THE USE OF AMPHOTERICIN B IN SELECTED CASES OF CHORIORETINITIS*

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COINCIDENT with the advent of antibiotics and steroids the ophthalmologist has been confronted with an increased incidence of ocular fungus disease. Any therapeutic agent which exhibits fungicidal properties, therefore, warrants careful appraisal by our discipline. This is particularly significant in that most fungus diseases of the eye have been relatively resistant to current antifungal therapy.

Amphotericin B, an antibiotic derived from soil *Streptomyces*, exhibits a most promising antifungal spectrum. Of pertinent interest to this investigation is the specificity that this agent shows toward the organism *Histoplasma capsulatum*. The available evidence implicating *Histoplasma capsulatum* as an ocular pathologic agent is admittedly tenuous. The particular characteristic, however, of this organism to exhibit widespread involvement of the reticuloendothelial system and its unique mimicry of tuberculosis makes it appear quite likely that it may be pathologic to ocular tissues. Histoplasmosis has previously been implicated as a probable cause of human iridocyclitis and chorioretinitis. It is the purpose of this presentation to summarize a limited and preliminary experience with Amphotericin B** as a therapeutic agent in the management of suspected histoplasmosis chorioretinitis.

AMPHOTERICIN B

HISTORY

Gold (1) and his co-workers isolated Amphotericin A and B from Venezuelan soil in 1955. It soon became apparent that these agents possessed no antibacterial action. Laboratory and clinical evidence quickly accumulated, however, indicating that these antibiotics pos-

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sessed important fungicidal properties. Amphotericin A presented a much wider antifungal spectrum than B, but the latter exhibited greater potency against the common deep fungal pathogens including: *Histoplasma capsulatum*, *Coccidioides immitis*, *Candida albicans*, and *Cryptococcus neoformans* (1).

Oral administration of Amphotericin B proved fairly efficacious in the management of the deep mycoses, but because of erratic gastrointestinal absorption therapeutically desirable blood serum or cerebrospinal fluid levels were not consistently obtained (2). A water-insoluble intravenous preparation became available in 1956, and early in 1957 a water-soluble Amphotericin B mixture was developed (3). The employment of these two forms resulted in exciting clinical and experimental developments.

ADMINISTRATION

At present most clinicians administer Amphotericin B by intravenous infusion. The exact dosage, amount of diluent, and timing of administration have not been completely ascertained. Most clinicians recommend dosages between 0.50 and 1.5 mg./Kg. of body weight given daily and diluted in at least 10 c.c. of 5 percent glucose per milligram of Amphotericin B (2, 4, 6). Drs. Harrell and Curtis (7) of the University of Michigan Medical School, Department of Dermatology, have successfully evolved the following regimen: Daily intravenous infusion of 50 mg. of the drug in 500 c.c. of 5 percent glucose for 10 to 25 days. Adequate serum and cerebrospinal fluid levels can be maintained for 24 to 36 hours in this manner (2, 6).

Vogel (6) was able to therapeutically inhibit *Histoplasma capsulatum* in two of his cases by administering the drug on alternate days. Many of the toxic side effects of the drug, moreover, can be minimized when it is so administered. Curtis (8), and more recently Christie (9), have recommended the employment of the sulfonamides in the treatment of histoplasmosis. Christie has presented evidence revealing that triple sulfonamides, used alone, have been successful in the treatment of a number of cases of systemic disease. It is not known if these two agents, sulfadiazine and Amphotericin B, used in combination would be more efficient therapeutically although experimental evidence suggests that this may be the case (19).

SIDE EFFECTS

Seabury (11), in a careful analysis of the side effects of Amphotericin B therapy in 18 cases, tabulated in the order of their frequency the

following: chills and fever, 17 patients; anorexia, 10; abdominal pain, 8; headaches, 7; nitrogen retention, 6; nausea, 4; vomiting, 1; melena, 1; phlebitis, 1; and hemorrhagic gastroenteritis, 1. One case of exfoliative dermatitis, purpura, and death was reported by this author.

The kidney appears to be the organ most vulnerable to Amphotericin B toxicity. This is manifested by an azotemia. Prolonged therapy produces a rising blood urea nitrogen which fortunately is reversible upon cessation of therapy. Once the blood urea nitrogen has returned to normal it is believed safe to resume administration.

Squibb Institute for Medical Research workers have reported that Amphotericin B can produce diffuse gastrointestinal hemorrhages in dogs. Seabury (11) found gastrointestinal bleeding in a male treated with Amphotericin B for *blastomycosis*. Autopsy of the individual revealed lesions similar to those that occurred experimentally in the dog. It was believed, however, that death was due to *blastomycosis* in this patient. The same author encountered melena in another patient.

Various measures to counteract many of these side effects have been employed. Seabury used large doses of salicylates in combination or alone with Phenergan, Benadryl, and concomitant steroid administration, while Lerner (12) reduced chills and fever with 1 Gm. of aspirin given with the infusion and repeated every three hours as necessary.

It is apparent that Amphotericin B therapy is not without danger and, in fact, could possibly cause death. The decision to use Amphotericin B in the treatment of ocular histoplasmosis is not to be lightly made and if undertaken warrants extremely cautious and alert observation.

HISTOPLASMOSIS

Human infestation with *Histoplasma capsulatum* is startlingly prevalent (Figure 1). It has been estimated that over one-fifth of this country's population is infected and recently an authority suggested that as many as 500,000 cases occur yearly (13).

Darling (14) reported the first case but failed to recognize that the etiologic agent was a fungus. It was DeMonbreun (15) who laboriously and ingeniously demonstrated this fact.

Histoplasmosis was long considered a uniformly fatal disease until Amos Christie (16) recognized the relation of histoplasmosis sensitivity to pulmonary calcification in nonreactors to tuberculin. It soon was realized that a benign, nonprogressive form of the disease existed and was undoubtedly far more common than the fatal progressive type.

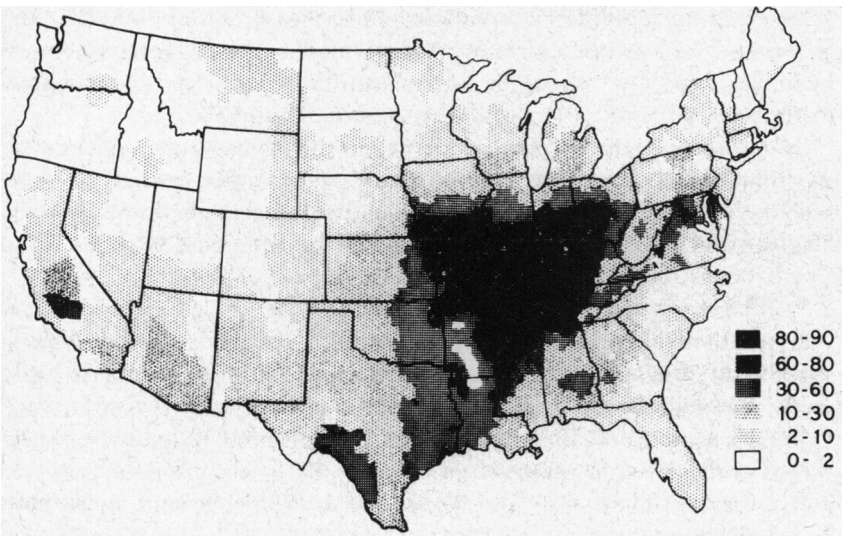

FIGURE 1. ILLUSTRATION OF DISTRIBUTION OF *Histoplasma capsulatum* INFESTATION IN THE UNITED STATES (MODIFIED FROM FURCOLOW)

PATHOLOGY

The causative organism, *Histoplasma capsulatum*, is parasitic (yeast phase) to the reticuloendothelial system of the body and exists as a mold form (mycelial phase) at room temperatures. The pathologic response is a granuloma accompanied by giant cell formation, mimicking the tubercle of tuberculosis. Generalized miliary dissemination may occur, but usually the pulmonary system only is involved. Apical pulmonary cavitation may result from progression, or possibly from reinfections.

EPIDEMIOLOGY

The disease is worldwide in distribution but better than 50 percent of the cases have been reported from the Missippi Valley area (Figure 1). *Histoplasma capsulatum* apparently is endemic, living in the soil, and is transmitted to man without any intermediate host, usually via the pulmonary route. Agricultural workers exposed to chicken dung, silos, storm cellars, and so forth are particularly vulnerable.

CLINICAL MANIFESTATIONS

It is beyond the scope of this paper to present a detailed analysis of the clinical variations of human histoplasmosis. The reader, therefore,

is referred to Furcolow's excellent summarization (13) of the five recognized categories: (i) mild histoplasmosis; (ii) moderately severe histoplasmosis; (iii) epidemic histoplasmosis; (iv) acute disseminated histoplasmosis, and (v) chronic progressive histoplasmosis.

The disease may involve, aside from the pulmonary system, the gastrointestinal tract, the genitourinary system, the central nervous system (brain), middle ear, skin, skeletal system, joints, and adrenals. The possibility of ocular involvement will be discussed later.

DIAGNOSIS

A positive diagnosis of histoplasmosis, of course, requires demonstration of *Histoplasma capsulatum* through culture or microscopic study. Serologic tests, both precipitation and complement fixation, are valuable adjuncts to the diagnosis. A histoplasmin skin test and the blood studies are not positive until four to six weeks after the onset of active disease. These tests and agents are available through most state health departments.

A positive skin test can be looked upon as a valuable screening procedure and only indicates the presence of the disease in the individual at some time in life, while a complement fixation of greater than 1:8 is considered indicative of the presence of active disease.

Woods (17), in his well-written monograph, notes that to prove ocular histoplasmosis one would need to directly demonstrate the fungus in the intraocular issues, fluids, or exudates. Realizing the difficulty of obtaining such material, he outlined the provisions for making a tentative diagnosis of histoplasmosis as follows: (i) exclusion of other factors causing uveitis; (ii) the presence of pulmonary calcification; (iii) anergy to tuberculin; (iv) positive immunologic test for histoplasmosis.

TREATMENT

Until the discovery of Amphotericin B the treatment of histoplasmosis was often inadequate. Sulfadiazine, Stilbamidine, and Nystatin gave sporadic cures. It was not until the use of the intravenous preparation of Amphotericin B that consistent therapeutic successes were reported. Friedman (18), Miller *et al.* (19), and Greedyke and his group (20) each reported cases of systemic histoplasmosis resistant to previous regimens of treatment which responded dramatically to the employment of Amphotericin B. Seabury (1) likewise found complete healing in the patients who received intravenous therapy but no improvement in one patient treated with the oral preparation. Lehan's group (21) published results on five patients with systemic histoplas-

mosis who received intravenous Amphotericin B, all of whom showed distinct improvement while receiving the drug.

As the use of this agent has become more widespread the documented cases of proven histoplasmosis treated with Amphotericin B have demonstrated the importance of this drug in our therapeutic armamentarium against the organism *Histoplasma capsulatum.*

OCULAR HISTOPLASMOSIS

As previously intimated, the evidence implicating *Histoplasma capsulatum* as a causative agent in the production of ocular disease is still presumptive. In this vein Woods (17) has written, "While *Histoplasma capsulatum* has not as yet been isolated from a human eye with granulomatous uveitis, thus fulfilling Koch's postulates, nevertheless the accumulated evidence points strongly to the probability that histoplasma infection is an actual cause of granulomatous uveitis, and in this respect may ultimately prove to be the most important of the fungi."

Experimental evidence is available that *Histoplasma capsulatum* can produce uveitis in laboratory animals. Day (22) produced a granulomatous uveitis in rabbits by injecting *Histoplasma capsulatum* into their anterior chambers. He also reported data on four patients who exhibited positive histoplasmin skin tests, pulmonary calcification, and granulomatous uveitis. The patients failed to exhibit evidence implicating other causative agents.

A meticulous survey of the available literature reveals only three patients who have had culturally proven histoplasmosis and a concomitant uveitis. Reid (23) described a patient exhibiting: "small, white, irregular areas surrounded by hemorrhage in the ocular fundi . . . not unlike tubercles." Salvin and Furcolow (24) reported the presence of a "retinitis" in a patient, and a "nodular iritis" in another individual, both affected with proven histoplasmosis. In the latter two cases, however, a diagnosis of sarcoidosis was considered.

Krause (25) postulated the diagnosis of histoplasmosis uveitis in a patient who had exhibited the following findings: exacerbation of granulomatous uveitis following histoplasmin skin testing and disseminated discrete pulmonary calcification. The latter suggested either healed histoplasmosis or military tuberculosis. The tuberculin test was negative and, more important, a positive histoplasma complement fixation test was secured. Krause concluded that "the etiology of the patient's right macular chorioretinitis was evidently due to an infection with *Histoplasma capsulatum.*"

A survey of the literature did not disclose that Amphotericin A or B had been used to treat cases of presumptive ocular histoplasmosis. Foster and his associates (26), however, treated a postoperative cataract extraction endophthalmitis in one human eye with intraocular, subcutaneous, and subconjunctival Amphotericin B. The eye was salvaged but was amaurotic. A *Volutella* species of fungus was cultured from the involved eye.

Harrell and Curtis's (7, 27) encouraging and successful management of systemic and dermatologic deep mycoses stimulated us to treat certain cases of granulomatous uveitis with this agent. Under the guidance and advice of these dermatologists patients were selected who exhibited the following findings: ophthalmoscopically suspicious chorioretinitis; a positive histoplasmin skin test; a negative or positive tuberculin and skin test; and disseminated pulmonary calcification. Failure of the lesion to respond to other forms of therapy also strongly influenced selection of the patient, particularly antituberculous regimens in the patients who exhibited a positive tuberculin reaction. Complement fixation tests for histoplasmosis had to be secured through the State Health Department Laboratory. Since these reports were not infrequently long delayed, a positive histoplasmin complement fixation was therefore not required as an immediate requisite for eligibility for treatment with Amphotericin B.

The pertinent facts concerning the nine cases of histoplasmosis chorioretinitis treated with intravenous Amphotericin B are summarized below in tabular form.

Case I

Sex	Male
Age	42
Residence	Michigan

Pretreatment ocular findings. The patient presented ophthalmoscopic evidence of active central chorioretinitis, right eye, and inactive central chorioretinitis, left eye. The corrected visual acuity was 20/20 right eye and counts fingers left eye. The visual field exhibited a large paracentral scotoma in the right eye (2/1,000 red) and a dense, moderate-sized central scotoma in the left eye (2/1,000 white).

Uveitis survey. The patient presented a positive histoplasmin skin test, a positive histoplasma complement fixation test (1:8), and pulmonary calcification compatible with histoplasmosis.

Therapy. Amphotericin B 0.5 Gm. was given intravenously in 10 divided doses over an interval of 10 days. Vasodilators and steroids

(Prednisilone) were also employed in addition to Phenergan and Aspirin.

Therapeutic side effects. The patient exhibited mild drowsiness. The blood urea nitrogen was elevated mildly as was the bromsulphalein test.

Post-treatment ocular findings. The patient's visual acuity at the time of discharge was 20/40 right eye with no change in the visual field. He was discharged on steroids and vasodilators. The lesion revealed activity at the end of one month. The lesion was quiescent eight months later; the visual acuity was 20/200, and a large, dense central scotoma (2/1,000 white) was present. The lesion exhibited extensive scarring. The complement fixation test now was negative.

Case II

Sex	Female
Age	43
Residence	Ohio

Pretreatment ocular findings. Active central chorioretinitis, right eye; inactive central chorioretinitis, left eye. Visual acuity was 20/200 right eye and 20/200 left eye. The visual fields revealed a large central scotoma (2/1,000 white).

Uveitis survey. The histoplasmin skin test was positive; the histoplasma complement fixation test was positive 1:8; the chest film showed evidence of old inflammatory pulmonary disease.

Therapy. Amphotericin B 0.5 Gm. in 10 equally divided doses was given over an interval of 17 days.

Therapeutic side effects included temperature spiking, anorexia, nausea, headache, and chills. Mild elevation of the blood urea nitrogen, increased bromsulphalein retention, and a minimal fall in the hematocrit reading were also seen. All findings reverted to normal upon cessation of therapy.

Post-treatment ocular findings. The right visual acuity was count fingers at 3 ft. and left eye 20/200. The patient was discharged on Medrol and vasodilators. A large central scotoma, 2/1,000 white, was present in both eyes. The lesions in both eyes presented a gliotic, slightly elevated scar with minimal pigment migration.

Case III

Sex	Male
Age	40
Residence	Ohio

Pretreatment ocular findings. An active perifovealor chorioretinitis and a nongranulomatous iridocyclitis were present in the right eye; the visual acuity was 20/20 in both eyes; visual field presented a large perimacular scotoma 2/1,000 white in the right eye.

Uveitis survey. A positive histoplasmin and tuberculin skin test were obtained. Chest X-ray films revealed pulmonary calcification. The histoplasma complement fixation test was 1:16 (three months after initiation of therapy).

Treatment. Amphotericin B 0.5 Gm. in 10 equally divided doses was given over an interval of 14 days: Meticorten 15 mg. four times a day, and Atropine and Neo-deltacortef drops; Isoniazid 100 mg. three times a day.

Therapeutic side effects. The patient experienced dizziness, drowsiness, and temperature spiking.

Post-treatment ocular findings. The visual acuity was 20/15, right eye, and 20/20, left eye three months after discharge. No activity was noted and only minimal pigment mottling was observed in the area of the original activity. No scotoma was demonstrable.

Case IV

Sex	Male
Age	44
Residence	Michigan

Pretreatment ocular findings. Active central choriorentinitis right eye; inactive central chorioretinitis left eye. The visual acuity was 20/20–1 right eye, and 20/50–2 (eccentric) left eye. The visual fields presented a small central scotoma 1/2/1,000 white right eye and a dense small central scotoma 18/1,000 white, left eye.

Uveitis survey. A histoplasmin skin test was positive. The chest X-ray films presented equivocal evidence of old inflammatory disease. The histoplasma complement fixation test was positive, 1:8.

Therapy. Amphotericin B 0.5 Gm. in 10 equally divided doses was given over a 10-day period. Thiamin chloride and nicotinic acid were administered. Decadron 1.0 mg. was given orally every six hours for a period of two weeks and then slowly tapered.

Therapeutic side effects. The patient experienced spiking fever, headache, chills, anorexia, and back pain.

Post-treatment ocular findings. The visual acuity was 20/20 right eye and 20/50–2 left eye; the ophthalmoscope revealed only pigment clumping in the macular area left eye; the lesion was quiescent. Complement fixation test reverted to negative.

Case V

Sex	Female
Age	42
Residence	Michigan

Pretreatment ocular findings. Disseminated old chorioretinitis, both eyes; active central chorioretinitis left eye; the vitreous was very cloudy in the latter eye. The corrected visual acuity was 20/20 right eye and 20/70 left eye. The left eye presented a temporal hemianopic defect including the fixation area on visual field examination.

Uveitis survey. A histoplasmin skin test was positive. The chest X-ray film revealed calcium changes typical of old histoplasmosis and a complement fixation of 1:8 was obtained.

Therapy. Amphotericin B 0.7 Gm. was given in 14 divided doses over a period of 17 days. The patient had been treated prior to her admission with steroids and Isoniazid by her local physician.

Therapeutic side effects. The patient experienced headache, nausea, backache, chills, spiking fever, diaphoresis, and a mild elevation of the blood urea nitrogen.

Post-treatment ocular findings. The vitreous haze cleared during Amphotericin B therapy in the left eye and a hemispherical raised lesion suggesting a malignant melanoma was observed. P32 uptake studies were positive. Visual acuity was 20/100 and the visual field was unchanged. Enucleation was performed and pathologic study revealed a spindle cell type A malignant melanoma of the choroid perforating the sclera along the vortex veins. Culture for *Histoplasma capsulatum* was negative. The histoplasma complement fixation test was 1:16 three months after enucleation.

Case VI

Sex	Male
Age	35
Residence	Michigan

Pretreatment ocular findings. An active central chorioretinitis was present in the right eye; the left retina was normal. The corrected visual acuity was 20/30 right eye and 20/20 left eye. The visual fields revealed a small central scotoma 1/1,000 red right eye.

Uveitis survey. A positive histoplasmin skin test, a positive histoplasma complement fixation test (1:8) and a chest X-ray film presenting calcified nodes and scattered bilateral pulmonary calcification and scarring suggestive of histoplasmosis were obtained.

Therapy. The patient received 0.5 Gm. of Amphotericin B in ten

divided doses over a 10-day interval. Nicotinic acid, thiamin chloride, and Medrol 2 mg. twice daily were also used.

Therapeutic side effects. The patient experienced spiking fevers, chills, and diaphoresis.

Post-treatment ocular findings. At the time of completion of treatment the visual acuity was 20/20 and a small pericentral scotoma 1/1,000 red was present. The patient was continued on small doses of steroids for three months following discharge. The visual acuity was 20/70 right eye three months after treatment and 20/80 five months later. The lesion showed no activity at the latter time.

Case VII

Sex	Female
Age	22
Residence	Michigan

Pretreatment ocular findings. An active central chorioretinitis was present in the left eye; no pathology was seen in the right eye. The corrected visual acuity was 20/15 right eye and 20/60 and Jaeger 11 left eye. The visual field presented a large central scotoma in the left eye 1/1,000 white.

Uveitis survey. A positive histoplasmin and tuberculin skin test, a negative histoplasma complement fixation test, and a chest X-ray film compatible with old inflammatory disease of the chest were secured.

Therapy. Amphotericin B 1.0 Gm. was administered in 20 divided doses over a 20-day interval. In addition Typhoid H Antigen, thiamin chloride, and nicotinic acid were employed.

Therapeutic side effects. The patient experienced mild anorexia, nausea, diarrhea, temperature spiking and malaise.

Post-treatment ocular findings. The fundus showed less activity. The visual field and acuity of the left remained the same immediately following treatment. One year after completion of treatment the lesion was quiescent and the visual acuity was count fingers at three feet.

Case VIII

Sex	Female
Age	23
Residence	Michigan

Pretreatment ocular findings. An acute exacerbation of an old central chorioretinitis lesion was noted in the left eye; the ocular findings in the right eye were negative for pathology. The visual field presented a small pericentral scotoma (1/1,000 red). The corrected visual acuity was 20/20–1 in each eye.

Uveitis survey. A positive histoplasmin skin test, a negative complement fixation test and chest X-ray findings previously diagnosed as histoplasmosis (1957) were obtained.

Therapeutic side effects. The patient experienced chills, fever, nausea, vomiting, headache, and depressed platelet count. The drug was stopped because of decreased hemoglobin and increased blood urea nitrogen. No further medication was given when the complement fixation test was read as negative for histoplasma.

Post-treatment ocular findings. The ocular findings were much as before treatment except less vitreous haze was noted and the activity was less. The visual acuity was 20/20–1 in both eyes.

Case IX

Sex	Female
Age	39
Residence	Michigan

Pretreatment ocular findings. An acute central chorioretinitis was present in both eyes. The corrected visual acuity was 20/30 right eye and 20/80 left eye. The visual fields exhibited a paracentral scotoma in the right eye (2/1,000 red) and a large central scotoma in the left eye.

Uveitis survey. The patient exhibited a very positive histoplasmin and mildly positive tuberculin skin test. The chest film was negative and the histoplasma complement fixation test was negative.

Therapy. The patient had received streptomycin, para-amino-salicylic acid and Isoniazid for several months without result. Amphotericin B 0.5 Gm. in 10 divided doses over an 11-day period was administered. Decadron was also employed.

Therapeutic side effects. The patient experienced headaches, abdominal cramping, spiking fever, chills, phlebitis (intravenous arm), lethargy, diaphoresis, and an elevated blood urea nitrogen.

Post-treatment ocular findings. The visual acuity improved to 20/25 in the left eye and decreased to 20/50 in the right eye. The lesion was quiescent in the left eye but continued to exhibit activity in the right eye as late as five months after therapy.

COMMENT

All of the nine cases presented exhibited a positive skin test to histoplasmin, but only six of these demonstrated a significant positive histoplasma complement fixation titer. The nine patients thus fall into

two groups: (1) those presenting a positive histoplasmin skin test and a positive histoplasma complement fixation test (I–VI) and (2) those presenting only a positive histoplasmin skin test (VII–IX). Little response to Amphotericin B therapy was encountered in the latter group. The former group (I–VI) however deserve closer scrutiny since the positive histoplasma complement fixation test suggests activity of the disease. In the group of six patients, two (Cases III and IV) demonstrated objective improvement in visual acuity and fields; two poorer visual acuity (Cases I and II) but subsidence of activity of the lesions; and one patient (Case V) had the diagnosis altered (malignant melanoma) after sufficient improvement in the vitreous haze resulted to permit more accurate visualization. One case (VI) had the same visual acuity immediately after treatment but this deteriorated later while on steroid therapy despite quiescence of the chorioretinitis.

Ideally, only those cases in whom one can obtain serologic evidence of active histoplasmosis should be treated with Amphotericin B. This was not done in our cases since it was not thought, at first, expedient to wait for the complement fixation test results. It is amazing that six of the nine cases actually did exhibit, eventually, a positive histoplasma complement fixation test. It is evident that a certain number of patients with active chorioretinitis and only a positive histoplasmin skin test will receive ill-advised therapy. Through experience the authors feel strongly that since Amphotericin therapy is an expensive, rigorous, and dangerous therapy it should not be instigated unless strong presumptive evidence of histoplasmosis activity is available to the physician.

Since several of the patients, including Cases III and IV, received steroid therapy in conjunction with the administration of the Amphotericin B it is freely admitted that it was impossible to determine to what degree the latter agent was responsible for the clinical observed subsidence. It is regrettable that steroids were employed, but their utilization was dictated by threatened destruction of the macular area. It is to be pointed out however that, in our experience, a certain number of such cases treated solely with long-term steroid administration continued to exhibit activity and on occasion the chorioretinitis would actually exacerbate, leading to phthisis. It would be, of course, most desirable to secure a series of cases presenting peripheral chorioretinitis in patients manifesting presumptive evidence of histoplasmosis and treated with Amphotericin B alone. Such a series would possibly answer many of the questions which this study cannot.

Amphotericin B therapy, as previously emphasized, is not an innocuous regimen. A survey of the complications encountered in the

nine reported patients revealed the following significant signs and symptoms: (i) spiking fever (8 out of 9); (ii) chills (6 out of 9); (iii) elevated blood urea nitrogen (5 out of 9); (iv) headache (5 out of 9); (v) nausea (4 out of 9); (vi) anorexia (3 out of 9); (vii) dizziness (3 out of 9); (viii) drowsiness (3 out of 9); (ix) diaphoresis (3 out of 9); (x) increased bromsulphalein (2 out of 9); and (xi) decreased hemoglobin, platelet count, phlebitis, and abdominal pain (1 out of 9). The majority of the latter signs and symptoms occurred in one patient (Case VIII) which necessitated cessation of therapy which was not resumed when the histoplasma complement fixation test was reported as negative. These reactive signs and symptoms returned to normal in all nine cases following cessation of treatment and no detectable evidence of permanent deleterious effect to any organ or system has been found. Christie's evidence that sulfonamide therapy is of specific value in the management of systemic histoplasmosis should stimulate its use in cases of chorioretinitis. As a result of our experience with Amphotericin B and motivated by Christie's report employing sulfonamides the following therapeutic regimen of suspected cases of histoplasmosis chorioretinitis is suggested.

(*a*) A careful medical survey of the patient should be made, particularly ruling out nephritic, hepatic, and hematopoietic pathology.

(*b*) Intravenous Amphotericin B in 5 percent glucose utilizing 1 mg. per kilogram of body weight, not to exceed 75 mg., usually 50 mg. per administration, should be given. Daily or alternate daily injection may be employed depending on the patient's systemic response to the drug. A total of 1.0 Gm. of the drug, probably, should be used.

(*c*) During the interval of therapy the kidney, liver and bone marrow function should be carefully followed. This may be done by alternate daily blood urea nitrogen, hematocrit, white blood count, and cellular differentiation determinations. Bromsulphalein retention and phenolsulfonphthalein clearance studies should be obtained weekly. A blood urea nitrogen greater than 30 mg. percent or evidence of moderate hepatocellular or bone marrow depression should dictate cessation of therapy. Should these findings return to normal, therapy may then be reinstituted. In an attempt to minimize side effects of the drug, the following ancillary regimen may be employed: Phenergan 25 mg. by mouth and acetylsalicylic acid grains 10 by mouth three hours prior to intravenous administration of Amphotericin B and repeated every three hours as necessary. In recalcitrant cases Benadryl 50 mg. may be mixed with intravenous preparation.

(*d*) Steroid therapy is to be administered only when macular or ocular destruction is imminent.

(*e*) Sulfadiazine 1 Gm. four times a day should be started seven days prior to cessation of Amphotericin B infusions and continued on a long term basis with or without steroids when the patient is discharged from the hospital. Repeated careful urinalyses must be performed in association with this dosage of sulfonamides and in addition the patient should be warned to maintain a high fluid intake.

This paper has not established, other than on speculative and presumptive evidence, that histoplasmosis affects the eye. The presence of an active chorioretinitis associated with (i) a positive histoplasmin skin test, (ii) a positive histoplasma complement fixation test, (iii) roentgenographic evidence of pulmonary histoplasmosis, and (iv) the absence of other causative factors is, however, as good as or better than the evidence usually available to implicate other granulomata causing agents. *Histoplasma capsulatum* has not been recovered from ocular tissues, but when consideration is accorded to the widespread involvement of other body tissues and organs by this agent it seems extremely plausible that the eye may likewise be affected.

Considerable debate is occurring as to the significance of a histoplasma complement fixation test positive in 1:8 dilution. At present many authorities consider this as positive evidence of active disease. Further clinical correlation, however, is required.

The penetrability of Amphotericin B into the human eye is still unproven and before one can definitely assign ocular therapeutic properties to this drug this problem must be answered. Since Amphotericin B has been detected in the cerebrospinal fluid it might be postulated that it can also appear in the aqueous. Montana and Sery (28) found no evidence of such penetration into the anterior chamber of rabbits no matter what the route of administration, but studies related to levels of the drug in the coats of the eye have not been obtained.

It is apparent that this paper has produced no confirmatory evidence that ocular histoplasmosis is an entity. The paucity of treated cases, the short period of follow-up, the high incidence of destructive scarring of the involved retina, and observed exacerbation of the lesion in several cases leaves much to speculation as to the efficiency of Amphotericin B in the treatment of the reported cases. Suffice it to say that an agent, successful elsewhere in treating systemic histoplasmosis, has been employed in the therapeusis of certain cases of chorioretinitis. It appeared, with and without the use of steroids, to effect quiescence of the chorioretinitis. Further experience and study are apparently necessary to answer the numerous questions that have arisen about the use of the drug.

SUMMARY

Nine selected cases of chorioretinitis, presumably caused by *Histoplasma capsulatum*, were subjected to Amphotericin B therapy with and without steroid supplement. Subsidence of the chorioretinitis activity resulted in most cases. Systemic reactions to Amphotericin B were encountered and were summarized. These drug reactions produced no permanent sequelae but were alarming and left no doubt that the drug is not innocuous, but rather one that requires the most meticulous care in its administration.

CONCLUSION

Amphotericin B, an antibiotic with proven antifungal activity, has been successfully employed in the treatment of systemic histoplasmosis. The results of its employment in the treatment of selected cases of chorioretinitis, although far from striking, suggest that further trial of the drug in cases of suspected histoplasmosis of the eye is warranted.

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DISCUSSION

DR. ALSON E. BRALEY. I shall attempt to discuss these two papers together, but this may present a problem, as you may have already guessed.

In 1932, while I was taking my residency in Pathology and Bacteriology, I did a postmortem on a man who had supposedly died of Hodgkin's disease and pneumonitis. Many organisms were found in the sections, and I was fortunate enough to take many cultures from the lung tissue and lymph nodes and grew the organism of histoplasmosis. This case was subsequently reported. Since then I have retained an interest in this elusive disease. I call it elusive because few but the fatal cases have been proven. As Dr. Woods pointed out in the presentation, the introduction of the skin test has shown that a nonfatal form must be common in many sections of the world. This

is true of my own state of Iowa, where positive skin tests to histoplasmin are common.

It is inviting to speculate that many of Dr. Woods' patients may have had ocular histoplasmosis, particularly those in Groups I and II.

In the benign form of histoplasmosis there is postulated a blood stream infection during some phase of the disease. If the organisms are screened out in all reticuloendothelial tissue, then one would guess that the choroid of the macula might also catch some of these organisms. The organism will either grow and produce a zone of inflammation, or die out and leave a sensitized tissue, which can then respond allergically, as Dr. Woods has pointed out. In our area, officials of our State Department of Health state that more than half of the population show positive skin tests. Similar findings are present in another elusive disease: brucellosis. It is nearly impossible to demonstrate in a uveitis sample a higher prevalence of positive skin tests than in the normal population.

I have treated one patient during the past four years who had a choroidal lesion similar to those described by Dr. Woods. This young woman, I believe, showed some regression of the inflammatory signs when treated with small doses of histoplasmin. I would like to hear Dr. Woods comment on treatment once the presumptive diagnosis is made.

Macular lesions involving the choroid and retina have been of considerable interest to me for several years. We eagerly await the day we will have an opportunity to grow organisms from these eyes or to use this tissue for fluorescein-tagged antibody studies. Dr. Woods is again to be congratulated in bringing to our attention another group of cases of granulomatous uveitis for which a possible etiologic agent may be found.

In regard to Dr. Falls' presentation, I should like to quote from his paper: "The decision to use Amphotericin B in the treatment of ocular histoplasmosis is not to be lightly made and if undertaken warrants extreme caution and alert observation."

If the organism disappears quickly from the lesions, why should treatment be of value?

DR. ALGERNON B. REESE. I have one question: is it possible that Boeck's sarcoid belongs to the histoplasmosis group?

DR. DAVID PATON. In the absence of Dr. von Sallmann, and particularly in view of Dr. Braley's closing remarks, I should like to mention a case of histoplasmosis which I believe is pertinent to this discussion.

A 60-year-old man was recently admitted to the National Institutes of Health with disseminated acute disease. Although skin tests and complement fixation tests were negative for histoplasmosis, positive cultures of the fungus were obtained from the spinal fluid and from bone marrow. The patient was treated for eight weeks or more with Amphotericin B in appropriately high doses. A remarkable recovery resulted, the cultures became

negative. During the course of his treatment visual loss occurred and a severe granulomatous type uveitis was found to have developed. There were iris nodules, many keratitic precipitates, flare, and vitreous opacities which prevented examination of the fundi which were previously apparently normal. An anterior chamber paracentesis was performed; culture of the aqueous was negative.

The patient is now fully recovered from other evidence of active disease, but his uveitis remains unchecked by topical steroids. His complement fixation and skin tests remain negative.

DR. DUPONT GUERRY, III. I should like to address one quick query to the authors: have they had any experience with the new fungicidal drug, griseofulvin, which has been recently used so effectively by the dermatologists? This drug, as you may know, is a derivative of penicillin, and is apparently not very toxic.

DR. ROBERT DAY. I have just one brief question. At the time of the experimental work that Dr. Woods referred to there was some cross-sensitization of *Histoplasma* with other fungi, notably *Blastomyces*, and I wonder what is the current status of that cross-sensitization. One of the difficulties in making a diagnosis and fulfilling Koch's postulates, as Dr. Woods mentioned, is that of identifying the organism in the infected tissue. The rabbits which I used developed a very severe granulomatous uveitis; if they were infected with a mycelial fungus, this was converted in a week to a spore form. This was difficult to identify with the ordinary staining techniques. However, the capsule of the spore contains a polysaccharide which shows up very well with polysaccharide stains, and it might be worth while for those people who have large collections of acute uveitis slides to restain them with these stains; they might identify some organisms which have hitherto been unrecognized.

I enjoyed Dr. Woods' and Dr. Falls' papers very much.

DR. WOODS. I have enjoyed Dr. Falls' paper. We have treated some five cases so far with Amphotericin B, and our results are the same as his. He has outlined beautifully the precautions which have to be taken. He has also outlined the use of sulfadiazine as an adjuvant. Dr. Braley has been good enough to outline the theory that I mentioned as to the pathogenesis of the disease, which is purely hypothetical.

In answer to Dr. Reese's question, these patients were all carefully explored, and there was no evidence of Boeck's sarcoid in any of them; there was no change in the A-G ratio—nothing was found.

In answer to the question on the use of histoplasmin, we have treated one case with histoplasmin desensitization, with a conspicuously good result. The man had bilateral lesions; his vision was threatened, but under desensitization therapy his symptoms have subsided. "One swallow does not make a summer."

In relation to staining the organisms with a polysaccharide stain, these various granulomatous lesions were stained by every stain known; they were studied by Drs. Zimmerman and Wilder and no organisms could be found.

In regard to the complement fixation reaction, I can speak with a good deal of conviction. I have used complement fixation reactions personally for many years in a variety of ocular infections. I started in 1913 working with tuberculosis, brucellosis, and gonorrhea, in the days when there was a lot of gonorrheal uveitis. The complement fixation is a weak reed to lean on! The results often vary greatly. It requires most careful titration in order to get consistent results, and often the results appear to vary with the weather, the state of the crops, and what the technician had for breakfast! They vary in the same patient in different laboratories. Schwartz believes a positive fixation reaction is only of value when it shows a rising titer. We have done complement fixation reactions on a number of the cases here reported. Some were positive, and others completely negative. I think the answer is this. Unless you have widespread infection there is insufficient antigenic stimulus in a small focus in the eye to excite the formation of complement fixing antibodies to the extent that they can be detected in the blood stream.

Again I should like to emphasize that in this paper Koch's postulates have not been fulfilled. I dislike drawing conclusions on purely clinical evidence, but I am highly doubtful that we will ever get the proof of the presence of this organism in these ocular lesions. If we can judge by experimental work, it is almost impossible to demonstrate the parasites in older lesions of ocular histoplasmosis.

DR. FALLS. Dr. Braley asked about treatment. Treatment with Amphotericin B was instigated for the following reasons: (1) failure of the typical chorioretinitis to respond to steroid therapy; (2) progressive destruction of central vision; (3) availability of a proven antifungal agent Amphotericin B, and (4) a desire to learn if Amphotericin B had any therapeutic role in the management of certain types of chorioretinitis.

I have no experience with the new antifungal drug which Dr. Guerry recommended, but we expect to investigate this particular agent before we do further studies.