

REVIEW ARTICLE

MEDICAL PROGRESS

OPHTHALMOLOGY

DON C. BIENFANG, M.D., LISA D. KELLY, M.D.,
DON H. NICHOLSON, M.D.,
AND ROBERT B. NUSSENBLATT, M.D.

THIS article reviews some currently important topics in ophthalmology, chosen either because they are of general interest or because they concern the ophthalmologic expressions of systemic diseases. We obviously cannot cover the entire field of ophthalmology, nor do we attempt to cover all the details of each complicated problem.

THE CORNEA AND CONJUNCTIVA

Inclusion Conjunctivitis

Inclusion conjunctivitis is a common, sexually transmitted disease caused by *Chlamydia trachomatis* serotypes D through K. There is an adult and a neonatal form of infection; in infants the eye is inoculated directly by cervical fluids during passage through the birth canal. Eye-to-eye transmission and indirect transmission in poorly chlorinated swimming pools have been reported but are uncommon.¹

Ophthalmia neonatorum, or inflammation of the ocular surface in the first month of life, may be caused by bacteria, fungi, viruses, or toxic insult, but chlamydial inclusion conjunctivitis is the most common cause in the United States. Eight to 20 percent of pregnant women have active cervical inclusion disease at the time of delivery, and the rate of transmission from infected mother to infant is 20 to 70 percent.² Infection becomes clinically apparent 5 to 13 days post partum, with the acute onset of unilateral or bilateral swelling of the lids, conjunctival hyperemia, and a variable amount of mucopurulent discharge. The ocular disease is usually benign and self-limited, but conjunctival scarring and corneal micropannus may occur.

It is impossible to distinguish chlamydial infection from other causes of neonatal conjunctivitis on the basis of physical examination alone, and the length of time from birth to presentation is not a reliable criterion for determining the causative organism. Therefore, all patients with ophthalmia neonatorum must have a microbiologic workup. Cell-culture isola-

tion is the diagnostic standard for chlamydial infection, but the diagnosis may also be made by identifying paranuclear inclusion bodies on Giemsa staining of conjunctival scrapings. The direct monoclonal fluorescent antibody test and the enzyme immunosorbent assay are other specific tests for chlamydia.³

Because of the association of neonatal inclusion conjunctivitis with neonatal pneumonia, simple topi-

Glossary:

Anterior chamber	The space in front of the iris and behind the cornea.
Aqueous humor	A fluid secreted by the ciliary-body processes. It provides nutrition to the lens, passes through the pupil, and leaves by the trabecular meshwork and Schlemm's canal, ultimately entering the aqueous veins.
Astigmatism	An irregularity in the shape of the eye. It is usually the cornea that has different radii of curvature.
Blepharitis	Any diffuse inflammation of the lids.
Ciliary body	A structure directly behind the iris that secretes the aqueous humor and contains the ciliary muscle that changes the shape and thus the power of the lens by tightening and relaxing the tension on the lens zonule.
Diskiform keratitis	A discrete, round area of inflammation of the corneal stroma.
Geographic ulceration	A corneal ulcer with an irregular and lobulated border.
Hyperopia (farsightedness)	An error of refraction in which the refractive surfaces of the eye — the cornea and the lens — focus the image behind the retina.
Interstitial keratitis	An inflammation of the corneal stroma, usually the deeper layers, that is usually associated with ingrowth of blood vessels.
Keratitis	Any inflammation of the cornea.
Micropannus	A vascular sheet of tissue on the cornea.
Myopia (nearsightedness)	An error of refraction in which the resting refractive surfaces of the eye — the cornea and lens — focus the image in front of the retina.
Posterior chamber	The space behind the iris and in front of the vitreous body. It is occupied by the lens, its zonules, and the aqueous humor.
Trabeculoplasty	An operation on the trabecular meshwork, which is the site of egress of the aqueous humor, for treatment of glaucoma.
Trophic ulceration	A noninfectious ulceration due to repeated damage to the epithelium and underlying Bowman's membrane.
Vitreous body	A structure composed of collagen fibrils and a gel (vitreous humor). It occupies the space behind the lens and in front of the retina.

From Brigham and Women's Hospital (D.C.B.) and the Massachusetts Eye and Ear Infirmary (L.D.K.), both in Boston; the Bascom Palmer Eye Institute, Miami (D.H.N.); and the National Eye Institute, Bethesda, Md. (R.B.N.). Address reprint requests to Dr. Bienfang at Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

cal therapy is inadequate. The recommended treatment is topical erythromycin or tetracycline ointment and systemic erythromycin (30 to 50 mg per kilogram of body weight per day for three weeks).¹ The mother and her sexual partners should also be treated for chlamydial infection.

Adult inclusion conjunctivitis (Fig. 1) is a common cause of ocular infection, although its exact incidence in the United States is unknown. Typically, the disease occurs in young, sexually active adults and may occur in conjunction with other sexually transmitted diseases. The disease presents as a bilateral follicular conjunctivitis, with hyperemic bulbar conjunctiva, mucopurulent discharge, and painless swelling of regional lymph nodes. As the disease progresses, the cornea may become involved, with epithelial keratitis, subepithelial infiltrates, and superior pannus formation. As many as 60 percent of patients have concurrent genitourinary symptoms.⁴

The recommended treatment is oral tetracycline (250 mg four times a day) or doxycycline (100 mg twice a day) for three weeks.⁵ In pregnant women, erythromycin (500 mg four times daily) should be administered orally for three weeks.^{1,2} All sexual partners must also be treated to avoid reinfection. Since chlamydia may be found in association with other sexually transmitted diseases, gynecologic evaluation is recommended.

Radial Keratotomy

Radial keratotomy (Fig. 2) is a form of refractive surgery in which deep corneal incisions are made in a bicycle-spoke pattern, causing the cornea to flatten and thereby decreasing the degree of myopia, or nearsightedness. The procedure is performed under local or topical anesthesia and consists of 4, 8, or 16 radial incisions that extend from the edge of a predetermined central optical zone toward, but not across, the limbus (the junction between the cornea and sclera). The amount of corneal flattening is a function of the number and depth of the incisions and the diameter of the central optical zone. Radial keratotomy typically has 2 to 6 diopters of hyperopic effect (a diopter is the reciprocal of the focal length of the lens) and is most appropriate for patients with myopia in this range.⁶ Radial keratotomy is not recommended for patients with any type of corneal dystrophy, ocular surface disease, or scarring.

In 1980 the National Eye Institute funded a prospective evaluation of radial keratotomy to investigate the safety and efficacy of this procedure.⁷ The study was designed as a five-year, multicenter, prospective clinical trial of radial keratotomy in 435 patients with -2 to -8 diopters of myopia. All the surgeons in the study used an eight-incision technique with an optical zone that varied with the patients' refractive errors. After four years of follow-up, 76 percent of the patients had visual acuity of 20/40 or better without glasses. Fifty-five percent of the patients were within 1 diopter of emmetropia (no refractive error), 28 per-

cent had undercorrection (residual myopia), and 17 percent had overcorrection (induced hyperopia, or farsightedness) by more than 1 diopter.⁸ Complications of radial keratotomy include diurnal fluctuation in visual acuity, glare, decrease in best corrected acuity, overcorrection and undercorrection, delayed bacterial keratitis, corneal perforation, recurrent epithelial erosion, and irregular astigmatism (inability of the lens to focus light rays to a point).^{9,10} The patients' degree of satisfaction after radial keratotomy was high: 90 percent were moderately to very satisfied with the result one year later.¹¹ Satisfaction has been noted even among patients who did not see as well postoperatively as preoperatively. This suggests that psychological factors may play a part in certain cases independently of the actual refractive outcome. Patients requesting radial keratotomy are in general well educated, are of relatively high socioeconomic status, and for occupational, avocational, or cosmetic reasons want good vision without dependence on contact lenses or spectacles.¹² Because the procedure is performed on healthy eyes and has poor predictability and unknown long-term effects, ophthalmologists have not reached consensus about its use.¹³ Physicians who offer radial keratotomy to their patients have an obligation to ensure that patients have tried spectacles or contact lenses for myopia before considering surgical intervention.

Microbial Keratitis Associated with the Use of Contact Lenses

There are more than 19 million contact-lens wearers in the United States, the majority of whom are young, healthy persons with myopia who wear lenses for cosmetic reasons. Microbial keratitis (Fig. 3) is the most serious complication of contact-lens use; it may result in permanent visual loss due to corneal scarring.¹⁴

Microbial keratitis has been found in association with all types of contact lenses, but the risk of infection appears to be higher with extended-wear soft contact lenses than with soft contact lenses that are removed daily. Poggio and coworkers have estimated the annual incidence of microbial keratitis as 20.9 per 10,000 users of extended-wear lenses and 4.1 per 10,000 users of daily-wear lenses.¹⁵ Gram-negative organisms, especially *Pseudomonas*, predominate in contact-lens-related ulcers. In a series of 64 culture-positive cases of corneal ulcers of this type, Alfonso et al. found that 78 percent were caused by gram-negative organisms (62.5 percent *Pseudomonas*).¹⁶ There have been rare reports of fungal keratitis in association with contact-lens use. In these cases the fungus has grown into the matrix of the lens.¹⁷ Contact-lens wearers are also at higher risk for *Acanthamoeba* infection. *Acanthamoeba* is a free-living protozoan and an infrequent cause of corneal infection. In an epidemiologic review, Stehr-Green et al. were able to document only 213 cases in the United States; nevertheless, 85 percent had occurred in contact-lens wearers.¹⁷ Home-

made saline solutions for contact lenses and tap water are common sources of acanthamoeba, and patients should be advised against their use.

Improper handling of contact-lens equipment and solutions is a cause of microbial contamination. Donzis et al. found that 52 percent of asymptomatic contact-lens wearers had microbial colonization of their contact-lens systems, including the lens cases and solutions.¹⁸ The risk of infection decreases with hand-washing, appropriate use of lens disinfectant, and avoidance of contamination of the contact-lens solution.¹⁴ A red, painful eye in a contact-lens wearer must be considered to result from infectious keratitis until proved otherwise. Because of the virulence of the organisms associated with contact-lens-associated infections, cultures for bacteria, fungi, and acanthamoeba must be prepared promptly, and appropriate antibiotic therapy initiated. An empirical regimen of topical cefazolin (133 mg per milliliter hourly) and tobramycin (14 mg per milliliter hourly) is often used until the offending organism and drug sensitivities are identified.

Herpes Simplex Keratitis

Herpes simplex keratitis is the most common infectious cause of corneal blindness in developed countries. There are as many as 500,000 cases annually in the United States alone.¹⁹ Ocular involvement is usually due to herpes simplex virus type 1. In neonatal infection acquired during passage through the birth canal, however, 80 percent of cases are due to herpes simplex virus type 2. The initial ocular infection with herpes simplex causes a follicular conjunctivitis, and ulcerative vesicular blepharitis may also be present. Epithelial keratitis may develop. The treatment of primary disease in the absence of corneal involvement is prophylactic antiviral ointment (discussed below) applied three times a day. If the cornea is involved, the affected corneal epithelium should be gently debrided, and antiviral drops applied for 14 to 21 days. Antibiotic drops (such as gentamicin) or ointment (erythromycin or polymyxin B-bacitracin) should be used once daily to help prevent secondary bacterial infection.

After the initial ocular exposure, the virus remains in the trigeminal ganglion and possibly the cornea without causing signs or symptoms. Various poorly understood stress-related factors can reactivate the virus, causing recurrent ocular herpetic disease. It is the recurrent form of the disease that causes corneal scarring and visual impairment. The findings in recurrent ocular herpes simplex include active viral replication causing epithelial disease, noninfectious trophic corneal ulceration, immune reaction to viral antigen in the corneal stroma, and immune reaction in the anterior chamber, with cells and flare. The treatment of infectious epithelial disease, which includes dendritic and geographic ulceration, is the same as for the initial infection with corneal involvement. In cases of trophic ulceration, since there is no active infection, treatment

consists of copious lubrication, patching, or use of a "bandage" contact lens. Diskiform keratitis (Fig. 4) and interstitial keratitis both have an immune rather than infectious cause and should be treated with the least amount of topical steroid necessary to control the disease. Antiviral and antibiotic prophylaxis is usually given with steroid treatment. Iridocyclitis (inflammation of the iris and ciliary body) is managed nonspecifically with mydriatic drugs and topical steroids if necessary.¹⁹

The topical antiviral agents available are trifluridine drops (nine times daily), idoxuridine drops (every two hours), and vidarabine ointment (five times daily). All three are very effective against herpes simplex types 1 and 2.²⁰ There is no proved benefit in adding systemic acyclovir to the treatment of herpetic keratouveitis. Oral acyclovir is effective in treating epithelial infectious disease, but so are the less expensive topical agents. The systemic administration of acyclovir has no effect on latent virus in the ganglia, and there is no clear evidence that it alters the course of stromal disease or uveitis.²¹ Injudicious systemic use of this drug may select for resistant strains of the virus.

Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus is the term given to herpes zoster occurring in the first division of the trigeminal nerve. Involvement of the ophthalmic division of the trigeminal nerve accounts for up to 56,000 of the 300,000 cases of zoster occurring annually in the United States and is associated with severe, chronic ocular complications as well as postherpetic neuralgia.²²

Ophthalmic manifestations of herpes zoster ophthalmicus include cicatricial lid retraction, paralytic ptosis, conjunctivitis, keratitis, scleritis, iridocyclitis, retinitis (hemorrhagic vasculitis), choroiditis, optic neuritis, abnormal pupillary light responses, glaucoma, and palsies of the third, fourth, and sixth cranial nerves. Corneal disease is the most common complication and is present in 66 percent of cases.²² There is a wide range of corneal findings, such as epithelial abnormalities (including dendritic ulceration), edema of the corneal stroma, white-cell infiltration of the stroma, and loss of corneal sensation, all of which may resemble ocular herpes simplex clinically. There is no evidence that commercially available topical antiviral agents are beneficial in the treatment of herpes zoster. Topical acyclovir has demonstrated benefit but is not available commercially in the United States. Topical steroids are useful for the treatment of associated immunologic reactions in the corneal stroma,²³ but the role of systemic steroids is less clear. Postherpetic neuralgia is thought to result from perineural scarring after the initial inflammation. Systemic steroid therapy may prevent scarring. The efficacy of steroids in the prevention of postherpetic neuralgia is uncertain. Systemic steroids probably are not indicated for children and young adults, who are at low

risk for postherpetic neuralgia, or for immunocompromised patients, who are at risk for viral dissemination.

Cobo et al.²⁴ have shown that oral acyclovir, if given within 72 hours after skin eruption, decreases the duration of viral shedding and the incidence and severity of both keratitis and uveitis; however, it has no effect on the incidence of postherpetic neuralgia. The recommended dose for immunocompetent patients is 600 mg five times a day for 10 days, and for immunocompromised patients, 1500 mg per square meter of body-surface area per day for 7 days.¹ The Food and Drug Administration is currently reviewing the use of acyclovir in the treatment of herpes zoster ophthalmicus. Since the degree of toxicity associated with such therapy is low and the benefits are observed only when treatment is initiated within the first 72 hours, it is advisable to proceed with early treatment when herpes zoster is suspected.

GLAUCOMA

Almost all patients with glaucoma have an obstruction to the normal egress of aqueous humor from the eye. In the most common form — open-angle glaucoma — the drainage channels, called the trabecular meshwork, appear to be normal and unobstructed when examined grossly. In the other common variety — angle-closure glaucoma — the iris itself or scars from inflammatory disease or injury appear to cover the trabecular meshwork. Unfortunately, the most common symptom of glaucoma is severe visual loss. Only very high intraocular pressure, as seen with acute angle-closure glaucoma, causes pain.

Automated Perimetry

Although the diagnosis of glaucoma is based on the findings of elevated intraocular pressure, progressive changes in the optic-nerve head, and alteration of the anterior-segment anatomy, the goal of therapy is the prevention of visual-field loss. To that end perimetric examination of the visual field is a cornerstone of the evaluation of therapy. Automated perimetry sets new levels of standardization, allows exquisite quantitation, and can present random stimuli at variable intensities,²⁵ since it is clear that both long-term and short-term variation in visual-field loss are common in glaucoma.²⁶ However, this new technique is limited by its cost and by the patient's ability to cooperate.

Anatomy of the Optic-Nerve Head

The sight-threatening damage of glaucoma occurs at the optic-nerve head through the enlargement of the optic cup (Fig. 5). Initially, there is a vertical elongation of the cup; later, the nerve fibers from the macula on the temporal portion of the cup are lost, leading to a loss of acuity. A continuing area of attention is the measurement of the remaining neuroretinal rim.²⁷

It is not clear how the axon loss that results in the enlargement of the cup and the loss of visual field occurs.²⁸⁻³⁰ Is it a direct effect of the elevated pressure

on the nerve, or is there an ischemic intermediary?³¹ In this regard it is of interest that ischemia of the optic-nerve head, such as that seen with anterior ischemic optic neuropathy unrelated to elevated intraocular pressure, can result in enlargement of the cup. A characteristic of an acute infarction of the optic-nerve head is disk hemorrhage. Disk hemorrhages have also proved to be an unfavorable prognostic sign in glaucoma.^{32,33}

Drug Therapy

Ophthalmic beta-blockers, such as timolol maleate, levobunolol, and betaxolol, are popular with patients and physicians because of their ease of use and absence of local side effects. They seem to work by suppressing the production of aqueous humor in the eye, but there is enough systemic absorption to cause a crossover effect on the opposite eye,³⁴ the lung (bronchospasm),^{35,36} the central nervous system (depression),³⁷ and the heart (bradycardia).³⁸ Thus, it is important to use the lowest effective concentration.³⁹ Some but not all of these systemic side effects may be avoided with the cardioselective β_1 -adrenergic blocker betaxolol, but in some patients betaxolol seems to have a limited effect on the intraocular pressure.⁴⁰ The adrenergic receptors of the eye seem to be mainly of the β_2 subtype. It is important for those dispensing systemic beta-blockers to remember that they may lower elevated intraocular pressure.

Since all glaucoma medications used topically produce a systemic blood level, their use during pregnancy and lactation must be considered carefully. In pregnant patients it may be necessary to stop drug therapy and use argon-laser trabeculoplasty earlier than usual. Systemic inhibitors of carbonate dehydratase, such as acetazolamide, dichlorphenamide, ethoxzolamide, and methazolamide, are powerful medications in the control of elevated intraocular pressure but almost always produce side effects.^{41,42} The most common of these are fatigue, weight loss, a sensory neuropathy, and calcium phosphate nephrolithiasis. There is no controlled study showing that reversal of the metabolic acidosis with sodium bicarbonate is helpful. A topical carbonate dehydratase inhibitor will be welcome.⁴³

Neodymium:Yttrium-Aluminum-Garnet Laser

The laser has enabled ophthalmologists to use an optical device for surgery on an optical organ. The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser creates a microexplosion at its point of focus. It is commonly used to make an opening in an opacified lens capsule after cataract surgery. It can be used alone or in combination with the argon laser for iridectomy.⁴⁴⁻⁴⁷ The Nd:YAG laser can also be used to reopen fistulas created by glaucoma surgery.^{48,49}

Argon Laser

In contrast to the Nd:YAG laser, the argon laser uses thermal energy to create a lesion. Burns placed

next to or on the trabecular meshwork improve the drainage of aqueous humor from the eye. This has become the therapeutic step most commonly used after medical management for patients with primary open-angle glaucoma.⁵⁰ In all cases, however, the decision on the order of therapy (medication, laser, and surgery) is based on clinical experience and the individual features of the case. The mechanism by which laser trabeculoplasty lowers intraocular pressure is not clear. The trabecular meshwork may be stretched open by neighboring scar contraction, or a metabolic change may be induced in the meshwork.⁵¹⁻⁵⁴ Argon-laser therapy is so remarkably free of complications that there are some who advocate it as first treatment. Late failures are common, however, especially among blacks.⁵⁵

Filtration Surgery

When glaucoma progresses despite laser therapy and the maximal tolerated drug therapy, the creation of a surgical fistula connecting the anterior chamber to the subconjunctival space should be considered. Complications from this surgery, especially cataracts, are common enough to limit its use to patients who have not responded to other forms of therapy.

Destruction of the Ciliary Body

Cryotherapy to the ciliary body has been used in the past for patients who have severe glaucoma, often those with little functional vision. Yet the idea of reducing the production of aqueous humor by the controlled destruction of part of the ciliary body is appealing. The Nd:YAG laser can be used through the sclera or the pupil, and ultrasonography can be used through the sclera to accomplish this.⁵⁶⁻⁵⁸

CATARACTS

Causes

The cause of most cataracts remains unclear. Near-ultraviolet radiation present in sunlight and in commonly used artificial light has recently received attention as a contributory influence.⁵⁹ Exposure to x-rays can cause cataracts. The first opacities appear along the posterior cortical suture lines within hours to months after exposure. Higher doses of radiation cause the changes to appear more rapidly. As little as 2 Gy (200 rad) in a single dose or 5.5 Gy (550 rad) in divided doses is sufficient. Thus, the lens tolerates a series of low doses better than a single high dose.⁶⁰

Convincing evidence of the association between the use of systemic corticosteroids and posterior subcapsular cataracts came from the appearance of these cataracts in children treated with steroids. Such cataracts appear to develop more slowly in adults, but it has been hard to calculate a dosage and exposure pattern because there seems to be a wide range of susceptibility. These cataracts are difficult to induce in animals.⁶¹ They will not regress after cessation of the steroid therapy, but they may cease to progress. The

patient notices glare and decreased vision under conditions that induce miosis, such as exposure to bright lights or reading. The physician can see this type best with a +10 lens in the ophthalmoscope, in which case it appears as a granular patch against the red reflex (Fig. 6).

The hydroxymethylglutaryl-coenzyme A reductase inhibitor lovastatin depresses cholesterol synthesis, which occurs chiefly in the liver. In 10 percent of dogs, but not in rats, mice, or monkeys, exposed to 60 times the usual dose in humans, opacities were noted at the posterior suture lines after three to seven weeks of treatment.⁶² The cataracts were preceded by liver damage. However, after 2.5 years of lovastatin therapy, the increase in lenticular opacities in 744 patients matched that expected as a result of aging.⁶³

Preventive Therapy

Cataracts may develop in young patients with diabetes who have uncontrolled glucose levels. The excess glucose is converted by aldose reductase to sorbitol, which causes osmotic stress on the lens.⁶⁴ Because this stress is very low in humans, sorbinil, an aldose reductase inhibitor, is unlikely to prevent this problem.⁶⁵ Patients with rheumatoid arthritis have a reduced incidence of lens opacities,⁶⁶ but this effect is not due to the aspirin they take.⁶⁷

Surgery

Modern cataract surgery uses an extracapsular method. The entire posterior capsule of the lens and some of the peripheral anterior capsule with the supporting zonules of the lens capsule are left behind. Some surgeons prefer to emulsify and aspirate the nucleus of the lens, and others remove the nucleus intact. The latter technique requires a larger incision than the former. In almost all cases an intraocular lens is implanted on or within the capsule left behind. In 90 percent of patients, vision improves by two lines or more on a Snellen chart; improved mental status and timed performance of manual tasks also improve.⁶⁸ Extracapsular surgery has permitted the use of better intraocular lenses and has resulted in a decrease in retinal complications as compared with intracapsular surgery, in which the capsule and lens are completely removed.

There have been some new problems, however. Extracapsular surgery with placement of an intraocular lens in the posterior chamber has more inherent variables than the largely outdated intracapsular operation. Thus, it is a harder technique to learn. The preservation of the posterior capsule, which serves both as support for the implant and as a barrier to the vitreous, creates a risk of late opacification and thus the necessity for opening this membrane, usually with an Nd:YAG laser. Cataract surgery must be done under the magnification of an operating microscope. The intense light directed into the dilated pupil may damage the retina.⁶⁹ The major factors in the production of photic retinal damage are the duration of exposure and the intensity of the light. Recent

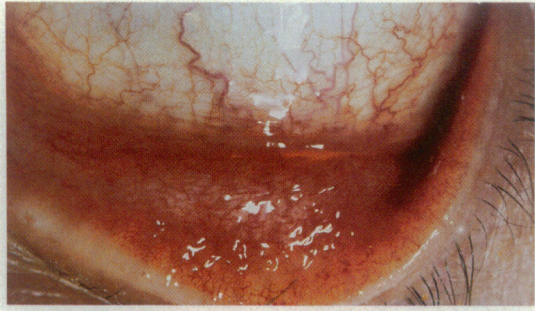


Figure 1. Inferior Tarsal Conjunctiva in Chlamydial Follicular Conjunctivitis.

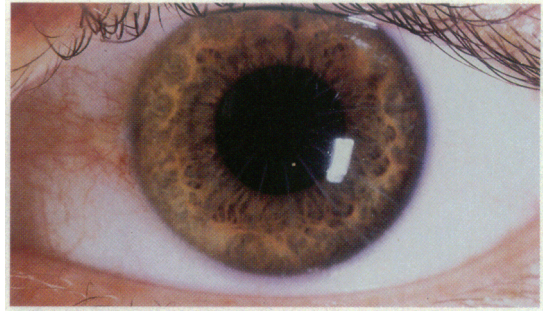


Figure 2. Radial-Keratotomy Incisions.

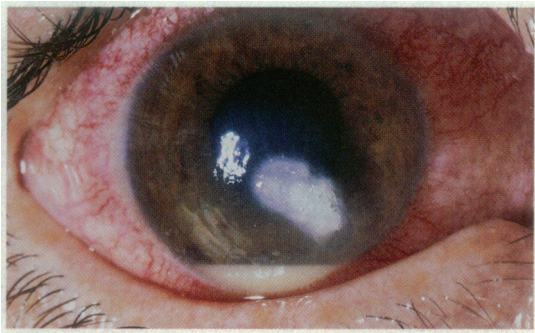


Figure 3. Corneal Ulcer with Hypopyon.

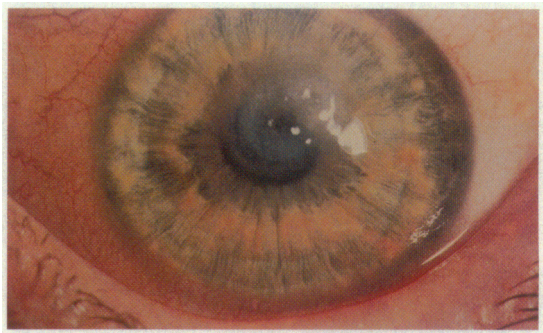


Figure 4. Diskiform Keratitis in Herpes Simplex.



Figure 5. A Disk Damaged by Glaucoma.
Note that the superior vessels dip into an extension of the normal cup superotemporally.

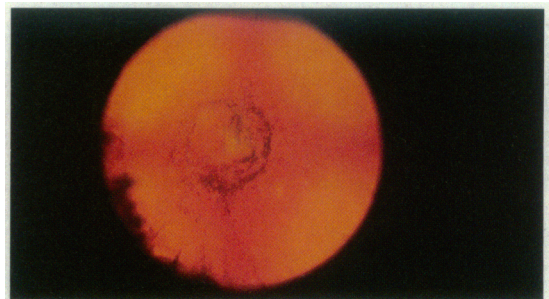


Figure 6. Posterior Subcapsular Cataract against the Red Reflex.

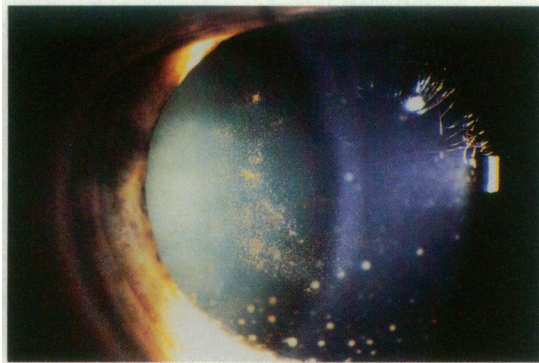


Figure 7. Anterior Segment of an Eye with the Manifestations of Sarcoidosis.

Multiple "mutton-fat" keratic precipitates can be seen on the endothelial surface of the eye.

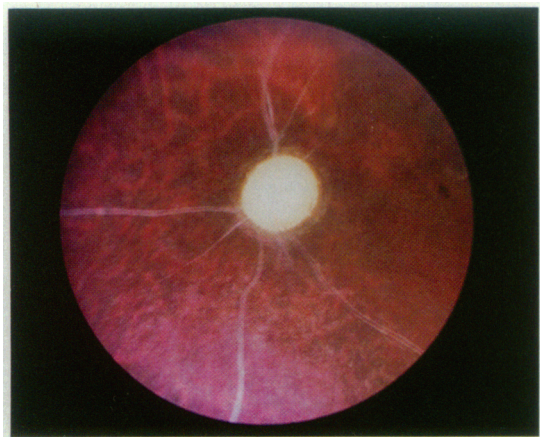


Figure 8. Fundus of the Eye of a Patient with a Long History of Intraocular Inflammatory Disease Due to Behçet's Syndrome. There is a pale disk, with attenuated, whitened vessels. The retina is thinned, and the mottled pigment seen to the left of center represents clumps of retinal pigmented epithelial cells, a response often seen after severe ocular inflammation affecting the posterior segment of the eye.



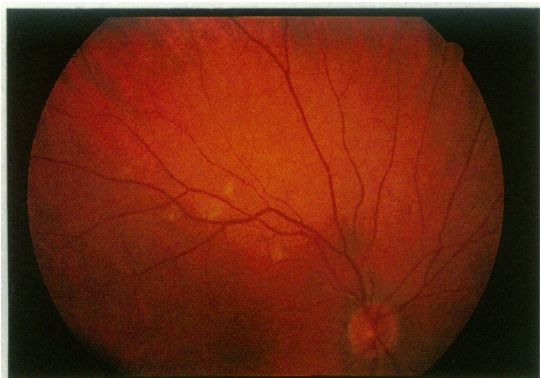
Figure 9. Fundus of an Eye with Birdshot Retinochoroidopathy. This disease, associated with HLA-A29, typically causes multiple deep oval or circular cream-colored lesions in the retina that are associated with a concomitant uveitis, as well as retinal vascular changes.



Figure 10. Nonproliferative Diabetic Retinopathy with Macular Edema. Note the hard exudates superior and temporal to the fovea.



Figure 11. Proliferative Diabetic Retinopathy. There is neovascularization above the macula and on the nasal and inferior sides of the optic disk. A fresh hemorrhage into the vitreous cavity lies parallel to the inferotemporal vascular arcade.



A



B

Figure 12. Retinal Lesions in AIDS.

Cotton-wool spots can be seen in Panel A adjacent to the fovea and vascular arcades. Panel B shows the focus of cytomegalovirus retinitis in the same patient six months later (vision, 20/25). There is the characteristic confluent white zone of retinal necrosis, with scattered flame-shaped hemorrhages on the surface and white granular lesions at peripheral borders.

data suggest that the high concentration of oxygen in the inspired air during surgery may aggravate the damage.⁷⁰ Viscous materials are now routinely used at the time of surgery to separate tissue planes and protect the cornea when the eye is opened. In some patients in whom viscous material is used there is a short-term increase in intraocular pressure on the day after surgery. The pressure may be high enough to cause symptoms reminiscent of acute angle-closure glaucoma.⁷¹ Fortunately, this increase rarely causes permanent complications. Modifications have already been made in the implanted lens to allow it to be folded and then inserted through a smaller incision. Although this technique offers all the advantages inherent in any operation with a smaller incision, it is unlikely that the patient's vision will be any better than if a larger incision had been used. The future holds the promise of implants that are injectable and perhaps even flexible enough to allow true accommodation.

UVEITIS

Uveitis is a general term denoting any type of intraocular inflammatory disease and in no way indicates the cause of the inflammation. It is the cause of approximately 10 percent of the cases of legal blindness in the United States.⁷² The disease can be due to infectious agents, such as toxoplasma or cytomegalovirus, or can be endogenous, possibly caused by autoimmune mechanisms, as is the case in Behçet's syndrome and the Vogt-Koyanagi-Harada syndrome. Uveitis can be readily observed by ophthalmologists, and the anatomical location and severity of the uveitis can be recorded. The Intermediate Uveitis Study Group⁷³ has recently suggested the use of "anterior," "intermediate," and "posterior" uveitis to indicate the location of the inflammatory response. This determination is made on the basis of the clinical examination. A diagnosis of anterior uveitis indicates that the inflammatory activity is centered in the anterior and posterior chamber of the eye, whereas a diagnosis of intermediate uveitis indicates that the most intense inflammation is noted on examination to be in the vitreous. A diagnosis of posterior uveitis indicates that the inflammation is located in the retina or choroid. In addition, the inflammatory response in the anterior segment of the eye can be categorized as being granulomatous or nongranulomatous, depending on the type of keratic precipitate seen on slit-lamp examination (Fig. 7). Granulomatous keratic precipitates are the larger of the two, have a "mutton-fat" appearance, and are largely composed of histiocytes and epithelioid cells. Nongranulomatous keratic precipitates are made up of lymphocytes and plasma cells. The diagnosis of uveitis is based primarily on clinical impressions. In addition to the potential risk to vision posed by the ongoing inflammatory response, sight-threatening sequelae of the inflammation include corneal decompensation, glaucoma, cataracts, vitreal opacities, vitreal hemor-

rhages, retinal and subretinal neovascularization, optic atrophy, and cystoid macular edema.

HLA and Animal Models

The underlying mechanisms leading to uveitis, particularly of the endogenous type, have yet to be fully delineated. HLA typing of patients with uveitis has demonstrated that some clinical entities have strong associations with certain antigens determined by the major histocompatibility complex. Perhaps the HLA association most familiar to nonophthalmologists is that of HLA-B27 with ankylosing spondylitis, a disease with anterior uveitis as part of its clinical presentation (relative risk among whites, 100).⁷⁴

Nongranulomatous anterior uveitis in whites without rheumatologic disease is also associated with HLA-B27, though less frequently (relative risk, 23.01).⁷⁵ However, other ocular inflammatory disorders have other HLA associations. Behçet's syndrome (Fig. 8), a disorder with severe, explosive episodes of retinal vasoocclusive inflammation as an ocular manifestation, has been associated in the Japanese with HLA-B51 (relative risk, 5.75).⁷⁶ More recently, restriction-fragment-linkage analysis with an HLA-DQ probe has found an association between a 1.9-kilobase fragment and severe, sight-threatening Behçet's syndrome.⁷⁷ Japanese patients with the Vogt-Koyanagi-Harada syndrome, characterized by severe anterior and posterior uveitis, hearing loss, leukocytosis of the central nervous system, alopecia, and vitiligo, have a 100 percent incidence of MT-3 (HLA-DR53)⁷⁸; however, the prevalence of this antigen was not significantly increased in American patients, although the antigens HLA-DR4/DQw3 were.⁷⁹ A purely ocular condition — birdshot retinochoroidopathy (Fig. 9) — a disease whose damage is centered in the posterior segment of the globe, is strongly associated with HLA-A29 in whites (relative risk, 50).^{80,81}

Further clarification of the mechanisms leading to endogenous intraocular inflammatory disorders has been aided immensely by the identification of several uveitogenic antigens found in the eye.⁸² To date, two retinal antigens, the retinal S-antigen and the interphotoreceptor binding protein, have proved to be most efficient in inducing uveitis when injected into lower mammals and nonhuman primates. The diseases induced in animals by immunization with these antigens have many of the characteristics seen in humans with uveitis, including not only the active inflammatory component, but many of the sequelae, such as cataracts and subretinal neovascularization.⁸³ Dissection of an animal model has demonstrated a central role for T-cell participation.⁸⁴ Lymphocytes from some patients with uveitis who have retinal involvement demonstrate *in vitro* proliferative responses to the S-antigen or other retinal antigens,⁸⁵ and this phenomenon is observed in essentially all patients with birdshot retinochoroidopathy who are tested.^{80,86} Fragments of these molecules that are uveitogenic in

lower mammals have been identified,^{87,88} but the fragments to which patients with uveitis may respond still need to be identified.

Association with Systemic Disease

Many uveitic conditions are local expressions of systemic disease. The ophthalmologist's observations can help immeasurably in attempts to differentiate between overlapping conditions, although the same can be stated for internists. The ocular presentation of the various rheumatologic disorders can be quite distinctive. Although the anterior uveitis associated with ankylosing spondylitis may affect both eyes, it initially presents as an episodic, nongranulomatous inflammation that is unilateral and painful. The anterior uveitis associated with pauciarticular arthritis often has a chronic, insidious course.⁸⁹ The ocular manifestation of most concern in Behçet's syndrome is an explosive, episodic, vasoocclusive retinitis that is usually bilateral.⁹⁰

Recent Approaches to Intraocular Inflammatory Therapy

Although therapy at one time centered around antimicrobial agents, steroids — administered topically, periocularly, or systemically — have become the basis for therapy in most forms of endogenous uveitis. More recent strategies for immunosuppression have capitalized on observations from animal studies that T-cell mediation of the disease process appears to be an important mechanism and that cyclosporine, an agent mediating most of its effect through the T cell, prevents the expression of experimental autoimmune uveitis.⁹¹ This agent has been used in the treatment of severe, sight-threatening endogenous intermediate and posterior uveitis, with favorable clinical results.⁹² It is particularly efficacious in treating the ocular manifestations of Behçet's syndrome.⁹³ These initial observations are supported by two randomized, masked studies.^{94,95} Although nephrotoxicity remains a constant concern,⁸⁰ recent reports have suggested that a lower starting dose of cyclosporine may decrease the incidence of this complication. The National Eye Institute is currently evaluating the effectiveness of systemic cyclosporin G in the treatment of uveitis, an agent known to be almost as effective as cyclosporine in the experimental model of autoimmune uveitis⁹⁶ and thought to be less nephrotoxic.⁹⁷

RETINA

Diabetic Retinopathy

Diabetic retinopathy⁹⁸⁻¹⁰⁰ occurs in two forms — nonproliferative (Fig. 10) and proliferative (Fig. 11). Each threatens vision in a different manner, and both may occur in the same eye. The ophthalmoscopic hallmark of nonproliferative diabetic retinopathy is the microaneurysm. Leakage from capillaries in the vicinity of microaneurysms produces retinal edema (thickening and hard exudates). Central vision (that used for reading or driving) is impaired when retinal edema

involves the macula. Both focal and diffuse forms of macular edema can be treated successfully with the laser. "Success," however, is defined as the stabilization of visual acuity, with a reduction in the rate of subsequent visual loss. Since substantial improvement in vision after treatment is unusual, early detection and appropriate treatment are essential.

Proliferative diabetic retinopathy occurs when newly formed vessels extend across the anterior surface of the retina or optic disk and, together with supporting fibroglial tissue, proliferate between the vitreous and the retina. Visual loss due to proliferative diabetic retinopathy usually begins with hemorrhage into the vitreous cavity. Laser treatment (panretinal photocoagulation) induces regression of new vessels and reduces the frequency of severe loss of vision by 50 percent in patients at high risk. If vitreous blood does not clear sufficiently to permit laser treatment or if fibroglial proliferation detaches the retina, surgical vitrectomy can often restore useful vision.

Early, treatable stages of diabetic retinopathy may not cause visual symptoms, so careful examination of asymptomatic patients with dilated pupils by well-trained ophthalmoscopists must be included in the primary care of all patients with diabetes. The National Diabetes Advisory Board recommends ophthalmologic referral for all patients with Type II diabetes and for patients with Type I who have had diabetes for more than five years.⁹⁸ Proliferative diabetic retinopathy is especially likely to appear suddenly and progress rapidly in patients with Type I diabetes who are between the ages of 17 and 25 years, during the last trimester of pregnancy, and when diabetic nephropathy becomes evident clinically. Asymptomatic patients in any of these three categories who have never been examined by an ophthalmologist should be referred for examination.

Retinopathy of Prematurity

Extreme prematurity, perhaps coupled with transient exposure of the premature retina to high concentrations of oxygen, triggers a proliferation of abnormal peripheral retinal vessels and fibroglial tissue that in some cases rapidly progresses to traction retinal detachment and total blindness.¹⁰¹ First recognized by the end-stage appearance (retrolental fibroplasia), the spectrum of retinal alterations in low-birth-weight infants is now understood to include at the milder end minimal vascular proliferation that regresses spontaneously and leaves the infant with normal visual potential. Careful screening with indirect ophthalmoscopy of premature neonates can identify those at high risk at an early stage. A nationwide collaborative clinical trial has recently proved that retinal cryotherapy in premature infants at high risk reduces the risk of progression by about half.¹⁰² Vitamin E (α -tocopherol) therapy, in vogue a few years ago, has generally been abandoned. Surgical reattachment of the retina in older infants with more ad-

vanced disease is possible, but the degree of visual recovery is often disappointing.

Age-Related Macular Degeneration

Visual loss due to age-related macular degeneration has been the subject of intensive clinical investigation and increasing public awareness in recent years.¹⁰³ Degenerative changes in the pigmentary epithelium of the retina may be related in some way to exposure to sunlight.¹⁰⁴ After the age of 50, yellowish punctate excrescences (drusen) appear in the fundi of predisposed persons as the ophthalmoscopic substrate of age-related macular degeneration. Daily self-testing of central vision and periodic ophthalmologic examination, with fluorescein angiography when indicated, are the screening methods used to identify patients at risk who will benefit from laser treatment. This is the only form of treatment proved thus far to delay the loss of central vision, and it is useful in only a small fraction of patients with visual loss due to age-related macular degeneration. Several vitamin and mineral nutritional supplements have been suggested for prophylaxis, and a preliminary clinical trial of high doses of oral zinc showed a limited treatment benefit.¹⁰⁵ Whether zinc therapy has any role in prophylaxis awaits the outcome of the large-scale, long-term, strictly controlled collaborative studies that are now under way. Because peripheral vision remains intact, patients with advanced macular degeneration can usually care for themselves and walk unaided. Various types of magnifying lenses help them derive optimal benefit from whatever central vision remains.

The Acquired Immunodeficiency Syndrome

Cotton-wool spots (Fig. 12A) and hemorrhages, the most frequent ocular manifestations of infection with the human immunodeficiency virus (HIV), are observed in more than half the patients with established acquired immunodeficiency syndrome (AIDS).¹⁰⁶ They correlate with a low ratio of T helper cells to suppressor cells and may thus be an important clinical sign of the severity of HIV-related disease.¹⁰⁷ The most devastating ocular complication of AIDS — cytomegalovirus retinitis — was observed in 29 percent of 157 patients with AIDS and was the initial diagnostic opportunistic infection in 3 percent.¹⁰⁸ Primary physicians caring for patients with AIDS should be familiar with the ophthalmoscopic appearance of cytomegalovirus retinitis (Fig. 12B), since infections originating in the retinal periphery may not cause symptomatic loss of vision initially.¹⁰⁹ Areas of extensive confluent necrosis are white or yellow, with frequent splashes of flame-shaped hemorrhage. At the margin of the confluent white zone of retinal necrosis are white, granular, punctate lesions. The inexorable progression of cytomegalovirus retinitis can be arrested by intravenous ganciclovir therapy in more than half of infected patients.¹¹⁰ One problem has been the

combined use of ganciclovir and zidovudine, since both are toxic to bone marrow. Preliminary reports suggest that foscarnet¹¹¹ and intravitreal ganciclovir¹¹² may also suppress cytomegalovirus retinitis. Any of these antiviral regimens must be continued indefinitely, since the drugs are virostatic and recurrence regularly follows the suspension of drug therapy. Other forms of infectious retinitis that occur in patients with AIDS and may mimic infections with cytomegalovirus are syphilis,¹¹³ toxoplasmosis,¹¹⁴ and among intravenous drug abusers, endogenous bacterial or fungal endophthalmitis. When active cytomegalovirus infection resolves after treatment, the thin atrophic retina tears easily, causing retinal detachment. As the AIDS epidemic continues, the syndrome is likely to be manifested in the eye in new and unexpected ways. In patients who are not immunosuppressed, we have recently recognized a similar pattern of intense retinitis and vitritis followed by tearing and detachment of the retina — the syndrome of acute retinal necrosis. Herpesviruses have been isolated or identified immunohistochemically from some of these patients.¹¹⁵ Unlike cytomegalovirus retinitis, acute retinal necrosis improves with systemic acyclovir therapy.

We are indebted to Deborah Pavan Langston, M.D., Massachusetts Eye and Ear Infirmary, for her expert assistance in the preparation of part of this manuscript, and to Drs. Harry W. Flynn, Jr., and Elaine Chuang for referral of their patients.

REFERENCES

1. Tabbara KF. Chlamydial conjunctivitis. In: Tabbara KF, Hyndiuk RA, eds. *Infections of the eye*. Boston: Little, Brown, 1986:431-4.
2. Fedukowicz HB, Stenson S. External infections of the eye: bacterial, viral, mycotic with noninfectious and immunologic diseases. 3rd ed. Norwalk, Conn.: Appleton-Century-Crofts, 1985:88-90.
3. Sheppard JD, Kowalski RP, Meyer MP, Amortegui AJ, Slifkin M. Immunodiagnosis of adult chlamydial conjunctivitis. *Ophthalmology* 1988; 95:434-42.
4. Stenson S. Adult inclusion conjunctivitis: clinical characteristics and corneal changes. *Arch Ophthalmol* 1981; 99:605-8.
5. Wilson FM II. Varicella and herpes zoster ophthalmic. In: Tabbara KF, Hyndiuk RA, eds. *Infections of the eye*. Boston: Little, Brown, 1986:369-86.
6. Arrowsmith PN, Sanders DR, Marks RG. Visual, refractive, and keratometric results of radial keratotomy. *Arch Ophthalmol* 1983; 101:873-81.
7. Waring GO III, Lynn MJ, Gelender H, et al. Results of the Prospective Evaluation of Radial Keratotomy (PERK) Study one year after surgery. *Ophthalmology* 1985; 92:177-98, 307.
8. Waring GO III, Lynn MJ, Fielding B, et al. Results of the Prospective Evaluation Radial Keratotomy (PERK) Study 4 years after surgery for myopia. *JAMA* 1990; 263:1083-91.
9. Waring GO III, Lynn MJ, Culbertson W, et al. Three-year results of the Prospective Evaluation of Radial Keratotomy (PERK) Study. *Ophthalmology* 1987; 94:1339-54.
10. Shivitz IA, Arrowsmith PN. Delayed keratitis after radial keratotomy. *Arch Ophthalmol* 1986; 104:1153-5.
11. Bourque LB, Cosand BB, Drews C, Waring GO III, Lynn M, Cartwright C. Reported satisfaction, fluctuation of vision, and glare among patients one year after surgery in the Prospective Evaluation of Radial Keratotomy (PERK) Study. *Arch Ophthalmol* 1986; 104:356-63.
12. Bourque LB, Rubenstein R, Cosand B, et al. Psychosocial characteristics of candidates for the Prospective Evaluation of Radial Keratotomy (PERK) Study. *Arch Ophthalmol* 1984; 102:1187-92.
13. Diagnostic and therapeutic technology assessment (DATTA): radial keratotomy for simple myopia. *JAMA* 1988; 260:264-7.
14. Driebe WT Jr. Contact lenses. *Ophthalmology* 1987; 94:1355-9.
15. Poggio EC, Glynn RJ, Schein OD, et al. The incidence of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. *N Engl J Med* 1989; 321:779-83.

16. Alfonso E, Mandelbaum S, Fox MJ, Forster RK. Ulcerative keratitis associated with contact lens wear. *Am J Ophthalmol* 1986; 101:429-33.
17. Stehr-Green JK, Bailey TM, Visvesvara GS. The epidemiology of acanthamoeba keratitis in the United States. *Am J Ophthalmol* 1989; 107:331-6.
18. Donzis PB, Mondino BJ, Weissman BA, Bruckner DA. Microbial contamination of contact lens care systems. *Am J Ophthalmol* 1987; 104:325-33.
19. Pavan-Langston D. Viral diseases: herpetic infections. In: Smolin G, Thoft RA, eds. *The cornea: scientific foundations and clinical practices*. 2nd ed. Boston: Little, Brown, 1987:240-66.
20. Kaufman HE, Centifanto-Fitzgerald YM, Varnell ED. Herpes simplex keratitis. *Ophthalmology* 1983; 90:700-6.
21. Schwab IR. Oral acyclovir in the management of herpes simplex ocular infections. *Ophthalmology* 1988; 95:423-30.
22. Womack LW, Liesegang TJ. Complications of herpes zoster ophthalmicus. *Arch Ophthalmol* 1983; 101:42-5.
23. Scheie HG. Herpes zoster ophthalmicus. *Trans Ophthalmol Soc U K* 1970; 90:899-930.
24. Cobo LM, Foulks GN, Liesegang T, et al. Oral acyclovir in the treatment of acute herpes zoster ophthalmicus. *Ophthalmology* 1986; 93:763-70.
25. Enger C, Sommer A. Recognizing glaucomatous field loss with the Humphrey STATPAC. *Arch Ophthalmol* 1987; 105:1355-7.
26. Flammer J, Drance SM, Zulauf M. Differential light threshold: short- and long-term fluctuation in patients with glaucoma, normal controls, and patients with suspected glaucoma. *Arch Ophthalmol* 1984; 102:704-6.
27. Airaksinen PJ, Drance SM, Schulzer M. Neuroretinal rim area in early glaucoma. *Am J Ophthalmol* 1985; 99:1-4.
28. Chandler PA, Grant WM. *Glaucoma*. 2nd ed. Philadelphia: Lea & Febiger, 1979:66.
29. Grant WM, Burke JF Jr. Why do some people go blind from glaucoma? *Ophthalmology* 1982; 89:991-8.
30. Quigley HA, Addicks EM. Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. *Arch Ophthalmol* 1981; 99:137-43.
31. Minckler DS, Spaeth GL. Optic nerve damage in glaucoma. *Surv Ophthalmol* 1981; 26:128-48.
32. Diehl DL, Quigley HA, Miller NR, Sommer A, Burney EN. Prevalence and significance of optic disk hemorrhage in a longitudinal study of glaucoma. *Arch Ophthalmol* 1990; 108:545-50.
33. Drance SM, Fairclough M, Butler DM, Kottler MS. The importance of disc hemorrhage in the prognosis of chronic open angle glaucoma. *Arch Ophthalmol* 1977; 95:226-8.
34. Kwitko GM, Shin DH, Ahn BH, Hong YJ. Bilateral effects of long-term monocular timolol therapy. *Am J Ophthalmol* 1987; 104:591-4.
35. Weinreb RN, van Buskirk EM, Cherniak R, Drake MM. Long-term betaxolol therapy in glaucoma patients with pulmonary disease. *Am J Ophthalmol* 1988; 106:162-7.
36. Harris LS, Greenstein SH, Bloom AF. Respiratory difficulties with betaxolol. *Am J Ophthalmol* 1986; 102:274-5.
37. Lynch MG, Whitson JT, Brown RH, Nguyen H, Drake MM. Topical beta-blocker therapy and central nervous system side effects: a preliminary study comparing betaxolol and timolol. *Arch Ophthalmol* 1988; 106:908-11.
38. Novack GD. Ophthalmic beta-blockers since timolol. *Surv Ophthalmol* 1987; 31:307-27.
39. Boozman FW III, Carriker R, Foerster R, Allen RC, Novack GD, Batoosingh AL. Long-term evaluation of 0.25% levobunolol and timolol for therapy for elevated intraocular pressure. *Arch Ophthalmol* 1988; 106:614-8.
40. Allen RC, Hertzmark E, Walker AM, Epstein DL. A double-masked comparison of betaxolol vs timolol in the treatment of open-angle glaucoma. *Am J Ophthalmol* 1986; 101:535-41.
41. Daniels BS, Ferris TF. The use of diuretics in nonedematous disorders. *Semin Nephrol* 1988; 8:342-53.
42. Higginbotham EJ. Topical carbonic anhydrase inhibitors. *Ophthalmol Clin North Am* 1989; 2:113-30.
43. Higginbotham EJ, Kass MA, Lippa EA, Batenhorst RL, Panebianco DL, Wilensky JT. MK-927: a topical carbonic anhydrase inhibitor. Dose response and duration of action. *Arch Ophthalmol* 1990; 108:65-8.
44. Abraham RK, Miller GL. Outpatient argon laser iridectomy for angle closure glaucoma: a two-year study. *Trans Am Acad Ophthalmol Otolaryngol* 1975; 79:OP-529-OP-538.
45. Bonner RF, Meyers SM, Gaasterland DE. Threshold for retinal damage associated with the use of high-power neodymium-YAG lasers in the vitreous. *Am J Ophthalmol* 1983; 96:153-9.
46. Robin AL, Pollack IP, Quigley HA, D'Anna S, Addicks EM. Histologic studies of angle structures after laser iridotomy in primates. *Arch Ophthalmol* 1982; 100:1665-70.
47. Pollack IP. Laser iridotomy: current concepts in technique and safety. *Int Ophthalmol Clin* 1981; 21:137-44.
48. Praeger DL. The reopening of closed filtering blebs using the neodymium: YAG laser. *Ophthalmology* 1984; 91:373-7.
49. Dailey RA, Samples JR, Van Buskirk EM. Reopening filtration fistulas with the neodymium-YAG laser. *Am J Ophthalmol* 1986; 102:491-5.
50. Traverso CE, Spaeth GL, Starita RJ, Greenidge KC, Poryzees E, Fellman RL. Factors affecting the results of argon laser trabeculoplasty in open-angle glaucoma. *Ophthalmic Surg* 1986; 17:554-9.
51. Wilensky JT, Jampol LM. Laser therapy for open angle glaucoma. *Ophthalmology* 1981; 88:213-7.
52. Wise JB. Glaucoma treatment by trabecular tightening with the argon laser. *Int Ophthalmol Clin* 1981; 21:69-78.
53. *Idem*. Long-term control of adult open angle glaucoma by argon laser treatment. *Ophthalmology* 1981; 88:197-202.
54. Schwartz AL, Whitten ME, Bleiman B, Martin D. Argon laser trabecular surgery in uncontrolled phakic open angle glaucoma. *Ophthalmology* 1981; 88:203-12.
55. Krupin T, Patkin R, Kurata FK, et al. Argon laser trabeculoplasty in black and white patients with primary open-angle glaucoma. *Ophthalmology* 1986; 93:811-6.
56. Burgess SE, Silverman RH, Coleman DJ, et al. Treatment of glaucoma with high-intensity focused ultrasound. *Ophthalmology* 1986; 93:831-8.
57. Patel A, Thompson JT, Michels RG, Quigley HA. Endolaser treatment of the ciliary body for uncontrolled glaucoma. *Ophthalmology* 1986; 93:825-30.
58. Zarbin MA, Michels RG, de Bustros S, Quigley HA, Patel A. Endolaser treatment of the ciliary body for severe glaucoma. *Ophthalmology* 1988; 95:1639-48.
59. Zigman S. The role of sunlight in human cataract formation. *Surv Ophthalmol* 1983; 27:317-25.
60. Lipman RM, Tripathi BJ, Tripathi RC. Cataracts induced by microwave and ionizing radiation. *Surv Ophthalmol* 1988; 33:200-10.
61. Urban RC Jr, Cotlier E. Corticosteroid-induced cataracts. *Surv Ophthalmol* 1986; 31:102-10.
62. MacDonald JS, Gerson RJ, Kornbrust DJ, et al. Preclinical evaluation of lovastatin. *Am J Cardiol* 1988; 62:16J-27J.
63. Tobert JA. Efficacy and long-term adverse effect pattern of lovastatin. *Am J Cardiol* 1988; 62:28J-34J.
64. Brown NA, Bron AJ. Medical therapy in the prevention of cataract. *Trans Ophthalmol Soc U K* 1985; 104:748-54.
65. Seland JH, Chylack LT Jr. Acute glucose-derived osmotic stress in rabbit lenses. *Acta Ophthalmol (Copenh)* 1986; 64:533-9.
66. Van Heyningen R, Harding JJ. Do aspirin-like analgesics protect against cataract? A case-control study. *Lancet* 1986; 1:1111-3.
67. West SK, Munoz BE, Newland HS, Emmett EA, Taylor HR. Lack of evidence for aspirin use and prevention of cataracts. *Arch Ophthalmol* 1987; 105:1229-31.
68. Applegate WB, Miller ST, Elam JT, Freeman JM, Wood TO, Gettlefinger TC. Impact of cataract surgery with lens implantation on vision and physical function in elderly patients. *JAMA* 1987; 257:1064-6.
69. Khwarg SG, Linstone FA, Daniels SA, et al. Incidence, risk factors, and morphology in operating microscope light retinopathy. *Am J Ophthalmol* 1987; 103:255-63.
70. Jaffe GJ, Irvine AR, Wood IS, Severeinghaus JW, Pino GR, Haugen C. Retinal phototoxicity from the operating microscope: the role of inspired oxygen. *Ophthalmology* 1988; 95:1130-41.
71. Naeser K, Thim K, Hansen TE, Degen T, Madsen S, Skov J. Intraocular pressure in the first days after implantation of posterior chamber lenses with the use of sodium hyaluronate (Healon). *Acta Ophthalmol (Copenh)* 1986; 64:330-7.
72. National Advisory Eye Council. Support for vision research: interim report of the National Advisory Eye Council. Bethesda, Md.: Public Health Service, 1976:20-2. (DHEW publication no. (NIH) 76-1098.)
73. Bloch-Michel E, Nussenblatt RB. Intermediate Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. *Am J Ophthalmol* 1987; 103:234-5.
74. Brewerton DA, Hart FD, Nicholls A, Caffrey M, James DC, Sturrock RD. Ankylosing spondylitis and HL-A 27. *Lancet* 1973; 1:904-7.
75. Brewerton DA, Caffrey M, Nicholls A, Walters D, James DC. Acute anterior uveitis and HL-A 27. *Lancet* 1973; 2:994-6.
76. Ohno D, Matsuda H. Studies of HLA antigens in Behcet's disease in Japan. In: Lehner T, Barnes CG, eds. *Recent advances in Behcet's disease: proceedings of conference no. 103*. London: Royal Society of Medicine, 1986:11-6.
77. Numaga J, Matsuki K, Mochizuki M, Minami M, Juji T. An HLA-D region restriction fragment associated with refractory Behcet's disease. *Am J Ophthalmol* 1988; 105:528-33.
78. Ohno S. Immunological aspects of Behcet's and Vogt-Koyanagi-Harada's diseases. *Trans Ophthalmol Soc U K* 1981; 101:335-41.

79. Davis JL, Mittel KK, Mellow SD, Nussenblatt RB. Association of HLA-DR52 with Vogt-Koyanagi-Harada disease and sympathetic ophthalmia in a mixed race population. *Ophthalmology* 1989; 96:Suppl:171.
80. Nussenblatt RB, Mittal KK, Ryan S, Green WR, Maumenee AE. Birdshot retinochoroidopathy associated with HLA-A29 antigen and immune responsiveness to retinal S-antigen. *Am J Ophthalmol* 1982; 94:147-58.
81. Baarsma GS, Kijlstra S, Oosterhuis JA, Kruit PJ, Rothova A. Association of birdshot retinochoroidopathy and HLA-A29 antigen. *Doc Ophthalmol* 1986; 61:267-9.
82. Gery I, Mochizuki M, Nussenblatt RB. Retinal specific antigens and immunopathogenic processes they provoke. In: Osborne NN, Chader GJ, eds. *Progress in retinal research*. Vol. 5. Oxford, England: Pergamon Press, 1986:75-109.
83. Caspi RR, Roberge FG, Chan CC, et al. A new model of autoimmune disease: experimental autoimmune uveoretinitis induced in mice with two different retinal antigens. *J Immunol* 1988; 140:1490-5.
84. Caspi RR. Basic mechanisms in immune-mediated uveitic disease. In: Lightman SE, ed. *Immunology of eye diseases*. London: MTP Press, 1989:61-86.
85. Nussenblatt RD, Gery I, Ballintine EJ, Wacker EB. Cellular immune responsiveness of uveitis patients to retinal S-antigen. *Am J Ophthalmol* 1980; 89:173-9.
86. Le Hoang P, Donnefort N, Foucault C, et al. Association between HLA-A29 antigen and birdshot retinochoroidopathy. In: *Proceedings of the 25th International Congress of Ophthalmology, Rome, 1986*. Amsterdam: Kugler and Ghendi, 1987:45-6.
87. Donoso LA, Merryman CF, Sery TW, et al. S-antigen: characterization of a pathogenic epitope which mediates experimental autoimmune uveitis and pinealitis in Lewis rats. *Curr Eye Res* 1987; 6:1151-9.
88. Singh VK, Nussenblatt RB, Donoso LA, Yamaki K, Chan CC, Shinohara T. Identification of a uveitopathogenic and lymphocyte proliferation site in bovine S-antigen. *Cell Immunol* 1988; 115:413-9.
89. Cassidy JT, Levinson JE, Bass JC, et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. *Arthritis Rheum* 1986; 29:274-81.
90. Nussenblatt RB, Palestine AG. *Uveitis: fundamentals and clinical practice*. Chicago: Year Book Medical, 1989:212-32.
91. Nussenblatt RB, Rodrigues MM, Wacker WB, Cevario SJ, Salinas-Carmona MC, Gery I. Cyclosporin A: inhibition of experimental autoimmune uveitis in Lewis rats. *J Clin Invest* 1981; 67:1228-31.
92. Nussenblatt RB, Palestine AG, Rook AH, Scher I, Wacker WB, Gery I. Treatment of intraocular inflammatory disease with cyclosporin A. *Lancet* 1983; 2:235-8.
93. Nussenblatt RB, Palestine AG, Chan CC, Mochizuki M, Yancey K. Effectiveness of cyclosporin therapy for Behçet's disease. *Arthritis Rheum* 1985; 28:671-9.
94. Masuda K, Nakajima A, Urayama A, Nakae K, Kogure M, Inaba G. Double-masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behçet's disease. *Lancet* 1989; 1:1093-6.
95. BenEzra D, Nussenblatt RB, Timonen P. *Optimal use of Sandimmune in endogenous uveitis*. Berlin: Springer-Verlag, 1988.
96. Nussenblatt RB, Caspi RR, Dinning WJ, Palestine AG, Hiestand P, Borel J. A comparison of the effectiveness of cyclosporine A, D, and G in the treatment of experimental autoimmune uveitis in rats. *J Immunopharmacol* 1986; 8:427-35.
97. Calne RY, White DJG, Thiru S, Rolles K, Drakopoulos S, Jamieson NV. Cyclosporin G: immunosuppressive effect in dogs with renal allografts. *Lancet* 1985; 1:1342.
98. Klein R. Recent developments in the understanding and management of diabetic retinopathy. *Med Clin North Am* 1988; 72:1415-37.
99. Davis MD. Diabetic retinopathy: a clinical overview. *Diabetes Metab Rev* 1988; 4:291-322.
100. Merimee TJ. Diabetic retinopathy: a synthesis of perspectives. *N Engl J Med* 1990; 322:978-83.
101. Flynn JT. Retinopathy of prematurity. *Pediatr Clin North Am* 1987; 34:1487-516.
102. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multi-center trial of cryotherapy for retinopathy of prematurity: preliminary results. *Pediatrics* 1988; 81:697-706.
103. Bressler NM, Bressler SB, Fine SL. Age-related macular degeneration. *Surv Ophthalmol* 1988; 32:375-413.
104. Young RW. Solar radiation and age-related macular degeneration. *Surv Ophthalmol* 1988; 32:252-69.
105. Newsome DA, Swartz M, Leone NC, Elston RC, Miller E. Oral zinc in macular degeneration. *Arch Ophthalmol* 1988; 106:192-8.
106. Pivetti-Pezzi P, Tamburi S, D'Offizi GP, Mezzaroma I, Aiuti F. Retinal cotton-wool-like spots: a marker for AIDS? *Compr Ther* 1988; 14:41-4.
107. Freeman WR, Chen A, Henderly DE, et al. Prevalence and significance of acquired immunodeficiency syndrome-related retinal microvasculopathy. *Am J Ophthalmol* 1989; 107:229-35.
108. Jabs DA, Enger C, Bartlett JG. Cytomegalovirus retinitis and acquired immunodeficiency syndrome. *Arch Ophthalmol* 1989; 107:75-80.
109. Bloom JN, Palestine AG. The diagnosis of cytomegalovirus retinitis. *Ann Intern Med* 1988; 109:963-9.
110. Mills J, Jacobson MA, O'Donnell JJ, Cederberg D, Holland GN. Treatment of cytomegalovirus retinitis in patients with AIDS. *Rev Infect Dis* 1988; 10:Suppl 3:S522-S531.
111. Walmsley SL, Chew E, Read SE, et al. Treatment of cytomegalovirus retinitis with trisodium phosphonoformate hexahydrate (Foscarnet). *J Infect Dis* 1988; 157:569-72.
112. Cantrill HL, Henry K, Melroe NH, Knobloch WH, Ramsay RC, Balfour HH Jr. Treatment of cytomegalovirus retinitis with intravitreal ganciclovir: long-term results. *Ophthalmology* 1989; 96:367-74.
113. Passo MS, Rossenbaum JT. Ocular syphilis in patients with human immunodeficiency virus infection. *Am J Ophthalmol* 1988; 106:1-6.
114. Holland GN, Engstrom RE Jr, Glasgow BJ, et al. Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome. *Am J Ophthalmol* 1988; 106:653-67.
115. Culbertson WW, Blumenkranz MS, Pepose JS, Stewart JA, Curtin VT. Varicella zoster virus is a cause of the acute retinal necrosis syndrome. *Ophthalmology* 1986; 93:559-69.