The Role of Steroids in the Management of *Acanthamoeba* Keratitis, Fungal Keratitis, and Epidemic Keratoconjunctivitis

Roberto Pineda II, M.D.
Claes H. Dohlman, M.D.

Debate over the use of corticosteroids in infectious corneal disease has existed since the introduction of these agents in the late 1940s [1–3]. The central controversy around topical steroid use has been the risk of augmenting an infection versus the benefit of controlling the inflammatory response. We have chosen to examine the literature regarding corticosteroid use in *Acanthamoeba* keratitis, fungal keratitis, and epidemic keratoconjunctivitis (EKC). Recent advances in the development of animal models for these diseases have allowed a better understanding of the interplay among cornea, infectious agent, and corticosteroids, thus permitting a more objective analysis of the usefulness of corticosteroids in treating patients. In this chapter, we review the currently available data pertaining to corticosteroids and these three infectious corneal entities and offer our own opinions as to their appropriateness.

■ *Acanthamoeba* Keratitis

Pathological Features

Acanthamoeba keratitis is an uncommon, chronic, painful infection caused by a ubiquitous resilient amoeba, found commonly in soil, freshwater, and seawater (Fig 1). Additionally, *Acanthamoeba* has been identified in swimming pools [4] and hot tubs [5]. The organism has two forms,—the trophozoite or active form and a cyst or vegetative form, which it assumes when it is environmentally stressed—making treatment of *Acanthamoeba* keratitis difficult. Five different species of *Acanthamoeba* are implicated in

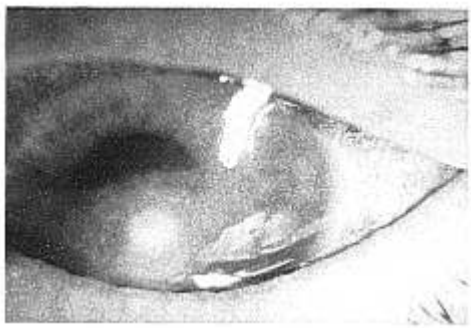

Figure 1 Acanthamoeba *keratitis with a dense central corneal infiltrate and immune ring.*

human keratitis: *A. castellani, A. culbertsoni, A. hatchetti, A. polyphaga,* and *A. rhysodos* [6]. Of these, *A. castellani* and *A. polyphaga* are reported to be the most commonly involved in human keratitis [7]. Interestingly, it has been observed that the total sterol counts of virulent strains of *Acanthamoeba* trophozoites are higher compared to the nonpathogenic strains and species [8].

Sources for contamination in *Acanthamoeba* keratitis include trauma associated with vegetable matter, exposure to freshwater, hot tub use, and exposure to swimming pool water [9, 10]. However, the strongest risk factor remains soft contact lens wear, owing to poor cleaning habits and the use of tap water or homemade saline solutions [11, 12].

Prevention and Treatment

Since *Acanthamoeba* was recognized as an agent of infectious keratitis nearly 20 years ago [13], treatment of the entity has not been satisfactory and has posed a therapeutic dilemma. The mediocre response to currently available drugs and difficulty in diagnosis has only compounded the management problems of this disease. Patients often are treated for herpes simplex keratitis before *Acanthamoeba* keratitis is suspected or confirmed [14]. Lack of standardized methods and models in this disease are only now being addressed in the literature. For these reasons, use of corticosteroids in the treatment of *Acanthamoeba* keratitis remains controversial and has been clouded by anecdotal case reports of its use.

Currently, authors agree that prevention or elimination of risk factors is the best defense against *Acanthamoeba* keratitis [14–16]. However, most authors believe that once *Acanthamoeba* has seeded the cornea, early recognition and aggressive topical treatment with a multidrug regimen are critical in neutralizing the infection [17]. Most protocols for *Acanthamoeba* keratitis advocate multidrug therapy and include propamidine isethionate 0.1% (Brolene®) and neomycin drops. Several other antibiotic and antifungal agents have been helpful in treating *Acanthamoeba* infections, including ketoconazole, clotrimazole, miconazole, paramomycin, and itraconazole

[14]. Recently, polyhexamethylene biguanide (PHMB), a new drug used in the treatment of *Acanthamoeba* in Europe, has shown excellent in vitro sensitivity and moderate clinical results [18].

Because of delayed diagnosis and often inadequate response to medical therapy, however, penetrating keratoplasty often is necessary in affected patients. Recurrence in the graft is not unusual. Ficker and colleagues [19], in a recent article, examined retrospectively 13 eyes of 11 patients with *Acanthamoeba* keratitis to determine the risk factors for penetrating keratoplasty. They found that graft survival was significantly better in quiet eyes than in eyes inflamed by recurrent infection. Six of seven inflamed eyes required regrafting, whereas none of the quiet eyes had graft failures. The authors cited delayed clinical diagnosis as a serious risk factor in predicting final outcome in patients with *Acanthamoeba* keratitis.

New potential hypothesized treatments include the use of proteinase inhibitors [20] and magainin, a peptide present in the skin of the clawed frog *Xenopus laevi.* A synthetic analog, magainin G, has shown excellent cysticidal and trophocidal activity against *A. castellani* [21].

The role of steroids in managing and treating *Acanthamoeba* remains obscure and is still being debated [9]. Most patients in the literature have received topical steroids as adjunctive therapy, including the first case of successfully medically treated *Acanthamoeba* keratitis, reported by Wright and colleagues [22]. However, most authors either urge care with steroid use [9, 14] or strongly discourage such use altogether [23].

Animal Models Recently, animal models have been developed for *Acanthamoeba* keratitis using rabbit, rat, and pig. This has allowed more objective evaluation of therapeutic agents as well as a better understanding of the pathogenesis of this disorder. Font and coworkers [24], in 1981, developed the first experimental model of *Acanthamoeba* keratitis in rabbits using corticosteroids, but Badenoch and associates [25] now report development of a rat model without steroid pretreatment. Interestingly, Badenoch's model of experimental *Acanthamoeba* keratitis required coinjection of *Corynebacterium xerosis,* a bacterium that has been previously isolated from the corneas of patients with *Acanthamoeba* keratitis [26]. The possible role of commensal bacteria in the pathogenesis of *Acanthamoeba* keratitis has been postulated by others [27].

He and coworkers [28] reported the use of the Yucatan micropig as an animal model in which disease is transmitted via a contaminated contact lens, 1 of 11 species tested (other than humans) to display this property in vitro. In another study, Cote and colleagues [29] intrastromally inoculated the corneal stroma of 12 rabbits with *A. castellani.* These rabbits then received either topical and subconjunctival steroids or subconjunctival placebo. The results showed that steroid treatment did not enhance the severity of the keratitis or affect the rate of culture isolation of *Acanthamoeba.*

Osato and coworkers [30], in an initial in vitro study, demonstrated

that dexamethasone altered the timing of morphogenesis and inhibited the replication of *Acanthamoeba*. Such an effect by corticosteroids in vivo would be efficacious in treating the keratitis as some authors believe that the trophozoites encyst when therapy is begun and, in such a state, are more refractory to antimicrobial therapy [31–33]. Unfortunately, these observations were not supported in subsequent animal models by Osato.

In another study by John's group [34], 20 New Zealand white rabbits received intrastromal injections of *A. castellani.* These were divided into three groups. Group A received no corticosteroids, group B received intracorneal dexamethasone, and group C received subconjunctival injections of dexamethasone on days 0, 14, and 21. All rabbits developed *Acanthamoeba* keratitis in the experimental eye. Greater amounts of corneal infiltrate and neovascularization were seen in the rabbits that received the dexamethasone, suggesting a detrimental effect of corticosteroids to the host. In addition, dexamethasone did not seem to affect, to any appreciable degree, morphogenesis of *Acanthamoeba* from the cyst to the trophozoite form in vivo. In fact, proliferation appeared to be enhanced.

The importance of host resistance to *Acanthamoeba* was emphasized in a recent experiment by Silvany and associates [35] when their group demonstrated lysis of *A. castellani* by rat neutrophils and T-cell cytokine-activated macrophages. This observation argues against the use of corticosteroids in *Acanthamoeba* keratitis as steroids inhibit neutrophil and macrophage response.

Thus, current experimental data imply a possible detrimental effect to the host from the use of corticosteroids in *Acanthamoeba* keratitis. Steroid use in animal models of *Acanthamoeba* keratitis appears to have a potentiating effect that may relate to enhanced pathogenicity or decreased host defense. Recently, a study found that antifungal agents used to treat *Acanthamoeba* keratitis are impaired by topical steroids in experimental fungal keratitis [36]. This finding discourages corticosteroid use and may cripple the few moderately effective agents currently available for treatment of this disease.

Clinical Findings The clinical literature offers little help when evaluating the usefulness of corticosteroids in *Acanthamoeba* keratitis. There are equal numbers of cases suggesting clinical improvement on topical steroids or progressive deterioration with steroid therapy. This most likely explanation for such discrepancies relates to variable length of follow-up, use of combined medical and surgical approaches, duration and intensity of therapy, and lack of controlled clinical data.

In one clinical study, Rabinovitch and coauthors [37] reviewed the outcome of *Acanthamoeba* keratitis as it related to intensity of treatment, time of diagnosis, and the use of corticosteroids. Using multivariate analysis, steroid use was the only factor associated with poor outcome ($p <$

0.0001), suggesting that use of corticosteroids was the single most important factor in predicting failure of medical treatment.

Summary In summary, it can be concluded that the literature concerning the role of steroids in *Acanthamoeba* keratitis remains ambiguous. Although several authors strongly discourage steroid use, we maintain that there is a role for steroids in *Acanthamoeba* keratitis. When the eye is inflamed, steroids help to quiet the eye. In addition, they are very useful prior to keratoplasty for progressive disease and play an integral part following keratoplasty, preventing graft rejection and reducing postoperative inflammation. Until more controlled data become available, judicious use of corticosteroids in *Acanthamoeba* seems rational.

■ Fungal Keratitis

Fungal keratitis continues to be a clinical challenge because of the difficulties in diagnosis and treatment (Fig 2). Of the existing controversies, there is less debate over the use of corticosteroids in fungal keratitis than in other infectious corneal diseases. That corticosteroids promote fungal growth has been recognized for more than three decades [38, 39]. Recent laboratory studies using animal models and in vitro pharmacological experiments confirm this fact [40], with numerous clinicians echoing this finding from their own practical experience.

Pathological Features

Although relatively uncommon in the United States, fungal keratitis appears to have increased in incidence in recent decades [41]. The widespread use of corticosteroids has been implicated as one cause of this rise in cases [42]. Three major groups of fungal ocular pathogens have been identified [42]. The first are the filamentous fungi, which possess hyphae with or without septa. These include the septate genera *Fusarium, Aspergillus, Penicillium,* and *Cephalosporium* (a cardinal group causing keratomyco-

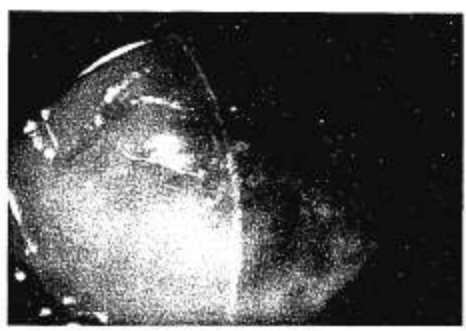

Figure 2 *Fungal corneal ulcer treated with topical steroids* (Fusarium).

sis) and the nonseptate genera *Rhizopus, Mucor,* and *Absidia.* The second group are the unicellular yeast organisms, which include *Cryptococcus* and *Candida* species. *Candida* is the principal corneal pathogen in this group. The third group encompasses the diphasic organisms—*Blastomycoses, Coccidioides,* and *Histoplasma*—which play a negligible role in corneal disease. Thus, the principal fungal corneal pathogens are yeast and filamentous septate fungi.

Treatment

It is currently agreed that corticosteroids potentiate mycotic infections, at least in part, by reducing tissue resistance through altered host cellular defense mechanisms. Numerous animal studies have demonstrated enhanced virulence of fungal pathogens when corticosteroids are administered [43–47].

Few reports have substantiated any claims of benefit from corticosteroid use in fungal keratitis, either clinically or experimentally. In a study by Newmark and colleagues [48], using a rabbit model of *Aspergillus* fungal keratitis, low-dose dexamethasone sodium phosphate (0.001%) combined with 5% pimaricin and 2% potassium iodide effectively suppressed ocular inflammation and appeared to improve infection resolution without promoting mycotic proliferation or interfering with the antifungal agent. O'Day and coworkers [49], in a case report, described the use of combined corticosteroid-antifungal therapy to quiet an eye before a successful therapeutic penetrating keratoplasty was performed in a patient with a deep fungal corneal abscess (*Aspergillus*). In this article, routine use of corticosteroids was not recommended.

It has been shown that phagocytic competence plays a large role in antifungal defense [50]. In light of this and the well-known fact that corticosteroids inhibit neutrophil and macrophage function, the role of corticosteroids would seem to be contraindicated in mycotic infections. This is particularly important as most antifungal agents are primarily fungistatic in nature and, therefore, intact antimicrobial body defenses are crucial.

In an enlightening article by O'Day and associates [36], the influence of corticosteroids on the efficacy of various antifungal agents was evaluated using a quantitative rabbit model of *Candida* keratitis. In the study, 1% prednisolone acetate exacerbated the fungal keratitis when administered alone and negatively influenced topical 5% natamycin, 1% flucytosine, and 1% miconazole when administered jointly. However, amphotericin B in concentrations of 0.5% and 0.15% appeared to be unaltered in efficacy with simultaneous corticosteroid use. This study demonstrated that highly efficacious antifungal drugs are not hindered in the presence of corticosteroids but that the effect of marginal antifungal agents is diminished or ablated, most likely due to impaired host response. The role of synergism between antifungal agents was not addressed.

It should be remembered that all current topical antifungal medications have poor corneal penetration and often do not reach fungicidal concentrations in the cornea. This fact as well as the previously cited literature strongly argue against the application of corticosteroids in keratomycosis. We concur that there is no role for steroids at any stage of fungal keratitis, as our own clinical experience with steroids even late in the course of such disease has been very discouraging.

■ Epidemic Keratoconjunctivitis

Pathological Features

EKC is a highly contagious and communicable disease that carries significant morbidity and occasionally results in visual disturbances that persist for months or, very rarely, years. EKC is not, however, associated with the blinding potential of *Acanthamoeba* or fungal keratitis and is considered an acute or subacute self-limiting entity. Fuchs [51] described this entity in 1889 and called it *keratitis punctata superficialis,* but it was not until 1955 that adenovirus was identified by Jawetz and coworkers [52, 53] as the causative agent of EKC. The term *epidemic keratoconjunctivitis* was coined by Hogan and Crawford [54] in the early 1940s after a review of the literature.

EKC is caused by the globally found adenovirus family of which 42 serotypes have been identified [55]. Clinically, three distinct adenovirus ocular infections are recognized: epidemic keratoconjunctivitis, pharyngoconjunctival fever, and nonspecific follicular conjunctivitis [56]. EKC is most commonly associated with serotypes 8 and 19, but several other serotypes have also been isolated in this disease [57]. Currently, there is no effective antiviral therapy available for adenoviral ocular disease, and the role of topical corticosteroids has been debated. Good hygienic care is the best preventive of this contagious disease. During the acute stage of the infection, making the patient comfortable is the main objective.

In most cases, topical steroids in EKC usually are not necessary. The extended use of topical corticosteroids is of particular concern to clinicians owing to the possibility of superinfection, glaucoma, and cataract formation. The potential for misdiagnosis in the acute phase of EKC is another reason for the objection to topical steroids.

The clinical course of EKC has been amply described [58, 59]. After an average incubation period of 8 days, patients present with conjunctival infection, foreign-body sensation with watery discharge, and a conjunctival follicular reaction. Small petechial hemorrhages on the tarsal conjunctiva, as well as preauricular adenopathy, are often seen. A pseudomembrane may develop in very severe cases and can result in cicatrization with symblepharon formation (Fig 3).

The cornea usually is not involved in the first 3 days of the infection.

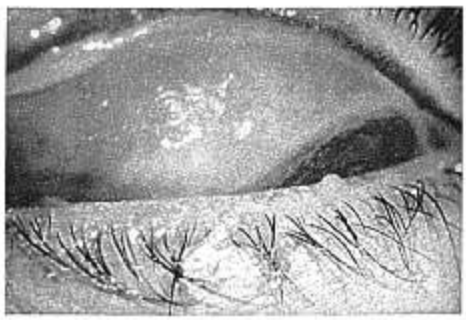

Figure 3 *Everted upper eyelid with a pseudomembrane due to epidemic keratoconjunctivitis.*

Then a fine diffuse epithelial keratitis that does not stain may ensue, generally resolving by the end of the first week. It may be followed by the development of a focal epithelial keratitis that lasts 1 week or so. This does stain and is easily seen with biomicroscopy. These focal epithelial lesions have been shown to harbor active virus [60] and persist in the presence of topical steroids, as opposed to the superficial punctate keratitis of Thygeson's disease that readily responds to low-dose topical steroid therapy [56]. Two to three weeks after the onset of the disease, corneal subepithelial infiltrates develop in the area underlying the focal epithelial keratitis. These infiltrates may persist for months, years, or even decades [59]; however, most gradually resolve (Fig 4).

It has been suggested that viral antigens are adsorbed by the corneal stroma from the overlying infected epithelial cells, leading to the formation of subepithelial infiltrates when sensitized T lymphocytes react with these antigens [61]. Two histopathological studies of EKC-related subepithelial infiltrates have demonstrated lymphocytic or histiocytic infiltration and fibroblastic cells with no evidence of virus particles, intracellular inclusions, or indirect immunofluorescence of the virus [62, 63]. The histological findings suggest an immunological basis for the subepithelial infiltrates. Steroids would thus suppress the lymphocytic response, resulting in clearing of the infiltrate; when discontinued with no further immunosuppression, the infiltrates would be expected to reappear. The fibroblastic re-

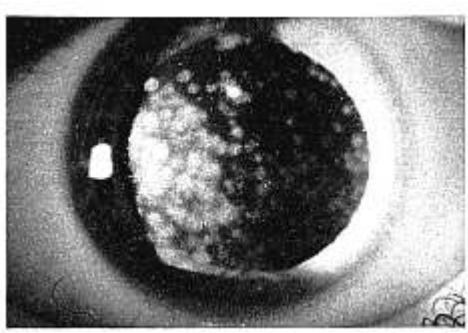

Figure 4 *Visually significant subepithelial infiltrates in epidemic keratoconjunctivitis.*

sponse most likely reflects a chronic inflammatory state, causing permanent scarring, which explains why, at times, these infiltrates fail to respond to topical steroid therapy.

Treatment

Several authors believe patients with pseudomembranes and potential symblepharon formation benefit from a short course of topical steroids [56, 59]. Laibson [59] recommends 0.25% prednisone with 10 to 15% sulfacetamide drops two to four times daily, used for as long as the patient is highly symptomatic and weaned after 7 to 10 days. In another study, Murrah [64] treated 15 EKC patients with a topical antibiotic-steroid mixture for supportive treatment and was convinced that topical steroids relieved discomfort in most cases, with no reported sequelae. In our own experience, no case of EKC treated with topical steroids in the acute stage has displayed any obvious complications from this regimen. In addition, our patients claim to have felt almost immediate relief from the symptoms when started on steroids, and this amelioration is clinically very significant.

Studies have demonstrated the ability of topical steroids to reduce or prevent the appearance of subepithelial infiltrates in EKC, but this is transitory; the lesions recur after cessation of the steroids. Laibson and colleagues [65] examined 32 eyes with EKC prior to the appearance of subepithelial infiltrates in a double-blind study using Prednefrin Forte or Liquifilm. Four weeks after therapy was started, 13 of 16 eyes developed subepithelial deposits on Liquifilm, whereas only 6 of 16 steroid-treated eyes developed subepithelial infiltrates. Two weeks after medication was stopped, the steroid-treated patients developed subepithelial lesions that resolved with reinstitution of the steroid therapy but later reappeared after the steroids were stopped. This effect could be seen from 1 year after the initial infection. In this article, steroids were not recommended unless photophobia and tearing were incapacitating or the infiltrates involved the deep stroma over the pupil. It was also pointed out that these were uncommon scenarios in EKC.

A second publication from Germany examined in a prospective random study 53 patients with adenovirus type 8 EKC using artificial tears or topical steroids for 6 weeks [66]. Their findings were similar to those of Laibson [65]. There was no difference in the course of the conjunctivitis or frequency of superficial punctate keratitis. Moreover, there was a high incidence of permanent dry eye in the postinfective period. The investigators suggested only limited topical steroid use in severe cases to relieve symptoms.

Experimentally, productive viral infections with human adenovirus have been documented using cells from other species. This has been expanded to corneal organ cultures using New Zealand rabbits in which permissive viral infection of adenovirus types 8 and 19 have been demon-

strated [67]. More recently, two promising animal models of ocular adenovirus infection have been published [68, 69]. Using New Zealand rabbits, Gordon and colleagues [68] intrastromally inoculated a clinical isolate of adenovirus type 5 into the corneal stroma. This model produced an acute reproducible ocular infection, that included conjunctivitis, corneal edema, subepithelial infiltrates, and iritis, comparable to human ocular adenovirus disease. Similarly, Tsai and coworkers [69] demonstrated typical EKC features in the eyes of cotton rats inoculated with adenovirus types 5 and 8. In contrast, Gordon failed to observe these changes in his cotton rat model with adenovirus type 5.

These encouraging animal models will allow further analysis of the role of topical corticosteroids in EKC. Many external disease experts remain wary of steroid use in EKC despite the fact that adverse effects have not been convincingly shown. We have never seen side effects of short-term steroid therapy in EKC, whereas the benefits of these drugs in reducing morbidity and discomfort are substantial. It is our conviction that topical steroids can be used safely during the acute phase of EKC and tapered over 2 to 4 weeks. Should subsequent stromal infiltrates cause glare or reduce vision, very low doses of steroids can be given safely for months.

■ Conclusion

Although the literature is ambivalent, we believe there is a role for topical corticosteroids in *Acanthamoeba* keratitis. Corticosteroids help reduce inflammation, may inhibit trophozoite conversion, giving antimicrobials a better opportunity to act, and prevent immune reactions following keratoplasty for progressive disease. It is also our opinion that steroids should be avoided at all costs in fungal keratitis as they can change a steady course into a disaster. This sentiment is strongly documented in the literature. Finally, we have no objections to topical steroid use at any stage of EKC, particularly to reduce morbidity in the acute phase. When pseudomembranes are present, a short course of high-dose topical steroids is absolutely necessary. With subepithelial infiltrates, low-dose steroids can be used to suppress glare and improve visual acuity; the drug is then tapered slowly.

■ References

1. Aronson SB, Moore TE. Corticosteroid therapy in central stromal keratitis. Am J Ophthalmol 1969;67(6):873–896
2. Jones DB. Decision-making in the management of microbial keratitis. Ophthalmology 1981;88:814–820
3. Stern GA, Buttross M. Use of corticosteroids in combination with antimicrobial

drugs in the treatment of infectious corneal disease. Ophthalmology 1991;98: 847–853
4. Lyons TB III, Kapur R. *Limax amoebae* in public swimming pools of Albany, Schenectady, and Rensselaer counties, New York: their concentration, correlations and significance. Appl Environ Microbiol 1977;33:551–555
5. Samples JR, Binder PS, Luibel FJ, et al. *Acanthamoeba* keratitis possibly acquired from a hot tub. Arch Ophthalmol 1984;102:707–710
6. Moore MB, Ubelaker JE, Martin JH, et al. In vitro penetration of human corneal epithelium by *Acanthamoeba castellani:* a scanning and transmission electron microscopy study. Cornea 1991;10(4):291–298
7. Center for Disease Control. *Acanthamoeba* keratitis associated with contact lenses—United States. MMWR 1986;35:405–408
8. Mehdi H, Garg HS, Garg NK, Bhakuni DS. Sterols of *Acanthamoeba* culbertsoni strain A-1. Steroids 1988;51:551–558
9. Auran JD, Starr MB, Jakobiec FA. *Acanthamoeba* keratitis. A review of the literature. Cornea 1987;6(1):2–26
10. Stehr-Green JK, Barley TM, Visvesvara GS. The epidemiology of *Acanthamoeba* keratitis in the United States. Am J Ophthalmol 1989;107:331–336
11. Moore MB, McCulley JP, Luckenbach M, et al. *Acanthamoeba* keratitis associated with soft contact lenses. Am J Ophthalmol 1985;100:396–403
12. Moore MB, McCulley JP, Newton C, et al. *Acanthamoeba* keratitis is a growing problem in soft and hard contact lens wearers. Ophthalmology 1987;94:1654–1661
13. Jones DB, Visvesvara GS, Robinson NM. *Acanthamoeba polyphaga* keratitis and *Acanthamoeba* uveitis associated with fatal meningoencephalitis. Trans Ophthalmol Soc UK 1975;95:221–232
14. Brady SE, Cohen EJ. *Acanthamoeba* keratitis. Ophthalmol Clin North Am 1990;3(4): 537–544
15. Doren GS, Cohen EJ, Higgens SE, et al. Management of contact lens–associated *Acanthamoeba* keratitis. CLAO J 1991;17(2):120
16. Cohen EJ, Higgens SE, Arentsen JJ, et al. Clinical course of *Acanthamoeba* keratitis. Rev Infect Dis 1991;13(suppl 5):S426
17. Cohen EJ, Parlato CJ, Arentsen JJ, et al. Medical and surgical treatment of *Acanthamoeba* keratitis. Am J Ophthalmol 1987;103:615–625
18. Elder MJ, Kilvington S, Dart JKG. A clinicopathological study of in-vitro sensitivity testing and *Acanthamoeba* keratitis. Invest Ophthalmol Vis Sci 1993;34(suppl 4):695
19. Ficker LA, Kirkness C, Wright P. Prognosis for keratoplasty in *Acanthamoeba* keratitis. Ophthalmology 1993;100:105–110
20. James ER, Mitro K. *Acanthamoeba* trophozoites secrete serine and cysteine proteinases. Invest Ophthalmol Vis Sci 1991;32(suppl 4):2515
21. Hwang DG, Nakamura T, Huang CM, et al. Efficacy of a synthetic magainin analog against trophozoites and cysts of *Acanthamoeba.* Invest Ophthalmol Vis Sci 1991; 32(suppl 4):2517
22. Wright P, Warhurst D, Jones BR. *Acanthamoeba* keratitis successfully treated medically. Br J Ophthalmol 1985;69:778–782
23. Moore MB, McCulley JP. *Acanthamoeba* keratitis associated with contact lenses: six consecutive cases of successful management. Br J Ophthalmol 1989;73:271–275
24. Font RL, Tapert MJ, Robinson NM, et al. An animal model of *Acanthamoeba* keratitis. Invest Ophthalmol Vis Sci 1981;20(suppl):8
25. Badenoch PR, Johnson AM, Christy PE, Coster DJ. A model of *Acanthamoeba* keratitis in the rat. Rev Infect Dis 1991;13(suppl 5):S445
26. Badenoch PR, Johnson AM, Christy PE, Coster DJ. Pathogenicity of *Acanthamoeba* and a *Corynebacterium* in the rat cornea. Arch Ophthalmol 1990;108:107–112
27. Larkin DFP, Easty DL. External eye flora as a nutrient source for *Acanthamoeba.* Graefes Arch Clin Exp Ophthalmol 1990;228:458–460

28. He YG, Mellan J, Pidherney M, et al. A pig model of *Acanthamoeba* keratitis. Invest Ophthalmol Vis Sci 1991;32(suppl 4):2516
29. Cote MA, Irvine JA, Rao NA, Trousdale MD. Evaluation of the rabbit as a model of *Acanthamoeba* keratitis. Rev Infect Dis 1991;13(suppl 5):S443–444
30. Osato M, Robinson N, Wilhelmus K, Jones D. Morphogenesis of *Acanthamoeba castellani.* Titration of the steroid effect. Invest Ophthalmol Vis Sci 1986;27(suppl 3):37
31. Badenoch PR. The pathogenesis of *Acanthamoeba* keratitis. Aust NZ J Ophthalmol 1991;19(1):9–20
32. Nagington J, Richards JE. Chemotherapeutic compounds and acanthamoebae from eye infections. J Clin Pathol 1976;29:648–651
33. Osato MS, Robinson NM, Wilhelmus KR, Jones DB. In vitro evaluation of antimicrobial compounds for cysticidal activity against *Acanthamoeba.* Rev Infect Dis 1991; 13(suppl 5):S431–435
34. John T, Lin J, Sahm D, Rockey JH. Effects of corticosteroids in experimental *Acanthamoeba* keratitis. Rev Infect Dis 1991;13(suppl 5):S440–442
35. Silvany R, Stewart GL, McCulley JP, et al. Lysis of *Acanthamoeba castellani* by ray neutrophils and macrophages and the chemotactic potential of parasite extracts. Invest Ophthalmol Vis Sci 1991;32(suppl 4):2450
36. O'Day DM, Ray WA, Robinson R, Heads WS. Efficacy of antifungal agents in the cornea: II. Influences of corticosteroids. Invest Ophthalmol Vis Sci 1984;25: 331–335
37. Rabinovitch T, Weissman SS, Ostter HB, et al. *Acanthamoeba* keratitis: clinical signs and analysis of outcome. Rev Infect Dis 1991;13(suppl 5):S427
38. Mitsui Y, Hanbusar J. Corneal infections after cortisone therapy. Br J Ophthalmol 1955;39:244
39. Zimmerman LE. Keratomycosis. Surv Ophthalmol 1963;8:1–25
40. O'Day DM, Ray WA, Head WS, et al. Influences of corticosteroids on experimentally induced keratomycosis. Arch Ophthalmol 1991;109:1601–1604
41. Jones BR. Principles in the management of oculomycosis. Am J Ophthalmol 1975; 79:719–751
42. Johns KJ, O'Day DM. Pharmacologic management of keratomycosis. Surv Ophthalmol 1988;33:178–188
43. Francois J, Rijsselaere M. Corticosteroids and ocular mycoses: experimental study. Ann Ophthalmol 1974;6:207–217
44. Berson EL, Kobayashi GS, Becker B, Rosenbaum C. Topical corticosteroids and fungal keratitis. Invest Ophthalmol 1967;6:512–517
45. Forster RK, Rebell G. Animal model of *Fusarium solanae* keratitis. Am J Ophthalmol 1975;79:510–515
46. Ley AP. Experimental fungus infections of the cornea. A preliminary report. Am J Ophthalmol 1956;42:59
47. Burda CD, Fisher E. The use of cortisone in establishing experimental fungal keratitis in rats. Am J Ophthalmol 1959;48:330
48. Newmark E, Ellison AC, Kaufman HE. Combined pimaricin and dexamethasone therapy for keratomycosis. Am J Ophthalmol 1971;71:718–722
49. O'Day DM, Moore TM Jr, Aronson SB. Deep fungal corneal abscess—combined corticosteroid therapy. Arch Ophthalmol 1971;86:414–419
50. Diamond RD, et al. Damage to pseudohyphal forms of *Candida albicans* by neutrophils in the absence of serum in vitro. J Clin Invest 1978;61:349
51. Fuchs E. Keratitis punctata superficialis. Wien Klin Wochenschr 1889;2:837
52. Jawetz E, Kimura SJ, Hanna L, et al. Studies on the etiology of epidemic keratoconjunctivitis. Am J Ophthalmol 1955;40(2):200
53. Jawetz F, Kimura SJ, Nicholas A, et al. New type of APC virus from epidemic keratoconjunctivitis. Science 1955;122:1190

54. Hogan MJ, Crawford NJ. Epidemic keratoconjunctivitis: with a review of the literature and a report of 125 cases. Am J Ophthalmol 1942;25:1059
55. Baum SG. Adenovirus. In: Mandell GL, Douglas RG Jr, Bennett JE, eds. Principles and practice of infectious disease, ed 3. New York: Churchill Livingstone, 1990
56. Vastine DW, Wilner BI. Adenoviridae. In: Darrell RW, ed. Viral diseases of the eye. Philadelphia: Lea & Febiger, 1985
57. Center for Disease Control. Keratoconjunctivitis due to adenovirus type 19–Canada. MMWR 1974;23:185
58. Dawson CR, Hanna L, Wood TR, Despain R. Adenovirus type 8 keratoconjunctivitis in the United States: III. Epidemiologic, clinical and microbiologic features. Am J Ophthalmol 1970;63(3):473–480
59. Laibson PR. Ocular adenoviral infections. Int Ophthalmol Clin 1984;24(2):49–64
60. Dawson CR, Hanna L, Tongi B. Adenovirus type 8 infections in the United States: IV. Observations on the pathogenesis of lesions in severe eye disease. Arch Ophthalmol 1972;87:258–268
61. Jones BR. Adenovirus infections of the eye. Trans Ophthalmol Soc UK 1962;82:621
62. Lund OE, Stephani FH. Corneal histology after epidemic keratoconjunctivitis. Arch Ophthalmol 1978;96:2085–2088
63. Tullo AB, Lucas DR, Richards S. Histology of adenovirus type 8 keratitis. Cornea 1987;6(3):234
64. Murrah WF. Epidemic keratoconjunctivitis. Ann Ophthalmol 1988;20:36–38
65. Laibson PR, Dhiri S, Oconer J, Ortolan G. Corneal infiltrates in epidemic keratoconjunctivitis. Arch Ophthalmol 1970;84:36–40
66. Trauzettel-Klosinski S, Sundmacher R, Wigand R. Die Wirkung von steroiden bei keratoconjunctivitis epidemica: Ergebnisse einer kontrollierten prospektiven Studie. Klin Monatsbl Augenheilkd 1980;176:899–906
67. Schwartz HS, Yamashiroya HM. Adenovirus types 8 and 19 infection of rabbit corneal organ culture. Invest Ophthalmol Vis Sci 1979;18:956–963
68. Gordon YJ, Romanowski E, Araullo-Cruz T. An ocular model of adenovirus type 5 infection in the New Zealand rabbit. Invest Ophthalmol Vis Sci 1992;33:574–580
69. Tsai JC, Garlinghouse G, McDonnell PJ, et al. An experimental animal model of adenovirus-induced ocular disease. The cotton rabbit. Invest Ophthalmol Vis Sci 1991;32(suppl 4):1561