Disseminated Histoplasmosis Treated with Amphotericin B
Report of a Case
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Histoplasmosis has been classified clinically into acute and chronic forms. The acute form has been further grouped as acute localized and acute disseminated, according to the manifestations of the illness.

The acute disseminated form is generally fatal. This is the form in which the disease was first recognized and in which, until recently, the diagnosis was usually made at necropsy. Severe illness was considered to be the only manifestation of histoplasmosis until the observations of the frequency of pulmonary calcifications in tuberculin negative individuals started investigators on the way toward recognizing the much more common and benign forms of the disease. It is now known that most histoplasmosis infections are self-limited and spontaneously result in healing of the lesions and complete recovery of the patient. In 1957, Rubin, Lehan, and Furcolow reported a case of histoplasmosis treated with amphotericin B. This patient had acute pulmonary histoplasmosis from which he would have been expected to recover; however, the authors were sufficiently impressed by the prompt improvement in their patient to attach some significance to the effect of the drug.

This report concerns a patient who had acute disseminated histoplasmosis involving lung, liver, spleen, bone marrow, and probably central nervous system, and who appeared to be terminally ill at the time that amphotericin B therapy was started.

Case Report
J. A., a 69-year-old salesman, was admitted to Baylor University Medical Center in May, 1956. He complained of weight loss, anorexia, weakness, and fever since December, 1955. He had a

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**Amphotericin B used was kindly furnished by Squibb Research Laboratories.

Figure 1
Figure 2
Figure 1: Chest x-ray film, July 21, 1952, taken three years prior to the onset of the illness. Figure 2: Chest x-ray film, June 26, taken between the first two hospital admissions.
mild cough, productive of about one teaspoonful of clear sputum in the morning only. He had had a prostatectomy for benign hypertrophy in 1952, and extraction of senile cataract in each eye in August and December, 1955. He had been on acetazolamide for glaucoma since December, 1955.

Physical examination revealed a thin elderly man. There was no lymphadenopathy; no lesion of the mucous membrane of the mouth or was throat apparent; lungs were clear; and liver and spleen were not palpable.

In the hospital, his temperature was as high as 100.2° F. on each of several days. Hemoglobin, 13.5 gm. per cent; white blood count, 8,150/ cmm. with 3 per cent eosinophils, 1 myelocyte, 1 young form, 12 band forms, 47 segmented neutrophils, 25 lymphocytes, and 11 monocytes. Urinalysis: specific gravity, 1.014; albumin and sugar, negative; microscopic examination revealed a few white blood cells and frequent red blood cells in spun sediment per high-power field. Bromsulphalein liver test, 6.5 per cent dye in the serum in 45 minutes, using 5 mg. dye per kg. body weight. Blood culture was negative; urine culture grew out *Streptococcus hemolyticus*. Chest film suggested pulmonary fibrosis and emphysema with fibrotic scarring in the upper lobes.

His illness was thought to be chronic pyelonephritis, and he was given erythromycin, 250 mg. four times a day for two weeks. He continued to have fever and gradually felt worse, having the same symptoms as previously. Chest x-ray film taken on June 26, 1956, showed increase in the pulmonary fibrosis with soft nodularity in the upper lung lobes. No pulmonary calcification was present. He was readmitted in July, 1956, when hepatomegaly and splenomegaly became apparent for the first time.

Routine laboratory work was essentially the same as two months previously. Cephalin cholesterol flocculation was 4+ in 24 hours; thymol turbidity, 11.6 units. Bromsulphalein liver test, 24 per cent dye in the serum in 45 minutes. Albumin, 3.8 gm. per cent; globulin, 3.9 gm. per cent. Sputum Gram's stain and culture showed Neisseria and *Streptococcus viridans* and no acid-fast bacilli. Urine and blood cultures: no growth.

Old tuberculin skin test, 1:1000, negative; coccidioidin skin test, negative; histoplasmin skin test, positive.

Bone marrow aspiration was considered normal though there was an increase in mononuclear cells. Needle liver biopsy revealed multiple granuloma of the liver, consistent with sarcoidosis.

On July 20, 1956, he was started on prednisone, 10 mg. every eight hours, on the basis of a diagnosis of sarcoidosis. Within 48 hours there was disappearance of fever and a gratifying return of appetite and sense of well-being. He was discharged from the hospital and maintained on prednisone.

**FIGURE 3**

*Chest x-ray film, September 10, 1956, taken just prior to initiation of amphotericin B therapy.*

**FIGURE 4**

*Chest x-ray film, February 22, 1957, taken one week after completion of therapy.*
On September 1, 1956, fever and anorexia returned, along with extreme weakness. He rapidly became worse and was readmitted to the hospital.

A complement fixation test for histoplasmosis, which had been drawn on July 20, 1956, was reported at this time as being positive 1:512 phase 1; 1:256 phase 2 (yeast).

On physical examination, he was emaciated, weak, and chronically ill appearing. Temperature, 102° F. Blood pressure, 132/82. He was semi-comatose and bringing up mucoid sputum. The chest was emphysematous and there were dry rales over both lung apices, but no areas of dullness or bronchial breathing. Liver and spleen were both palpable. There was a positive Babinski reflex on the right.

On September 18, 1956, the following laboratory findings were obtained: hemoglobin, 12.4 gm. per cent; white blood count, 5,250/cmm. with 3 per cent young forms, 15 band forms, 45 neutrophils, 31 lymphocytes, 5 monocytes, and 4 eosinophils. Blood urea nitrogen, 23.8 mg. per cent; albumin, 3.6 gm. per cent; globulin 3.9 gm. per cent; CO₂ 28.8 mEq./L.; sodium, 120 mEq./L.; potassium, 4.4 mEq./L.; bilirubin, 0.075 mg. total; thymol turbidity, 7.1 units. By serum electrophoresis there was slight hypergamaglobulinemia.

Lumbar puncture opening pressure, 180 mm.; final pressure, 120 mm. of spinal fluid. Spinal fluid culture, no acid-fast bacilli or fungi, no growth on routine culture. White blood count, 3/cmm.; protein, 74 mg. per cent; sugar, normal; Wasserman, negative.

A bone marrow taken on September 14, 1956, prior to admission to the hospital, was reported to show intracellular Histoplasma capsulatum. Culture of this bone marrow later grew out Histoplasma capsulatum. Sputa, on September 18 and September 20, 1956, showed Histoplasma capsulatum on direct examination and culture.

On September 19, 1956, he was started on amphotericin B with the following dosage schedule:

- September 19 to September 25, 1956, 100 mg. intravenous daily; 1.0 gm. orally daily in 5 doses.
- September 26 to October 9, 1956, 50 mg. intravenous daily; 2.0 gm. orally daily.
- October 10 to November 18, 1956, 50 mg. intravenous every other day; 1.0 gm. orally daily.
- November 18 to December 18, 1956, 50 mg. intravenous once a week; 1.0 gm. orally daily.
- December 18, 1956, to February 15, 1957, 1.0 gm. orally daily.

The above schedule is equal to a total intravenous dose of 1.9 gm., or 30 mg./kg., and a total oral dose of 120 gm. It is likely that very little of the oral medication was absorbed.

Because he had previously been on adrenal steroid, and also because of the possibility of adrenal destruction by his disease, he was maintained on 10 mg. of prednisone daily. Certain aspects of his illness thereafter were attributed to possible toxic effects of amphotericin B. After each intravenous infusion, he had a hard chill, followed by elevation of temperature to 103° F.; this was associated with nausea and vomiting.

He was maintained on suitable intravenous fluids. The amphotericin B itself was dissolved in 500 ml. and an additional 1,000 to 3,000 ml. given, depending on oral intake. The blood urea nitrogen remained normal throughout. Hypopotassemia occurred on two occasions and was corrected quickly by adding potassium chloride to the infusions. On several occasions the CO₂ combining power fell to 18 mEq./L. and was corrected by the administration of 1/6 molar sodium lactate. It is impossible to say whether the electrolyte effects were specific results of amphotericin or rather a function of his severe illness and extended maintenance on parenteral fluids.

No evidence of renal irritation appeared in the urine. Prior to onset of therapy and after adequate hydration, his hemoglobin averaged 12.5 gm. per cent and his blood count, 4,500,000/cmm. on several occasions. On September 24, 1957, one week after initiation of therapy, the hemoglobin was 9.6 gm. per cent and red blood count was 3,900,000/cmm. Serum bilirubin was not increased. Three blood transfusions were given to maintain hemoglobin at 12 gm. per cent during the ensuing week.

After intravenous amphotericin B was discontinued there was no apparent toxic effect of the oral drug. By then, of course, he was much improved and eating reasonably well. The stools were continuously full of unabsorbed granules of amphotericin B.

**FIGURE 5:** Chest x-ray film, May 11, 1960, taken three years after completion of therapy.

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He had a slow return of strength and weight. He was continued on small doses of prednisone daily until 1958, when indigestion developed and a duodenal ulcer was demonstrated by x-ray. Prednisone was withdrawn and he became quite ill; vomiting, weakness, and hypotension ensued. The Kepler-Power water test was positive, 17-ketosteroids in urine were low, and hypotension was confirmed. Additional tests for adrenal insufficiency were considered to be contraindicated. He was started on cortisone, 12.5 mg. and 9-alpha-fluoro hydrocortisone, 0.025 mg. daily. There was marked improvement and he has remained quite well since.

Needle biopsy of the liver in January, 1957, showed complete healing of the granulomatous process and the liver and spleen were no longer palpable. Chest x-ray films since 1957 show marked clearing of nodular lesions and there has been no evidence of recurrence of histoplasmosis by x-ray film. Sputum cultures have all been negative for fungus since September 20, 1956.

The following complement fixation tests have been reported:

July 20, 1956, 1:512 phase 1 (histoplasmin);
1:256 phase 2 (yeast).

October 17, 1956, 1:512 phase 1; 1:512 phase 2.


October 9, 1957, 1:16 phase 1; negative phase 2.

April 7, 1958, negative phase 1; negative phase 2.

March 5, 1961, negative phase 1; negative phase 2.

In 1961, five years after the diagnosis of histoplasmosis was established, he has complaints commensurate with his age, but none referable to histoplasmosis.

REFERENCES


CRUSHED CHEST AND TRACHEAL RUPTURE

The problem is discussed from the points of view of: (1) air leak, (2) paradox, (3) airway and a case is selected to illustrate the main points of discussion. Unremitting attention to fundamental principles offers the best means of saving lives, too many of which are lost as a result of a failure to do this.


INFLUENCE OF CORTISONE ON PENETRATION OF C14 Labeled INH INTO THE BLOOD AND INTERNAL ORGANS OF HEALTHY GUINEA PIGS AND TUBERCULOUS GUINEA PIGS

Fifteen guinea pigs were given C14 labeled INH intramuscularly in doses of 5 mg. per kg. body weight. Fifteen other animals were given C14 labeled INH alone and served as controls. The animals were sacrificed one-half, one, three, five and ten hours after the administration of the drugs. The level of INH and its metabolites was determined by means of a Geiger-Muller counter in the homogenates of the liver, brain, heart, kidneys, muscles distal to the site of the injection and adjacent to the site of the injection of INH and cortisone, and in the urine. The results were presented as percentages of the mean distribution.

It was found that one hour after the administration of the drugs, cortisone inhibited the penetration of INH into the internal organs, but after three hours, there was a compensatory increase of the INH level which was higher than that in the control animals. After five hours, and ten hours, the levels became equal gradually in both groups of animals. During the whole experiment, cortisone inhibited the penetration of INH into the blood. The drug remained at the site of injection in higher concentration than that in the control group.