up of five years. One patient died of pulmonary emphysema nine years following wedge resection of focal histoplasmosis. We believe amphotericin B is not indicated in the treatment of focal histoplasmosis.

PULMONARY INFILTRATION Unresolved pulmonary infiltration without a definitive diagnosis is an indication for exploratory thoracotomy. Ten of the 13 patients were treated with surgery only. Three developed a post-operative complication and two had progression of disease with an average follow-up of 44 months. Three patients received adequate post-operative amphotericin B therapy along with surgery. They have been followed for a period of three to 10 years, with an average follow-up of seven years. They are well and active and there is no recurrence of disease.

We do not treat the patient with amphotericin B without a definite diagnosis of histoplasmosis established by positive sputum or positive histopathological examination. Most of the patients among the group of pulmonary infiltration due to histoplasmosis had negative sputum and thus did not qualify to receive amphotericin B pre-operatively even though histoplasmosis was strongly suspected. Our present policy is to treat this group of patients post-operatively with adequate doses of amphotericin B when the diagnosis of pulmonary histoplasmosis has been established by positive histopathological examination. We believe unresolved pulmonary infiltration (Fig. 2) due to histoplasmosis is a form of chronic progressive pulmonary histoplasmosis and, if untreated, will progress into cavitary disease (Fig. 3).

CAVITARY HISTOPLASMOSIS Cavitary histoplasmosis is the most frequent form of this disease for which we have performed surgical resection. Forty of the 76 patients with cavitary disease had positive sputum, and a definite diagnosis of cavitary histoplasmosis was established pre-operatively. In 19 patients the diagnosis of cavitary histoplasmosis was strongly suspected because of radiographic evidence of cavitary disease, positive histoplasmin skin test, positive complement fixation test, and negative tests for tuberculosis. In the remaining 17 patients the diagnosis of histoplasmosis was made post-operatively from positive histopathological examination. Seven of these 17 cases were diagnosed as cavitary pulmonary tuberculosis by positive sputum culture. Surgery was performed to treat the cavitary tuberculosis. Histopathological examination of the resected tissue yielded tubercle bacilli and *H. capsulatum*. In three patients the diagnosis of bronchogenic carcinoma was made from positive bronchoscopic

examination and biopsy. Methenamine silver stain of the resected tissue demonstrated *H. capsulatum*. Thus we operated on seven patients without any pre-operative diagnosis of cavitary disease of the lung, and histopathological examination of resected tissue yielded Histoplasma organisms.

The operative indications in 76 patients with cavitary disease are given in Table IX.

TABLE IX

SURGICAL INDICATIONS IN 110 PATIENTS WITH PULMONARY HISTOPLASMOSIS

	No.
Focal histoplasmosis	
Coin lesion	21
Pulmonary infiltration	
Unresolved pulmonary infiltration	8
Right middle lobe syndrome	1
Pleural involvement with persistent pleural effusion	1
Diagnostic biopsy	1
Associated carcinoma	2
Cavitary disease	
Resection of cavitary disease	50
Destroyed lung	5
Bronchiectasis	4
Empyema with bronchopleural fistula	3
Bronchial stenosis	1
Associated cavitary pulmonary tuberculosis	7
Associated bronchogenic carcinoma	5
Diagnostic biopsy for associated inoperable carcinoma	1

CAVITARY DISEASE As with pulmonary tuberculosis, surgical treatment for chronic cavitary histoplasmosis is indicated after maximum improvement with antifungal drug therapy, provided the lesions are sufficiently localized and the patient's pulmonary function is not yet seriously impaired by the development of pulmonary fibrosis and emphysema. Surgery was indicated to remove the cavitary disease in 50 patients.

DESTROYED LUNG Five patients presented radiographic evidence of destroyed lung due to extensive cavitary disease. Only in two was the diagnosis of histoplasmosis made pre-operatively by positive sputum. In the remaining three, the complement fixation tests for histoplasmosis and sputum cultures for tubercle bacilli and *H. capsulatum* were negative. In all five, pneumonectomy was performed to remove the destroyed lung. One patient died on the 10th post-operative day due to respiratory failure. Another died six months following surgery due to pneumonia. At necropsy there was no evidence of recurrence of disease. One patient had right pneumonectomy in 1956. He did well until July 1962, when chest radiographs showed pulmonary infiltration at the left apex. Readmission to the Sanatorium for possible amphotericin B therapy was advised, but he left town and was lost to follow-up. The other two patients are alive and well 13 years and 9 years respectively following surgery. There is no evidence of recurrence of disease to the opposite lung.

BRONCHIECTASIS Histoplasmic bronchiectasis appears to be a rare disease. In four cases in which we have done resection, the diagnosis was made before surgery by positive sputum, bronchoscopy, and bronchogram. These patients also had cavitary disease of the lung.

BRONCHIAL STENOSIS We have been able to demonstrate only one case of bronchial stenosis as a result of this disease compared to numerous reported cases of stenosis due to tuberculosis.

EMPYEMA WITH BRONCHOPLEURAL FISTULA Three patients were admitted to the Sanatorium because of empyema with bronchopleural fistula along with extensive cavitary disease of the lung. Culture from empyema fluid yielded *H. capsulatum* in all three. They were treated with tube drainage followed by thoracoplasty. Only one patient received an adequate dose of amphotericin B intravenously. Following tube drainage and thoracoplasty, the empyema and bronchopleural fistula healed spontaneously, and they were discharged as improved. One patient was lost to follow-up immediately. The other two died six months and three years respectively following surgery due to progression of the disease.

The role of collapse therapy in the treatment of cavitary histoplasmosis is not properly evaluated. We have performed three thoracoplasties, primarily to treat the empyema and bronchopleural fistula, with success. However, collapse therapy by thoracoplasty failed to control the disease.

COURSE OF UNTREATED, MEDICALLY TREATED, AND SURGICALLY TREATED CAVITARY HISTOPLASMOSIS The course and prognosis of untreated chronic cavitary histoplasmosis reveals that about one-third of the patients died of progression of their disease within four years (Furcolow, 1963). By the sixth anniversary, only 19% of these patients would not be expected to have died or developed progression of disease. Among those living after six years of follow-up, about two-thirds are disabled 50% or more.

Furcolow (1963) and Sutliff, Andrews, Jones, and Terry (1964) reported encouraging results in the therapy of chronic pulmonary histoplasmosis.

TABLE X

RESULTS OF TREATMENT IN 110 CASES OF PULMONARY HISTOPLASMOSIS

Type of Lesion	No. of Cases	Complications	Operative Mortality	Late Mortality due to Histoplasmosis	Progression of Disease	Average Follow-up (months)
Coin lesion						
Surgery only	21	0	0	0	0	60
Surgery+amphotericin B	0	0	0	0	0	0
Pulmonary infiltration						
Surgery only	10	3 (30%)	0	0	2 (20%)	44
Surgery+amphotericin B	3	0	0	0	0	84
Cavitary disease						
Surgery only	38	7 (18%)	2 (5%)	3 (8%)	9 (24%)	60
Surgery+amphotericin B	38	10 (26%)	0	2 (5%)	3 (8%)	58

with amphotericin B as shown by sputum conversion, radiological improvement, and reduced mortality. However, the results of the patient treated medically with amphotericin B is closely related to the total dosage. Those patients treated adequately have improved the four-year mortality rate to 15% as compared to those treated inadequately, who had a four-year mortality rate of 25%.

Diveley and McCracken (1966) reported 29 patients who had surgically treated cavitary histoplasmosis without amphotericin B coverage. Among this group there was no mortality and recurrence of disease in four patients with an average follow-up of 43 months. Palk, Cubiles, and Buckingham (1957) reported good results in 17 of the 21 operated cases for cavitary histoplasmosis. Ahn, Kilman, Vasko, and Andrews (1969) reviewed the literature and reported 9·6% mortality among the group of 114 patients treated with surgery without amphotericin B coverage. In our group of 38, treated with surgery without amphotericin B coverage, there had been two immediate post-operative deaths due to respiratory failure and three late deaths due to progression of disease, with an average follow-up of 60 months (Table X).

The effect of combined amphotericin B therapy together with surgery in regard to post-operative complications and progression of disease has not been defined. Ahn *et al.* (1969) reviewed the literature and found 15 resections for cavitary histoplasmosis with pre- and post-operative amphotericin B coverage. They reported 13% morbidity and 6% mortality in this group as compared to 20% morbidity and 9·6% mortality in the collected review of 114 patients treated with surgery alone. They concluded that in open cavitary histoplasmosis, resection with effective pre- and post-operative amphotericin B therapy reduced the incidence of post-operative complication and mortality. Beatty, Levene, Saliba, and Coelho (1962) reported nine cases with chronic cavitary histoplasmosis treated with surgical resection, four of whom received concomitant amphotericin B therapy. They concluded that in open cavitary histoplasmosis, resection with effective amphotericin B coverage reduced the incidence of post-operative complications.

Katz (1960), Gryboski, Crutcher, Holloway, Mayo, Segnitz, and Eiseman (1963), and Takaro (1967) recommended amphotericin B coverage for patients with cavitary disease treated surgically. However, they did not describe their clinical experience. On the other hand, Diveley and McCracken (1966) reported three post-operative complications and four recurrences among the 29 patients treated surgically, without amphotericin B coverage, with an average follow-up of 43 months. Levene, Slesh, Torres, and Saliba (1968) reported 24 patients, surgically treated and with cavitary histoplasmosis; 10 patients had concomitant amphotericin B and surgical therapy, and 12 had only post-operative amphotericin B therapy. There were six post-operative complications in each group, and they concluded that amphotericin

TABLE XI

RESULTS OF TREATMENT IN 76 CASES OF CAVITARY HISTOPLASMOSIS

Treatment Group	No. of Patients	Post-operative Complications	Late Mortality due to Histoplasmosis	Progression of Disease
Surgery only	38	7 (18%)	3 (8%)	9 (24%)
Surgery+adequate preop. amphotericin B	9	4 (44%)	0	0
Surgery+adequate postop. amphotericin B	5	1 (20%)	0	0
Surgery+inadequate post-op. amphotericin B	6	1 (20%)	1	1 (16%)
Surgery+adequate pre- and postop. amphotericin B	15	3 (20%)	1 (6·5%)	1 (6·5%)
Surgery+inadequate pre- and postop. amphotericin B	3	1 (33%)	0	1 (33%)

B offers little protection against the immediate post-operative complication but appears to have a beneficial effect on the long-term result.

Table XI summarizes our experience of 76 patients with cavitary histoplasmosis. Thirty-eight patients were treated with surgery alone and 38 patients received combined treatment of surgery with amphotericin B therapy. In the first group there were 18% complications, 8% late mortality, and 24% recurrence, as compared with 26% complications, 5% mortality, and 8% recurrence in the second group of patients. Twenty-nine of the 38 patients received adequate amphotericin B therapy; among this group there were 27% post-operative complications, 3·4% mortality, and 3·4% recurrence of disease; in comparison nine patients received inadequate therapy, and there were 22% post-operative complications, 11% mortality, and 11% recurrence of disease.

Further analysis of complications reveals that 30% of the 27 patients who received pre-operative amphotericin B developed post-operative complications, as compared to 18% of the 11 patients who received post-operative drug therapy and 18% of the 38 patients who were treated with surgery without amphotericin B.

Our study indicates that amphotericin B is of little value in the prevention of post-operative complications. However, we agree with several investigators that amphotericin B plays a major role in reducing mortality and recurrence of disease in long-term results.

It should be mentioned that amphotericin B is a toxic drug and must be administered intravenously over a prolonged period of time averaging from three to four months. Its renal toxicity, which is often reversible, and gastrointestinal toxicity are well recognized. The effect of amphotericin B on tissue healing is not properly studied to our knowledge. Increased post-operative complications among the group who received pre-operative amphotericin B might be related to poor tissue healing.

When the diagnosis of cavitary histoplasmosis is established by positive sputum before surgical resection, we believe that we are justified in treating the patient with amphotericin B before surgical resection even though there are numerous side-effects to this drug. We also believe it is worth while to wait for the sputum to be converted to a negative phase by this form of treatment, which appears to cause regression in the infiltration process surrounding the cavitary lesion. It has been our experience that, in the cavitary phase of this disease, the drug alone will not close cavities over 3 to 4 cm. in diameter, and these larger cavities ultimately require surgical resection to control the disease process.

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