We all have benefited enormously from the continuing flow of education in ophthalmology, within the elastic but structured framework of teaching and communication, that Edward Jackson and all those who followed his precepts have done so much to establish. This flow of thought, fact, and criticism, continuing in all directions, both from the higher to the lower and from the lower to the higher levels of seniority, has been the strength and the drive of American ophthalmology. We can see it as the imprint of Edward Jackson upon our profession.

As the first British Commonwealth Jackson Lecturer, and only the third non-American one, I am able uninhibitedly to express our gratitude and admiration for those principles in teaching which you enjoy so fully in the United States and which we, in the slightly older countries of Europe, have needed so badly to emulate and to adopt. It is especially in this sense that, in paying homage to Jackson, I am deeply grateful for the opportunity of expressing the thanks and appreciation of other countries for the American leadership in teaching in our field, so much of which has stemmed from him.

Fungal infection of the eye has been reported with increasing frequency during the last two decades (Fig. 1). It is not clear whether this is due to the widespread use of corticosteroids and wide-spectrum antibiotics, to improved recognition of the disease, or to the explosion of academic ophthalmology increasing the pressure to report cases.

There is, however, little merit in the publication of scattered cases unless they demonstrate some new fact in the mycology, pathology, epidemiology, or treatment of oculomycosis; so the present decade may see a falloff in reporting.

The subject of oculomycosis is complex and difficult for the practical ophthalmologist, so I shall only highlight some of the salient principles in the management of oculomycosis. The staggering range of nearly 100 different fungal species that can invade the eye by various routes,1-3 giving a variety of clinical presentations and problems, and the experimental nature of antifungal therapeutics, tends to be paralyzing when balanced against the relative infrequency of cases in the hands of most individual ophthalmologists.

The commonly disastrous outcome of most of the scattered cases, compared with the excellent results that can follow correct management, leads to the first principle that I will discuss. It makes a strong case for rapid referral of cases of oculomycosis to a relatively few especially equipped centers with clinical and surgical experience in oculomycosis and its pathologic understanding, with

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Fig. 1 (Jones). Reported cases of oculomycosis by decades.

Mycologic facilities for identification and the measurement of antifungal sensitivities to a wide range of antifungal substances, coupled with experience in antifungal chemotherapy that is still largely experimental. Our laboratory will measure the antifungal sensitivities in a fungus isolated from the lesion in a patient's eye; but this information may be insufficient, if other skills are lacking.

I wish to emphasize certain points in the recognition and diagnosis of keratomycosis by both clinical and laboratory methods; to indicate the main pathways to blindness in keratomycosis; to discuss certain general aspects of fungal infection and antifungal therapy as they influence management and prognosis; to consider certain antifungal drugs and their selection for use in oculomycosis; and to indicate some developments ahead.

Keratomycosis

Recognition and diagnosis—Any of the following clinical features should make us suspect a fungal causation: indolent recrudescent course; dry, crumbly, raised surface to a white or yellow ulceration; crenated edge; finger-like extensions into the stroma, misleadingly called "hyphate" edges; and satellite lesions or recurrent hypopyon.

But in any given case all the typical signs may be absent. This brings us to the second principle to be emphasized: each fungus, or even fungal strain, can cause its own disease that may differ in its clinical features and prognosis from all the others, and is in search of its own specific effective management.

A confusingly large and continually increasing number of fungal species infect the eye. In virulence, the filamentous fungi of environmental origin range from the potentially rapidly destructive Fusarium solani, which can completely destroy an eye in a few weeks, through many species including Cephalosporium, Allescheria, Aspergillus, Penicillium, and the like, to the more leisurely pathogens like Dreschlera rostrata and Phialophora which may have grown indolently in a cornea over a period of months.

If the inflammatory response is relatively slight, it may be possible to definitely recognize the presence in the cornea of individual hyphae of these fungi. They can be seen
with the X40 biomicroscope and photographed by using Brown’s method.  

*Candida albicans* differs in many respects from the other organisms causing oculomycosis. It produces both yeast-like forms and filamentous forms in the cornea. It has the alimentary tract and related mucosae of man as its main reservoir of infection. It is, therefore, more likely than the filamentous fungi to cause blood-borne chorioretinitis and the like. Its corneal lesions range from relatively benign thrush-like plaques, to deep and often perforating, though usually small and circumscribed ulcers. Even without perforating it can, like the filamentous fungi, invade both anterior and posterior chambers. It has been the cause of nearly all of the rare cases of bilateral corneal or intraocular mycosis.

The orbital and other phycomycoses caused by *Absidia*, *Mucor*, *Rhizopus*, and related organisms will not be discussed here.

Of the reported cases of keratomycosis nearly 50% have been due to *Aspergillus*, mainly *A. fumigatus*, nearly 25% to *C. albicans*, and the remaining 25% due to an astonishing diversity of fungi, among which *F. solani* is frequently identified. This remarkable spectrum of clinical presentations leads to another principle: suspect a fungal infection in almost any ocular inflammation and in every suppurative corneal ulcer. Whenever a fungal cause for an ulcer is suspected, we should scrape and culture for both fungi and bacteria.

**Laboratory diagnosis**—Scraping of corneal ulcers with direct microscopy of Giemsa- or gram-stained smears provides an immediate diagnosis of keratomycosis in about half the cases. Moreover, it proves the presence of fungus in the lesion, and the presence of both yeast-like forms and pseudohyphae establishes a diagnosis of *Candida* infection. It is important, however, to scrape the ulcer edge and base vigorously with a semisharp scraper, covering all areas. If the culture is negative, the collection should be repeated.

Our routine is to culture swabbings from the surface of an ulcer at 37°C on blood agar and in thioglycollate medium, and to culture scrapings at room temperature on blood agar, Sabouraud’s agar, and in brain-heart infusion with rotary shaking. Like others we have found that this combination gives a higher yield than any one method, and it is especially suitable for culturing aqueous or tissue fragments. Any organism growing on the solid medium rather than on the inoculation-streak should be disregarded.

The majority of cases of oculomycosis can be diagnosed by using simple methods known to every ophthalmologist: direct microscopy of Giemsa- or gram-stained smears of well-taken corneal scrapings and blood-agar cultures at both 37°C and room temperature for two or three weeks. The other methods yield only a small harvest of additional diagnoses.

Cultivation of the causative fungus permits species identification and measurement of antifungal sensitivities. The measurement of the antifungal sensitivities in the patient’s fungus is the key to rational specific antifungal therapy.

**Pathways to blindness**—Before considering the various therapeutic approaches to oculomycosis, we have to know the pathologic pathways to blindness that must be blocked. In keratomycosis there are two main pathways. The first, or “corneal pathway,” is both obvious and well understood: suppurative ulcerative keratitis leads to corneal opacity or to corneal perforation that may lead to glaucoma and cataract. The relevant therapeutic measures are specific antifungal therapy, and possibly anti-inflammatory drugs, conjunctival flap, or keratoplasty. The second, or “posterior chamber pathway,” is less obvious and less well known: many fungi have a predilection for growing in the posterior chamber; this growth of fungus with inflammatory exudation accumulates around the lens, secludes the posterior chamber, and binds the iris onto the lens. As aqueous humor in the anterior chamber
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Fig. 2 (Jones). Case 1. Dry, white, raised ulcer at presentation.

Fig. 4 (Jones). Case 1. Fungal malignant glaucoma relieved by lens extraction; *F. solani* grew from intraocular contents.

Fig. 3 (Jones). Case 1. Ten days after presentation, the eye was hard, painful, with no perforation but virtually no anterior chamber; exudate and iris pigment obscure pupil; fungal malignant glaucoma diagnosed.

drains out through normal channels, aqueous humor secreted behind the secluded lens-iris fungal mass relentlessly pushes this whole complex forward. It does not give the appearance of iris bombé because the iris is plastered onto the lens. The ominous clinical sign is progressive loss of anterior chamber without perforation and with a normal tension until the angle becomes blocked. This results in "fungal malignant glaucoma," commonly late perforation, and rupture of the globe, sometimes with invasion of the lens and anterior vitreous cavity. Therapeutic measures are specific antifungal therapy and possibly anti-inflammatory drugs. A conjunctival flap is useless in this situation which requires excisional keratoplasty, lens extraction, and anterior vitrectomy.

Case 1 illustrates this posterior chamber pathway to blindness.

**Case report**

*Case 1*—A 37-year-old woman had a small, raised, dirty-white, dry-looking corneal ulcer (Fig. 2). Cultures and scrapings were negative for bacteria and fungi, so intensive anti-bacterial treatment was given. She developed endophthalmitis with hypopyon and loss of the anterior chamber without perforation. Ten days later (Fig. 3), the eye was rock-hard and extremely painful with light perception. Fungal malignant glaucoma was relieved by lens extraction with sector iridectomy (Fig. 4). Culture from aqueous humor, iris, lens, and vitreous cavity all grew *F. solani*. Postoperatively, the keratitis and endophthalmitis progressed (Fig. 5), despite maximal amphotericin B therapy pushed to the limits of corneal and renal toxicity. Antifungal sensitivity tests then demonstrated resistance to amphotericin B (minimum inhibitory concentration [MIC]: > 50 μg/ml),
sensitivity to thiabendazole (MIC: 1.5 μg/ml), and partial sensitivity to pimaricin (MIC: 6 μg/ml). After administering these drugs, we found that cultures of intraocular fluids and tissues at each subsequent operation and after enucleation remained sterile. The fungal infection had been eliminated, and after a 10-mm penetrating graft, the eye improved but was eventually lost because of repeated, recurring forward displacement of iris and adherent thickened vitreous face (Fig. 6), leading to irreversible obliterations of the anterior chamber.

The hemisected enucleated eye revealed that aqueous humor, secreted from the posterior surface of the ciliary body, had pushed the thickened vitreous face and adherent iris forward to obliterate the anterior chamber (Fig. 7). Vitrectomy or grafting, at the time of extraction, would probably have obviated aphakic fungal malignant glaucoma and saved the eye.10,12

Comment—Inoculation of *F. solani* from this patient into the anterior chambers of rabbits led to the rapid development of a preferentially posterior chamber endophthalmitis (Fig. 8); injection into a gerbil cornea caused ongoing keratitis with endophthalmitis, seclusion of the posterior chamber, and fungal malignant glaucoma10 (Fig. 9).
The frequency of fungal malignant glaucoma in keratomycosis will be determined in prospective studies. However, this was the cause of failure in each of the three patient eyes with oculomycosis that I lost and it occurred in each of the five eyes in Professor Ashton's series of eyes lost from oculomycosis (Fig. 10). It occurred in Cases 1, 6, 20, and 24 of the 24 cases of keratomycosis in the present study.

Therefore, we must look for signs of the posterior chamber pathway to blindness in oculomycosis and take appropriate medical and surgical measures to avert fungal malignant glaucoma, a common cause of loss of eyes from fungal infection.

**General Therapy Considerations**

Oculomycosis is caused by a wide variety of organisms that are opportunistic pathogens. There are many organisms of rather low invasiveness, but they differ in different areas and seasons, and are dense in the environment. The most virulent fungal infections often occur in persons with no apparent defect in resistance, whereas the less virulent organisms, including *C. albicans*, tend to invade individuals who have a resistance defect, even of a temporary nature such as trauma, a factor in nearly half these cases. Minor defects of eyelid closure due to notches or other eyelid margin defects, especially if coupled with defects in Bell's phenomenon, or eye movements from dysthyroid eye disease, may be potent causes of reduced resistance, demanding active correction. Deficiencies in the tear film in Sjögren's syndrome, erythema multiforme, and the like, also predispose to infection. Defects in neutrophil leukocyte function may be a factor as may defects in macrophage function. Defects in cell-mediated immune responses are probably important, especially in candidiasis. Deficiencies in antibody production, especially IgA, may affect resistance. These various deficits in the immune mechanisms may be genetically determined, or may be iatrogenic from corticosteroids or more profound immunosuppressant therapy. Diabetes and alcoholism also reduce resistance to infection, and must be carefully controlled.
Any defects in resistance that may be present and remediable must be attended to, either medically or surgically. If they cannot be remedied, major deficits, including profound immunosuppression, indicate the need for more intensive and more prolonged antifungal therapy, and a guarded prognosis.

The next general principle concerns the nature of fungi and the drugs used to combat them. Fungi are plants and, like the higher plants, tend to endure. Patients invaded by these lowly plants require weeks, rather than days, of antifungal therapy. The available antifungal drugs reach fungistatic, but rarely fungicidal, levels in the tissue. The objective of antifungal therapy is to inhibit fungal growth over a long period so that the body's defense mechanisms can manage the fungus. If these defense mechanisms are crippled by immunosuppression, antifungal therapy may have to be maintained for many months while other microbial infections are watched for and treated.

Double infection or intercurrent infections by bacteria as well as fungi or even two fungi, must be watched for. We have seen the following combinations: *C. albicans* plus *Staphylococcus aureus*; *A. fumigatus* plus *S. aureus*; and *Alternaria* species, *Rhodotorula*, and *Acaligenes faecalis* (from a corneal abscess in a patient with defective eyelid closure and absence of Bell's phenomenon complicating dysthyroid disease, with the companion eye lost to a *Pseudomonas* infection). In each case, there was improvement with treatment.

The use of corticosteroid or other antiinflammatory treatment in oculomycosis is a vexed question. Corticosteroids can predispose to, or heighten, low-grade or latent fungal infection in the eye.13

Nevertheless, since we have been using the new, highly potent and nontoxic antifungal drugs, we have found that corticosteroids produce good results under certain conditions. Two of our three patients whose blinding *C. albicans* infections were cured with fluorocytosine (5-FC), with good visual acuity, had been receiving intensive corticosteroid therapy for other diseases (Cases 25 and 27).

Corticosteroid therapy in oculomycosis should be avoided unless the patient is receiving intensive and prolonged antifungal therapy that acts against his particular fungus, and if the ordained outcome or general health is markedly dependent on corticosteroid therapy.

When only polyene antibiotics and organic mercurials were available, the situation was dominated by the unacceptable toxicity and ineffectiveness of the mercurials and by the severely limiting toxicity of the polyenes, especially amphotericin B (Fungizone), that possibly did more harm than good. A major advance came in the late 1960s with pimarinicin, a nonirritant in the eye that cures many superficial corneal mycoses but cannot penetrate sufficiently well to cure the deeper ones (Table 1).

Therefore, to treat oculomycosis effectively, a drug must be nonirritating and nontoxic in the eye, must penetrate the eye well, and must have a high level of antifungal activity against at least one significant ocular pathogen.

Keratoplasty deals with perforation of an ulcer, or its threatened occurrence. Additionally, the excision of a disorganized area of cornea laden with fungus and inflammatory debris removes a possibly infective mass and a continuing stimulus to inflammation and vascularization. In some cases, such a

### TABLE 1

<table>
<thead>
<tr>
<th>Polyene Antifungal</th>
<th>Activity Spectrum</th>
<th>Activity Level</th>
<th>Ocular Irritancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Fair</td>
<td>High</td>
<td>Limitingly high</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Fair</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Pimaricin</td>
<td>Wide</td>
<td>Moderate</td>
<td>Very low</td>
</tr>
<tr>
<td>Etruscomycin</td>
<td>Wide</td>
<td>High</td>
<td>Unacceptably high</td>
</tr>
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</table>
procedure has led to resolution, without effective antifungal therapy, despite viable fungus and fungal hyphae extending to the border of this excision. A combination of effective antifungal therapy and early excisional keratoplasty could be advantageous if it becomes clear that the eye would otherwise be blind. However, rational use of the new antifungal drugs leads to remarkable resolution of inflammation and greatly reduces the optical need for keratoplasty.

Grafting, then, should not be rushed; it should be done if necessary to rid the eye of damaging disease or to give access for lens extraction and vitrectomy to deal with fungal malignant glaucoma.

In the absence of excision of debris, we have seen hemorrhages that developed during the healing stages of candidiasis responding to 5-fluorocytosine, either in the cornea (Case 25) or in the retina in Candida chorioretinitis (Case 27). While a case of A. fumigatus keratomycosis was healing with clotrimazole therapy, a hyperplastic mass that prevented further epithelialization developed at the site of ulceration and had to be shaved off, but contained no viable fungus (Case 4). During resolution of an intraocular F. solani infection by means of thiabendazole therapy, a gray fibrous membrane bridged across an iridectomy and narrowed down the pupil. It was mistaken for a hyphal mat but histologic examination and cultures of this excised eye revealed no fungus (Case 1).

Although these phenomena are not completely understood, the principle is that one must not take the development of hemorrhages, hyperplastic masses, or fibrous sheets in the region of healing fungal lesions as evidence of antifungal therapy failure. Rather, these signs should encourage continued treatment.

**Antifungal Drugs**

From other reports, and from our own experience, proven ocular antifungals apparently fall into three groups: polyene antibiotics, imidazoles, and a pyrimidine. After testing over 200 compounds against ocular fungi, we conclude that certain nonpolyene antibiotics and other chemicals, including some used for crop protection, deserve further study. Griseofulvin, the nonpolyene antibiotic, is not useful with ocular fungi and the nonimidazole compounds are not used against dermatophytes. All the organic mercurial compounds are too toxic for therapeutic use in the eye.

**Polyene antifungal antibiotics**—The polyene antibiotics are classified according to the number of double bonds. We have used amphotericin A and B, nystatin, pimaricin, candididin, hachimycin (Trichomycin), dermostatin, and lucymycin (Etruscomycin) clinically (Table 2). Many of them, especially Etruscomycin, pimaricin, and amphotericin B, possess attractive in vitro activity against ocular fungi (Figs. 11-13). Unfortunately, all are highly insoluble. Most are unstable and cannot be sterilized by heat. Nearly all are irritants in the eye. Etruscomycin has the widest spectrum of activity against ocular fungi, but is the most irritating of those we have tested topically in the eye.

**Table 2**

<table>
<thead>
<tr>
<th>Polyene antifungal antibiotics</th>
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<tbody>
<tr>
<td>Tetrones Heptenes</td>
</tr>
<tr>
<td>Antimycin</td>
</tr>
<tr>
<td>Chromine</td>
</tr>
<tr>
<td>Etruscomycin*</td>
</tr>
<tr>
<td>Fumagillin</td>
</tr>
<tr>
<td>Nystatin*</td>
</tr>
<tr>
<td>Pimaricin*</td>
</tr>
<tr>
<td>Rimocidin</td>
</tr>
<tr>
<td>Sistomycosin</td>
</tr>
<tr>
<td>Pentenes</td>
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<tr>
<td>Dermostatin*</td>
</tr>
<tr>
<td>Eurocidin</td>
</tr>
<tr>
<td>Filipin</td>
</tr>
<tr>
<td>Fungichromatin</td>
</tr>
<tr>
<td>Lagosin</td>
</tr>
<tr>
<td>Pentamycin</td>
</tr>
<tr>
<td>Unspecified Polynes</td>
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</table>

* Antifungals that we have used clinically.
eye: its toxicity for the corneal epithelium and conjunctiva is quite unacceptable. Pimaricin (Fig. 13), with the next widest spectrum, is the least irritating and the most stable (Table 1).

**Nystatin**—Nystatin is reasonably well tolerated in the eye as a 3.3% ointment. It has a medium level of activity against most *Candida* isolates and an occasional isolate of the other ocular fungal pathogens (Fig. 11); its level of activity is seldom sufficient to effect a cure other than in the most super-
Infections by the most sensitive organisms.

**Amphotericin B**—Amphotericin B has a high level of activity against *Candida* species and a small proportion of other ocular fungi (Fig. 12); because of poor penetration, it cures only superficial infections when applied topically. Moreover, eye drops (5%) prepared from Fungizone, which also contains desoxycholate sodium, are highly irritating and toxic in the eye. Their use soon leads to punctate epithelial erosions of the cornea. If administration is intensified, large epithelial ulcers develop (Fig. 5).

Subconjunctival injections of the drug are painful; more than 300 mg is poorly tolerated. Larger doses may lead to tissue necrosis and ulceration (Case 24, Fig. 14). Intraocular injections cause intolerable damage, and in any event such methods of administration could not be maintained long enough to effectively treat oculomycosis.15

Although almost entirely replaced by better drugs for topical use, amphotericin B may still have a place in the intravenous treatment of orbital phycomycoses and of intraocular infections by *C. albicans*, *Coccidioides immitis*, *Cryptococcus neoformans*, and other organisms for which the drug may have a minimum inhibitory concentration of 0.75 μg/ml, or lower. Although flucytosine is generally a better drug for such intraocular infections, resistant organisms may occur or develop. Combined flucytosine and amphotericin B therapy may be desirable.

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**Fig. 13 (Jones).** Cumulative percent ocular fungi isolates sensitive to various concentrations of pimaricin.

**Fig. 14 (Jones).** Case 24. Necrotic slough in conjunctiva and episcleral tissue at site of subconjunctival injection of 25 mg of amphotericin B.
However, whenever intravenous amphotericin B therapy is used, the guidelines set out by Drutz, Spikard, and Koening\textsuperscript{16} should be carefully followed. The keynote is to give only moderate doses below the level of toxicity and to maintain treatment long enough to effect a cure, that is, nine to 12 weeks.

The 50-mg vial of Fungizone should be completely dissolved in 10 ml of sterile water, without preservatives, to give a concentrate that is stored at $+4^\circ$C and used within a week. It is diluted in 500 to 1,000 ml of 5\% dextrose in water with 5 to 10 mg of heparin and administered in daily slow intravenous infusions over four to six hours by means of a small pediatric butterfly scalp vein needle placed in a different vein each day. If any precipitate forms at any stage the preparation must be discontinued. The daily doses should rise cautiously: day 1, 1 mg; day 2, 5 mg; day 3, 10 mg; and day 4, 15 mg, each in a 500-ml infusion. Thereafter, the gradually rising daily dose, for example, 20 to 40 mg in 1,000 ml, is governed by monitoring the patient’s serum level of amphotericin B and maintaining it in the 0.75 to 1.5 [Ag/ml range for pre- and postinfusion levels. The daily dose is determined also by the patient’s tolerance, renal function, and the clinical picture. Intolerance requires slower infusion, and possibly a lower dose gradually rising to the required level. The following side effects are common: thrombophlebitis, fever, and chills requiring diphenhydramine hydrochloride (Benadryl) therapy, and the like; or anorexia, nausea, or vomiting requiring promethazine hydrochloride (Phenergan) therapy, and the like. It is essential to monitor serum potassium, blood urea nitrogen (reduced dose if BUN > 50 mg/100 ml), and hematocrit level for anemia.

This schedule ranges around 0.5 mg/kg/day and avoids the previously recommended 1 mg/kg/day dosage that we, like others, have found impossible to sustain.

If the markedly less toxic derivative, amphotericin B methyl ester hydrochloride, becomes available, this may make the ocular therapeutic potential of amphotericin B a reality by both topical and intravenous routes (Fig. 12).

Fungizone is too toxic for local use in the eye but if it is administered intravenously, over a long period, according to precise instructions, and combined with fluconazole or other antifungal therapy, it may continue to be valuable for intraocular or other fungal infections by organisms, mainly \textit{C. albicans}, for which amphotericin B has a minimum inhibitory concentration of 1.0 \textmu g/ml or less.

\textbf{Pimaricin—}In the eye, pimaricin is the least irritating and the least toxic polyene. It is the most stable and resists sterilization by heat. It has the widest range of antifungal activity against ocular pathogens (Fig. 13); unfortunately, the level of activity is frequently marginal in relation to its solubilities and its grudging ability to penetrate the ocular tissues. It can certainly cure many superficial fungal infections but is ineffective against deeper infections in the cornea.\textsuperscript{6,17-21}

At present a 5\% suspension or possibly a 1\% pimaricin ointment can be an antifungal prophylactic in ocular injuries, especially in areas of higher prevalence of oculomycosis, provided the condition of the eye allows the use of such a preparation. It can also be used as first-line treatment in any suspected fungal infection, after the collection of appropriate diagnostic specimens to provide an isolate for guiding further therapy, if necessary.

Those patients who do not respond to pimaricin require treatment with other drugs, whose use should be guided by measurement of the antifungal sensitivities of the patient’s fungus.

\textbf{Imidazole antifungal drugs—}Following the lead given by the antifungal activity of thiabendazole (Fig. 15), a remarkably active and nontoxic anthelmintic, I directed a continuing search for comparable substances with antifungal action and tested them on ocular fungi. There were two promising groups of imidazole-containing compounds
explored as medical antifungals: the trityl imidazoles, from which clotrimazole has now emerged and the phenethylalcohol imidazoles, from which miconazole and econazole have now emerged. The search also revealed a large number of antifungal compounds used in agriculture; some of these deserve further study.

**Clotrimazole**—Clotrimazole (Canesten) is a chlorinated trityl (triphenylmethane) imidazole (Fig. 16) of low human toxicity with a broad spectrum of antifungal activities (Fig. 17).

The subject of a recent symposium in London presenting the results of various open and double-blind clinical trials, clotrimazole is clearly an active antimycotic that is at least as good as the polyenes or tolnaftate, when applied topically to the skin or mucosal surfaces.

Clotrimazole is also active systemically...
when given by mouth in doses of 60 mg/kg/day, increasing to 100 mg/kg/day. Children tolerate up to 150 mg/kg/day. Aside from some anorexia, nausea, occasional vomiting, and the necessity to monitor serum alkaline phosphatase and other factors of liver function, the drug appears to be well tolerated. It can be given to patients with renal dysfunction induced by amphotericin B, but should not be given during the first three months of pregnancy or to those with severe liver or adrenal disease. Unfortunately, the induction of drug-metabolizing enzymes in the liver usually limits the systemic levels that can be maintained beyond the first week or two.

Nevertheless, the biologically measured serum levels in our two patients whose ocular aspergillosis was treated with oral clotrimazole have ranged from 5.5 to 2.5 μg/ml in one, and 0.8 to 0.4 μg/ml in the other during the first few weeks. This coincided with clinical improvement in the intraocular inflammation. Therefore, treatment of severe intraocular infections with clotrimazole-sensitive fungi should begin with both topical and oral administration to achieve maximum intraocular levels during the first week or two, and then discontinuance of the oral dosage as clinical response and falling serum-levels may indicate.

The following is a summary of collected experience treating 15 patients with 1% clotrimazole in arachis oil.

CASE REPORTS

Case 2—A 37-year-old man developed a worsening corneal ulcer with recurring hypopyon (Fig. 18). After three months this was identified as fungal and *A. fumigatus* was grown (MIC: pimaricin, 6 μg/ml; nystatin, 25 μg/ml, amphotericin B, 3 μg/ml; and clotrimazole, 0.75 μg/ml). His condition worsened in the next month, despite administration of topically applied pimaricin, nystatin, and intravenously applied amphotericin B, every hour. Therefore, clotrimazole was administered orally, 60 mg/kg/day, increasing to 100 mg given for three weeks; the dosage was reduced to 60 mg/kg/day for four more weeks. During this time, we devised a satisfactory formulation of clotrimazole for topical use in the eye, by using animals and a human volunteer. This mixture of 1% clotrimazole in arachis oil was administered two weeks after oral therapy began (Fig. 19), every three hours for 13 weeks, until complete resolution (Fig. 20). Visual acuity improved from counting fingers at 0.5 meter, to 20/40 unaided.

Case 3—A 28-year-old man developed a worsening corneal ulcer after removal of a corneal foreign body. Recognized as fungal after four weeks, an ulcer culture grew *A. fumigatus* (MIC: pimaricin, 6 μg/ml; amphotericin B, 6 μg/ml; Etruscomycin, 1.5 μg/ml; and clotrimazole, 0.75 μg/ml). The patient was treated with Etruscomycin ointment, 500 IU/g, every two hours; there was no improvement and he developed severe toxic punctate corneal epithelial erosion four days later. He was changed to 1% clotrimazole in arachis oil, every three hours for 12 weeks, until complete resolution.
Fig. 20 (Jones). Case 2. Complete resolution after three months of clotrimazole therapy; visual acuity, 20/40.

Fig. 21 (Jones). Case 4. *A. fumigatus* ulcer with hypopyon and endophthalmitis worsening during pimaricin and amphotericin B therapy; visual acuity, counting fingers at 0.75 meter.

There was definite improvement within four days. Clotrimazole was then given orally, 60 mg, increasing to 100 mg/kg/day for five weeks. Visual acuity improved from 20/100 to 20/20.

Case 4—A 69-year-old man developed a worsening corneal ulcer after mulch had blown into his eye. Fungus was seen and scrapings grew *A. fumigatus* (MIC: pimaricin, 6 µg/ml; amphotericin B, >50 µg/ml; clotrimazole, 1.5 µg/ml; miconazole, 6 µg/ml; and econazole, 3 µg/ml). He was treated with topically applied pimaricin and amphotericin B, every three hours for three weeks, and 500 µg/ml of amphotericin B was administered subconjunctivally six times. Repeat scrapings were negative but the eye worsened with hypopyon and increasing posterior synechia (Fig. 21).

He was changed to clotrimazole therapy on arrival here, 100 mg/kg/day for one week, reduced to 60 mg/kg/day for five more weeks, with topical 1% clotrimazole, four times daily for nine weeks, until complete resolution. He also received oxyphenbutazone (Tanderil) topically and orally. The hypopyon cleared, the uveitis gradually resolved, and the ulcer healed slowly but a hyperplastic plaque developed over an area of severe endothelial damage (Fig. 22). It was excised to allow complete healing. Improvement in visual acuity from counting fingers at 0.75 meter to 20/200 was limited by corneal opacity and a dense, but incomplete, pupillary membrane (Fig. 23).

Case 5—A 52-year-old woman presented with a seed husk on her cornea and a marked anterior uveitis. The husk was removed and she was given atropine, betamethasone, and neomycin sulfate drops.

There was definite improvement within four days.

Fig. 22 (Jones). Case 4. Hyperplastic mass at site of healing ulcer after four weeks of clotrimazole therapy.

Fig. 23 (Jones). Case 4. Healed corneal scar, partial pupillary membrane, and cataract; visual acuity, 20/200.
four times daily. A week later, the uveitis had lessened but a culture from a yellow ulcer grew *A. fumigatus* (mic: pimaricin 6 µg/ml; amphotericin B, 12.5 µg/ml; clotrimazole, 0.75 µg/ml; miconazole, 12.5 µg/ml; and econazole, 0.75 µg/ml). She was treated with 1% clotrimazole, every two hours for eight weeks, and every four hours for four more weeks. The uveitis worsened and she developed hypopyon after cessation of corticosteroid drops. She was given 0.5% prednisolone drops, twice daily, and amphotericin B and alpha chymotrypsin drops, every four hours. A debridement of the raised ulcer surface was performed after 2 1/2 weeks of clotrimazole treatment. Despite *A. fumigatus* cultured from that material, the hypopyon and the lesion completely resolved, with visual acuity of 20/20.

Case 6—A 50-year-old man presented with a sore eye of five days' duration. In spite of subconjunctivally administered carbenicillin disodium (Pyopen) and intensive therapy of topical amphotericin, his corneal abscess worsened with hypopyon formation, shallowing of the anterior chamber, and raised intraocular pressure. *Aspergillus fumigatus* was grown from a corneal culture three times (mic: pimaricin, 6 µg/ml; amphotericin B, 50 µg/ml; clotrimazole, 1.5 µg/ml; and miconazole, 6 µg/ml). The hypopyon cleared and the abscess resolved within one week. There was complete resolution of inflammation with the clotrimazole drops eight weeks later, but he declined surgery other than a tarsorrhaphy. The tension remained high and the cornea quietly perforated 15 months later, presumably the end result of unrelieved malignant glaucoma of fungal origin that was already established when specific antifungal therapy began.

Case 7—A 50-year-old woman developed severe endophthalmitis after trauma to her eye with corneal laceration. An anterior chamber tap grew *Torulopsis* and *A. fumigatus*. She was treated with flucytosine without dramatic improvement. Another anterior chamber tap grew *A. fumigatus*. Topical treatment with 1% clotrimazole drops, every hour, was followed by striking resolution of the intracocular inflammation, although the corneal scar precluded useful vision. She was lost to follow-up.

Case 8—A 9-year-old girl had an exenteration of her orbit in October 1968, following two roentgen treatments that produced only temporary recession of a rhabdomyosarcoma. Because of the irradiation, no attempt was made to graft the cavity which slowly granulated. Bacterial infection was controlled with ampicillin but four months later she developed a hairy mold. *Aspergillus fumigatus* was repeatedly grown during the ensuing eight months, was held in check, not eradicated by frequent applications of amphotericin B, nystatin, and thimerosal (Merthiolate) (mic: pimaricin, 3 µg/ml; amphotericin B, 6 µg/ml; nystatin, 3 µg/ml; thiabendazole, 3 µg/ml; thimerosal, 0.75 µg/ml). Twelve months later, fungal invasion of the necrotic bone of the orbital roof was evident. The orbit was painted with 1% clotrimazole in arachis oil, three times a day. The visible fungus growth rapidly disappeared and 12 weeks later, all orbital cultures and washouts of exposed sinuses were negative for *Aspergillus*. She then underwent grafting procedures to line the orbit. Six years later, there has been no recurrence of the fungus infection or the tumor.

Case 9—A 45-year-old man developed a secondary infection in an indolent herpetic corneal ulcer (Fig. 24, top); a culture grew *A. wentii*. The condition worsened during 13 days of intensive treatment with topically applied pimaricin (Fig. 24, bottom). There was a striking improvement four days later with the administration of 1% clotrimazole drops (Fig. 25, top), every two hours for six months, to complete resolution (Fig. 25, bottom). Visual acuity improved from counting fingers at 1 meter to 20/100.

Case 10—A 37-year-old man presented with a corneal ulcer; a culture grew *A. flavipes* (Fig. 26,
Intensive topical treatment with nystatin, intravenously applied Fungizone, 10,000 IU daily, and 3 mg of prednisolone, twice daily, produced only slight improvement. On commencing 1% clotrimazole in arachis oil topically, every four hours, there was a dramatic improvement 12 weeks later with complete resolution. She developed an ocular cutaneous sensitivity reaction, but a patch test to the clotrimazole preparation was negative.

**Case 12**—A 65-year-old diabetic woman who had corneal scarring from herpetic keratitis was referred with perforation through a central suppurative corneal ulcer that worsened after six days of treatment with nystatin (Fig. 27, top). An ulcer culture grew *C. albicans* (mic: pimaricin, 6 μg/ml; amphotericin B, 0.35 μg/ml; nystatin, 6 μg/ml; clotrimazole, 0.75 μg/ml; and flucytosine, 0.35 μg/ml).

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**Case 11**—A 56-year-old woman who had had Sjögren's syndrome for six years was given prednisolone drops while on vacation. When seen by her ophthalmologist one month later, she had a dense corneal opacity with a white center; the ulcer grew rapidly, involving half the corneal thickness. Corneal scrapings revealed yeasts and pseudohyphae and a culture grew *C. albicans* (mic: pimaricin, 3 μg/ml; amphotericin B, 0.35 μg/ml; nystatin, 6 μg/ml; clotrimazole, 0.75 μg/ml; and flucytosine, 0.35 μg/ml). Intensive topical treatment with nystatin, intravenously applied Fungizone, 10,000 IU daily, and 3 mg of prednisolone, twice daily, produced only slight improvement. On commencing 1% clotrimazole in arachis oil topically, every four hours, there was a dramatic improvement 12 weeks later with complete resolution. She developed an ocular cutaneous sensitivity reaction, but a patch test to the clotrimazole preparation was negative.

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The following three cases are summarized by Jones.24

Case 13—A central corneal ulcer culture from a 40-year-old man grew *C. tropicalis* (MIC: pimaricin, 3 μg/ml; amphotericin B, 0.75 μg/ml; clotrimazole, 0.75 μg/ml; flucytosine, 0.35 μg/ml; miconazole, 0.35 μg/ml; and econazole, 0.75 μg/ml). He was treated with pimaricin for one day but developed a severe inflammatory response (Fig. 28, top). Administration of 1% clotrimazole topically, every two hours, resulted in subsidence of the reaction and a healed ulcer (Fig. 28, bottom), 23 days later. Visual acuity improved from 20/200 to 20/50.

Case 14—A 48-year-old man who had a second but opaque corneal graft for herpetic keratitis developed a large, yellowish-white corneal ulcer (Fig. 29, top) due to *Candida*. He was referred for treatment and started on 1% clotrimazole after diagnostic material had been collected. The ulcer responded dramatically (Fig. 29, bottom) and healed in five days. He remained on clotrimazole until complete resolution, 17 days later; visual acuity was again reduced to hand movements at 0.66 meter. The cultures grew *F. moniliforme* (MIC: pimaricin, 3 μg/ml; nystatin, 6 μg/ml; clotrimazole, 1.5 μg/ml; and flucytosine, 0.75 μg/ml). After topically administered 1% clotrimazole in arachis oil there was a dramatic improvement (Fig. 27, bottom), with complete resolution eight weeks later. Visual acuity improved from hand movements at 0.33 meter to an approximate pre-ulcer visual acuity of 1/200.

Fig. 27 (Jones). Case 12. Top, *C. albicans* infection; central perforation through suppurative ulcer; visual acuity, hand movements at 0.3 meter. Bottom, Healed corneal scar after eight weeks of clotrimazole therapy; visual acuity, 1/200.

Fig. 28 (Jones). Case 13. Top, *C. tropicalis* ulcer with chemosis after one day of pimaricin treatment; visual acuity, 20/200. Bottom, Healed corneal scar after eight weeks of topical clotrimazole; visual acuity, 20/50.
Fig. 29 (Jones). Case 14. Top, *F. moniliforme* ulcer in old opaque corneal graft. Bottom, Appearance after 17 days of topical clotrimazole therapy.

μg/ml; amphotericin B, > 50 μg/ml; nystatin, > 50 μg/ml; clotrimazole, 6 μg/ml; miconazole, 3 μg/ml; and econazole, 0.75 μg/ml).

Case 15—A 48-year-old man suffered a severe corneal laceration followed by severe endophthalmitis. An anterior chamber tap grew *P. variotii* (mic: pimaricin, 3 μg/ml; amphotericin B, 3 μg/ml; nystatin, 6 μg/ml; clotrimazole, 0.75 μg/ml; miconazole, 6 μg/ml; and econazole, 6 μg/ml). A regimen of intensive topical pimaricin, every hour, and amphotericin B, administered subconjunctivally, topically, and by anterior chamber lavage did not control the infection but it improved dramatically with topically applied 1% clotrimazole in arachis oil until complete resolution of inflammation, 64 days later. He had a quiet eye with visual acuity reduced to hand movements due to corneal opacity, with a fibrous scar extending back into the vitreous cavity.

Case 16—A 52-year-old man was struck in the eye by flying material when his golf club struck the ground. Treatment with dexamethasone (Decadron) drops and an intensive regimen of topical and oral antibacterial antibiotics improved the resultant ulcer at first, but then it relapsed. Topically applied corticosteroids and 30 mg of prednisolone daily were continued. When I saw him, three weeks after the injury, there was a shallow central ulcer with little infiltration (Fig. 30); the highest magnification on the slit lamp showed fine branching hyphae extending out from the lesion into the corneal stroma (Fig. 31, left). Scrapings grew *Dreschlera rostrata* (mic: pimaricin, 0.75 μg/ml; amphotericin B, 0.35 μg/ml; nystatin, 1.5 μg/ml; clotrimazole, 0.35 μg/ml; miconazole, 0.35 μg/ml; and econazole, 0.35 μg/ml). He was treated with 1% clotrimazole, every two hours. After three weeks the hyphae began disintegrating (Fig. 31, right). But as the corticosteroid therapy was reduced, inflammatory reaction increased. A curettage of the lesion during the fourth week of treatment gave negative cultures, so treatment with topical corticosteroids was resumed and the condition resolved in eight weeks. Visual acuity improved from 20/70 to 20/30.

Comment—In Cases 2, 6, 7, and 15, there was severe intraocular disease, confirmed by fungal isolation in Cases 7 and 15, and cured by topical clotrimazole alone, except in that Case 2 the patient was on a regimen of oral as well as topical medication. The organism in Case 13 (mic: 6 μg/ml) responded dramatically.

Topical 1% clotrimazole in oil or ointment,
administered every hour until a clinical response is elicited, then four times daily, for eight to 12 weeks, is the treatment of choice in *Aspergillus* infections of the eye. It is also highly effective with *Candida*, *Paecilomyces*, and *Dreschlera* organisms and probably in *Alternaria*, *Cladosporium*, and *Fonsecaea* species, and many other organisms. It can resolve *F. moniliforme* infection, but is ineffective against most *Fusarium* species.

For severe intraocular fungal infections topical treatment combined with oral administration (60 mg/kg/day increasing to 100 mg/kg/day) may be used for the first two weeks.

I recommend a regimen of topical clotrimazole for prophylactic use in injuries and as first-line treatment in areas like Britain where *Aspergillus* and *Candida* species cause most oculomycosis infections. However, in areas like southern Florida, where *Fusarium* species cause many severe cases, pimaricin probably will continue as the best prophylactic and first-line treatment, possibly with clotrimazole or econazole.

**Miconazole and Econazole**—Miconazole and econazole (Fig. 32) are two of a large series of substituted phenethylalcohol imidazoles with broad spectrum antifungal activity and low mammalian toxicity (Fig. 33). Furthermore, miconazole is as active as benzyl penicillin is against gram-positive bacilli and cocci. Miconazole (Brentan, Daktarin, Monistat, Micatin) is the more fully developed drug. Like clotrimazole, it is not significantly absorbed when topically applied to the skin or vaginal mucosa, but is absorbed somewhat at oral administration. A daily oral dose of 0.3 g has been well tolerated for several weeks with beneficial effects on cutaneous fungal infection. Unlike clotrimazole, miconazole and econazole do not induce drug-metabolizing enzymes in the liver, so the systemic levels can be maintained. In severe infections they can be given intravenously, dissolved in cremophor EL.

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**Fig. 31 (Jones). Case 16.** Corneal macrophotos of *D. rostrata* hyphae. Left, before, and right, after three weeks of topical clotrimazole therapy showing disintegration of hyphae.
Fig. 32 (Jones). Structural formulae of miconazole and econazole.

(Case 17). Topically applied miconazole has been as effective against vaginal candidiasis as nystatin and at least as effective as tolnaftate. Econazole (Pevaryl) is also active topically against dermatophytes.29-32

After experimenting with rabbit eyes, we used eye drops of 1% suspension of econazole and a similar suspension of econazole nitrate clinically. The latter suspension was irritating and was discontinued within a week (Case 22). The most satisfactory ocular preparation of either miconazole or econazole is, however, a 1% solution in arachis oil prepared by dissolving the solution in chloroform, mixing it with arachis oil, and driving off the chloroform with heat. Although these substances dissolve readily in cremophor EL, and are water miscible in all preparations, this vehicle causes brisk stinging in the eye, not prevented by topical antihistamines. The bases of each substance are better tolerated in the eye than the corresponding nitrates. Miconazole is somewhat less well tolerated than econazole; nevertheless, a patient with an A. fumigatus ulcer was cured by wearing an experimental, ocular therapeutic system delivering miconazole base at 6 µg/hour continually (Case 19).

Miconazole is approximately ten times more active against Candida species but econazole is more active against filamentous fungi including some Fusarium, Aspergillus, and Penicillium species, although it lacks the activity of miconazole against gram-positive bacteria.

When ocular preparations become available they will be a valuable addition to the antifungal armamentarium.

Case 17—For 15 years, a 53-year-old woman suffered recurring episodes of pain and swelling over her left lacrimal sac, three or four times a year, relieved by a lacrimal sac cast, passed into her nose. This material, and lacrimal passage syringing drippings from her nose, grew \( \text{P. gougerotii} \) (mic: pimaricin, 1.5 µg/ml; amphotericin B, 6 µg/ml; nystatin, 12.5 µg/ml; clotrimazole, 3 µg/ml; miconazole, 0.35 µg/ml; econazole, 0.35 µg/ml; thiabendazole, 0.75 µg/ml; and fluocytosine, 50 µg/ml). A 1% miconazole base in arachis oil was syringed through her lacrimal passages daily. She applied the drops, every hour, for 21 days. After one week of localized treatment, she received 600 mg of miconazole intravenously, each day for five days, commencing one hour before dacrystocystorhinostomy surgery. The serum levels of miconazole ranged from 0.69 to 0.24 µg/ml. Thereafter, all cultures, including swabblings of the sac and scraping of the sac wall taken at the time of surgery, and washings were free of fungus. She made an uneventful recovery, and has had no recurrence of positive-culture symptoms after 18 months of follow-up.

She was allergic to penicillin. On two occasions she had chest discomfort after intravenously administered miconazole and developed urticaria five days after cessation of treatment. She continued to apply miconazole, without reaction, so it is possible that the urticaria may have been related to the cremophor vehicle of the intravenously applied miconazole.
Case 18—A 55-year-old woman who had lost her left eye after a P. aeruginosa infection that complicated dysthyroid eye disease had a small, indolent, progressive central intrastromal abscess in her right cornea (Fig. 34). The abscess lay at the upper edge of a transverse band of opacity associated with corneal exposure due to poor eyelid closure and inability to look up. Corneal scrapings of this abscess grew the following three organisms: *Alternaria* (mic: pimaricin, 0.75 µg/ml; amphotericin B, 0.3 µg/ml; nystatin, 3 µg/ml; clotrimazole, 1.5 µg/ml; and miconazole, 0.3 µg/ml); *Rhodotorula* (mic: nystatin, 12.0 µg/ml; amphotericin B, 6 µg/ml; clotrimazole, 0.3 µg/ml; and miconazole, 3 µg/ml); and *A. faecalis* sensitive to carbenicillin disodium, chloramphenicol, and gentamicin hydrochloride. She was treated with drops of miconazole base 1% in arachis oil and gentamycin drops, every hour. A recession of her right inferior rectus muscle restored some degree of Bell's phenomenon. The corneal abscess gradually resolved after four weeks of therapy (Fig. 35). Visual acuity improved from counting fingers at 0.33 meter to 20/100.

Case 19—A 52-year-old man with right visual acuity of 20/70 due to quiescent herpetic keratitis developed a white raised corneal ulcer one week after a foreign body lodged in his left eye while digging in his garden (Fig. 36, left). An ulcer specimen grew *A. fumigatus* (mic: pimaricin, 6 µg/ml; amphotericin B, 1.5 µg/ml; clotrimazole, 0.35 µg/ml; and miconazole, 0.35 µg/ml). He received drops of 1% miconazole base in arachis oil, every hour, and wore an experimental therapeutic system delivering miconazole base, 6 µg/hour, constantly after an initial delivery period more than 25 µg/hour during the first 24 hours (Fig. 36, right). There had been some improvement in the main lesion during the miconazole in oil therapy; but an extension at its lower edge developed. The whole lesion, however, rapidly became inactive and healed during use of the miconazole delivery device. Visual acuity improved from 20/100 to 20/20 within eight days. Although a similar miconazole delivery device caused some stinging in a volunteer's eye, the patient has tolerated it without discomfort.
Comment—Topically applied miconazole base, either in arachis oil or in a therapeutic drug delivery system, is satisfactorily tolerated and cures infections due to sensitive fungi. Miconazole nitrate has been, in our experience, an ocular irritant and should not be administered topically.

Case 20—A man developed a worsening keratitis and hypopyon iritis with raised ocular tension after a penetrating injury. A penetrating corneal graft was performed to avert impending corneal perforation and *F. solani* was grown from the aspirated intraocular fluid (mic: pimaricin, 6 μg/ml; amphotericin B, 50 μg/ml; nystatin, 50 μg/ml; Etruscomycin, 0.75 μg/ml; clotrimazole, 50 μg/ml; miconazole, 12.5 μg/ml; and econazole, 0.75 μg/ml). He was treated with pimaricin and amphotericin B without effect. The posterior chamber became filled with a gluey abscess, the lens and iris moved forward, and the lens opacified. Cataract extraction with vitreous aspiration was done through the posterior chamber: cultures again were positive. Further revision of the anterior chamber with vitreous aspiration was done a week later; cultures again were positive. Two months after the corneal graft he was started on 1% econazole suspension, every hour. The inflammation subsided and cultures from further posterior chamber aspiration were negative after 16 days of econazole therapy. The eye quieted but the gluey exudate over the ciliary body organized, the eye became soft, and it was enucleated two years later.

Case 21—A 52-year-old man presented with a small yellow-white abscess in the periphery of his right cornea. No bacteria were recovered and despite energetic treatment with antibacterial antibiotics, the lesion persisted with recurrent hypopyon. After six weeks it slowly enlarged and the anterior uveitis increased. A corneal scraping grew a *Penicillium* species (mic: pimaricin, 12.5 μg/ml; amphotericin B, >50 μg/ml; nystatin, >50 μg/ml; clotrimazole, 50 μg/ml; miconazole, 1.5 μg/ml; econazole, 0.75 μg/ml; and econazole nitrate, 0.75 μg/ml). He was started on 1% econazole nitrate suspension, every two hours. The cornea and anterior chamber improved but after five days, irritation from the suspension increased and he was changed to 1% econazole base suspension. This was free of irritation and was continued, four times daily for six weeks, until it completely resolved. At commencement of antifungal therapy he was given 200 mg of orally administered econazole nitrate, three times a day for two weeks; serum levels ranged from 0.14 to 0.70 μg/ml. Visual acuity improved from 20/100 to 20/20.

mg/day, his condition improved during the first week but then relapsed with hypopyon and corneal infiltration that ulcerated. Scrapings gave no organisms but a week later, an anterior chamber tap grew *Pe. lilacinum* (mic: pimaricin, 50 μg/ml; amphotericin B, 50 μg/ml; nystatin, 50 μg/ml; clotrimazole, 12.5 μg/ml; miconazole, 12.5 μg/ml; econazole, 0.35 μg/ml; and thiabendazole, 6 μg/ml). He was treated with intensive pimaricin, amphotericin B, and subconjunctivally administered amphotericin B. Oral prednisolone was reduced to 20 mg/day. The condition relentlessly worsened and, a week later, his cornea perforated (Fig. 37). He was given 1% econazole, every 15 minutes. Within three days, the anterior chamber re-formed, the hypopyon was resolving (Fig. 38), and the cornea was clearing; the corneal abscess continued to shrink during the next ten days (Fig. 39). At this stage he developed exfoliative dermatitis, probably a reaction to chlorpropamide.

Case 22—A 52-year-old man presented with a small yellow-white abscess in the periphery of his right cornea. No bacteria were recovered and despite energetic treatment with antibacterial antibiotics, the lesion persisted with recurrent hypopyon. After six weeks it slowly enlarged and the anterior uveitis increased. A corneal scraping grew a *Penicillium* species (mic: pimaricin, 12.5 μg/ml; amphotericin B, >50 μg/ml; nystatin, >50 μg/ml; clotrimazole, 50 μg/ml; miconazole, 1.5 μg/ml; econazole, 0.75 μg/ml; and econazole nitrate, 0.75 μg/ml). He was started on 1% econazole nitrate suspension, every two hours. The cornea and anterior chamber improved but after five days, irritation from the suspension increased and he was changed to 1% econazole base suspension. This was free of irritation and was continued, four times daily for six weeks, until it completely resolved. At commencement of antifungal therapy he was given 200 mg of orally administered econazole nitrate, three times a day for two weeks; serum levels ranged from 0.14 to 0.70 μg/ml. Visual acuity improved from 20/100 to 20/20.

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**Fig. 35 (Jones). Case 18. Appearance after four weeks of topical miconazole therapy; visual acuity, 20/100.**

**Fig. 36 (Jones). Case 19. A. fumigatus infection resolving with continuous delivery of 6 μg of miconazole per hour from an experimental delivery system.**
Case 21—A 21-year-old diabetic man developed a marginal corneal ulcer that was unsuccessfully treated with carbolization and topically applied antibacterial antibiotics for five weeks. Corneal scrapings then grew *A. fumigatus* (mic: pimaricin, 0.75 μg/ml; amphotericin B, 12.5 μg/ml; nystatin, > 50 μg/ml; clotrimazole, 1.5 μg/ml; miconazole, 1.5 μg/ml; and econazole, 1.5 μg/ml). He was treated with 1% econazole suspension, every hour for one week, with marked improvement, then every two hours for four weeks, until complete resolution. Visual acuity improved from 20/70 to 20/15.

Comment—Econazole as a 1% watery suspension is well tolerated in the eye and is effective against sensitive fungi causing ocular disease.

Both miconazole and econazole are tolerated in the eye in a 1% solution in arachis oil, although econazole is less irritating. Both drugs cure infections by sensitive fungi and each may, if necessary, be given intravenously. In general, miconazole is more effective for *Candida* and bacteria species, whereas econazole is better for filamentous ocular fungi, especially *Fusarium, Aspergillus, Penicillium* species, and others. At
Thiabendazole—Thiabendazole, a thiazolyl benzimidazole²¹⁻³³ (Fig. 15) of low mammalian toxicity with high antihelmintic activity, is extensively used in the medical and veterinary fields (Mintezol). It is well absorbed orally and is, at 25 mg/kg/day, active against visceral larva migrans. Its high antifungal activity is used in agricultural crop protection. Although poorly soluble in water it penetrates the eye well in a 4% suspension that is nonirritating to the eye.³⁸ Thiabendazole is more selective in its action than clotrimazole, miconazole, or econazole and is particularly active against some ocular isolates of *Fusarium* species and other filamentous fungi including *Penicillium*, *Phialophora*, and *Cladosporium* species (Fig. 40).

We used thiabendazole only in two cases of advanced infection by *F. solani*: in each case extensive disorganizing intraocular invasion was present but the ocular fluids and tissues reverted from culture-positive to culture-negative within a week or two of treatment, having been repeatedly fungus-positive over a long period of time. However, we did not have an opportunity to evaluate the potential effectiveness of thiabendazole in saving sight in oculomycosis caused by a sensitive fungus.

*Case 1*—The case history of this patient was reviewed earlier in this study. The regimen of intense topical and oral thiabendazole therapy caused cessation of the inflammation and intraocular cultures became negative.

*Case 2*—A 73-year-old man got some material in his right eye while clearing his garden. A week later he had a painful eye with right visual acuity of 20/200, a small ulcer at 6 o’clock in the midzone, with hazy cornea, keratic precipitates, flare, massive posterior synechiae, and a raised ocular tension of 36 mm Hg. He worsened steadily during a week of intensive mydriatic, antibacterial, and topically applied corticosteroid treatment. He developed an extensive marginal corneal ulceration. His ophthalmologist reported that: “Two strains of *Penicillium* species have been isolated. These grew on one plate only (the one without suppressants). They are most likely the result of contamination.” Nevertheless, further corneal scrapings revealed hyphae. The patient was treated with 25 mg of amphotericin B administered subconjunctivally every two days, with further rapid deterioration and continuing high ocular tension.

On admission here (Fig. 41), this patient had keratomycosis, with massive corneal invasion and peripheral necrosis, and an advanced stage of fungal malignant glaucoma complicated by two sloughing areas of conjunctival and subconjunctival necrosis at the amphotericin B injection (Fig. 13). He had light perception but was treated intensively with a regimen of topical pimaricin and 1% clotrimazole therapy. After six more days of worsening, when massive corneal and scleral necrosis existed with a hard painful eye (Fig. 42), the mycologic results showed *F. solani* (mic: pimaricin, 3 μg/ml; amphotericin B, > 50 μg/ml; nystatin, 50 μg/ml;
Etruscomycin, 3 ng/ml; clotrimazole, 12.5 μg/ml; miconazole, 25 μg/ml; econazole, 3 μg/ml; and thiabendazole, 1.5 μg/ml). By entering the suprachoroidal space at the insertion of the recti, we eviscerated the anterior segment and choroid with contents intact, with a wide rim of apparently normal sclera. Hemisection confirmed the existence of fungal malignant glaucoma, with seclusion of the posterior chamber, and hyphal invasion of the lens and sclera up to the limits of excision.

Every part of this specimen grew *F. solani*. The socket was dressed daily with thiabendazole, pimaricin suspensions, and Etruscomycin ointment. Extension of scleral necrosis occurred and eight days after evisceration, culture from a scleral biopsy specimen grew *F. solani* (Fig. 43). Culture from a second biopsy remained sterile after 17 days on this topical treatment.

**Comment**—This case of ocular infection by *F. solani* was unusually virulent. This organism is also more virulent for animal eyes than most *F. solani* species. Thiabendazole probably contributed to the eradication of the fungus.

A 4% thiabendazole suspension is well tolerated in the eye, and can be given orally to back up intraocular penetration from topical administration. Its antifungal activity is high but selective. Intensive early administration of thiabendazole may prove to be effective in selected cases infected with sensitive fungi, especially certain *Fusarium* isolates.

**Flucytosine**—Flucytosine (fluorocytosine [5-FC]), a halogenated pyrimidine (Fig. 44), is well absorbed orally and is remarkably nontoxic in human beings because it is not metabolized but is excreted, unchanged, in the urine. Fungi that have a permease to allow the drug's entry and a deaminase to convert it within their bodies to the highly toxic 5-fluorouracil are highly sensitive to its action (Fig. 45): they include *Candida* species and *Cr. neoformans*. Resistant strains occur, or may arise, especially with low dosages, but this is less of a problem with *Candida* than with *Cryptococcus*. We have not encountered any resistant *Candida* in the eye. The simultaneous administration of amphotericin B may solve the problem of new resistant strains and has a synergistic effect on *C. albicans.* The interactions
among flucytosine, clotrimazole, and miconazole are still in an experimental stage.

Flucytosine is soluble in water (1.5%) and nonirritating in the eye. Although drops may be active in the cornea, they do not give good results at intraocular levels and subconjunctival administrations are disappointing. However, we have biologically measured levels of 10 and 40 µg/ml of flucytosine in the aqueous humor of patients receiving oral doses, 200 mg/kg/day. Oral administration, therefore, is relevant to ophthalmic disease. We successfully treated three patients with orally administered flucytosine: two had corneal candidiasis (one already had severe anterior and posterior chamber invasion) and the other chorioretinal candidiasis.

**Case 25**—A 29-year-old atopic woman developed a 3 × 4-mm deep white corneal ulcer in her only seeing eye in an area of herpetic keratitis that had been treated with idoxuridine and betamethasone drops. Ulcer scrapings revealed yeast forms and pseudohyphae. The eye worsened on nystatin ointment, three times daily, and there was a dense exudate occupying the upper pupillary area, while the lower was bound to the lens. *Candida albicans* was grown (mic: pimaricin, 6 µg/ml; nystatin, 6 µg/ml; amphotericin B, 0.75 µg/ml; candididin, 0.75 µg/ml; hamycin, 0.75 µg/ml; Trichomycin, 0.75 µg/ml; clotrimazole, 6 µg/ml; flucytosine, 0.75 µg/ml; miconazole, 12.5 µg/ml; and econazole, 25 µg/ml).

Intensive topical treatment with 5% candididin ointment, 1% pimaricin ointment, and 0.1% hamycin suspension was administered every half hour. Intravenously administered amphotericin B therapy of 0.25 to 0.8 mg/kg/day, every day, gave serum levels ranging from 1.3 to 2.5 mg/ml. There was some improvement on this regimen, but after two weeks mounting renal and corneal epithelial toxicity forced a reduction in therapy, with recrudescence of corneal, anterior chamber, and posterior chamber disease. In the third week, visual acuity had deteriorated to counting fingers at 2 meters (Fig. 46). Her regimen was changed to 1% flucytosine drops, every hour, and 150 to 200 mg/kg/day of
oral flucytosine. She improved within 24 hours (Fig. 47) and was continued on this therapy for five weeks, while receiving intensive systemic corticosteroid therapy to avert status asthmaticus. Orally administered flucytosine was given for two more weeks, when she exhibited a slight recrudescence three weeks after cessation of the initial course. Visual acuity improved from counting fingers at 2 meters to 20/70 (Fig. 48).

Case 26—A 57-year-old atopic woman receiving orally administered corticosteroid therapy for asthma for ten years as well as topical corticosteroid preparations for rosacea keratitis developed a small, deep white ulcer below the center of her right cornea. Treated with antibacterial antibiotics and a regimen of topical and subconjunctival corticosteroids, the patient’s deepening ulcer continued for four months with increasing uveitis, hypopyon, and raised ocular tension for which she was given acetzolamide (Diamox). Scrapings then revealed yeast and pseudohyphal forms. While an attempt was being made to evacuate a subconjunctival depot of corticosteroid, the cornea perforated; a conjunctival flap was raised and therapy with nystatin drops was administered every hour.

Three days later, the flap retracted from the ulcer which was full of exudate and necrotic material and the anterior chamber re-formed with heavy flare and 3+ cells. Swabblings grew a coagulase-negative S. albus and C. albicans (mic: pimaricin, 6 µg/ml; amphotericin B, 0.75 µg/ml; nystatin, 12.5 µg/ml; clotrimazole, 3 µg/ml; flucytosine, 0.75 µg/ml; miconazole, 6 µg/ml; and econazole, 12.5 µg/ml). She was treated with 1% flucytosine drops topically, every hour, and 200 mg/kg/day orally for ten weeks; she received only topically applied flucytosine for the week preceding keratoplasty. An unusually intense pharmacokinetic interaction occurred between flucytosine and the acetzolamide she was receiving because of threatened perforation. Her flucytosine serum levels ranged from 48 to 200 µg/ml, and averaged 100 µg/ml. An aqueous humor measurement showed a level of 55 µg/ml, biologically. In the first week of treatment the ocular cultures were negative for Candida but remained repeatedly positive for the coagulase-negative staphylococcus. The suppurative keratitis and uveitis improved slowly, but when systemically and topically applied penicillin was administered, the patient improved dramatically. A hazardous descemetocele and an organizing exudate were on the lens. Aqueous humor collected at the time of penetrating keratoplasty, after the patient had been on a one-week regimen of 1% flucytosine drops, every hour, contained no measureable level of flucytosine (< 0.125 µg/ml). Oral therapy was resumed, with
more normal pharmacokinetic handling of the drug; there was minimal interaction between flucytosine and acetazolamide. She made a routine recovery to a quiet eye, with visual acuity of 20/70, and flucytosine was discontinued after ten weeks (seven weeks postoperatively).

Case 27—A 26-year-old woman who was receiving systemic prednisolone therapy for polymyositis of two years' duration had had her daily dose reduced from 190 to 85 mg when she noticed black spots in the vision of her right eye: visual acuity was 20/20. There was a small white spot over the lower temporal artery just below the macula. Fluorescein angiography showed focal leakage from the lesion and nearby veins. Rapid progression of disease with uveitis, vitreous abscess formation, and extension of the retinal lesion with developing satellite lesion reduced visual acuity to 20/100 within a few days. An ulcerative lesion in her mouth and vaginal and rectal cultures grew C. albicans, although blood cultures remained sterile (mic: flucytosine, 0.35 µg/ml; amphotericin B, 0.75 µg/ml; miconazole, 1.5 µg/ml; clotrimazole, 3 µg/ml; and econazole, 6 µg/ml). Serum precipitins against C. albicans were present and agglutinins showed a titer of 1:64.

Impaired renal function made amphotericin therapy undesirable. She was treated with flucytosine, 200 mg/kg/day for ten weeks, and half this dose for eight more weeks. The serum levels of flucytosine ranged between 50 and 70 µg/ml during administration of the full dosage, and 30 to 40 µg/ml during half-dose administration. The anterior vitreous cavity cleared fairly promptly although the inflammatory exudate increased in the posterior vitreous cavity. A localized detachment of the vitreous cavity developed over the lesion and debris accumulated on the posterior vitreous face. Within six weeks the retinal lesion became less elevated and leakage of fluorescein from the retinal veins ceased though it persisted from the lesion. Visual acuity had improved to 20/70. The retinal lesion was flat and hemorrhages were visible in its base, after 12 weeks of therapy. By the 15th week the vitreous cavity was clearing well and visual acuity was 20/30. The patient was observed for a year and maintained a visual acuity of 20/20.

Flucytosine (200 mg/kg/day, and 1.5% aqueous drops, every hour), is the drug of choice for intraocular and deep corneal infections by Candida species if the patient's fungus is not resistant to the drug. Therapy must be maintained for 12 to 32 weeks, combined with amphotericin B or possibly clotrimazole or miconazole.

**Discussion**

The following points must be considered when managing an individual case of keratitis. The balance between host and invader may be delicately poised and may lie in favor of either one or the other, so that some fungal corneal infections probably recover spontaneously; others need only minimal help from poorly penetrating polyenes, or a boost to host defenses from a conjunctival flap, whereas other cases end disastrously unless a highly effective, non-damaging, and well-penetrating antifungal regimen is directed against each fungus at the earliest possible moment. In some cases with intraocular invasion, this medical treatment may be combined with excisional keratoplasty or evacuation of the posterior chamber and anterior vitreous body.

A highly effective and nondamaging compound is available for most cases. Nevertheless, some drugs that can save sight and eyes, in otherwise hopeless cases, have not yet been approved in many countries. Moreover, it will probably take time before a highly effective drug that acts against all ocular fungi is available. Meanwhile, there will be a continuing, but diminishing, place for the older and less potent polyene antifungals, especially pimaricin, amphotericin B, and others, in managing a residue of cases that should be readily identifiable by antifungal sensitivity tests.

When choosing antifungal drugs for individual fungi, as with bacteria, one institutes specific therapy on the basis of the probable sensitivities of a given species; but the sensitivity that occurs within species is so varied that therapy must be based on the sensitivity testing results of each patient's fungus. Our laboratory will provide test results on any ocular fungus.* While awaiting these results, the ophthalmologist should treat the infection intensively with pimaricin, or any other recommended drug.

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* Cultures should be sent airmail to Professor Barrie Jones, Institute of Ophthalmology, Moorfields Eye Hospital, City Road, London, EC1V 2PD, England, suitably packed, and marked "Urgent diagnostic medical specimen: no commercial value."
Candida species—Flucytosine is the drug of choice for C. albicans infections, other than those isolates that may be resistant to it (Fig. 49). Clotrimazole and miconazole are highly active against a proportion of Candida infections and penetrate sufficiently well for most Candida infections. Intravenously administered amphotericin B probably has a place in treating intraocular candidiasis, combined with flucytosine.
Aspergillus species—Clotrimazole is the drug of choice for Aspergillus infections (Fig. 50). Miconazole and econazole are also highly active and are preferable for some Aspergillus infections (Fig. 51).

Various ocular fungi—Choosing an initial management for individual fungal infections (Fig. 52)—other than Candida, Aspergillus, or Fusarium—will be easier when extensive isolate testing becomes more common. Meanwhile, ophthalmologists who encounter infections by the following filamentous ocular fungi—Alternaria, Cladosporium, Drechslera, Fonsecaea, Helminthosporium, Pasciomyces, Penicillium, and Phialophora—should use miconazole, econazole, possibly clotrimazole, and occasionally thiabendazole therapy, if pimaricin fails while awaiting the sensitivity test results.

Fusarium species—We do not yet have a drug that is nonirritating, penetrates well, and is highly active against many F. solani and other Fusarium species (Fig. 53). Treatment of Fusarium infections should always begin with pimaricin. Clotrimazole, miconazole, thiabendazole, and econazole are valuable in some cases, as indicated by sensitivity tests.

There are many ocular Fusarium isolates, but many are experimental compounds presently unavailable for human use, and many may be unsuitable for ocular use. One substance that deserves further investigation is furidazole 2-(2 furyl) benzimidazole, an agricultural antifungal used for plant disease, caused by F. nivale and F. culmorum, that is configurationally similar to thiabendazole.

To determine the efficacy and acceptability of new antifungals, we treated several patients each with a single drug selected by using the in vitro antifungal sensitivity of the patient's fungus and pharmacokinetic considerations. Beneficial combinations of drugs for ocular use are still in experimental stages.

Although present drugs cure many cases of oculomycosis, many challenging fungi remain, especially the Fusarium species; development of new drugs should concentrate on fungi that are resistant to present antifungals.

The very existence of effective drugs for most fungi forces us to define the magnitude, distribution, and etiology of suppurrative loss of eyes following ocular trauma in the less medically advanced nations. More eyes are lost to fungal infections in tropical rural areas...
han reports indicate, because diagnostic 
acilities are not available and, without treat-
ment, there has been little point in the pur-
uit of precise causation. Simple diagnostic 
ulture kits, distributed in these areas, may 
provide data to guide the provision of com-
bined antibacterial and antifungal prophyl-
axis for people in high-risk occupations.

To overcome the problems of low water 
solubility, oily solutions or ointment may be 
used. Ocular therapeutic drug delivery sys-
tems are being tested. Although miconazole
is somewhat irritating as a watery suspension, a patient with an *A. fumigatus* infection recovered dramatically while wearing a device (Fig. 36), with a steady delivery rate of 6 μg of miconazole per hour, without discomfort.

The drugs we now have are powerful and nondonamaging, some broad in action, others highly specific. But this specificity demands speed in sensitivity determination and precision in use. Few fungal infections of the eye are so trivial that they can be managed lightly, nor are they so severe that they should be despaired of, provided they are treated at a center with the combination of required skills.

**Summary**

Effective antifungal therapy must be long-term, nondonamaging, penetrating to the eye, and highly active against each patient's fungus. Results of antifungal sensitivity testing of 61 collected ocular fungal pathogens and observations in 25 cases treated with one of the nonpolyene antifungal drugs indicated that infection was rapidly controlled and eradicated with restoration of visual acuity, determined by the degree of disorganization present at the time of commencement of rational specific antifungal therapy.

Pimaricin has the widest spectrum, a medium level of activity, and rather poor penetration but is recommended as an antifungal prophylactic and as first-line therapy for ocular fungal disease while awaiting identification and sensitivity testing of the fungus. Flucytosine combined with amphotericin B, or possibly with clotrimazole or miconazole, is recommended for *Candida* infections. Clotrimazole is the drug of choice for *Aspergillus* species although miconazole and econazole are more effective with some isolates. Miconazole and econazole are recommended for miscellaneous filamentous fungi although clotrimazole or thiabendazole are superior in some cases. Each of these drugs may be useful in patients infected with *Fusarium* who do not respond to pimaricin. In these cases, drug use should be guided by the results of antifungal sensitivity testing. In addition to medical antifungal therapy some eyes may require excisional keratoplasty with the lens removal and evacuation of the posterior chamber and anterior vitreous cavity.

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**References**


