Fungal Endophthalmitis

An Experimental Study With a Review of 17 Human Ocular Cases

Thomas W. McGuire, MD; John D. Bullock, MD; J. David Bullock, Jr; B. Laurel Elder, PhD; James W. Funkhouser, MD

- *Pseudallescheria boydii* is an opportunistic fungus that is histologically indistinguishable from *Aspergillus fumigatus*. *Pseudallescheria boydii* has been reported to cause endophthalmitis, orbital cellulitis, and corneal ulceration and is, thus, important to the ophthalmologist. A clinical review of 17 patients with *P. boydii* ophthalmic infections is presented. In addition, animal models of endophthalmitides caused by *A. fumigatus* and *P. boydii* were created and compared. Dutch-Belted rabbits used for the experimental models were immunosuppressed with methylprednisolone acetate (Depomedrol). Exogenous and endogenous models of *P. boydii* endophthalmitis were created in immunocompetent and immunosuppressed animals. An exogenous model of *A. fumigatus* endophthalmitis was created in immunocompetent and immunosuppressed animals for comparison. The clinical and histopathologic features of *A. fumigatus* and *P. boydii* endophthalmitis are indistinguishable in the immunocompetent and immunosuppressed exogenously infected rabbits. Endogenous *P. boydii* endophthalmitis has a similar fundus appearance to that caused by *Nocardia asteroides.*


*Pseudallescheria boydii* (perfect [sexual] state) is a ubiquitous, opportunistic fungus with a low inherent virulence. In its asexual (imperfect) state it is known as *Scedosporium apiospermum*. It is found worldwide in soil, manure, and multiple water sources, including creeks contaminated with sewage, standing water, and tidewashed coastal areas. In tissue this organism is morphologically indistinguishable from the more commonly occurring fungus, *Aspergillus fumigatus*. The thin septate hyphae of *A. fumigatus* and *P. boydii* often exhibit dichotomous branching. In tissue section, these two organisms demonstrate the identical pathologic tissue reactions of suppuration and vascular invasion with infarction, hemorrhage, ischemia, and necrosis. The spectrum of disease produced by *P. boydii* is wide and encompasses virtually the entire range of human illness caused by the *Aspergillus* species, thus earning *P. boydii* the designation “the great imitator.” Both fungi exhibit rapid growth on Sabouraud’s agar at an optimal temperature range of 30°C to 37°C. In culture, *P. boydii* has a velvety white to smoky gray appearance while *A. fumigatus* is usually green.

*Pseudallescheria boydii* organisms cause mycetoma (also known as Madura foot); infection results from the traumatic implantation of the fungus into subcutaneous tissues. Disseminated infections occur almost exclusively in immunosuppressed hosts, with the lungs being the site of entry in most cases. *Pseudallescheria boydii* has been reported to cause endophthalmitis, orbital cellulitis, and corneal ulceration and, thus, is important to the ophthalmologist. 5,19

Human ophthalmic involvement from *P. boydii* can occur exogenously and endogenously. In the exogenous form, ocular pseudallescheriasis develops as a result of a superficial infection, traumatic implantation of the organism, or following intraocular surgery. Endogenous ocular pseudallescheriasis occurs when the organisms are spread to the eye hematogenously. Most of the reported cases have occurred with the exogenous form of the disease (11 of the 17 cases). Table 1 is a summary of the clinical and histopathologic findings in these previously reported cases.

A misconception exists that the unique diagnosis of aspergillosis can be made either “visualizing dichotomously branching septate hyphae in biopsy specimens or on the basis of a consistent clinical presentation.” 20 Because it is more common, aspergillosis is generally the presumptive diagnosis prior to cultural identification of the organism. 21,22 Since *P. boydii* and *A. fumigatus* may be sensitive to different antifungal agents (miconazole, the reported drug of choice for *P. boydii* infections, or ketoconazole and amphotericin B, respectively), the distinction is an important one and, thus, supports the necessity of a precise diagnosis by culture. 23

The purpose of this study was to compare animal models of endophthalmitides caused by *A. fumigatus* and *P. boydii*. Exogenous and endogenous experimental models of *P. boydii* endophthalmitis were created in immunocompetent and immunosuppressed rabbits. The clinical and histopathologic features of the model are compared and contrasted with an exogenous rabbit model of *A. fumigatus* endophthalmitis.
### Table 1.—Summary of the Clinical and Histopathologic Features of Previously Reported Cases of Patients With *Pseudallescheria boydii* Ocular Infections

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient No., Age, y/Sex</th>
<th>Involved Eye</th>
<th>Predisposing Factor(s)</th>
<th>Ocular Symptom(s)</th>
<th>Clinical Ocular Finding(s)</th>
<th>Source of Positive Culture</th>
<th>Histopathologic Feature(s)</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al⁴</td>
<td>1/4/M</td>
<td>L</td>
<td>Penetrating injury (from an oil can spout) to the orbit and frontal lobe</td>
<td>Eye pain</td>
<td>L upper eyelid laceration with edema and purulent drainage; visual acuity could not be determined</td>
<td>Orbital abscess</td>
<td>Day 16, IV amphotericin B; day 21, superior orbit debridement; day 22, IV miconazole</td>
<td>Mycelia and oil droplets in brain and orbital abscesses</td>
<td>1 y later the visual acuity was 20/30 OS</td>
</tr>
<tr>
<td>Bakerspigel⁵</td>
<td>2/41/M</td>
<td>R</td>
<td>Traumatic implantation of a wood particle</td>
<td>None</td>
<td>Corneal ulcer</td>
<td>Corneal tissue</td>
<td>&quot;Eye solution,&quot; then evascration</td>
<td>Cornea with septated hyphae in the stroma</td>
<td>Evisceration</td>
</tr>
<tr>
<td>Elliot et al⁶</td>
<td>3/26/M</td>
<td>L</td>
<td>Burn, secondary to molten aluminum</td>
<td>Pain and decreased vision</td>
<td>Early: corneal infiltrates and edema; Late: necrosis at the corneoscleral junction</td>
<td>Conjunctiva</td>
<td>Amphotericin B, then enucleation</td>
<td>Fungal hyphae and inflammatory cells in the corneal stroma, Descemet's membrane, and anterior chamber</td>
<td>Enucleation</td>
</tr>
<tr>
<td>Ernest and Rippon⁶</td>
<td>4/43/M</td>
<td>Not stated</td>
<td>None</td>
<td>Pain and redness</td>
<td>Hypopyon and corneal ulcer</td>
<td></td>
<td>Nystatin and amphotericin B; keratoplasty for a descemetic ocele</td>
<td>Conidiphores with ovoid conidia in the corneal ulcer</td>
<td>Healed, scarred cornea</td>
</tr>
<tr>
<td>Glassman et al⁷</td>
<td>5/48/F</td>
<td>L</td>
<td>Cataract surgery and diabetes mellitus</td>
<td>Pain and decreased vision</td>
<td>Conjunctival hyperemia; pus and tiny white spherules in anterior chamber; choroidal detachment</td>
<td>Anterior chamber</td>
<td>Day 1, topical and oral steroids and antibiotics; day 17, amphotericin B</td>
<td>None</td>
<td>Visual acuity of 20/30 8 mo after cataract surgery</td>
</tr>
<tr>
<td>Gordon et al⁸</td>
<td>6/27/M</td>
<td>L</td>
<td>Traumatic implantation of a fish scale in the eye</td>
<td>Pain, photophobia, lacrimation, and loss of vision</td>
<td>Aquous flare in the anterior chamber; corneal ulcer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levitt and Goldstein⁹</td>
<td>7/40/M</td>
<td>L</td>
<td>Unknown foreign body in the cornea</td>
<td>Pain and discomfort</td>
<td>Initially, a crater-like corneal ulcer; hypopyon at 5 wk, with perforation of the cornea</td>
<td>Anterior chamber</td>
<td>Day 1, dexamethasone and antibiotics; week 9, nystatin and amphotericin B</td>
<td>Aqueous smear showed &quot;saprophytic fungi&quot;</td>
<td>Scleratomy, iridectomy, lensectomy, and synechiectomy</td>
</tr>
<tr>
<td>Lutwick et al¹⁰</td>
<td>8/32/F</td>
<td>R</td>
<td>Systemic lupus erythematosus; prednisone, azathioprine therapy</td>
<td>Pain and decreased vision</td>
<td>Conjunctival edema; 4-mm proptosis; decreased visual acuity; anterior chamber pus; chorioretinal abscesses</td>
<td>Vitreous humor</td>
<td>Day 1, prednisone drops; day 3, amphotericin B and antibiotics; day 8, miconazole; day 16, enucleation</td>
<td>Chronic inflammation, and branching hyphae in vitreous</td>
<td>Uneventful recovery after enucleation</td>
</tr>
<tr>
<td>Meadow et al¹¹</td>
<td>9/15/F</td>
<td>L</td>
<td>Near drowning with aspiration pneumonia</td>
<td>None</td>
<td>Bilateral retinal degeneration with vitritis</td>
<td>Vitreous humor</td>
<td>Day 9, amphotericin B and topical antibiotic; day 14, vitrectomy; day 19, miconazole</td>
<td>No autopsy eye report; disseminated <em>P. boydii</em> in liver, lung, brain, kidney, and subcutaneous tissue</td>
<td>Death</td>
</tr>
<tr>
<td>Pautler et al¹²</td>
<td>10/39/M</td>
<td>L</td>
<td>None</td>
<td>Eye and jaw pain and tearing</td>
<td>Corneal ulcer with hypopyon</td>
<td>Corneal ulcer</td>
<td>Day 1, steroids and multiple antibiotics; day 12, enucleation</td>
<td>Anterior chamber exudate (inflammatory cells and septated fungal hyphae, with conidia)</td>
<td>Uneventful recovery after enucleation</td>
</tr>
</tbody>
</table>

### MATERIALS AND METHODS

*Pseudallescheria boydii* and *A. fumigatus* were obtained on Sabouraud's dextrose agar (Cambinet Clinical Laboratories, Dayton, Ohio). The culture was transferred to fresh Sabouraud's agar and grown for 96 hours at room temperature. The fungi were transferred from the agar plate and suspended in sterile saline, which was diluted to 10⁶ spores per milliliter. Quantitation of the spore count was based on a turbidity comparison to a predetermined standard that was previously verified using a hemocytometer.

Male and female Dutch-Belted rabbits (*Lepus europaeus*), aged 2 to 3 months and weighing from 1 to 2 kg, were kept in an
Table 1.—Summary of the Clinical and Histopathologic Features of Previously Reported Cases of Patients With Pseudallescheria boydii Ocular Infections 

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<th>Histopathologic Feature(s)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al</td>
<td>11/45/M</td>
<td>L</td>
<td>None</td>
<td>Pain</td>
<td>Hypopyon, retinitis, and vitritis</td>
<td>Vitreous humor</td>
<td>Vitrectomy with intravitreal amphotericin B; intravitreal and IV miconazole; fluconazole; encleavage</td>
<td>Fungi in outer layers of the retina</td>
<td>Death secondary to systemic pseudallescheriasis</td>
</tr>
<tr>
<td>Nunnerly et al</td>
<td>12/10/M</td>
<td>R</td>
<td>Penetrating injury (stick) to lower lid</td>
<td>None</td>
<td>Cicatricular ectrusion with scar-ring to the inferior orbital rim; fistulous tract with purulent drainage below lateral lid margin</td>
<td>Fistulous tract purulent drainage, and from surgical specimen</td>
<td>Multiple systemic and topical antibiotics; surgical debridement; miconazole after positive cultures</td>
<td>Hyphae in orbital tissues</td>
<td>Complete recovery, without complications</td>
</tr>
<tr>
<td>Caya et al</td>
<td>13/49/M</td>
<td>Both</td>
<td>Immunosuppression (azathioprine, and methylprednisolone) for renal transplantation</td>
<td>Pain and photophobia</td>
<td>R: visual acuity: light perception only; L: visual acuity: no light perception, Both: hazy media, and conjunctivitis with injection</td>
<td>Vitreous humor from both eyes</td>
<td>Bilateral vitreomycosis and intraocular amphotericin B; intravitreal and IV miconazole; L eye enucleation</td>
<td>Vitreous cavity with necrotic debris and hyphae, branching at 45°</td>
<td>Death secondary to septic shock</td>
</tr>
<tr>
<td>Gluckman et al</td>
<td>14/58/M</td>
<td>R</td>
<td>Diabetes mellitus</td>
<td>Painless loss of vision</td>
<td>Phthisis, exophthal-mos, exotropia, and visual acuity of light perception only</td>
<td>R maxillary sinus (no eye cultures were obtained)</td>
<td>IV amphoteracin B and cephalothin sodium</td>
<td>None</td>
<td>Blindness</td>
</tr>
<tr>
<td>Persaud and Holroyd</td>
<td>15/44/M</td>
<td>L</td>
<td>None</td>
<td>Conjunctival scrappings</td>
<td>Lower lid symblepharon, upper lid myome-toma; corneal scarring</td>
<td>None</td>
<td>Surgical lysis of adhesions and removal of the myome-toma</td>
<td>Subepithelial abscess with fungal colonies of septate branch-Iing hyphae and conidiophores</td>
<td>Not stated</td>
</tr>
<tr>
<td>Zapater and Albesi</td>
<td>18/19/M</td>
<td>L</td>
<td>Traumatic implantation of a foreign body</td>
<td>Pain, photophobia, and lacri-mation</td>
<td>Central corneal ulcer and hy-popyon</td>
<td>Corneal ulcer</td>
<td>Topical antibiotics and atropine, 5% natamycin; subconjunctival amphotericin B</td>
<td>None</td>
<td>Leukoma, with visual acuity of hand movements</td>
</tr>
<tr>
<td>Stern et al</td>
<td>17/31/M</td>
<td>R</td>
<td>&quot;Systemic stress secondary to multiple surgical interventions&quot;</td>
<td>Blurred vision</td>
<td>Visual acuity of hand motion only: hyperemic bulbar conjunctiva; deep anterior chamber with 4+ cells and 1+ flare; hypopyon; intraretinal fluffy white exudative lesions</td>
<td>Vitreous humor</td>
<td>Day 1: topical prednisolone acetate and cyclopentolate hydrochloride; day 3, IV acyclovir sodium; day 11, IV nafcillin sodium and tobramycin sulfate; day 12, lensectomy-vitreomcy; day 18, IV and intravitreal micon-azole</td>
<td>Reinitis with mononuclear and polymorphonuclear cellular infiltration; vitreous cavity with necrotic debris; fungal hyphae were absent in all sections studied</td>
<td>Death secondary to fungemia</td>
</tr>
</tbody>
</table>

IV indicates intravenous.

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approved animal facility with food and water ad libitum. Rabbits were used in this study because of the relatively large size of the eyes and carotid arteries and because standard human ophthalmoscopes and retinal cameras could be used to observe and photograph the retinas. Dutch-Belted rabbits were selected because the ocular appearance is similar to the human eye.

Preexperimental ocular examinations showed all rabbits to have clear media and normal fundi. Three days prior to the injection of the fungi, the rabbits were pretreated with either intramuscular saline or intramuscular steroid (10 mg/kg methylprednisolone acetate [Depomedrol]). The rabbits were anesthetized with ketamine hydrochloride (Vetalar), 40 mg/kg, intramuscularly. The neck area was shaved and a depilatory agent (Surgey) was applied to remove the residual hair. Following a povidone-iodine (Pharmadine) skin preparation and the subcutaneous injection of a local anesthetic (2% lidocaine hydrochloride), a 25-mm longitudinal incision was made in the neck to expose the right common carotid artery. For the carotid injection, a 25-gauge needle was used to puncture the common carotid artery and a 1-mL inoculum of 10⁶ spores per milliliter of P. boydii (or 1 mL of sterile saline) was injected over 10 seconds. After the injection, the needle was withdrawn, and the skin incision was closed.

For the intracocular injections, the animals were anesthetized with ketamine (as
The control group received 0.2 mL of sterile saline. Following both endogenous and exogenous inoculation, the animals were returned to their cages and given food and water ad libitum. To verify the viability and purity of the inoculum, 0.5 mL of the injectate was placed on Sabouraud's agar at room temperature.

The eyes and all grossly infected internal organs of rabbits that died or were killed with an intravenous injection of N-[2-(methoxy-phenyl)-2-ethyl-buty1]-11-gamma-hydroxy-butylramide, 4-methylene-bis (cyclohexl-trimethyl-ammonium-oxide), tetracaine hydrochloride, and dimethylformamide (Euthanasia T-61 Solution) were removed to 10% phosphate-buffered formaldehyde solution. Selected eyes with observed retinal lesions or endophthalmitis underwent vitreous aspiration for culture on Sabouraud's agar. The tissues were embedded in paraffin and microscopic sections were prepared. Sections were stained with hematoxylin, phloxine, and safranine, periodic acid-Schiff, and Gomori's methanamine silver. Microscopic sections were examined under oil immersion for evidence of fungal infection. Microscopic sections were photographed with color slide film (Ektachrome 50, Eastman Kodak Co, Rochester, NY).

Clinical observation and evaluation began 2 days after fungal inoculation and continued every other day thereafter. The rabbits' pupils were dilated with a combination of 0.67 mg of 2.5% phenylephrine hydrochloride (Neo-Synephrine), 0.15 mg of 1% tropicamide (Mydriacyl), and 0.10 mg of 2% homatropine hydrobromide (Isopto-Homatropine). One drop of each medication was instilled into the conjunctival sac of each eye, and prompt, wide pupillary dilatation was evident within 20 to 30 minutes. The retinas of each intra-arterially and intravitreally injected rabbit was observed using an indirect ophthalmoscope. Animals with chorioretinal lesions were photographed using a retinal camera (Kowa, Keeler Optical, Nishiki, Naka-ku, Nagoya, Japan) and color slide film (Kodachrome 64, Eastman Kodak Co). A 35-mm camera with an extender lens capable of one-to-one reproduction and color slide film (Kodachrome 25, Eastman Kodak Co) was used to photograph lesions of the anterior segment.

Photomicrographs of selected ocular tissues infected with either P boydii or A fumigatus were projected onto plain white paper. The projected fungal organisms were traced onto the paper and the angles of branching were measured with a protractor. The study was conducted in accordance with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research.

RESULTS

Immunocompetent rabbits that received intraocular injections of either P boydii or A fumigatus (groups 1 and 5, Table 2) had development of a fulminating endophthalmitis (Figs 1 and 2). Histopathologically, both organisms produced severe inflammation, with hyphae and hyphal fragments in the anterior segment and vitreous humor (Figs 3 and 4) that were indistinguishable from each other. Neither animal demonstrated systemic fungal infection at autopsy. In both animals, postmortem vitreal aspirates were culture positive.

Rabbits that were immunosuppressed and received intraocular injections of either P boydii or A fumigatus

Table 2.—Animal Immune Status, Route of Infection, and Fungus Injected in Experimental Pseudallescheria boydii and Aspergillus fumigatus Endophthalmitis

<table>
<thead>
<tr>
<th>Group No.</th>
<th>n</th>
<th>Immune Status</th>
<th>Route of Administration</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Competent</td>
<td>Exogenous</td>
<td>P boydii</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Suppressed</td>
<td>Exogenous</td>
<td>P boydii</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>Competent</td>
<td>Endogenous</td>
<td>P boydii</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>Suppressed</td>
<td>Endogenous</td>
<td>P boydii</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>Competent</td>
<td>Exogenous</td>
<td>A fumigatus</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Suppressed</td>
<td>Exogenous</td>
<td>A fumigatus</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>Suppressed</td>
<td>Endogenous</td>
<td>(Saline control)</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>Suppressed</td>
<td>Exogenous</td>
<td>(Saline control)</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>Competent</td>
<td>Endogenous</td>
<td>(Saline control)</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>Competent</td>
<td>Exogenous</td>
<td>(Saline control)</td>
</tr>
</tbody>
</table>

Fig 1.—External photograph of Pseudallescheria boydii endophthalmitis in an immunocompetent rabbit infected exogenously.

Fig 2.—External photograph of Aspergillus fumigatus endophthalmitis in an immunocompetent rabbit infected exogenously.
(groups 2 and 6, Table 2) also had development of a fulminant endophthalmitis (Figs 5 and 6). Histopathologically, both groups exhibited severe inflammation and hyphae and hyphal fragments in the anterior segment and vitreous humor that were indistinguishable from each other. Lens destruction was noted in one of the two *P. boydii*-infected eyes. The rabbit with *A. fumigatus* endophthalmitis (group 6) was noted at autopsy to have fungal lesions of the lungs and liver. In both groups, postmortem vitreal aspirates were culture positive.

Five immunocompetent rabbits that received carotid injections of *P. boydii* (group 3, Table 2) had a mean survival of less than 24 hours. No ocular lesions were noted, and no internal organ lesions were seen at autopsy.

Nine of 17 immunosuppressed rabbits that received an intracarotid injection of *P. boydii* (group 4, Table 2) had development of prominent ocular lesions in the posterior and/or anterior segment (Table 3). The animals that had development of a fulminant endophthalmitis presented clinically with hypopyon and leukokoria. Histopathologically, these animals exhibited severe inflammation, hyphae, and hyphal fragments in the anterior segment with destruction of the lens and lens capsule (Fig 7). Lesions of the retina and/or choroid also demonstrated inflammatory cells, hyphae, and hyphal fragments (Figs 8 through 10). Fungal lesions of the lungs, brain, kidneys,
Table 3.—Number and Location of Ophthalmic Lesions in Experimental *Pseudallescheria boydii* Endophthalmitis in Immunosuppressed and Endogenously Infected Rabbits

<table>
<thead>
<tr>
<th>Location</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>8</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1</td>
</tr>
<tr>
<td>Anterior segment</td>
<td>7*</td>
</tr>
<tr>
<td>Retinal</td>
<td>4*</td>
</tr>
<tr>
<td>Total eyes</td>
<td>10</td>
</tr>
</tbody>
</table>

*One eye had lesions in both locations.

and liver were seen in these animals at autopsy. Five rabbits had development of ataxia and/or nystagmus. Rabbits with fulminant endophthalmitis had culture-positive vitreal aspirates.

The angles of branching derived from the projected photomicrographs of the fungal organisms (Table 4) showed that *P. boydii* hyphae had a mean branching angle of 47°, a median of 43°, and a range that varied from 22° to 88°. Fifty-four *A. fumigatus* hyphae had a mean branching angle of 43°, a median of 40°, and a range that varied from 23° to 90°.

**COMMENT**

Clinical features of the 17 previously reported cases of patients with *P. boydii* eye infections are given in Table 1 and reveal a mean age of 33 years and a male-to-female ratio of 4.6:1. Fifteen of the 17 reported cases of eye infections were unilateral with a left eye preponderance (10:5). Numerous predisposing factors in these patients included trauma (penetrating injury, burn, or foreign body), a chronic underlying disease (diabetes mellitus or systemic lupus erythematosus), drowning with aspiration, immunosuppression (for renal transplantation), multiple surgical procedures, and cataract surgery. Ocular symptoms in these patients included pain, decreased visual acuity, lacrimation, redness, and photophobia. The clinical findings of the 17 infected eyes included 10 endophthalmitides, five corneal ulcers, and two orbital cellulitides. *Pseudallescheria boydii* was cultured in 17 of the 17 reported cases; 14 cultures were obtained from an ocular site, two cultures were obtained from an orbital abscess, and, in one instance, a culture was obtained from the maxillary sinus. The ocular histopathologic descriptions reported hyphae and/or conidia (spores) in 13 of the 17 cases. In four patients there were no ocular histopathologic findings reported, but in one of these, fungal hyphae were noted in the lung, liver, brain, kidney, and subcutaneous tissue.

Therapeutic surgical procedures included enucleation for five of the 17 eyes, with one instance each of lysis of adhesions and resection of a mycetoma, orbital débridement, evisceration, lensectomy, and keratoplasty; one patient required a sclerotomy, iridectomy, lensectomy, and synechietomy; two patients underwent a vitrectomy, and two underwent orbital débridement. A variety of antimicrobial agents and/or corticosteroids were
used therapeutically, either alone or in combination with the previously mentioned surgical procedures.

Antifungal agents were used in 14 of the 17 patients; however, the proper diagnosis of a *P. boydii* infection was delayed in all 17 patients. Miconazole (the reported drug of choice for *P. boydii* infections) was used in seven patients, five of whom used it following prior (discontinued) treatment with amphotericin B. In seven patients, amphotericin B (the reported drug of choice for *A. fumigatus* infections) was the sole antifungal agent used to treat the infection. Of the seven patients treated with only amphotericin B, one required enucleation to eradicate the infection; there were no deaths in this treatment group. Of the four patients treated with amphotericin B initially and then treated with miconazole, two underwent enucleation and two died. One patient who was treated with fluconazole following prior, discontinued treatment with amphotericin B and then miconazole underwent enucleation before death. In this series of ocular infections, four patients (all with disseminated disease) died. Because of the varied ocular diagnoses and the limited number of patients (17), a statistical comparison of the different antifungal agents and their outcomes was not meaningful.

We reviewed a series of 20 previously reported cases of patients with a variety of nonocular *P. boydii* infections and the treatment outcomes using miconazole or amphotericin B. In this series, four patients died and 16 survived. Of the four patients who died, two had disseminated fungal disease. Both of these were treated with amphotericin B. Two others had, initially, a fungal sinusitis; one patient was treated with amphotericin B and the other was treated with miconazole. The 14 patients who lived and were treated with either miconazole or ketoconazole had fungal disease involving one specific organ system (lung, joint, central nervous system, sinus, and bone); none of these patients had systemic fungal disease. The two patients who lived and were treated with amphotericin B had sinus and central nervous system fungal infections, respectively. A statistical analysis of these data, likewise, was not meaningful due to the varied diagnoses, severity, and treatment regimens. Of the eight patients in both the ocular and nonocular series who died, five were treated with miconazole and three were treated with amphotericin B.

Experimental data herein reported have demonstrated that the clinical and histopathologic appearances of exogenous *P. boydii* and *A. fumigatus* endophthalmitis are indistinguishable in immunocompetent rabbits (groups 1 and 5). In addition, systemic immunosuppression does not significantly alter the clinical or histopathologic features of the exogenous fungal endophthalmitis caused by either *P. boydii* or *A. fumigatus* (groups 2 and 6).

The sudden onset of death following the carotid injection of *P. boydii* in the immunocompetent rabbits (group 3) was probably secondary to a "toxic reaction" (similar to anaphylaxis) rather than to infection per se. We hypothesize that immunosuppression is a paradoxical protective mechanism in response to a large antigen challenge, in that it probably prevents the release of histamines and/or other mediators of presumed anaphylaxis.

*Pseudallescheria boydii* produced a severe endogenous endophthalmitis in nine of 17 immunosuppressed rabbits (group 4) following its injection into the carotid artery. A large number of animals in this group, compared with the other experimental groups, were required to establish the animal model for systemic *P. boydii* infections. Anterior segment infections occurred more often (1.75:1) than chorioretinal infections, with one animal having both occur in the same eye. The chorioretinal lesions produced by *P. boydii* were clinically identical to lesions produced in experimental nocardiosis.

The three instances of lens/lens capsule destruction in the endogenous group were similar to that seen in the exogenous *P. boydii* infection (group 2). Other researchers have hypothesized the presence of a *P. boydii* proteinase as the cause of corneal destruction. We postulate that *P. boydii* may produce a proteolytic enzyme that, likewise, dissolves the lens capsule (Fig 7).

The angles of branching of both *P. boydii* or *A. fumigatus* hyphae (Table 4) are indistinguishable; we believe, therefore, that a diagnosis of an aspergillus infection cannot be made on the basis of "visualizing dichotomously branching septate hyphae in biopsy specimens." This study indicates that *P. boydii* ocular infections mimic both clinically and histologically those caused by *A. fumigatus*. In cases of suspected fungal endophthalmitis, it would not be unreasonable for the clinician to suspect, prior to identification by culture, the more common aspergillus as the infective agent and treat empirically with amphotericin B. Since miconazole or ketoconazole is the reported treatment of choice for *P. boydii* infections, cultural identification (which can occur as early as 24 to 36 hours or as late as 4 to 5 days) is of extreme importance so

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**Table 4.** Means, Medians, and Ranges of Branching Angles of *Pseudallescheria boydii* and *Aspergillus fumigatus* (in Degrees)

<table>
<thead>
<tr>
<th>Organism</th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. boydii</em></td>
<td>51</td>
<td>47</td>
<td>43</td>
<td>22-88</td>
</tr>
<tr>
<td><em>A. fumigatus</em></td>
<td>54</td>
<td>43</td>
<td>40</td>
<td>23-90</td>
</tr>
</tbody>
</table>

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Fig 10. — Photomicrograph of same histopathologic section shown in Fig 9, at higher magnification, demonstrating hyphae and hyphal fragments of *Pseudallescheria boydii* (Gomori's methenamine silver, under oil immersion, × 1000).
that exact, often lifesaving, antifungal treatment can be given.

Our review of 17 ophthalmic and 20 nonophthalmic cases of 
P. boydii infections, however, does not substanti-
tiate a difference in the efficacy of miconazole and ketoconazole as 
compared with amphotericin B. In addi-
tion, this series of 17 ocular cases indicates that 
P. boydii is not an ex-
tremely rare cause of ophthalmic infec-
tion and is an organism worthy of 
familiarity and recognition by the 
ophthalmologist.

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From the Archives of the Archives

A look at the past...

The great majority of investigators believe that trachoma is an infectious disease 
caused by a specific micro-organism the identity of which has not yet been definitely estab-
ilished. Successful inoculation experiments on human beings and animals seem to 
prove the communicability of the disease beyond doubt. A great variety of organisms have 
been described as the cause of trachoma, but all have failed to produce the disease either 
in man or in experimental animals and have subsequently been shown to be only second-
ary invaders. The discovery, in 1907, by Haberstadter and von Prowazek1 of character-
istic intracellular inclusions in conjunctival scrapings from trachoma was a decided step 
forward, but the problem soon became complicated by the finding of similar inclusions 
in various types of nontrachomatous conjunctivitis. At present the inclusion theory does 
not receive wide acceptance.

SOURCE: Finoff WC, Thygeson P. Bacterium granulosis in trachoma. 

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