OPHTHALMOLOGY SECRETS IN COLOR

FOURTH EDITION

QUESTIONS YOU WILL BE ASKED

TOP 100 SECRETS ■ KEY POINTS ■ WEBSITES

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TOP 100 SECRETS

These secrets summarize the concepts, principles, and most salient details of ophthalmology.

1. The goal of refractive correction is to place the circle of least confusion on the retina.
2. To find the spherical equivalent of an astigmatic correction, add half the cylinder to the sphere.
3. Recheck if the axial length measures less than 22 mm or more than 25 mm or if there is more than a 0.3-mm difference between the two eyes. For each 1 mm in error, the intraocular lens (IOL) power calculation is off by 2.5 diopters (D). Recheck keratometry readings if the average K power is <40 D or >47 D or if there is a difference of more than 1 D between eyes. For every 0.25-D error, the IOL power calculation is in error by 0.25 D.
4. According to Kollner's rule, retinal diseases cause acquired blue-yellow color vision defects, whereas optic nerve diseases affect red-green discrimination.
5. A junctional scotoma is a unilateral central scotoma associated with a contralateral superotemporal field defect and is caused by compression of the contralateral optic nerve near the chiasm.
6. False-negative errors cause a visual field to appear worse than it actually is. False-positive errors cause a visual field to look better than it actually is.
7. Lesions anterior to the optic chiasm cause unequal visual acuity, a relative afferent papillary defect, and color abnormalities. The optic disc may also have asymmetric cupping and pallor.
8. A drop of 2.5% neosynephrine is a simple test to distinguish between episcleritis (these vessels will blanch) and scleritis (these vessels do not)—two entities with very different prognoses and evaluations. Because 50% of patients with scleritis have systemic disease, referral to an internist is necessary for further evaluation.
9. Immediately irrigate any patient with a chemical ocular injury from an alkali or an acid, even before checking visual acuity. Normalize the pH before examining the patient to prevent further damage to the eye.
10. Rule out uncontrolled hypertension or blood dyscrasias in patients with recurrent subconjunctival hemorrages.
11. A corneal ulcer is infectious until proven otherwise. You are never wrong to culture an ulcer; any ulcer not responding to therapy should be recultured.
12. Systemic treatment is necessary for gonococcal, chlamydial, and herpetic neonatal conjunctivitis because of the potential for serious disseminated disease. The mother and her sexual partners must be evaluated for other sexually transmitted diseases, including HIV.
13. Treatments that are effective for prophylaxis of gonococcal and chlamydial neonatal conjunctivitis include 1% silver nitrate, 0.5% erythromycin, and 1% tetracycline. Silver nitrate is rarely used, however, because of its potential for causing chemical conjunctivitis.
14. Topical steroids may promote herpetic keratitis if viral shedding is coincident with administration.
15. Steroid-induced increases in intraocular pressure occur in about 6% of patients on topical dexamethasone. This risk is higher in patients with known glaucoma or a family history of glaucoma.

16. Patients may be symptomatic with dry eye even with a normal slit lamp exam.
17. Ask about gastric bypass procedures in patients who have recent severe dry eye with no discernible cause. Vitamin A deficiency may be the reason. Similarly, patients after gastric bypass may present with Wernicke-Korsakoff syndrome (nyastmus, diplopia, ptosis and mental confusion) due to vitamin B1 deficiency.
18. If a patient presents with symptoms consistent with recurrent corneal erosion syndrome but no findings on slit lamp exam of the same, look for an underlying dystrophy, specifically epithelial basement membrane dystrophy.
19. If a patient with a corneal dystrophy is undergoing corneal transplantation but also has a clinically significant cataract, consider staging the cataract extraction a few months after the corneal transplant, offering the patient the advantage of better intraocular lens power calculation and postoperative refractive result. Alternatively, Descemet stripping endothelial keratoplasty, which does not alter corneal contour, may be combined with cataract surgery with a more predictable refractive outcome.
20. Corneal opacification in a neonate has a differential diagnosis of STUMPED: sclerocornea, trauma, ulcers, metabolic disorder, Peter's anomaly, endothelial dystrophy, and dermoid.
21. Most patients with keratoconus can be managed successfully with contact lens wear. Corneal transplantation is very successful in treating patients whose visual needs are not satisfied with glasses or contact lens correction.
22. As many as 30% to 50% of individuals with glaucomatous optic nerve damage and visual field loss have an initial intraocular pressure measurement less than 22 mm Hg.
23. The treatment of both primary open-angle glaucoma and low-tension glaucoma aims to preserve vision and quality of life through the lowering of intraocular pressure.
24. When evaluating a patient with angle-closure glaucoma, it is important to look at the fellow eye. Except for cases of marked anisometropia, the fellow eye should have a similar anterior chamber depth and narrow angle. If it does not, consider other nonrelative papillary block mechanisms of angle closure.
25. Patients with sporadic inheritance of aniridia need to be evaluated for Wilms tumor, as it is found in 25% of cases.
26. Allergy from topical medications can present months to years after starting the drop.
27. If a patient's glaucoma continues to worsen, even with seemingly reduced intraocular pressure during office visits, think of noncompliance.
28. Before trabeculectomy surgery, identify high-risk patients in whom sudden hypotony should be avoided: those with angle-closure glaucoma, shallow anterior chambers, very high preoperative intraocular pressure, elevated episcleral venous pressure, or high myopia. Hemorrhagic choroidals and expulsive hemorrhages are more likely.
29. Patients with traumatic ocular injuries must be evaluated for systemic injuries as well.
30. Posterior fractures most commonly occur in the posteromedial orbital floor.
31. Patients recovering from a traumatic hyphema are at increased risk for glaucoma and retinal detachments in the future. They need ongoing ophthalmic evaluation for the rest of their lives.
32. Always check the pressure in the contralateral eye in a patient with ocular trauma. Asymmetrically low intraocular pressure may be an important clue to a possible ruptured globe.
33. Complete systemic evaluation by a pediatrician is mandatory for any infant with a congenital cataract.
34. Patients must have a documented functional interference in quality of life from a visual standpoint before cataract surgery is indicated.

35. Glare testing can reveal significant functional visual problems even in patients with excellent visual acuity on Snellen testing.
36. Amblyopia is a diagnosis of exclusion. If amblyopia is associated with an afferent pupillary defect, a lesion of the retina or optic nerve should be suspected and ruled out.
37. The critical period of visual development is from birth through age 6 to 7 years. Amblyopia is most successfully treated during this time. However, treatment can be successful at older ages with good compliance. Atropine penalization can be as effective as patching.
38. Early treatment for congenital esotropia gives the best chance for the development of binocular vision. Be certain that a patient with a partial accommodative esotropia is wearing the maximum tolerated hyperopic prescription.
39. Check the light reflex test and cover test to determine if a true deviation exists. If the light reflex is in the appropriate place and there is no refixation on cover testing, the patient is orthophoric.
40. A young patient with asthenopia should be evaluated for exophoria at near (convergence insufficiency) as well as for his or her cycloplegic refraction for undercorrected hyperopia (accommodative insufficiency).
41. Any patient with chronic progressive external ophthalmoplegia needs an electrocardiogram to rule out heart block. These patients may need a pacemaker to prevent sudden death.
42. A patient with acute onset of any combination of third, fourth, fifth, and sixth cranial nerve palsies; extreme headache; and decreased vision must be immediately placed on intravenous steroids and referred to neurosurgery for pituitary apoplexy.
43. The signs of endophthalmitis typically appear 1 to 4 days after strabismus surgery and include lethargy, asymmetric eye redness, eyelid swelling, and fever.
44. Before evaluating for strabismus, make sure patients with double vision have binocular diplopia. Strabismus does not cause monocular diplopia.
45. Always consider myasthenia gravis and thyroid eye disease in patients presenting with diplopia and normal pupils.
46. When performing surgery on both oblique and rectus muscles, hook the obliques first.
47. In a recess–resect procedure, the recession should be done first.
48. If a patient has a significant deviation in primary gaze or an abnormal head posture, strabismus surgery is indicated in most incomitant strabismus cases.
49. Try for fusion of all patients with nystagmus. Aim for exophoria with fusion.
50. Smoking is a controllable risk factor for thyroid eye disease.
51. All patients with optic neuritis should experience some improvement in vision. However, 5% of patients who presented with visual acuity of less than 20/200 were still 20/200 or less at 6 months.
52. An abnormal magnetic resonance imaging (MRI) in a patient with optic neuritis is the strongest predictor of developing multiple sclerosis (MS). Fifty-six percent of patients with optic neuritis and a white matter lesion on MRI will develop MS within 10 years.
53. The closer a patient stands to a visual-field testing screen, the smaller the field should be. This is helpful in determining a malingering patient.
54. Any patient suspected of giant cell arteritis should immediately be started on high doses of steroids to prevent involvement of the other eye even if the temporal artery biopsy cannot be done beforehand.

55. Dacryocystitis must be treated emergently to prevent cellulitis or intracranial spread of the infection.
56. Computed tomography (CT) scanning is superior to MRI in most cases of orbital disease owing to better bone–tissue delineation.
57. The most common cause of unilateral or bilateral proptosis is thyroid eye disease (Graves ophthalmopathy). Most patients with thyroid-related ophthalmopathy (TRO) will not require surgery for their disease; it will burn out with time.
58. The most common cause of unilateral proptosis in children is orbital cellulitis.
59. A child with rapidly progressive proptosis, inferior displacement of the globe, and upper eyelid edema should have immediate neuroimaging followed by an orbital biopsy to rule out rhabdomyosarcoma.
60. Suspect TRO in patients with nonspecific redness and inflammation of the eyes even if there is no history of a systemic thyroid imbalance.
61. Myositis, a nonspecific inflammation of an extraocular muscle, can be distinguished from thyroid-associated ophthalmopathy (TAO) by the location of muscle inflammation. TAO demonstrates thickening of the muscle belly, but only myositis shows thickening of the tendon insertion as well.
62. Persistent proptosis and progression of orbital infection while on intravenous antibiotics for orbital cellulitis should prompt a repeat CT scan to rule out an orbital abscess.
63. The sinuses are the most common source of an orbital infection. The ethmoid sinus is the most frequent culprit as its lateral wall is the thinnest orbital wall, the lamina papyracea.
64. Surgical drainage should be undertaken in orbital cellulitis if sinuses are completely opacified, response to antibiotics is poor by 48 to 72 hours, vision decreases, or an afferent pupillary defect presents.
65. Mild ptosis associated with miosis and neck or facial pain should raise suspicion of a carotid artery dissection, prompting an urgent workup.
66. Acute ptosis and ocular misalignment mandate a careful evaluation of the pupil to rule out pupil-involving third-nerve palsy. A dilated pupil requires neurologic evaluation for a compressive aneurysm.
67. Basal cell carcinoma is the most common malignant eyelid tumor. It has a 3% mortality rate because of invasion into the orbit and brain via the lacrimal drainage system, prior radiation therapy, or clinical neglect.
68. Squamous cell carcinoma may metastasize systemically.
69. Keratoacanthomas often resolve spontaneously but should be removed surgically if near the lid margin to prevent permanent deformity.
70. Rule out sebaceous cell carcinomas in a patient with a recurrent chalazion in the same spot.
71. Young patients with xanthelasma should be evaluated for diabetes mellitus and hypercholesterolemia.
72. All patients who have anterior uveitis must have a dilated examination to exclude associated posterior segment disease.
73. Consider masquerade syndromes in the very young, the elderly, and in patients who have uveitis that does not respond to treatment. Uveitis in patients with acquired immunodeficiency syndrome is almost invariably part of a disseminated systemic infection. Lymphoma may masquerade as retinitis.

74. Never aspirate subretinal exudates for diagnostic purposes in a patient with potential Coats disease unless retinoblastoma has been absolutely ruled out. It may take as long as 1 to 2 years for exudation to clear after successful treatment of the abnormal peripheral retinal vessels.
75. The five trauma-related breaks are horseshoe tears, operculated tears, dialyses, retinal dissolution, and macular holes.
76. The globe is most likely to rupture at the limbus, underneath a rectus muscle, or at a previous surgical site.
77. A break in the Bruch membrane is necessary for a choroidal neovascular membrane to form.
78. Age-related macular degeneration (ARMD) is the leading cause of legal blindness in the Western world. The leading epidemiologic risk factors for ARMD are increasing age, smoking, and genetic predisposition.
79. Threshold disease of retinopathy of prematurity (ROP) is five contiguous or eight cumulative clock hours of stage 3 ROP in zone I or II in the presence of plus disease.
80. When ROP reaches ETROP Study Type 1 (high-risk disease), indirect laser photocoagulation dramatically reduces the risk of blindness.
81. Newborns weighing less than 1500 g at birth and/or born at or before 28 weeks' gestational age should be screened for ROP at 4 to 6 weeks after birth or 31 to 33 weeks postconceptual age and followed until the retinal vascularization has fully matured.
82. The most common cause of vision loss in diabetic retinopathy is macular edema.
83. Neovascularization of the iris is an ominous finding in proliferative diabetic retinopathy and requires prompt treatment with panretinal photocoagulation, intravitreal anti-vascular endothelial growth factor (VEGF) injections, or both.
84. Clinically significant macular edema is defined as one of the following: retinal thickening within 500 μm of the center of the fovea, hard yellow exudate within 500 μm of the fovea and adjacent retinal thickening, or at least one disc area of retinal thickening, any part of which is within one disc diameter of the center of the fovea. It is based on fundus exam and is NOT related to visual acuity or optical coherence tomography findings.
85. Most central retinal artery obstructions are thrombotic; most branch retinal artery obstructions are embolic. Systemic disease must be ruled out in any patient with retinal artery obstruction.
86. First-line treatment for macular edema from retinal venous occlusive disease is intravitreal anti-VEGF injections. However, there is an emerging role for intravitreal corticosteroid treatment, especially in refractory cases.
87. In patients with central retinal venous occlusions, argon laser photocoagulation is indicated only when neovascularization develops; it is not for prophylaxis.
88. Perform iris examination and gonioscopy before dilation in a patient with a central retinal vein occlusion. Neovascular glaucoma is the most feared complication of a central retinal vein occlusion.
89. Branch and central retinal venous occlusions are classified as ischemic or nonischemic. Patients with ischemic occlusions lose vision primarily from macular edema. Vision loss in nonischemic occlusions is due to macular nonperfusion, vitreous hemorrhage, tractional retinal detachments, and neovascular glaucoma.
90. The classic symptoms of a retinal break are flashes and floaters. Pigmented cells or blood in the vitreous strongly suggests the possibility of a retinal break. Risk factors for rhegmatogenous retinal detachment (RRD) include previous cataract surgery, lattice degeneration, myopia, trauma, family history, and fellow eye with an history of an RD.

91. Pneumatic retinopexy for an RRD should be avoided if patients are at high risk of significant vitreoretinal traction, i.e., early PVR, highly elevated flap tears, multiple tears, lattice degeneration, or sizable vitreous hemorrhage.
92. Retinoblastoma is the leading eye cancer in children. About 98% of children with retinoblastoma in the United States and developed nations survive owing to early detection and proper management.
93. Most children with unilateral retinoblastoma have a somatic mutation and are managed with enucleation or intra-arterial chemotherapy.
94. Most children with bilateral retinoblastoma have a germ-line mutation and are managed with intravenous or intra-arterial chemotherapy.
95. The presence of dilated, tortuous episcleral blood vessels warrants a complete exam to rule out an underlying ciliary body or peripheral choroidal tumor.
96. Ultrasound findings of low-to-medium internal reflectivity and collar-button shape can confirm diagnosis of a choroidal melanoma and differentiate it from other choroidal lesions.
97. Uveal melanomas with epithelioid cells have a poorer prognosis. Seventy percent of uveal metastases are from breast or lung cancer.
98. Most periocular lymphomas are B cell, extranodal marginal zone lymphoma, also known as mucosal-associated lymphoid tissue lymphoma.
99. Management of orbital lymphoma is largely based on two factors: the particular histologic subtype and the stage of disease.
100. Based on recent data, the treatment of choice for optic nerve sheath meningioma is stereotactic radiotherapy.

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CLINICAL ANATOMY OF THE EYE

Kenneth B. Gum

CHAPTER 1

I. GENERAL

1. **Name the seven bones that make up the bony orbit and describe which location is most prone to damage in an orbital blow-out fracture.**
   The seven orbital bones are the frontal, zygoma, maxillary, sphenoid, ethmoid, palatine, and lacrimal. A true blow-out fracture most commonly affects the orbital floor posteriorly and medially to the infraorbital nerve. The ethmoid bone of the medial wall is often broken.

2. **Which nerves and vessels pass through the superior orbital fissure? Which motor nerve to the eye lies outside the annulus of Zinn, leaving it unaffected by retrobulbar injection of anesthetic?**
   The superior orbital fissure transmits the third, fourth, and sixth cranial nerves as well as the first division of the fifth cranial nerve, which has already divided into frontal and lacrimal branches. The superior ophthalmic vein and sympathetic nerves also pass through this fissure. The fourth cranial nerve, supplying the superior oblique muscle, lies outside the annulus. This position accounts for residual intorsion of the eye sometimes seen during retrobulbar anesthesia (Fig. 1-1).

3. **A 3-year-old is referred for evaluation of consecutive exotropia after initial bimedial rectus recessions for esotropia performed elsewhere. Review of the operative notes discloses that each muscle was recessed 4.5 mm for a 30-prism diopter deviation. Unfortunately, the child had mild developmental delay and presents with a 25-prism diopter exotropia. You decide to advance the recessed medial rectus of each eye back to its original insertion site. Where is this site in relation to the limbus? Identify the location of each of the rectus muscle insertion sites relative to the limbus.**
   Reattach each medial rectus muscle 5.5 mm from the limbus. Insertion of the inferior rectus is 6.5 mm from the limbus, the lateral rectus is 6.9 mm from the limbus, and the superior rectus, 7.7 mm. The differing distances of rectus-muscle insertions from the limbus make up the spiral of Tillaux. An important caveat in developmentally delayed children is to postpone muscle surgery until much later, treating any amblyopia in the interim. Early surgery frequently leads to overcorrection.

4. **What is the most common cause of both unilateral and bilateral proptosis in adults?**
   Thyroid orbitopathy is the most common cause. Many signs are associated with thyroid eye disease, which is probably caused by an autoimmune reactivity toward the epitope of thyroid-stimulating hormone receptors in the thyroid and orbit. The order of frequency of extraocular muscle involvement in thyroid orbitopathy is as follows: inferior rectus, medial rectus, lateral rectus, superior rectus, and obliques. There is enlargement of the muscle belly with sparing of the tendons.

5. **You have just begun a ptosis procedure. A lid crease incision was made, and the orbital septum has been isolated and opened horizontally. What important landmark should be readily apparent? Describe its relation to other important structures.**
   The orbital fat lies directly behind the orbital septum and directly on the muscular portion of the levator (Fig. 1-2). A separate medial fat pad often herniates through the septum in later years.

6. **To what glands do the lymphatics of the orbit drain?**
   There are no lymphatic vessels or nodes within the orbit. Lymphatics from the conjunctivae and lids drain medially to the submandibular glands and laterally to the superficial preauricular nodes.

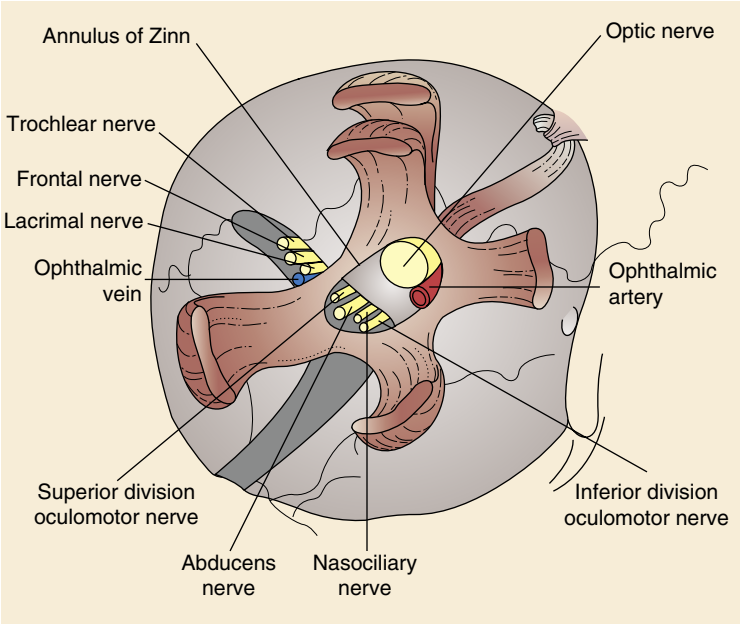

Figure 1-1. The annulus of Zinn and surrounding structures. *(From Campolattaro BN, Wang FM: Anatomy and physiology of the extraocular muscles and surrounding tissues. In Yanoff M, Duker JS [eds]: Ophthalmology, ed 2, St. Louis, Mosby, 2004.)*

7. What is the orbital septum?

The septum is a thin sheet of connective tissue that defines the anterior limit of the orbit. In the upper lid it extends from the periosteum of the superior orbital rim to insert at the levator aponeurosis, slightly above the superior tarsal border (see Fig. 1-2). The lower lid septum extends from the periosteum of the inferior orbital rim to insert directly on the inferior tarsal border.

8. A 70-year-old patient presents with herpes zoster lesions in the trigeminal nerve distribution. Classic lesions on the side and tip of the nose increase your concern about ocular involvement. Why?

This sign, called Hutchinson's sign, results from involvement of the infratrochlear nerve. The infratrochlear nerve is the terminal branch of the nasociliary nerve, which gives off the long ciliary nerves (usually two) that supply the globe.

9. Where is the sclera the thinnest? Where are globe ruptures after blunt trauma most likely to occur?

The sclera is thinnest just behind the insertion of the rectus muscles (0.3 mm). Scleral rupture usually occurs opposite the site of impact and in an arc parallel to the limbus at the insertion of the rectus muscles or at the equator. The most common site of rupture is near the superonasal limbus.

10. Describe the surgical limbus and Schwalbe's line.

The surgical limbus can be differentiated into an anterior bluish zone that extends from the termination of Bowman's layer to Schwalbe's line, which is the termination of Descemet's membrane. The posterior white zone overlies the trabecular meshwork and extends from the Schwalbe's line to the scleral spur.

11. You are preparing to do an argon laser trabeculoplasty. Describe the gonioscopic appearance of the anterior chamber angle.

The ciliary body is a visible concavity anterior to the iris root. The scleral spur appears as a white line anterior to the ciliary body. Above this are the trabecular meshwork and canal of Schlemm. Treatment is applied to the anterior trabecular meshwork.

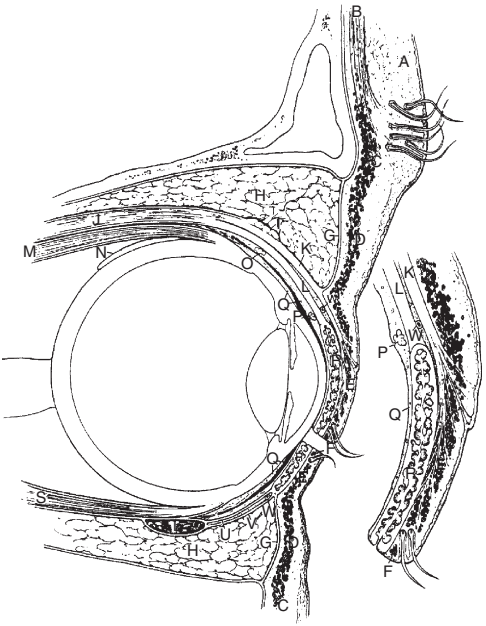

Figure 1-2. Schematic cross-section of eyelids and anterior orbit. *A,* Skin; *B,* frontalis muscle; *C,* orbicularis muscle (orbital portion); *D,* orbicularis muscle (preseptal portion); *E,* orbicularis muscle (pretarsal portion); *F,* orbicularis muscle (muscle of Riolan); *G,* orbital septum; *H,* orbital fat; *I,* superior transverse ligament; *J,* levator muscle; *K,* levator aponeurosis; *L,* Müller's muscle; *M,* superior rectus muscle; *N,* superior oblique tendon; *O,* gland of Krause; *P,* gland of Wolfring; *Q,* conjunctiva; *R,* tarsus; *S,* inferior rectus muscle; *T,* inferior oblique muscle; *U,* inferior tarsal muscle; *V,* capsulopalpebral ascia; *W,* peripheral arterial arcade. *(From Beard C: Ptosis, ed 3, St. Louis, Mosby, 1981.)*

12. After a filtering procedure, your patient develops choroidal effusions. Explain the distribution of these fluid accumulations based on uveal attachments to the sclera.

The uveal tract is attached to the sclera at the scleral spur, the optic nerve, and the exit sites of the vortex veins. The fluid dissects the choroid from the underlying sclera but retains these connections.

13. Describe the structure of Bruch's membrane. Name two conditions in which defects develop in this structure spontaneously.

The Bruch's membrane consists of five layers: internally, the basement membrane of the pigment epithelium, the inner collagenous zone, a central band of elastic fibers, and the outer collagenous zone; externally, the basement membrane of the choriocapillaris. Pseudoxanthoma elasticum and myopia may cause spontaneous defects in this membrane, making the patient prone to development of choroidal neovascularization.

KEY POINTS: BRUCH'S MEMBRANE

1. Composed of five layers.
2. Spontaneous breaks can occur in pseudoxanthoma elasticum and myopia.
3. Defect in Bruch's membrane in age-related macular degeneration may lead to the exudative form.
4. Trauma may cause a break in the membrane, leading to a choroidal neovascular membrane.

14. Less laser power is required for photocoagulation in darkly pigmented fundi. What determines this pigmentation?

The pigmentation of the fundus seen ophthalmoscopically is largely determined by the number of melanosomes in the choroid. The darker macular area results from taller pigment epithelial cells that contain more and larger melanosomes than the periphery.

15. What is the blood–retinal barrier?

The inner blood–retinal barrier consists of the retinal vascular endothelium, which is nonfenestrated and contains tight junctions. The outer blood–retinal barrier is the retinal pigment epithelium. Bruch's membrane is permeable to small molecules.

16. Name the 10 classically described anatomic layers of the retina and the cells that make up the retina.

The retina may be divided into 10 layers, starting just above the choroids and extending to the vitreous:

- Retinal pigment epithelium
- Outer segments of the photoreceptors
- External limiting membrane
- Outer nuclear layer
- Outer plexiform layer
- Inner nuclear layer
- Inner plexiform layer
- Ganglion cell layer
- Nerve fiber layer
- Internal limiting membrane

Within these layers lie the photoreceptors, horizontal cells, bipolar cells, amacrine cells, retinal interneurons, ganglion cells, and the glial cells of the retina, Müller cells.

17. Which retinal layer is referred to as the fiber layer of Henle in the macular region?

The outer plexiform layer, which is made up of connections between photoreceptor synaptic bodies and horizontal and bipolar cells, becomes thicker and more oblique in orientation as it deviates away from the fovea. At the fovea this layer becomes nearly parallel to the retinal surface and accounts for the radial, or star-shaped, patterns of exudate in the extracellular spaces under pathologic conditions causing vascular compromise, such as hypertension.

18. What are three clinically recognized remnants of the fetal hyaloid vasculature?

Mittendorf's dot, Bergmeister's papilla, and vascular loops (95% of which are arterial).

19. A patient presents with a central retinal artery occlusion and 20/20 visual acuity. How do you explain this finding?

Fifteen percent of people have a cilioretinal artery that supplies the macular region. Thirty percent of eyes have a cilioretinal artery supplying some portion of the retina. These are perfused by the choroidal vessels, which are fed by the ophthalmic artery and thus are not affected by central retinal artery circulation.

20. Where do branch retinal vein occlusions occur? Which quadrant of the retina is most commonly affected?

Branch retinal vein occlusions occur at arteriovenous crossings, most commonly where the vein lies posterior to the artery. The superotemporal quadrant is most often affected because of a higher number of arteriovenous crossings on average.

21. Discuss the organization of crossed and uncrossed fibers in the optic chiasm.

Inferonasal extramacular fibers cross in the anterior chiasm and bulge into the contralateral optic nerve (Willebrand's knee). Superonasal extramacular fibers cross directly to the opposite optic tract. Macular fibers are located in the center of the optic nerve. Temporal macular fibers pass uncrossed through the chiasm, whereas nasal macular fibers cross posteriorly. However, in albinism, many temporal fibers also cross.

22. Describe the location of the visual cortex.

The visual cortex is situated along the superior and inferior lips of the calcarine fissure. This area is called the striate cortex because of the prominent band of geniculocalcarine fibers, termed the stria of Gennari after its discoverer.

23. What is the most likely anatomic location of pathology associated with downbeat nystagmus?

Downbeat nystagmus is usually indicative of cervicomedullary structural disease. The most common causes are Arnold-Chiari malformation, stroke, multiple sclerosis, and platybasia. Any patient with this finding should have neuroimaging studies done.

24. A patient presents with a chief complaint of tearing and ocular irritation. As she dumps the plethora of eyedrops from her purse, she explains that she has seen seven different doctors and none has been able to help her. The exam shows mild inferior punctate keratopathy but a normal tear lake and normal Schirmer's test. Of interest, she had blepharoplasty surgery 6 months previously. What is the diagnosis?

You are already patting yourself on the back as you ask if the irritation is worse in the morning or evening. She replies emphatically that it is much more severe upon awakening. You ask her to close her eyes gently and see 2 mm of lagophthalmos in each eye. This is a frequently overlooked cause of tearing in otherwise normal eyes.

25. During orbital surgery, a patient's lacrimal gland is removed. Afterward, there is no evidence of tear deficiency. Why not?

Basal tear production is provided by the accessory lacrimal glands of Krause and Wolfring. Krause's glands are located in the superior fornix, and the glands of Wolfring are located above the superior tarsal border. They are cytologically identical to the main lacrimal gland.

26. Describe the anatomy of the macula and fovea.

The macula is defined as the area of the posterior retina that contains xanthophyllic pigment and two or more layers of ganglion cells. It is centered approximately 4 mm temporal and 0.8 mm inferior to the center of the optic disc. The fovea is a central depression of the inner retinal surface and is approximately 1.5 mm in diameter.

27. Fluorescein angiography typically shows perfusion of the choroid and any cilio-retinal arteries prior to visualization of the dye in the retinal circulation. Why?

Fluorescein enters the choroid via the short posterior ciliary arteries, which are branches of the ophthalmic artery. The central retinal artery, also a branch of the ophthalmic artery, provides a more circuitous route for the dye to travel, resulting in dye appearance in the retinal circulation 1 to 2 seconds later.

28. Explain why visual acuity in infants does not reach adult levels until approximately 6 months of age, based on retinal differentiation.

The differentiation of the macula is not complete until 4 to 6 months after birth. Ganglion cell nuclei are initially found directly over the foveola and gradually are displaced peripherally, leaving this area devoid of accessory neural elements and blood vessels as neural organization develops to adult levels by age 6 months. This delay in macular development is one factor in the inability of newborns to fixate, and improvement in visual activity parallels macular development.

29. A neonate presents with an opacification in her left cornea. What is the differential diagnosis?

Neonatal cloudy cornea usually falls into one of the following categories (which can easily be recalled by using the mnemonic *STUMPED*): sclerocornea, trauma, ulcers, metabolic disorder, Peters' anomaly, endothelial dystrophy, and dermoid.

30. Describe the innervation of the lens.

The lens is anatomically unique because it lacks innervation and vascularization. It depends entirely on the aqueous and vitreous humors for nourishment.

31. Describe the innervation of the cornea.

The long posterior ciliary nerves branch from the ophthalmic division of the trigeminal nerve and penetrate the cornea. Peripherally, 70 to 80 branches enter the cornea in conjunctival, episcleral, and scleral planes. They lose their myelin sheath 1 to 2 mm from the limbus. The network just posterior to the Bowman's layer sends branches anteriorly into the epithelium.

32. What are the three layers of the tear film? Where do they originate?

- The *mucoid layer* coats the superficial corneal epithelial cells and creates a hydrophilic layer that allows for spontaneous, even distribution of the aqueous layer of the tear film. Mucin is secreted principally by the conjunctival goblet cells but also from the lacrimal gland.

- The *aqueous layer* is secreted by the glands of Kraus and Wolfring (basal secretion) and the lacrimal gland (reflex secretion). The aqueous layer contains electrolytes, immunoglobulins, and other solutes, including glucose, buffers, and amino acids.
- The *lipid layer* is secreted primarily by the meibomian glands and maintains a hydrophobic barrier that prevents tear overflow, retards evaporation, and provides lubrication for the lid/ocular interface.

33. What are the differences in the structure of the central retinal artery and retinal arterioles?

The central retinal artery contains a fenestrated internal elastic lamina and an outer layer of smooth muscle cells surrounded by a basement membrane. The retinal arterioles have no internal elastic lamina and lose the smooth muscle cells near their entrance into the retina. Hence, the retinal vasculature has no autoregulation.

34. Where is the macula represented in the visual cortex?

Macular function is represented in the most posterior portion at the tip of the occipital lobe. However, there may be a wide distribution of some macular fibers along the calcarine fissure.

35. What is macular hole formation?

Macular hole formation is a common malady that can result in rapid loss of central vision. Approximately 83% of cases are idiopathic, and 15% are due to some sort of trauma.

36. Describe the stages of macular hole formation as proposed by Gass, as well as the changes in our understanding of the disease process since the development of optical coherence tomography (OCT).

Gass's theory proposed that the underlying causative mechanism was centripetal tangential traction by the cortical vitreous on the fovea. He also proposed the following stages:

- **Stage 1a:** Tractional elevation of the foveola with a visible yellow dot
- **Stage 1b:** Enlargement of the tractional detachment with foveal elevation. A yellow ring becomes visible
- **Stage 2:** Full-thickness retinal defect less than 400 μm
- **Stage 3:** Full-thickness retinal defect larger than 400 μm
- **Stage 4:** Stage 3 with complete posterior vitreous detachment

OCT analysis has revealed that some patients have perifoveal vitreous detachment with a remaining attachment of the fovea. Occasionally patients may develop an intraretinal split with formation of a foveal cyst. This cyst may evolve into a full-thickness hole with disruption of the inner retinal layer and opening of the foveal floor. These findings suggest a complex array of both anterior–posterior and tangential vector forces as an etiology for molecular hole formation.

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ANATOMY OF THE ORBIT AND EYELID

Edward H. Bedrossian, Jr.

CHAPTER 2

ORBIT

1. **Name the bones of the orbit** (see Fig. 2-1).
   - **Medial wall:** Sphenoid, ethmoid, lacrimal, maxillary
   - **Lateral wall:** Zygomatic, greater wing of the sphenoid
   - **Roof:** Frontal, lesser wing of the sphenoid
   - **Floor:** Maxillary, zygomatic, palatine
2. **What are the weak spots of the orbital rim?**
   - Frontozygomatic suture
   - Zygomaticomaxillary suture
   - Frontomaxillary suture
3. **Describe the most common location of blow-out fractures.**
   The posteromedial aspect of the orbital floor.
4. **What is the weakest bone within the orbit?**
   The lamina papyracea portion of the ethmoid bone.
5. **Name the divisions of cranial nerve V that pass through the cavernous sinus.**
   - Ophthalmic division (V1)
   - Maxillary division (V2)

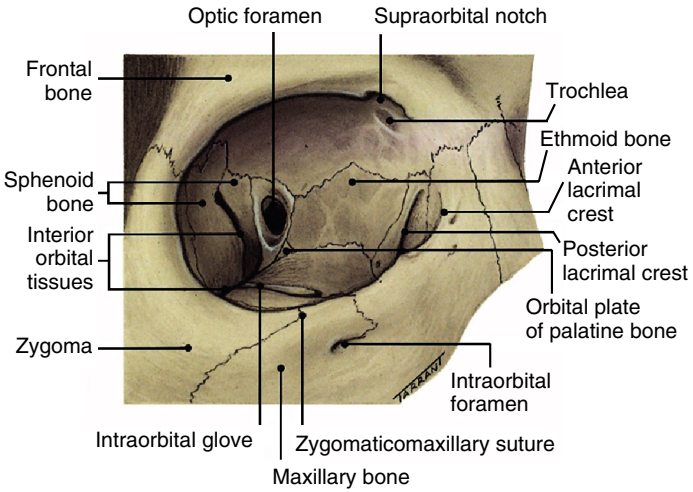

Figure 2-1. Anatomy of the orbit. *(From Kanski JJ: Clinical Ophthalmology: A Systematic Approach, ed 7, London, Elsevier, 2011.)*

6. **What is the annulus of Zinn?**
The circle defined by the superior rectus muscle, inferior rectus muscle, lateral rectus muscle, and medial rectus muscle.

7. **What nerves pass through the superior orbital fissure but outside the annulus of Zinn?**
Frontal, lacrimal, and trochlear nerves.

EYELID

8. **List the factors responsible for involutional entropion.**
- Lower lid laxity
- Override of the preseptal orbicularis oculi muscle onto the pretarsal orbicularis oculi muscle
- Dehiscence/disinsertion of the lower lid retractors
- Orbital fat atrophy

9. **Describe the sensory nerve supply to the upper and lower eyelids.**
- The ophthalmic nerve (V1) provides sensation to the upper lid.
- The maxillary nerve (V2) provides senssation to the lower lid.

10. **What are the surgical landmarks for locating the superficial temporal artery during temporal artery biopsies?**
The superficial temporal artery lies deep to the skin and subcutaneous tissue but superficial to the temporalis fascia.

11. **What structures would you pass through during a transverse blepharotomy 3 mm above the upper eyelid margin?**
- Skin
- Pretarsal orbicularis muscle
- Tarsus
- Palpebral conjunctiva (see Fig. 2-2)

12. **What is meant by the phrase *lower lid retractors*?**
The lower lid retractors consist of the capsulopalpebral fascia and the inferior tarsus muscle. The capsulopalpebral fascia of the lower lid is analogous to the levator complex in the upper lid. The inferior tarsus muscle of the lower lid is analogous to the Müller's muscle in the upper lid.

13. **What structures would be cut in a full-thickness lower-lid laceration 2 mm below the lower tarsus?**
- Skin
- Preseptal orbicularis oculi muscle
- Conjoint tendon (fused orbital septum and lower lid retractors)
- Palpebral conjunctiva

14. **What structures would be cut in a full-thickness lower-lid laceration 6 mm below the lower tarsus?**
- Skin
- Preseptal orbicularis oculi muscle
- Orbital septum
- Fat
- Lower lid retractors (capsulopalpebral fascia and inferior tarsus muscle)
- Conjunctiva

15. **Discuss the bony attachments of the Whitnall's superior suspensory ligament.**
Medially, it attaches to the periosteum of the trochlea. Laterally, the major attachment is to the periosteum at the frontozygomatic suture. It also sends minor attachments to the lateral orbital tubercle.

16. **What structure separates the medial fat pad from the central (also called the preaponeurotic) fat pad in the upper eyelid?**
The superior oblique tendon.

17. **Lester Jones divided the orbicularis oculi muscle into three portions. Name them.**
- Orbital portion
- Preseptal portion
- Pretarsal portion

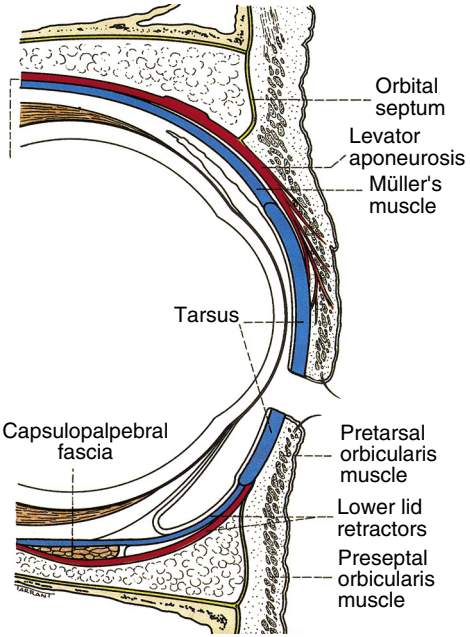

Figure 2-2. Eyelid structures. *(From Kanski JJ: Clinical Ophthalmology: A Systematic Approach, ed 5, New York, Butterworth-Heinemann, 2003.)*

18. What portions of the orbicularis oculi muscle are important in the lacrimal pump mechanism?

The preseptal and pretarsal portions.

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CHAPTER 3

OPTICS AND REFRACTION

Janice A. Gault

1. **What is the primary focal point (F_1)?**
   The primary focal point is the point along the optical axis at which an object must be placed for parallel rays to emerge from the lens. Thus, the image is at infinity (Fig. 3-1).

2. **What is the secondary focal point (F_2)?**
   The secondary focal point is the point along the optical axis at which parallel incoming rays are brought into focus. It is equal to 1/lens power in diopters (D). The object is now at infinity (Fig. 3-2).

3. **Where is the secondary focal point for a myopic eye? A hyperopic eye? An emmetropic eye?**
   The secondary focal point for a **myopic** eye is anterior to the retina in the vitreous (Fig. 3-3, *A*). The object must be moved forward from infinity to allow the light rays to focus on the retina. A **hyperopic** eye has its secondary focal point posterior to the retina (Fig. 3-3, *B*). An **emmetropic** eye focuses light rays from infinity onto the retina.

4. **What is the far point of an eye?**
   The term *far point* is used only for the optical system of an eye. It is the point at which an object must be placed along the optical axis for the light rays to be focused on the retina when the eye is not accommodating.

5. **Where is the far point for a myopic eye? A hyperopic eye? An emmetropic eye?**
   The far point for a **myopic** eye is between the cornea and infinity. A **hyperopic** eye has its far point beyond infinity or behind the eye. An **emmetropic** eye has light rays focused on the retina when the object is at infinity.

6. **How do you determine which lens will correct the refractive error of the eye?**
   A lens with its focal point coincident with the far point of the eye allows the light rays from infinity to be focused on the retina. The image at the far point of the eye now becomes the object for the eye.

7. **What is the near point of an eye?**
   The near point is the point at which an object will be in focus on the retina when the eye is fully accommodating. Moving the object closer will cause it to blur.

8. **Myopia can be caused in two ways. What are they?**
   - **Refractive myopia** is caused by too much refractive power owing to steep corneal curvature or high lens power.
   - **Axial myopia** is due to an elongated globe. Every millimeter of axial elongation causes about 3 D of myopia.

9. **The power of a proper corrective lens is altered by switching from a contact lens to a spectacle lens or vice versa. Why?**
   Moving a minus lens closer to the eye increases effective minus power. Thus, myopes have a weaker minus prescription in their contact lenses than in their glasses. Patients near presbyopia may need reading glasses when using their contacts but can read without a bifocal lens in their glasses (see question 45). Moving a plus lens closer to the eye decreases effective plus power. Thus, hyperopes need a stronger plus prescription for their contact lenses than for their glasses. They may defer bifocals for a while. The same principle applies to patients who slide their glasses down their nose and find that they can read more easily. They are adding plus power. This principle works for both hyperopes and myopes.

10. **What is the amplitude of accommodation?**
    The total number of diopters that an eye can accommodate.

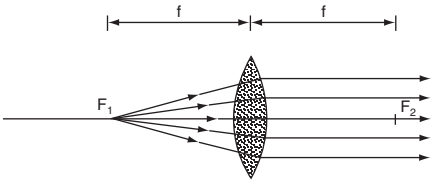

Figure 3-1. The primary focal point (F_1), which has an image at infinity. *(From Azar DT, Strauss L: Principles of applied clinical optics. In Albert DM, Jakobiec FA [eds]: Principles and Practice of Ophthalmology, vol. 6, ed 2, Philadelphia, W.B. Saunders, 2000, pp 5329–5340.)*

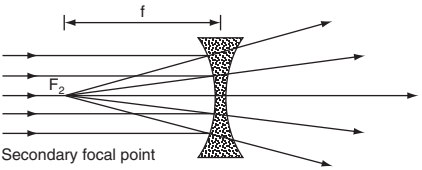

Figure 3-2. The secondary focal point (F_2), which also has an object at infinity. *(From Azar DT, Strauss L: Principles of applied clinical optics. In Albert DM, Jakobiec FA [eds]: Principles and Practice of Ophthalmology, vol. 6, ed 2, Philadelphia, W.B. Saunders, 2000, pp 5329–5340.)*

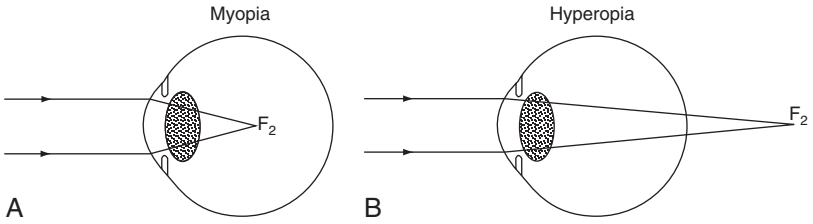

Figure 3-3. A, The secondary focal point of a myopic eye is anterior to the retina in the vitreous. **B,** In hyperopia, the secondary focal point is behind the retina. *(From Azar DT, Strauss L: Principles of applied clinical optics. In Albert DM, Jakobiec FA [eds]: Principles and Practice of Ophthalmology, vol. 6, ed 2, Philadelphia, W.B. Saunders, 2000, pp 5329–5340.)*

11. What is the range of accommodation?
The range of clear vision obtainable with accommodation only. For an emmetrope with 10 D of accommodative amplitude, the range of accommodation is infinity–10 cm.

12. How does a diopter relate to meters?
A diopter is the reciprocal of the distance in meters.

13. What is the near point of a 4-D hyperope with an amplitude of accommodation of 8?
The far point is 25 cm (¼ D) behind the cornea. The patient must use 4 D of accommodation to overcome hyperopia and focus the image at infinity on the retina. Thus, he or she has 4 D to accommodate to the near point, which is 25 cm (¼ D) anterior to the cornea. However, when wearing a +4.00 lens, he or she has the full amplitude of accommodation available. The near point is now 12.5 cm (⅛ D).

14. What is the near point of a 4-D myope with an amplitude of accommodation of 8?
The far point is 25 cm (¼ D) in front of the eye. The patient can accommodate 8 D beyond this point. The near point is 12 D, which is 8.3 cm (1/12 D) in front of the cornea.

15. When a light ray passes from a medium with a lower refractive index to a medium with a higher refractive index, is it bent toward or away from the normal?
It is bent toward the normal (Fig. 3-4).

16. What is the critical angle?

The critical angle is the incident angle at which the angle of refraction is 90 degrees from normal. The critical angle occurs only when light passes from a more dense to a less dense medium.

17. What happens if the critical angle is exceeded?

When the critical angle is exceeded, total internal reflection is the result. The angle of incidence equals the angle of reflection (Fig. 3-5).

18. Give examples of total internal reflection.

Total internal reflection at the tear–air interface prevents a direct view of the anterior chamber. To overcome this limitation, the critical angle must be increased for the tear–air interface by applying a plastic or glass goniolens to the surface. Total internal reflection also occurs in fiber-optic tubes and indirect ophthalmoscopes.

19. What is the formula for vergence?

$$U + P = V,$$

where U is the vergence of light entering the lens, P is the power of the lens (the amount of vergence added to the light by the lens), and V is the vergence of light leaving the lens. All are expressed in diopters. By convention, light rays travel left to right. Plus signs indicate anything to the right of the lens, and minus signs indicate points to the left of the lens.

20. What is the vergence of parallel light rays?

The vergence of parallel light rays is zero. Parallel light rays do not converge (which would be positive) or diverge (which would be negative). Light rays from an object at infinity or going to an image at infinity have zero vergence.

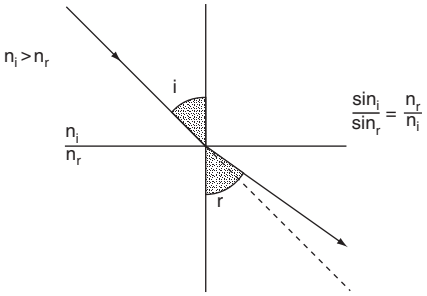

Figure 3-4. When light passes from a medium with a lower refractive index (n_i) to a medium of higher refractive index (n_r), it slows down and is bent toward the normal to the surface. Snell's law determines the amount of bending. *i* is the angle of incidence, *r* is the angle of refraction. *(From Azar DT, Strauss L: Principles of applied clinical optics. In Albert DM, Jakobiec FA [eds]: Principles and Practice of Ophthalmology, vol. 6, ed 2, Philadelphia, W.B. Saunders, 2000, pp 5329–5340.)*

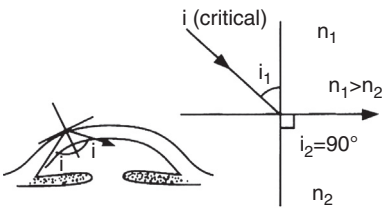

Figure 3-5. Total internal reflection occurs when the critical angle is exceeded. *(From Azar DT, Strauss L: Principles of applied clinical optics. In Albert DM, Jakobiec FA [eds]: Principles and Practice of Ophthalmology, vol. 6, ed 2, Philadelphia, W.B. Saunders, 2000, pp 5329–5340.)*

21. What is the image point if an object lies 25 cm to the left of a +5.00 lens?

Everything must be expressed in diopters: 25 cm is 4 D (1/0.25 m). Because the image is to the left of the lens,

$$U = -4D$$

$$P = +5D$$

$$-4 + 5 = 1$$

The vergence of the object is +1 D. Converted to centimeters, the object lies 1 m to the right of the lens (1/1 D = 1 m = 100 cm).

22. Draw the schematic eye, with power, nodal point (np), principal plane, f and f′, refractive indices, and respective distances labeled.

See Fig. 3-6.

23. How is the power of a prism calculated?

The power of a prism is calculated in prism diopters (Δ) and is equal to the displacement in centimeters of a light ray passing through the prism measured 100 cm from the prism. Light is always bent toward the base of the prism. Thus, a prism of 15 Δ displaces light from infinity 15 cm toward its base at 100 cm.

24. What is Prentice's rule?

$$\Delta = hD$$

The prismatic power of a lens (Δ) at any point on the lens is equal to the distance of that point from the optical axis in centimeters (*h*) multiplied by the power of the lens in diopters (*δ*). It follows that a lens has no prismatic effect at its optical center; a light ray will pass through the center undeviated (Fig. 3-7).

25. How is Prentice's rule used in real life?

In a patient who has anisometropia, the reading position may cause hyperdeviation of one eye owing to the prismatic effect.

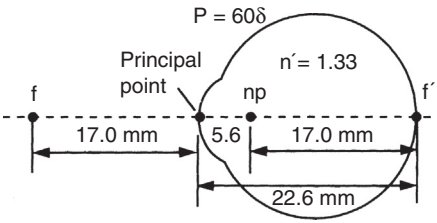

Figure 3-6. The reduced schematic eye. *(From Azar DT, Strauss L: Principles of applied clinical optics. In Albert DM, Jakobiec FA [eds]: Principles and Practice of Ophthalmology, vol. 6, ed 2, Philadelphia, W.B. Saunders, 2000, pp 5329–5340.)*

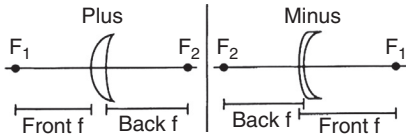

Figure 3-7. Prismatic effect of a lens according to Prentice's rule. Δ is the induced prism (measured in prism diopters), *h* is the distance from the optical center in centimeters, and *D* is the power of the lens in diopters. *(From Azar DT, Strauss L: Principles of applied clinical optics. In Albert DM, Jakobiec FA [eds]: Principles and Practice of Ophthalmology, vol. 6, ed 2, Philadelphia, W.B. Saunders, 2000, pp 5329–5340.)*

KEY POINTS: HOW TO ALLEVIATE SYMPTOMATIC ANISOMETROPIA

1. Contact lenses
2. Lowering optical centers
3. Slab-off

26. How can the prismatic effect be alleviated?

- Contact lenses move with the eye and allow patients to see through their optical center, preventing the prismatic effect.
- Lowering the optical centers decreases the *h* of Prentice's rule.
- Slab-off (removing the prism inferiorly from the more minus lens) helps to counteract the prismatic effect.

27. How does Prentice's rule affect the measurement of strabismic deviations when the patient is wearing glasses?

Plus lenses decrease the measured deviation, whereas minus lenses increase the measured deviation. The true deviation is changed by approximately 2.5 *D*%, where *D* is the spectacle power. The plus lenses have the base of the prism peripherally, whereas the minus lenses have the base of the prism centrally.

28. Bifocals can cause significant problems induced by the prismatic effect. What is the difference between image jump and image displacement?

- **Image jump** is produced by the sudden introduction of the prismatic power at the top of the bifocal segment. The object that the patient sees in the inferior field suddenly jumps upward when the eye turns down to look at it. If the optical center of the segment is at the top of the segment, there is no image jump. Image jump is worse in glasses with a round-top bifocal because the optical center is far from the distance lens's optical center. A flat-top bifocal is better because the optical center is close to the distance optical center.
- **Image displacement** is the prismatic effect induced by the addition of the bifocal and the distance lenses in the reading position. Image displacement is more bothersome than image jump for most people. A flat-top lens is essentially a base-up lens, whereas a round-top lens is a base-down lens. A myopic distance lens has base-up prismatic power in the reading position; thus, image displacement is worsened with a flat-top lens. The prism effects are additive. Similarly, a hyperopic correction is a base-down lens in the reading position; thus, a round-top lens makes image displacement an issue.

29. Should a hyperope use a round-top or flat-top reading lens?

A plus lens will have significant image displacement with a flat-top lens. Image displacement is lessened with a round-top lens. Although image jump will be present, it is the less disturbing of the two.

30. Should a myope use a flat-top or round-top reading lens?

A round-top lens has significant image displacement with a minus lens. A flat-top lens minimizes image displacement and image jump.

31. What is the circle of least confusion?

Patients with astigmatism have two focal lines formed by the convergence of light rays. The first focal line is nearer the cornea and created by the more powerful corneal meridian. The second focal line is farther away, created by the less powerful meridian. The circle of least confusion is the circular cross-section of the Sturm's conoid, dioptrically midway between the two focal lines (Fig. 3-8). The goal of refractive correction is to choose a lens that places the circle of least confusion on the retina.

32. What is the spherical equivalent of $-3.00 + 2.00 \times 125$?

Take half the cylinder and add it to the sphere. The spherical equivalent is –2.00 sphere.

33. Change the following plus cylinder refraction to the minus cylinder form: $-5.00 + 3.00 \times 90$.

First, add the sphere and cylinder to each other. Then change the sign of the cylinder, and add 90 degrees to the axis. Thus, the minus cylinder form is $-2.00 - 3.00 \times 180$.

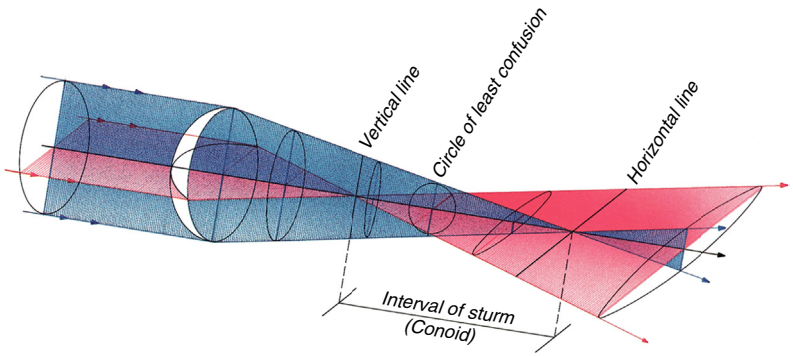

Figure 3-8. The circle of least confusion. *(From Azar DT, Strauss L: Principles of applied clinical optics. In Albert DM, Jakobiec FA [eds]: Principles and Practice of Ophthalmology, vol. 6, ed 2, Philadelphia, W.B. Saunders, 2000, pp 5329–5340.)*

34. After large incision extracapsular cataract surgery, a patient has the following refraction: +1.00 + 3.00 × 100. Does the patient have with-the-rule or against-the-rule astigmatism?

With-the-rule astigmatism is corrected with a plus cylinder at 90 degrees (±15 to 20 degrees). Against-the-rule astigmatism is corrected with a plus cylinder at 180 degrees (±15 to 20 degrees). The patient has with-the-rule astigmatism.

35. How should you proceed with the patient's care?

Check the remaining sutures. Cutting the 11:00 suture will relax the wound and decrease the amount of astigmatism.

36. What if another patient has a refraction of +2.00–2.00 × 90 after large incision extracapsular cataract extraction? Where should you cut the suture?

Changing the refraction to the plus cylinder form, you see that the patient is plano + 2.00 × 180 and has against-the-rule astigmatism. You cannot cut any sutures to relax the astigmatism. The only option is to do a relaxing incision of the cornea, but it is likely that the patient will tolerate glasses, especially if the refraction is close to the preoperative correction. Also, check the preoperative keratometry. The patient may have had against-the-rule astigmatism before surgery.

37. Thick lenses have aberrations. List them.

- **Spherical aberration:** The rays at the peripheral edges of the lens are refracted more than the rays at the center, thus causing night myopia. The larger pupil at night allows more spherical aberration than the smaller pupil during daylight.
- **Coma:** A comet-shaped blur is seen when the object and image are off the optical axis. Coma is similar to spherical aberration but occurs in the nonaxial rays.
- **Astigmatism of oblique incidence:** When the spherical lens is tilted, the lens gains a small astigmatic effect that causes curvature of the field (i.e., spherical lenses produce curved images of flat objects). This effect is helpful in the eye because the retina has a similar curvature (Fig. 3-9).
- **Chromatic aberration:** Each wavelength has its own refractive index; the shortest wavelengths are bent the most (Fig. 3-10).
- **Distortion:** The higher the spherical power, the more significantly the periphery is magnified or minified in relation to the rest of the image. A high plus lens produces pincushion distortion; a high minus lens produces barrel distortion.

38. Are red or green light rays refracted more by a plus lens?

The shorter green rays are bent more than the longer red rays. This distinction causes chromatic aberration and is the basis for the red–green duochrome test. Green rays are focused 0.50 D closer to the lens than red rays. When a corrected myopic patient is fogged to prevent accommodation, the red letters should be clearer than the green. Slowly add more minus in 0.25 increments until the green and red letters are equal in clarity. This technique prevents overcorrection of myopia.

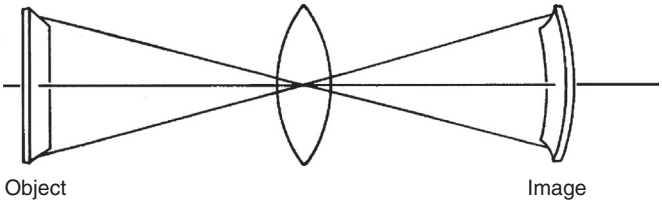

Figure 3-9. The aberration caused by the astigmatism of oblique incidence is helpful in the eye because the curvature of the field that it induces is almost identical to the retinal curvature.

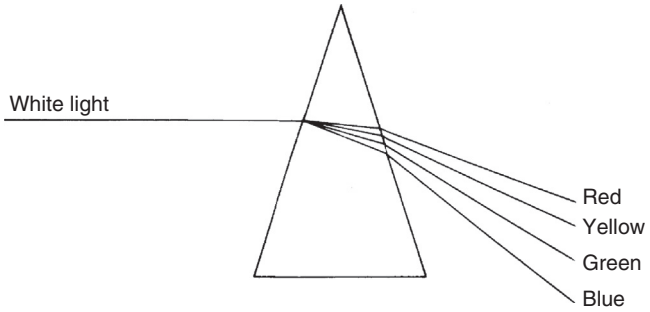

Figure 3-10. Because each wavelength has a different refractive index, light passing through a prism will reveal the characteristic visible spectrum. *(From American Academy of Ophthalmology: Basic and Clinical Science Course. Section 3. Optics, Refraction, and Contact Lenses. San Francisco, American Academy of Ophthalmology, 1992.)*

39. A myopic patient tilts his glasses to see in the distance. What does this tell you?

The patient is using the principle of astigmatism of oblique incidence to strengthen the power of his or her glasses. He or she needs a refraction. Tilting a minus lens induces a minus cylinder with axis in the axis of tilt. Tilting a plus lens induces a plus cylinder with axis in the axis of tilt. A small amount of additional sphere of the same sign is induced as well.

40. What measurements are necessary in determining the intraocular lens implant calculation?

Axial length in millimeters and keratometry readings in diopters. The desired postoperative refraction is also necessary. The SRK formula is commonly used. For emmetropia, the formula is $P = A - 2.5(\text{axial length}) - 0.9(K_{avg})$, where P equals the implant power, A is the implant constant as determined by the manufacturer, and K_{avg} is the average of the keratometry readings. The A constant also can be individualized by analysis of previous cases. For each diopter of desired ametropia, add 1.25–1.50 D. For example, if the SRK formula reveals a calculation of +18.0 D for emmetropia, implant a +19.50 D lens for –1.00 D.

41. How does an axial error that is incorrect by 0.1 mm affect the intraocular lens calculation?

For every 0.1 mm error, the calculation is affected by 0.25 D. Recheck the A-scan if the axial length is less than 22 mm or more than 25 mm or if there is more than a 0.3-mm difference in the measurement between the two eyes.

42. How does an error in keratometry readings affect the intraocular lens calculation?

For every error of 0.25 D, the calculation is in error by 0.25 D. Recheck the keratometer measurements if the average corneal power is less than 40 D or more than 47 D. Also check if there is a difference of more than 1 D in the average keratometer readings between eyes.

43. What is the formula for transverse magnification?

Also known as linear or lateral magnification, transverse magnification equals $I/O = v/u$, where I is the size of the image, O is the size of the object, v is the distance from the lens to the image, and u is the distance of the object from the lens. All are measured in millimeters.

44. What is the formula for axial magnification?
Axial magnification is the square of the transverse magnification. Magnification along the visual axis causes distortion in three-dimensional images.

45. What is the effect of axial magnification on accommodative requirements for a given near-viewing distance?
Hyperopes must accommodate more through glasses than through contact lenses, because the stronger plus prescription required in the contact lens provides more axial magnification of the image compared with the prescription for glasses. Conversely, myopes must accommodate less through glasses than through contact lenses. This effect can be clinically significant in early presbyopic years. The effect is greatest with high refractive errors. For example, a −5.00 myope may be able to read without bifocal glasses but require reading glasses with contact lenses. Conversely, a hyperope may be able to forego reading glasses with contact lenses but need bifocal glasses.

46. What is angular magnification?
Angular magnification is the magnification of a simple magnifier, such as viewing something with an eye or a single lens. Magnification is $D/4$, where D is the power of the lens used.

47. What is the magnification of a direct ophthalmoscope?
The examiner uses the optics of the patient's eye as a simple magnifier. Estimating the power of the eye as +60 D, the magnification is 15×. Thus, the retina appears 15 times larger than it is.

48. Does an astronomic telescope form an upright or an inverted image?
It forms an inverted image, which has few uses in ophthalmic optics.

49. Does a Galilean telescope form an upright or an inverted image?
It forms an upright image, which is used often in ophthalmic optics. An aphakic eye corrected with spectacles or a contact lens is an example. The eyepiece is the aphakic eye estimated to be −12.50 D, and the objective is the corrective lens.

50. What is the magnification formula for a telescope?

$$\text{Magnification} = \text{Deyepiece/D objective}$$

This formula applies to both astronomic and Galilean telescopes. For the aphakic eye with a spectacle correction of +10.00 D, the magnification is 1.25 or 25%. For a contact lens, this translates to +11.75 D, accounting for the vertex distance of 10 mm. Magnification now is 1.06 or 6%. Thus, aniseikonia with a contact lens is better tolerated than aniseikonia with glasses if the patient needs less powerful correction in the other eye.

51. When using the direct ophthalmoscope, which patient provides the larger image of the retina—the hyperope or the myope?
The myope functions as a Galilean telescope and provides extra magnification. The eyepiece (spectacle lens) is a minus lens, and the objective (the patient's own lens) is a plus lens. The hyperope functions as a reverse Galilean telescope and provides minification in comparison. In this situation, the eyepiece is a plus lens, and the objective is a minus lens.

52. What do you need to determine the best low-vision aid for a patient?
Best refraction, visual acuity, visual field, and practical needs of the patient.

53. What are the advantages and disadvantages of using a high add in a bifocal for a low-vision aid?
The advantages include a large field of view. Disadvantages include a short reading distance, as well as significant cost.

54. What are the advantages and disadvantages of using a high-power single-vision lens as a low-vision aid?
High-power single-vision lenses come in monocular and binocular forms. They also afford a large field of view but have a short reading distance.

55. How do you estimate the strength of plus lens needed to read newspaper print without accommodation?
The reciprocal of the best Snellen acuity is equal to the plus power of the lens required. For example, if a patient can read 20/60, a +3.00 D will suffice. The reciprocal of the diopter power gives the reading distance (i.e., 33 cm).

56. What adjustment is necessary when a binocular high-power single-vision lens is used?
Base in prisms to augment the natural ability to converge. Otherwise, patients develop exotropia at near when looking through high plus lenses.

57. What are the advantages and disadvantages of handheld magnifiers for low-vision aids?
Handheld magnifiers have a variable eye-to-lens distance and are easily portable. They enjoy a high rate of acceptability. However, they have a small field of view when the lens is held far from the eye and are difficult to manipulate by patients with tremors and arthritis. A stand magnifier may be more useful for such patients.

58. What are the advantages and disadvantages of using loupes as a low-vision aid?
Loupes are basically prefocused telescopes. They allow a long working distance and keep the hands free. But they have a small field of view, have a limited depth of field, and are expensive.

59. The devices mentioned thus far are for magnifying at near. What is available for distance aids?
The only magnifying device for distance is a telescope. Telescopes are monocular or binocular and can be handheld or mounted on glasses. They also have an adjustable focus. Unfortunately, they have a restricted field of view (approximately 8 degrees). Thus, the object of regard may be difficult to find.

60. Do convex mirrors add plus or minus vergence?
Convex mirrors add minus vergence, like minus lenses. Concave mirrors add plus vergence, like plus lenses. Plane mirrors add no vergence.

61. What is the reflecting power in diopters of a mirror?
$D = 2/r$, where r is the radius of curvature. The focal length is one-half the radius.

62. What instrument uses the reflecting power of the cornea to determine its readings?
The keratometer uses the reflecting power of the cornea to determine the corneal curvature. The formula is $D = (n - 1)/r$, where D is the reflecting power of the cornea and n is the standardized refractive index for the cornea (1.3375).

63. How much of the cornea is measured with a keratometer?
Only the central 3 mm. A peripheral corneal scar or defect may be missed by using a keratometer instead of a cornea map.

64. Why does a keratometer use doubling of its images?
A keratometer doubles its images to avoid the problems of eye movement in determining an accurate measurement. Doubling is done with prisms.

65. What is a Geneva lens clock?
A Geneva lens clock is a device to determine the base curve of the back surface of a spectacle. It is often used clinically to detect plus cylinder spectacle lenses in a patient used to minus cylinder lenses. It is specifically calibrated for the refractive index of crown glass. A special lens clock is available for plastic lenses.

66. Do you measure the power of spectacles in a lensmeter with the temples toward you or away from you?
The distance is measured with the temples facing away from you (back vertex power). The add is measured with the temples pointing toward you (front vertex power). You must measure the difference between the top and the bottom segments, especially if the patient has a highly hyperopic prescription.

67. If you obtain "with" movement during retinoscopy, is the far point of the patient in front of the peephole, at the peephole, or beyond the peephole?
It is beyond the peephole. The goal is neutralization of the light reflex so that the patient's far point is at the peephole. The light at the patient's pupil fills the entire space at once. More plus must be added to the prescription to move the far point to neutralization. "Against" movement means that the far point is in front of the peephole; more minus must be added to move the far point to neutralization.

68. What does a pachymeter measure?
It measures the corneal thickness or anterior chamber depth.

69. How does the Hruby lens give an upright or inverted image?
A Hruby lens is −55 D and gives an upright image. The Goldman lens is −64 D and also provides an upright image. The Volk 90 D lens provides an inverted image.

70. Why does the indirect ophthalmoscope provide a larger field of view than the direct ophthalmoscope?
The condensing lens used with the indirect ophthalmoscope captures the peripheral rays to give a field of view of 25 degrees or more depending on the lens power used. The direct ophthalmoscope does not use the condensing lens and thus provides only a 7 degree field of view.

71. What are the wavelengths of the spectrum of visible light?
The range is from 400 nm for violet light to 700 nm for red light. Anything shorter than 400 nm is considered ultraviolet, and anything longer than 700 nm is in the infrared spectrum.

72. Antireflective coatings on spectacle lenses are based on what principle?
Interference. Antireflective coatings use destructive interference. The crest of one wavelength cancels the trough of another.

73. What is the most effective pinhole diameter?
A pinhole diameter of 1.2 mm neutralizes up to 3 D of refractive error. A 2 mm pinhole neutralizes only 1 D. An aphakic patient may need a +10 D lens in addition to the pinhole to obtain useful visual acuity.

74. When is a cycloplegic refraction indicated?
- For patients younger than 15 years, especially if they have strabismus. Make sure to measure the deviation before cycloplegia.
- For hyperopes younger than 35 years, especially if they experience asthenopia.
- For patients with asthenopia suggestive of accommodative problems.

Note: Check accommodative amplitudes and reading adds before cycloplegia.

75. Which cycloplegic agent lasts the longest? The shortest?
Atropine lasts for 1 to 2 weeks. Watch for toxic effects in small children and elderly patients. Tropicamide (Mydriacyl) lasts 4 to 8 hours and is not strong enough for cycloplegia in children. One or two diopters of hyperopia may remain. Cyclogyl lasts 8 to 24 hours, homatropine 1 to 3 days, and scopolamine 5 to 7 days.

76. What are the signs and symptoms of systemic intoxication from cycloplegic medications? How are they treated?
Signs and symptoms of systemic intoxication include dry mouth, fever, flushing, tachycardia, nausea, and delirium. Treatment includes counteraction with physostigmine.

77. When is it important to measure the vertex distance in prescribing glasses?
Measure the vertex distance when the patient has a strong prescription of more than ±5.00 D.

78. What is the threshold for prescribing glasses in a child with astigmatism?
When visual acuity is not developing properly, as noted by amblyopia or strabismus, give the full correction. Children tolerate full correction better than adults. Most often, amblyopia or strabismus occurs with at least 1.50 D of astigmatism. Anisometropia that presents with 1.00 D or more of hyperopic asymmetry also requires full correction.

79. What may cause monocular diplopia?
- Corneal or lenticular irregularity
- Decentered contact lens
- Inappropriate placement of reading add
- Transient sensory adaptations after strabismus surgery
- Distortion from retinal lesions (rare)

80. What conditions may give a false-positive reading with a potential acuity meter?
Macular scotomas in a patient with amblyopia or retinal disease, such as age-related macular degeneration, may give a false positive. Acute macular edema also may elevate the reading, but the elevation disappears with chronic edema. An irregular corneal surface can falsely improve the potential acuity; however, wearing a contact lens may help.

81. What do you check when patients complain that their new glasses are not as good as their previous pair?

- Ask specifically what the complaint is: Distance reading? Near problems? Asthenopia? Diplopia? Pain behind the ears or at the nose bridge from ill-fitting glasses?
- Read the new and old glasses on the lensmeter and compare. Make sure that the old glasses did not have any prism. Check the patient for undetected strabismus with cover testing.
- Refract the patient again, possibly with a cycloplegic agent if the symptoms warrant.
- Check the optical centers in comparison with the pupillary centers.
- Check whether the reading segments are in the correct position—level with the lower lid.
- Make sure that the new glasses fit the patient correctly.
- Check whether the old glasses were made with plus cylinder by using the Geneva lens clock.
- Check whether the base curve has changed with the Geneva lens clock.
- Evaluate the patient for dry eye.
- If the patient has a high prescription, check the vertex distance. Often it is easier to refract such patients over their old pair of glasses to keep the same vertex distance.
- Check the pantoscopic tilt. Normally the tilt is 10 to 15 degrees so that when the patient reads, the eye is perpendicular to the lens. If the tilt is off, especially in relation to the old glasses, the patient may notice.
- With postoperative glasses, evaluate for diplopia in downgaze due to anisometropia.
- Perhaps the add is too strong or too weak. Check the patient using trial lenses and reading material.
- Sometimes if the diameter of the lens is much larger in the newer frames, the patient notices significant distortion in the peripheral lens. Encourage a small frame. However, too small a frame can make progressive bifocals very difficult. It is best to keep a frame size fairly consistent.
- Did the patient change bifocal types? Round top, flat top, executive style, and progressives all require different adaptations. Patients often have trouble when changing styles.
- Above all, try to test the new prescription in trial frames with a walk around the office. You do not want to go through this process again.

82. If after repeat refraction the patient suddenly develops more hyperopia than you previously noted, what do you look for?

Look for a cause of acquired hyperopia, such as a retrobulbar tumor, central serous retinopathy, posterior lens dislocation, or a flattened cornea from a contact lens.

KEY POINTS: CAUSES OF MONOCULAR DIPLOPIA

1. Corneal or lenticular irregularity
2. Decentered contact lens, intraocular implant, or refractive surgery
3. Inappropriate placement of reading add
4. Sensory problems after strabismus surgery
5. Retinal lesions (very rare)

83. What if the patient has more myopia than previously noted?

Check the cycloplegic refraction to make sure that it is true. Acquired myopia may be caused by diabetes mellitus, sulfonamides, nuclear sclerosis, pilocarpine, keratoconus, a scleral buckle for retinal detachment, and anterior lens dislocation.

84. What about acquired astigmatism?

Lid lesions such as hemangiomas, chalazions, and ptosis may cause acquired astigmatism. A pterygium or keratoconus may reveal a previously undetected astigmatism. And, of course, healing cataract wounds may change the previous astigmatism.

85. If the astigmatism has changed and the patient has difficulty with tolerating the new prescription, what are the options?

If the astigmatism is oblique, try rotating the axis toward 90° or toward the old axis. The astigmatic power may be reduced, but keep the spherical power the same. Sometimes a gradual change in prescription over time may allow the patient to adapt. For example, if a patient's prescription is $-3.00 + 2.00 \times 110$, a possibility is $-2.50 + 1.00 \times 90$. The spherical equivalent of -2.00 D has been maintained.

86. What does laser stand for?
Laser stands for light amplification by stimulated emission of radiation.

87. To steepen a contact lens fit, do you increase the diameter of the lens or the radius of curvature?
Increasing the diameter of the lens or decreasing the radius of curvature will steepen the lens (Fig. 3-11). This information is useful for lenses that fit too tightly.

88. How many seconds of arc does the "E" on the 20/20 line of the Snellen eye chart subtend?
It subtends 5″. The Snellen eye chart measures the minimal separable acuity.

89. When the Jackson cross is used to define the astigmatic axis, is the handle of the lens parallel to the axis or 45 degrees from it?
It is parallel. To define the astigmatic power, the handle is 45 degrees to the axis. Define the axis before the power.

90. A 25-year-old patient has a manifest refraction of +0.50 OU and complains of asthenopia. What do you do?
Check the patient's accommodative amplitude and look for an exophoria at near to evaluate for convergence insufficiency. Then do a cycloplegic refraction to check for undercorrection. On exam, the amplitude of accommodation is 3 D OU. Because this value is low for a young person, suspect undercorrection of hyperopia. Indeed, the cycloplegic refraction is +2.50 OU. The patient has accommodative spasm. Try giving one-half of the cycloplegic findings. Sometimes atropine is needed to break the spasm.

91. What instrument is useful to measure the accommodative amplitude?
Accommodative amplitude is measured with the Prince rule.

92. A 35-year-old man has 20/40 uncorrected vision. With +0.50 glasses, he is 20/20. He will remain 20/20 with a +1.50 manifest refraction. With cycloplegia, he has a refraction of +4.00. Define absolute hyperopia, facultative hyperopia, manifest hyperopia, and latent hyperopia
- **Total hyperopia:** Found by cycloplegia, +4.00
- **Manifest hyperopia:** Found without cycloplegia; more plus will blur vision, +1.50

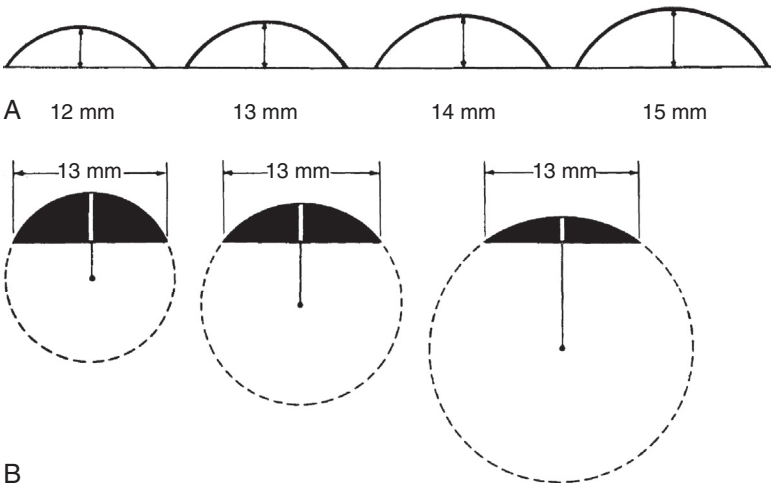

Figure 3-11. A, When the radius of curvature is kept constant while the diameter of the contact lens is increased, the fit steepens. **B,** Conversely, increasing the radius of curvature while maintaining the same diameter allows a flatter fit. *(From American Academy of Ophthalmology: Basic and Clinical Science Course. Section 3. Optics, Refraction, and Contact Lenses. San Francisco, American Academy of Ophthalmology, 1992.)*

- **Latent hyperopia:** Total minus manifest hyperopia, +2.50
- **Absolute hyperopia:** The minimal correction that the patient needs to see distances, +0.50
- **Facultative hyperopia:** Manifest minus absolute hyperopia; compensation accomplished by accommodation, +1.00

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COLOR VISION

Mitchell S. Fineman

CHAPTER 4

1. **What are photons?**
   Atoms consist of a nucleus (composed of protons and neutrons) and electrons, which revolve around the nucleus in orbits of more or less fixed diameter. An electron can move to a higher orbit if it receives energy from an external source (e.g., heating). However, it remains in the higher orbit for only one-hundred-millionth of a second. As it falls back to its original lower orbit, it releases its excess energy by emitting a small "packet" of energy called a quantum or a photon.

2. **Describe the physical properties of photons.**
   In a vacuum, all photons move at the speed of light. As they travel, they vibrate, causing measurable electric and magnetic effects (wave properties). The farther an electron falls to reach its original lower orbit, the greater its frequency of vibration, and the shorter its wavelength (λ), which is the straight-line distance a photon moves during one complete vibration. Frequency and wavelength are related by the formula $f = c/\lambda$, where f is the frequency of vibration, λ is the wavelength, and c is the speed of light. Thus, f and λ are inversely proportional (i.e., as frequency increases, wavelength decreases). For example, γ-rays have a very high frequency and a very short wavelength, and radio waves have a very low frequency and a rather long wavelength.

3. **What is the electromagnetic spectrum?**
   Light, x-rays, γ-rays, and radio waves are all forms of electromagnetic energy. When photons (quanta) are classified according to their wavelength, the result is the electromagnetic spectrum. The photons with the longest wavelengths are radio and television waves; those with the shortest are γ-rays. The photons we see (visible light) are near the middle of the spectrum.

4. **Why can we "see" light, but not other types of electromagnetic energy?**
   The rods and cones of the retina (photoreceptors) contain pigments that preferentially absorb photons with wavelengths between 400 and 700 nm (a nanometer is a billionth of a meter) and convert their energy into a neuronal impulse that is carried to the brain. Wavelengths longer than 700 nm and shorter than 400 nm tend to pass through the sensory retina without being absorbed (Fig. 4-1).

5. **What is the light spectrum?**
   Photons can be classified not only by their wavelength but also by the sensation they cause when they strike the retina. Photons of the shortest wavelengths that we can see are perceived as blue and green; those of longer wavelengths are perceived as yellow, orange, and red.

6. **How does a prism break white light into the colors of the rainbow?**
   Photons travel at the speed of light in a vacuum, but if they enter a denser medium, such as glass, their wavelength and speed decrease. The frequency of vibration remains the same. The shorter the wavelength, the more the speed is decreased. For example, imagine two photons traveling through a vacuum, one of wavelength 650 nm and the other of wavelength 450 nm. As long as they remain in a vacuum, they keep pace with one another. When they strike the glass perpendicularly, the 450 nm photon is slowed down more than the 650 nm photon. If they enter the glass obliquely, their paths are bent in proportion to how much their speed is slowed. In other words, the shorter the wavelength, the greater the bending. The blue is bent more and is separated from the red.

7. **How do rods differ from cones?**
   Both rods and cones are photoreceptors, which are defined as retinal cells that initiate the process of vision. Rods function best when the eye is dark-adapted (i.e., for night vision). They cannot distinguish one color from another. Cones, on the other hand, function when the retina is light-adapted (i.e., for day vision).

8. **What are the visual pigments?**
   There are four visual pigments: rhodopsin, which is present in rods, and the three cone pigments. All visual pigments are made up of 11-*cis* retinal (vitamin A aldehyde) and a protein called an opsin.

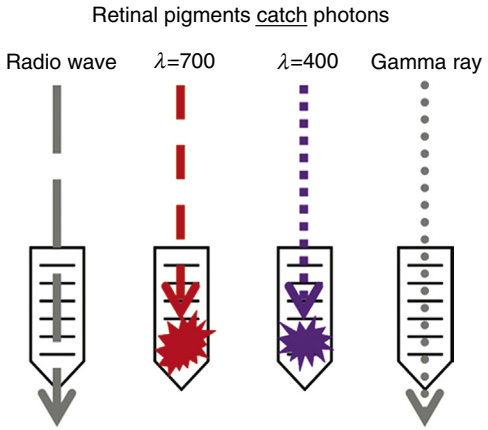

Figure 4-1. Photoreceptors are stimulated only by certain wavelengths of light.

When a photon is absorbed, the 11-*cis* retinal is converted to the all-*trans* form and is released from the opsin, initiating an electrical impulse in the photoreceptor that travels toward the brain. The eye then resynthesizes the rhodopsin.

9. Describe the three cone pigments.

Our ability to distinguish different colors depends on the fact that there are three different kinds of cone pigment. All visual pigments use retinal, but each has a different opsin. The function of the different opsins is to rearrange the electron cloud of retinal, thereby changing its ability to capture photons of different wavelengths. Red-catching cones (R cones) contain erythrolabe, which preferentially absorbs photons of long wavelengths. It is best stimulated by 570-nm photons, but also absorbs adjoining wavelengths. Blue-catching cones (B cones) contain cyanolabe, which absorbs the shortest wavelengths best. Its maximal sensitivity is at 440 nm. Green-catching cones (G cones) contain chlorolabe, which is most sensitive to the intermediate wavelengths. Its maximal sensitivity is at 540 nm.

10. How does the sensation of light get to the brain?

The electrical signals initiated by absorption of photons by the photoreceptors are transmitted to bipolar cells and then to ganglion cells. Horizontal and amacrine cells modify these messages. For example, if a cone is strongly stimulated, it sends inhibitory messages by way of a horizontal cell to neighboring cones, thereby reducing "noise" and sharpening up the message the brain receives. Bipolar cells send similar inhibitory messages by way of amacrine cells. The axons of ganglion cells form the optic nerve, which carries information to the brain. In the brain is the "hue center" (Fig. 4-2), which adds up the information from the different color channels and determines which color we see. In general, the hue we see depends on the relative numbers of photons of different wavelengths that strike the cones.

11. What three attributes are necessary to describe any color?

To accurately describe any color, one must specify three attributes: hue, saturation, and brightness.

12. What is hue?

Hue is synonymous with "color" and is the attribute of color perception denoted by blue, red, purple, and so forth. Hue depends largely on what the eye and brain perceive to be the predominant wavelength present in the incoming light. In simplest terms, this means that if light of several wavelengths strikes the eye and more light of 540 nm is present than is light of other wavelengths, we will see green.

13. What is saturation?

Saturation (chroma) corresponds to the purity or richness of a color. When all the light seen by the eye is the same wavelength, we say that a color is fully saturated. Vivid colors are saturated. If we add white to a saturated color, the hue does not change, but the color is paler (desaturated). For example, pink is a desaturated red.

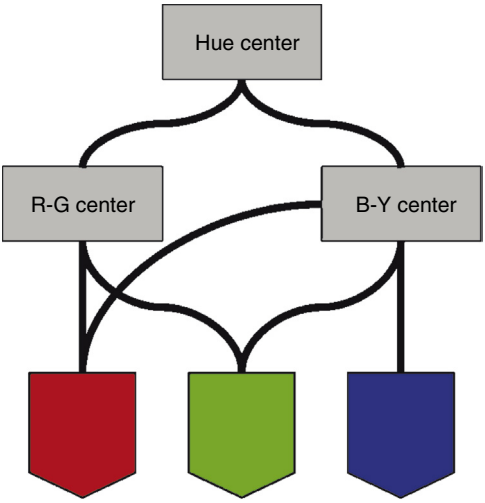

Figure 4-2. Illustration of the hue center.

14. What is brightness?

Brightness (luminance, value) refers to the quantity of light coming from an object (the number of photons striking the eye). If we place a filter over a projector or gradually (with a rheostat) lower its intensity, the brightness decreases.

15. What are complementary colors?

When equal quantities of complements are added, the result is white. Blue-green and red are complements as are green and magenta. (We are talking of colored lights, not paints.)

16. What is the color wheel?

The color wheel is made up of all hues arranged in a circle so that each hue lies between those hues it most closely resembles and complementary hues lie opposite each other. Using the color wheel, we can predict the color that will result when two different lights are mixed. When noncomplements are mixed, the resultant color lies between the two original colors. The exact color seen depends on the quantity of each color used. For example, equal quantities of red and green result in yellow, whereas a large quantity of red and a relatively small quantity of green result in orange.

17. How does the eye differ from the ear?

Unlike the ear, which can distinguish several musical instruments playing at once, our eye and brain cannot determine the composition of a color we see. For example, if we present the eye with a light composed purely of 589 nm photons, the eye sees yellow. However, if we mix green and red lights in the proper proportions, the eye also sees yellow and cannot differentiate this from the other. Similarly, when two complements are mixed, we see white and cannot distinguish this white from the white seen when equal quantities of all wavelengths are present. Further, if we add white light to our original 589 nm yellow, the eye still sees yellow. Similarly, a light composed only of 490 nm photons is seen as blue-green and cannot be distinguished from an appropriate mixture of blue and green.

18. What are the primary colors?

When speaking of colored lights, the primary hues (also called the additive primaries) are red, green, and blue. Any color, including white, can be produced by overlapping red, green, and blue lights on a screen in the proper proportions. The reflecting screen can be regarded as a composite of an infinite number of tiny projectors. The eye, bombarded by all these photons, "adds up" their relative contributions. The color we see is determined by how many quanta of each wavelength reach the eye. Color television relies on this ability of the eye to add up tiny adjacent points of light. If one looks at a color

television from 6 inches away, one sees tiny dots of only three colors: red, green, and blue. If one then backs away, the full range of colors becomes apparent and the eye can no longer distinguish the tiny dots. It synthesizes (adds up) the adjacent colors (e.g., tiny dots of red and blue = purple; red and green = yellow; red and green and blue = white; and so forth).

19. Where is the final determination of color made?

The hue center, localized in the cortex, synthesizes information it receives from two "intermediate centers": the R–G center and the B–Y center. The information sent to the hue center from the R–G center depends on the relative stimulation of the R and G cones. For example, when light of 540 nm strikes the retina, it will stimulate both R and G cones. However, because the G cones are stimulated much more than the R cones, the message received by the hue center is predominantly "green." On the other hand, if light of 590 nm strikes the retina, the R cones are stimulated more than the G cones and we see yellow. When light of 630 nm strikes the retina, the G cones are not stimulated at all and we see red. The B cones send information to the B–Y center. The Y information does not come from Y cones because there are no Y cones. Information from R and G cones has the effect of yellow in the B–Y center.

20. Why is brown, which is definitely a color, not on the color wheel?

Because brown is a yellow or orange of low luminance.

21. Describe the Bezold-Brucke phenomenon.

As brightness increases, most hues appear to change. At low intensities, blue-green, green, and yellow-green appear greener than they do at high intensities, when they appear bluer. At low intensities, reds and oranges appear redder and at high intensities, yellower. The exceptions are a blue of about 478 nm, a green of about 503 nm, and a yellow of about 578 nm. These are the wavelengths of invariant hue.

22. What is the Abney effect?

As white is added to any hue (desaturating it), the hue appears to change slightly in color. All colors except a yellow of 570 nm appear yellower.

23. What are the relative luminosity curves?

The relative luminosity curves illustrate the eye's sensitivity to different wavelengths of light. They are constructed by asking an observer to increase the luminance of lights of various wavelength until they appear to be equal in apparent brightness to a yellow light whose luminance is fixed. When the eye is light-adapted, yellow, yellow-green, and orange appear brighter than do blues, greens, and reds. The cones' peak sensitivity is to light of 555 nm. A relative luminosity curve can also be constructed for the rods in a dark-adapted eye, even though the observer cannot name the various wavelengths used. The rods' peak sensitivity is to light of 505 nm (blue).

24. Define lateral inhibition.

As mentioned above, as cones of one kind (e.g., R cones) are stimulated, they may send an inhibitory message by way of horizontal and amacrine cells to adjacent cones of the same kind (e.g., other R cones). Therefore, when a purple circle is surrounded by a red background, the R cones in the purple area are inhibited, making the purple (a combination of red and blue) appear bluer than it really is. If the purple is surrounded by blue, it appears redder.

25. What are afterimages?

If one stares at a color for 20 seconds, it begins to fade (desaturate). Then, if one gazes at a white background, the complement of the original color (afterimage) appears (Fig. 4-3). These two phenomena depend on the fact that even when cones are not being stimulated, they spontaneously send a few signals toward the brain. For example, when red light is projected onto the retina, the eye sees red because the R cones are stimulated much more than the G cones and B cones. The G and B contribution to the hue center is far outweighed by the R. After several seconds, the red color fades (becomes desaturated) because the red cones, being more strongly stimulated, cannot regenerate their pigment fast enough to continue to send such a large number of signals (fatigue). Now the G and B cone contribution to the hue center increases relative to that of the R cones and the brain "sees" a desaturated or paler red. It is as if we added blue-green light to the red. (Recall that blue-green is the complement of red and that mixing complements yields white.) When the red light is turned off, the frequency of the spontaneous messages sent to the brain by the fatigued R cones is far less than that sent by the G and B cones, so the brain sees blue-green, or cyan, the complement of red (Fig. 4-4).

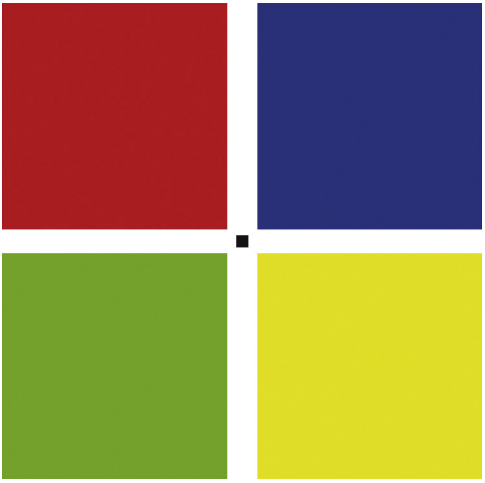

Figure 4-3. Stare at the black dot for 30 seconds and then look at a blank white area. The afterimage seen is the complement of each color.

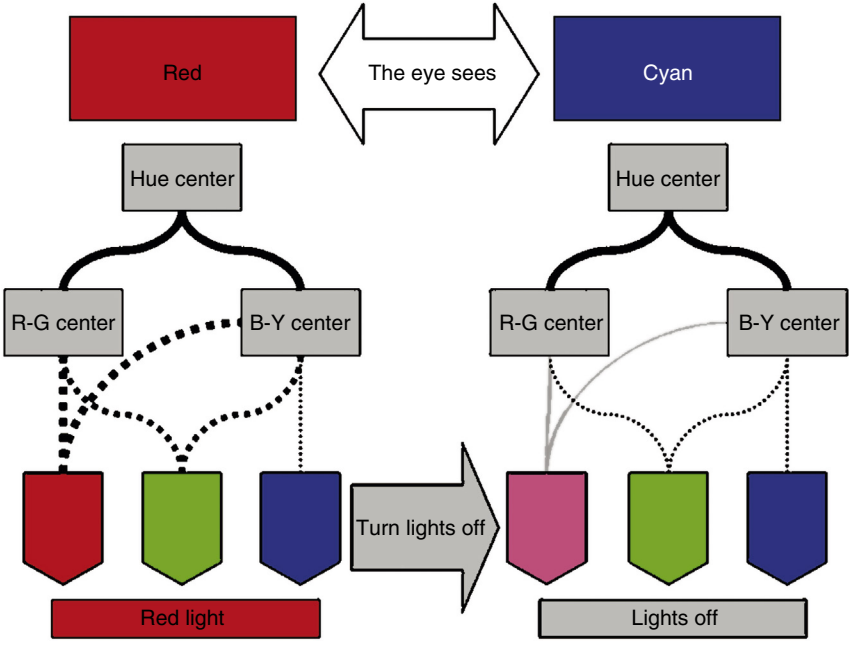

Figure 4-4. Afterimages are formed when certain photoreceptors cannot regenerate pigment quickly enough, allowing other photoreceptors to appear relatively more stimulated.

26. Why are white flowers white?

The color of any object that is not white or black depends on the relative number of photons of each wavelength that it absorbs and reflects. Our ambient light, derived from the sun, contains approximately equal numbers of all the photons that make up the light spectrum. White paint reflects all photons equally well, and white flowers appear white.

27. Why is charcoal black?

Charcoal absorbs most of the light that strikes it. Because very few photons are reflected toward the eye, the photoreceptors are not stimulated and no color is seen.

28. Why are blue flowers blue?

The pigments in blue flowers absorb red and yellow photons best, green next best, and blue least of all; therefore, more blue photons are reflected than others, and the eye sees blue. A green leaf is green because chlorophyll strongly absorbs blue and red and reflects green.

29. Why does mixing red and blue-green lights result in white, but mixing red and green paint results in brown?

Oil paints are made by mixing (suspending) tiny clumps of pigment in an opaque medium (the binder). Pigments reflect and absorb some wavelengths of light better than others. The dominant wavelength reflected is the color of the paint. When two lights are mixed, we speak of an "additive" mixture. But when two paints are mixed, each pigment subtracts some of the light the other would reflect. The resultant mixture is darker than either of the two originals. Red paint mixed with green paint results in brown because enough light is subtracted that the eye sees a yellow of low luminance.

30. Why does mixing paints yield unpredictable results?

An artist or home decorator never knows the exact absorption spectrum of the originals. Two greens may appear to be the same but, because their pigments are not identical, do not yield the same color when mixed with the same yellow.

31. Why do colors appear different under fluorescent light as opposed to incandescent light?

Tungsten (incandescent) lightbulbs emit relatively more photons of the longer (red) wavelengths than of the shorter (blue) wavelengths, whereas fluorescent lightbulbs emit relatively more light in the blue and green wavelengths. A shopper who picks out material for drapes in a store that has fluorescent lighting may be surprised to find out that the material looks quite different at home. A purple dress appears redder under incandescent light than it does under fluorescent light.

KEY POINTS: COLOR VISION

1. Rods function best in the dark-adapted state and cones function in the light-adapted state.
2. Any color can be produced by overlapping red, green, and blue lights in the proper proportions.
3. Afterimages appear as the complement of the original color.
4. Deuteranopes and tritanopes have difficulty distinguishing red from green.
5. All red-green disorders are inherited in an X-linked recessive pattern.

32. Why is the sky blue?

The sun emits light of all of the spectral colors. If an astronaut in space looks at the sun, it appears white. If the astronaut looks away from the sun, he sees that the outer space is black, because the photons not coming directly at him pass through space unhindered and are not reflected toward him. On Earth, the atmosphere, which contains ozone, dust, water droplets, and many other reflecting molecules and substances, is interposed between the sun and our eyes. The atmosphere scatters blue light more than it does green, yellow, or red. Therefore, if during the daytime we look away from the sun, we see the blue photons that are being bent toward us and the sky appears to be blue.

33. Why is the sunset red?

At dusk, to reach us, the light from the sun has to pass through much more of the earth's atmosphere than it does during the daytime. Therefore, even more of the blue and green photons are

bent away from the atmosphere. The red and yellow photons penetrate better. If some of these are eventually reflected toward us by clouds or dust, we see a red sky. Similarly, the sun appears red.

34. Define trichromats.

Trichromats are the 92% of the population who have "normal" color vision. They have all three different kinds of cones, normal concentration of the cone pigments, and normal retinal wiring.

35. What is congenital dichromatism?

In dichromats, the cones themselves are normal, but one of the three contains the wrong pigment. For example, in deuteranopes, the G cones are normal in every way except that they contain erythrolabe (red pigment) instead of chlorolabe (green pigment). In protanopes, the R cones are normal in every way except that they contain chlorolabe (green pigment) instead of erythrolabe (red pigment). Tritanopia is a defect of the B cones.

36. Why do deuteranopes have difficulty in distinguishing red from green?

In deuteranopia, because both R and G cones contain the same pigment, when red light strikes the retina, the R and G cones are stimulated equally and send an equal number of messages to the R–G center. Similarly, there is an increased R input to the B–Y center, where the R input now equals the G input. In other words, the hue center thinks that equal quantities of red and green light are striking the retina. When green or blue-green light strikes the retina, the R and G cones are again stimulated equally. An accurate analysis of the mechanics of color vision abnormalities would require a computer, but it should be apparent that because both red and green light stimulate the R and G cones equally, the information the hue center receives from the R–G center is not useful and the deuteranope would have difficulty distinguishing red from green. Similarly, protanopes also have difficulty distinguishing red from green.

37. What is anomalous trichromatism?

In anomalous trichromatism, two of the three cone pigments are normal, but the third functions suboptimally. Depending on which pigment is abnormal, the affected persons are termed *protanomalous, deuteranomalous,* or *tritanomalous.* Anomalous trichromats can distinguish between fully saturated colors but have difficulty distinguishing colors of low saturation (pastels) or low luminance (dark colors), or both. Deuteranomaly is present in approximately 5% of the population; deuteranopia, protanopia, and protanomaly in 1% each; and tritanopia or tritanomaly in only 0.002%.

38. How is abnormal color vision inherited?

All red-green disorders are inherited in a sex-linked recessive pattern. This means that men almost exclusively manifest the disorder. Women are carriers. In other words, the women have perfectly normal color vision, but approximately 50% of their sons are abnormal. Both men and women can have the tritan disorders, which are inherited as autosomal dominant traits (Table 4-1).

Table 4-1. Inherited Color Vision Defects

DEFECT	INCIDENCE	INHERITANCE
Deuteranomaly	5% (of males)	XR
Deuteranopia	1% (of males)	XR
Protanomaly	1% (of males)	XR
Protanopia	1% (of males)	XR
Tritanomaly and tritanopia	0.002%	AD

AD, Autosomal dominant; *XR*, X-linked recessive.

39. What is Kollner's rule?

As a very general rule, the errors made by persons with optic nerve disease tend to resemble those made by protans and deutans, whereas those made by persons with retinal disease resemble those made by tritans.

WEBSITE

http://retina.umh.es/webvision/

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OPHTHALMIC AND ORBITAL TESTING

Caroline R. Baumal and Michael D. Tibbetts

CHAPTER 5

1. What is the electroretinogram?

The electroretinogram (ERG) is a recording of the electrical discharges from the retina elicited by a flash of light. This response is secondary to transretinal movement of ions induced by the light stimulus.

2. How is an electroretinogram performed?

Light is delivered uniformly to the entire retina. Ganzfeld or full-field stimulation is achieved with a bowl perimeter. The light-induced electrical discharges from the eye are recorded with a corneal contact lens electrode.

KEY POINTS: COMPONENTS OF THE FULL-FIELD ERG

1. The **a wave** is the initial negative ERG waveform arising from photoreceptor cells.
2. The positive **b wave** following the a wave is generated by the Müller cells and bipolar cells in the outer retina.
3. **Oscillatory potentials** are small wavelets that may be superimposed on the b wave and arise from cells in the midretinal layers (Fig. 5-1).
4. Under certain recording conditions, additional waveforms may be noted, such as the **c wave** following the b wave. This reflects electrical activity at the level of the retinal pigment epithelium and is recorded in the dark-adapted eye.
5. The **early receptor potential** is a rapid transient waveform that occurs immediately after a light stimulus. This response originates from the bleaching of photopigments at the level of the photoreceptor outer segments.

3. What parameters are measured during evaluation of an electroretinogram?

Two major ERG parameters, **amplitude** and **implicit time,** are measured. The amplitude (microvolts) of the a wave is measured from baseline to the trough of the a wave. The b-wave amplitude is measured from the trough of the a wave to peak of the b wave. The implicit time (milliseconds) is the time from the stimulus onset to peak of the response.

4. How is the electroretinogram amplitude affected in retinal disorders?

The **full-field light-evoked** ERG is a mass response reflecting activity from the entire retina. The amplitude of the ERG is proportional to the area of functioning retina stimulated and is abnormal only when large areas of the retina are functionally impaired.

5. Describe different stimulus conditions and the associated photoreceptor response.

Certain light stimuli allow the isolation of either the cone or the rod responses so that each photoreceptor type can be studied independently (Table 5-1 and Fig. 5-2). After sufficient dark adaptation (known as **scotopic** conditions), the rod responses are optimized. Under light-adapted or **photopic** conditions, the rods are sufficiently dampened so that the response is primarily from the cones.

6. What five responses are evaluated during a standard full-field electroretinogram?

- Rod response (dark-adapted)
- Maximal combined rod–cone response (dark-adapted)
- Oscillatory potentials
- Single-flash cone response (light-adapted)
- 30-Hz flicker cone response

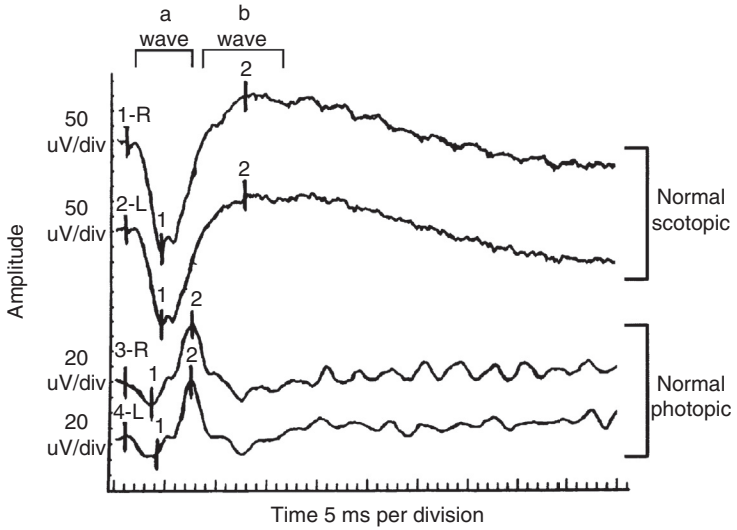

Figure 5-1. Nocturnal scotopic (dark-adapted) and photopic ERG responses to a high-intensity (0 dB) light flash demonstrating the a wave and b wave. Oscillatory potentials are present on the ascending limb of the b wave. The implicit time is measured from the stimulus onset to the peak of the a wave (1) or b wave (2). The a-wave amplitude is measured from the baseline to the trough of the a wave, and the b-wave amplitude is measured from the trough of the a wave to the peak of the b wave.

Table 5-1. Photoreceptor Response Associated with Various Stimulus Conditions

STATE OF ADAPTATION	LIGHT STIMULUS	PHOTORECEPTOR RESPONSE
Scotopic	Dim white (24 dB)	Rod
Scotopic	Dim blue (10 dB)	Rod
Scotopic	Bright white (0 dB)	Mixed response: Maximal rod and cone
Scotopic	Red (0 dB)	Mixed response: early cone, late rod
Scotopic	Bright white (0 dB)	Cone oscillatory potentials
Photopic	Bright white (0 dB)	Cone
Photopic	White flicker at 30 Hz	Pure cone

dB, Decibels; *Hz*, hertz.

7. How is the electroretinogram affected in age-related macular degeneration?
When age-related macular degeneration is characterized by small localized perimacular lesions, the full-field ERG is normal. The entire retina is stimulated by the bright flash in the Ganzfeld and, as a consequence, the full-field ERG is not affected when small areas of the retina are damaged.

8. What does the electroretinogram demonstrate in retinal ganglion cell disease?
The ganglion cells do *not* play a role in generation of the full-field ERG. Thus, disorders primarily affecting ganglion cells, such as glaucoma, do not alter the full-field ERG. On occasion, the b wave may be reduced in optic atrophy or central retinal artery occlusion, This is postulated to result from transsynaptic degeneration from ganglion to the bipolar cell layer.

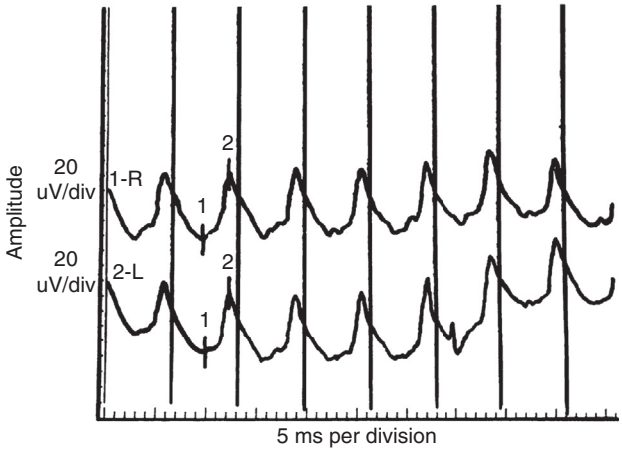

Figure 5-2. The normal ERG cone response to a flicker light stimulus at 30 Hz.

9. Describe the clinical situations in which an electroretinogram is utilized.

- To diagnose a generalized degeneration of the retina
- To evaluate family members for a known hereditary retinal degeneration
- To assess decreased vision and nystagmus present at birth
- To assess retinal function in the presence of opaque ocular media or vascular occlusion
- To evaluate functional visual loss

10. List the retinal degenerations in which an electroretinogram can help clarify the diagnosis.

- Retinitis pigmentosa and related hereditary retinal degenerations
- Retinitis pigmentosa sine pigmento
- Retinitis punctata albescens
- Leber's congenital amaurosis
- Choroideremia
- Gyrate atrophy of the retina and choroid
- Goldman-Favre syndrome
- Congenital stationary night blindness
- X-linked juvenile retinoschisis
- Achromatopsia
- Cone dystrophies
- Disorders mimicking retinitis pigmentosa

11. What are the clinical and electroretinogram features of retinitis pigmentosa?

Retinitis pigmentosa (RP) is an inherited retinal disorder of the photoreceptors and other retina cell layers. Inheritance may be autosomal dominant, autosomal recessive, or X-linked. Both the rods and, to a lesser extent, the cones are abnormal in retinitis pigmentosa. Clinical features include decreased night vision (nyctalopia), visual field loss, and abnormal ERG (Fig. 5-3). Ocular features include waxy pallor of the optic nerve, attenuated retinal vessels, mottled retinal pigment epithelium with bone-spicule pigmentation, cellophane maculopathy, cystic macular edema, pigment cells in the vitreous, and cataracts.

The ERG shows reduced amplitude (usually b wave) and prolonged photopic implicit time in early RP. Over time, the ERG becomes extinguished with no detectable rod or cone responses to bright white light.

12. What does the electroretinogram demonstrate in female carriers of X-linked retinitis pigmentosa?

ERG abnormalities are noted in the majority of female carriers, including prolonged photopic b-wave implicit time and/or a reduction in the amplitude of the scotopic b wave in the dark-adapted eye. Retinal examination in this group may be normal or demonstrate milder retinal findings without subjective complaints.

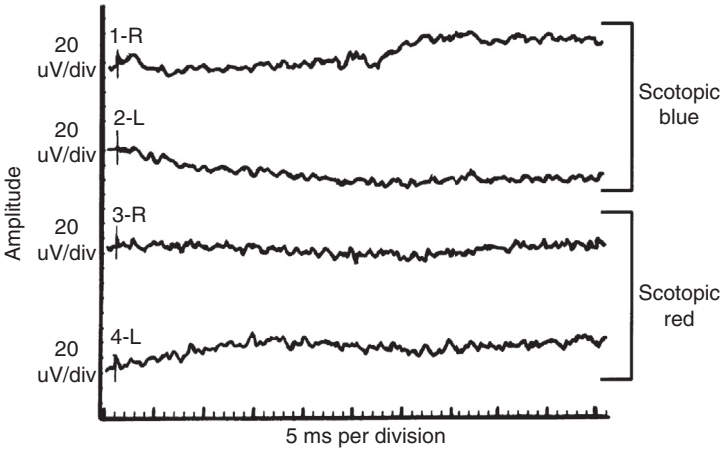

Figure 5-3. The ERG in retinitis pigmentosa reveals an extinguished response to scotopic blue and scotopic red light stimuli.

13. What does the electroretinogram reveal in congenital rubella syndrome?

Diffuse pigmentary retinal changes in congenital rubella syndrome may be confused with retinitis pigmentosa. However, the ERG is normal in congenital rubella. Other ocular signs of rubella include deafness and congenital cataracts.

14. Describe the electroretinogram in X-linked retinoschisis.

ERG reveals reduced scotopic and photopic b-wave amplitude, reflecting widespread midretinal anatomic changes induced by the schisis or splitting of the retina. Clinical findings include peripheral retinoschisis cavities in 50% of cases and foveal cystic changes in almost all cases.

15. What does the electroretinogram demonstrate in progressive cone dystrophy?

The ERG shows markedly reduced photopic flicker response and a normal rod scotopic response. This disorder initially affects peripheral cones, progressing to involve central cones. When the central cones are intact, the visual acuity and color vision are preserved; however, the acuity eventually decreases to the 20/200 range.

16. Why is the electroretinogram useful in patients with congenitally decreased vision?

Three disorders characterized by nystagmus, congenitally reduced vision, and normal retinal examination can be diagnosed with an ERG:

- **Achromatopsia** (also known as rod monochromatism) is a nonprogressive autosomal-recessive near absence of cones. The ERG reveals absent cone function and normal rod function.
- **Leber's congenital amaurosis** is a congenital autosomal recessive form of retinitis pigmentosa. The ERG is markedly reduced or extinguished with profound visual impairment.
- **Congenital stationary night blindness** is an inherited retinal disorder (autosomal dominant, X-linked recessive, or autosomal recessive) that primarily affects rods. The ERG reveals normal photoreceptors with a normal a wave, but an abnormal bipolar cell region as demonstrated by the absent b wave.

17. How can the electroretinogram measure retinal function in the presence of opaque ocular media?

The full-field ERG can be used to assess the retinal function when the retina cannot be visualized, owing to cataracts or corneal or vitreous opacities. A normal ERG provides information regarding the overall retinal function, but does not indicate whether central vision is normal because macular degeneration and optic atrophy typically do not affect the ERG amplitude. A cataract or corneal opacity may act as a diffuser of light, on occasion producing a "supernormal" ERG.

18. List the disorders that may demonstrate an extinguished electroretinogram.

- Retinitis pigmentosa and related disorders
- Ophthalmic artery occlusion
- Diffuse unilateral subacute neuroretinitis
- Metallosis
- Total retinal detachment
- Drugs such as phenothiazines or chloroquine
- Cancer-associated retinopathies

19. List the disorders that may demonstrate normal a-wave and reduced b-wave amplitude.

- Congenital stationary night blindness
- X-linked juvenile retinoschisis
- Central retinal vein or artery occlusion
- Myotonic dystrophy
- Oguchi's disease
- Quinine intoxication
- Transsynaptic degeneration from the ganglion to the bipolar cell layer (i.e., secondary to optic atrophy or central retinal artery occlusion)

20. List the disorders characterized by an abnormal photopic electroretinogram and a normal scotopic electroretinogram.

- Achromatopsia (also known as rod monochromatism)
- Cone dystrophy

21. Name three variations of the standard electroretinogram.

- The **focal electroretinogram** is induced by a focal-directed flash of light and measures the response from the central cone photoreceptors and outer retina.
- The **pattern electroretinogram** (PERG) measures the electrical response to an alternating pattern stimulus that has a constant overall retinal luminance. The response appears to be localized to retinal ganglion cells. The PERG is extinguished after transection of the optic nerve, whereas the full-field ERG is not altered. The PERG may be used to diagnose or monitor disorders such as glaucoma, ocular hypertension, optic neuritis, optic atrophy, and amblyopia.
- The **multifocal ERG** provides an objective equivalent to the visual field by simultaneously assessing the retinal electrical response at multiple locations. The resultant local responses contain components from all levels of the retina.

22. What is an electro-oculogram?

The **electro-oculogram** (EOG) is an indirect measure of the standing potential of the eyes (Fig. 5-4). This standing potential exists because of a voltage difference between the inner and the outer retina. The EOG is measured by placing electrodes near the medial and lateral canthi of each eye. The patient then moves his or her eyes back and forth over a specific distance.

The clinical measurement of the EOG relies on the fact that the amplitude of the response changes when the luminance conditions are varied. After dark adaptation, the response progressively decreases, reaching a trough in 8 to 12 minutes. With light adaptation, there is a progressive rise in amplitude, reaching a peak in 6 to 9 minutes. The greatest EOG amplitude achieved in light (light peak) is divided by the lowest amplitude in the dark (dark trough). This calculated ratio is the **Arden ratio**. Normal subjects have an **Arden ratio** value of 1.80 or greater, whereas a ratio of less than 1.65 is distinctly abnormal.

23. Where is the electro-oculogram response generated?

The electrical response in the EOG is generated by the retinal pigment epithelium, with the light peak being produced by a depolarization of the basal portion of the retinal pigment epithelium. To generate the EOG potential, it is necessary to have intact photoreceptors in physical contact with the retinal pigment epithelium.

24. What are the clinical uses for the electro-oculogram?

The most important clinical use for the EOG is the diagnosis of Best disease (also known as vitelliform dystrophy). Best disease is inherited autosomal dominantly with phenotypic variability. Individuals with Best disease usually have an EOG Arden ratio less than 1.5, but the ERG is normal. The EOG light rise

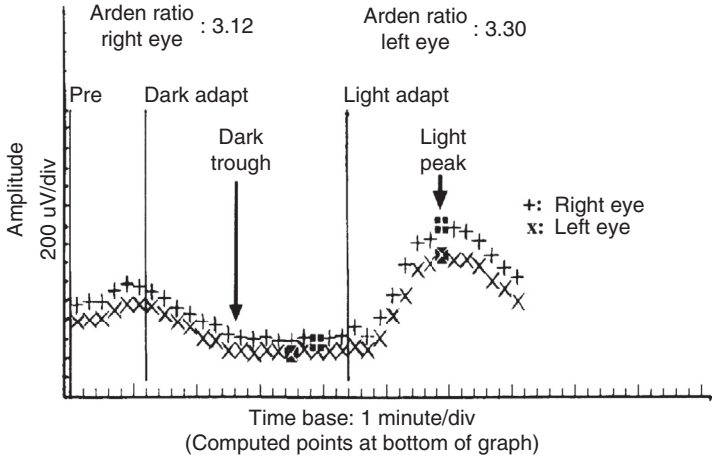

Figure 5-4. Normal EOG demonstrating the dark trough and the light peak.

is almost completely dependent on rod function, so it is normal in disorders of cone dysfunction. The EOG is abnormal in most other retinal disorders when the ERG is abnormal, thus, it has limited clinical utility aside from diagnosing Best disease.

25. What does the electro-oculogram demonstrate in pattern dystrophies?

The EOG light-peak to dark-trough Arden ratio in pattern dystrophy is usually either normal or minimally subnormal. This finding may help distinguish pattern dystrophy from Best's disease, in which the Arden ratio is always abnormal.

26. How are the electroretinogram and electro-oculogram affected by chloroquine and hydroxychloroquine use?

Abnormal findings in the ERG and EOG have been reported in patients receiving these antimalarial drugs, which are frequently used for immune-mediated arthritides and other autoimmune disorders.

27. What are the characteristics of dark adaptation?

Dark adaptometry measures the absolute threshold of cone and rod sensitivity and is tested with the Goldmann-Weekers adaptometer. Initially, the subject is adapted to a bright background light, which is then extinguished. In the dark, the patient is presented with a series of dim lights. The threshold at which the light is just perceived is plotted against time. The normal dark-adaptation curve (Fig. 5-5) is biphasic. The first curve represents the cone threshold and is reached in 5 to 10 minutes. The second curve represents the rod threshold and is reached after 30 minutes. The rod–cone break is a well-defined point between these two curves. Dark adaptometry is useful to evaluate retinal disorders with night blindness and some conditions with cone dysfunction.

28. What are the indications for ophthalmic ultrasonography?

- Evaluation of the anterior or posterior segment in eyes with opaque ocular media
- Assessment of ocular tumor dimensions as well as their tissue characteristics, such as calcium in retinoblastoma or choroidal osteoma
- Evaluation of orbital disorders such as thyroid ophthalmopathy and orbital pseudotumor
- Detection and localization of intraocular foreign bodies
- Measurement of distances within the eye and orbit (also known as biometry)

29. What frequency is used for standard ophthalmic ultrasonography?

Ultrasound is an acoustic wave that consists of an oscillation of particles within a medium. In standard ophthalmic ultrasound, frequencies are in the range of 8 to 10 MHz. This high frequency produces short wavelengths, which allow precise resolution of small ocular structures.

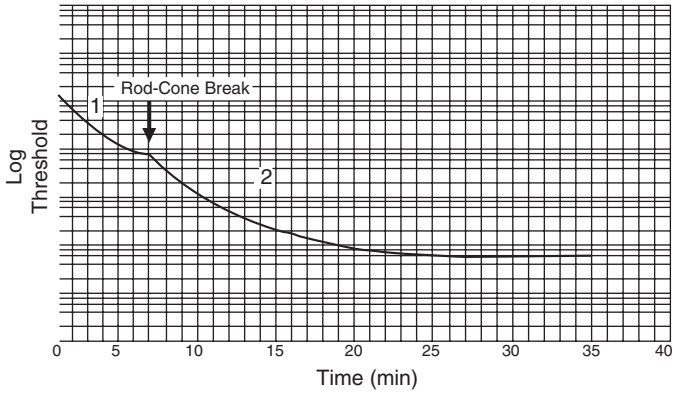

Figure 5-5. Normal dark adaptation curve demonstrates the rod-cone break at 7 minutes, separating the cone threshold (1) and the rod threshold (2).

30. What are the principles of ultrasonography?

Ultrasound is based on physical principles of tissue–acoustic impedance mismatch and pulse–echo technology. As the acoustic wave is propagated through tissues, part of the wave may be reflected toward the source of the emitted wave (i.e., the probe). This reflected wave is referred to as an echo. Echoes are generated at adjoining tissue interfaces that have differential acoustic impedance. The greater the difference in acoustic impedance, the stronger the echo. For example, strong reflections occur at the interface between retinal tissue and vitreous fluid.

31. How is the clinical ophthalmic ultrasound displayed?

The reflected echoes are received, amplified, electronically processed, and displayed in visual format as an A-scan or a B-scan (Fig. 5-6):

- **A-scan ultrasonography**, or the A mode, is a one-dimensional, time–amplitude display. The horizontal baseline represents the distance and depends on the time required for the sound beam to reach a given interface and for its echo to return to the probe. In the vertical dimension, the height of the displayed spike indicates the amplitude or strength of the echo.
- **B-scan ultrasonography**, or the B mode, produces a two-dimensional, cross-sectional display of the globe and orbit. The image is displayed in variable shades of gray, and the shade depends on the echo strength. Strong echoes appear white, and weaker reflections are seen as gray.

The A-scan is used predominantly for tissue characterization, whereas the B-scan is used to obtain architectural information. A-scans are used to determine axial lengths for intraocular lens power calculations for cataract surgery.

32. What lesion features are evaluated during the ultrasound examination?

1. The **topography** (location, configuration, and extension) of a lesion is evaluated by the two-dimensional B-scan.
2. The **quantitative features** include the reflectivity, internal structure, and sound attenuation of a lesion.
   - The **reflectivity** is evaluated by observing the height of the spike on an A-scan and the signal brightness on a B-scan. The internal reflectivity refers to the amplitude of echoes within a lesion and correlates with histologic architecture.
   - The **internal structure** refers to the degree of variation in histologic architecture within a lesion. Regular internal structure indicates a homogeneous architecture and is noted by minimal or no variation in the height of spikes on the A-scan and a uniform appearance of echoes on the B-scan. In contrast, an irregular internal structure is characterized by a heterogeneous architecture and variations in the echo appearance.
   - **Sound attenuation** occurs when the acoustic wave is scattered, reflected, or absorbed by a tissue and is noted by a decrease in the strength of echoes either within or posterior to a lesion. It is indicated by a decrease in spike height on the A-scan or a decrease in the brightness of echoes on the B-scan. Sound attenuation may produce shadowing seen as a void posterior to

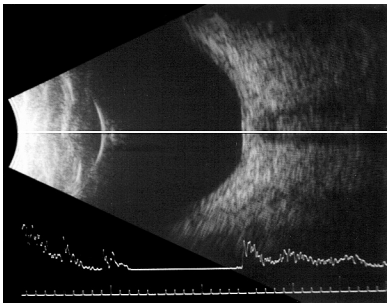

Figure 5-6. A-scan *(bottom)* and B-scan *(top)* of the normal globe. A cross-sectional anterior–posterior view is presented in the B-scan. The lens capsule is seen toward the left of the display, and the optic nerve is seen toward the right. A vector line through the B-scan demonstrates the position of the A-scan information.

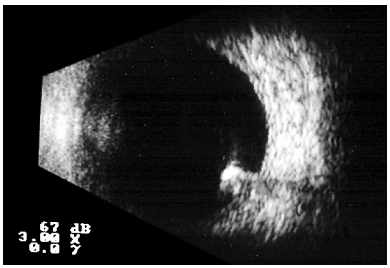

Figure 5-7. B-scan showing a metallic foreign body on the retina surface. A bright echo is produced by the foreign body with shadowing of the structures posteriorly.

the lesion. Substances such as bone, calcium, and foreign bodies typically produce sound attenuation (Fig. 5-7).

33. How is ultrasound used in preoperative cataract evaluation?

The A-scan is used to measure the axial length of the globe, which is required in the formula to calculate the intraocular lens power. The B-scan is useful if the ocular media are opaque to assess for a retinal disorder that may affect visual outcome after cataract surgery.

34. How is ultrasound used to assess intraocular tumors?

Ultrasound may be used for diagnosis, to plan treatment, and to evaluate tumor response to therapy. Specifically the tumor shape, dimensions (such as thickness and basal diameter), and tissue characteristics are evaluated, along with the presence of extraocular extension.

35. What are the characteristic features of a choroidal melanoma on ultrasound?

- Collar button or mushroom shape on B-scan (Fig. 5-8)
- Low-to-medium internal reflectivity on A-scan (Fig. 5-8)
- Regular internal structure
- Internal blood flow (vascularity)

36. Describe the ultrasound patterns in the differential diagnosis of choroidal melanoma.

Ultrasound is often used in the evaluation of choroidal melanoma, choroidal hemangioma, metastatic choroidal carcinoma, choroidal nevus, choroidal hemorrhage, and a disciform lesion. It should be combined with clinical information because there are more tumor types than differentiating ultrasound patterns (Table 5-2).

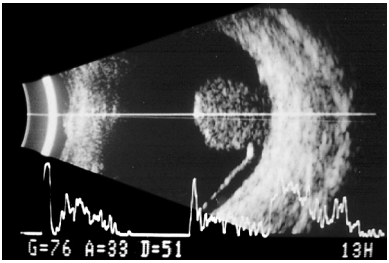

Figure 5-8. A-scan and B-scan of choroidal melanoma. The B-scan reveals a collar-button-shaped mass with regular internal structure. A serous retinal detachment extends from the margin of the tumor. The A-scan reveals a strong initial echo from the retinal tissue overlying the tumor followed by a rapid decline in the A-scan echo amplitude (low internal reflectivity) within the tumor tissue. High reflectivity is noted again at the level of the sclera and orbital fat.

Table 5-2. Ultrasound Patterns in the Differential Diagnosis of Choroidal Melanoma

LESION	LOCATION	SHAPE	INTERNAL REFLECTIVITY	INTERNAL STRUCTURE	VASCULARITY
Melanoma	Choroid and/or ciliary body	Dome or collar button	Low to medium	Regular	Yes
Choroidal hemangioma	Choroid, posterior pole	Dome	High	Regular	No
Metastatic carcinoma	Choroid, posterior pole	Diffuse, irregular	Medium to high	Irregular	No
Choroidal nevus	Choroid	Flat or mild thickening (usually <2 mm)	High	Regular	No
Choroidal hemorrhage	Choroid	Dome	Variable	Variable	No
Disciform lesion	Macula	Dome, irregular	High	Variable	No

37. Describe the ultrasound features of a choroidal hemangioma.

Within a choroidal hemangioma, the adjoining cell and tissue layers have marked differences in acoustic impedance (acoustic heterogeneity). This creates large echo amplitudes at each interface. The A-scan reveals high internal reflections within the tumor, and lesions appear solid white on the B-scan.

38. Describe the ultrasound features of a retinal detachment.

A detached retina produces a bright, continuous, folded appearance on B-scan (Fig. 5-9). When detachment is total or extensive, the retina inserts into both the optic nerve and the ora serrata. The A-scan reveals a 100% high spike. There is motion of the detached retina with voluntary eye movement. Chronic retinal detachment may show intraretinal cysts, calcification, or cholesterol debris in the subretinal space.

39. Describe the ultrasound features that differentiate retinal detachment, posterior vitreous detachment, and choroidal detachment.

See Table 5-3.

40. What ocular conditions may demonstrate calcification on ultrasound?

- Tumors (retinoblastoma, choroidal osteoma, optic nerve sheath meningioma, choroidal hemangioma, choroidal melanoma)
- Toxocara granuloma
- Chronic retinal detachment
- Optic nerve head drusen
- Disciform retinal lesion
- Vascular occlusive disease of the optic nerve
- Phthisis bulbi
- Intumescent cataractous lens[1]

41. When is ultrasound used to evaluate ocular trauma?

Ultrasound may be used to evaluate the position of the lens and the status of the retina if visualization is impeded by an opaque cornea, hyphema, or vitreous hemorrhage resulting from

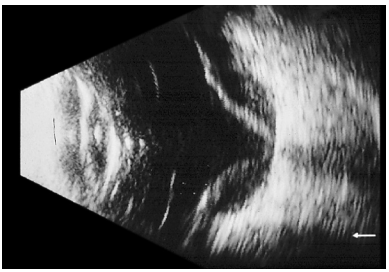

Figure 5-9. B-scan of total retinal detachment. The anteroposterior view reveals the characteristic V-shaped appearance with attachment to the optic nerve. A cataract is also present.

Table 5-3. Ultrasound Features That Differentiate Retinal Detachment, Posterior Vitreous Detachment, and Choroidal Detachment

ULTRASOUND FEATURES	RETINAL DETACHMENT	POSTERIOR VITREOUS DETACHMENT	CHOROIDAL DETACHMENT
Topographic (B-scan)	Smooth or folded surface	Smooth surface	Smooth, dome, or flat surface
	Open or closed funnel with insertion at optic nerve	Open funnel with or without optic disc or fundus insertion	No optic nerve insertion
	Inserts at ora serrata	Inserts at ora serrata or ciliary body	
	With or without intraretinal cysts	Inserts at ora serrata or ciliary body	
Quantitative (A-scan)	Steep 100% high spike	Variable spike height that is <100%	Steeply rising, thick, double-peaked 100% high spike
Mobility after eye movement	Moderate to none	Marked to moderate	Mild to none

trauma. It also may diagnose a posterior rupture site in the globe and assess for an intraocular foreign body.

The globe should be evaluated visually by the slit lamp technique before ultrasonography to determine whether ocular integrity has been severely disrupted and whether ultrasound examination is indicated. Given that the ultrasound probe contacts the eyelid and may apply pressure on the eye, ultrasound should be used cautiously if there is any evidence of a ruptured globe.

42. What are the ultrasound findings with an intraocular foreign body?

Foreign bodies have high reflectivity when the ultrasound probe beam is perpendicular to a reflective surface of the foreign body (see Fig. 5-7). On the B-scan, a metallic foreign body produces a bright echo that persists when the gain of the ultrasound output is decreased. Shadowing is often present behind a foreign body because of nearly complete reflection of the examining probe beam. Ultrasound is particularly useful with a nonmetallic intraocular foreign body that may not be visible on x-ray or computed tomography (CT) scan.

43. What is ultrasound biomicroscopy?

Ultrasound biomicroscopy (UBM) is a B-scan method that uses high frequencies in the range of 50 to 100 MHz. The depth of penetration is 5 to 7 mm. This technique produces high-resolution images of anterior segment structures (Fig. 5-10) and has been used to characterize the mechanism of secondary glaucoma.

44. How is color-Doppler ultrasonography used in ophthalmologic evaluation?

Color-Doppler ultrasonography is a noninvasive approach to evaluate ocular blood flow. It is useful for assessing morphologic and velocimetric data from the ophthalmic artery, central retinal artery, central retinal vein, and posterior ciliary vessels. This technique has been used to evaluate many ocular disorders, including glaucoma, optic nerve disorders, diabetes, hypertension, ocular ischemia, and the presence of arterial emboli.

45. What is required when you order orbital magnetic resonance imaging studies?

- Surface coil (orbital or head coil) for better visualization of structures of the orbit
- Precontrast axial, coronal, and sagittal T1-weighted images
- Axial, coronal T2-weighted images (fast spin-echo sequences)
- Postcontrast axial coronal T1-weighted images with fat-suppression techniques
- Sedation in children

46. What are paramagnetic agents?

Paramagnetic agents produce proton relaxation enhancement by shortening the intrinsic T1 and T2 relaxation times of the tissues in which they are present. Therefore, tissues containing paramagnetic agents will present with increased signal intensity, best seen on T1-weighted images. Melanin, methemoglobin, protein, and gadolinium are the most common paramagnetic agents. For example, a dermatoid cyst with a high proteinaceous content shows a higher signal intensity on T1- and T2-weighted images than a clear inclusion cyst does.

47. Which ocular and orbital tissues *do not* normally enhance on postcontrast magnetic resonance imaging studies?

- Lens
- Vitreous
- Retina

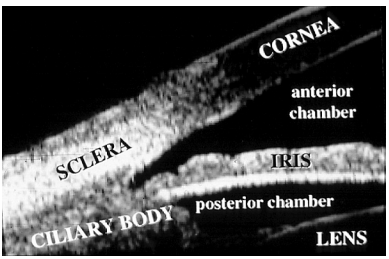

Figure 5-10. Ultrasound biomicroscopic image of the anterior-segment angle structures.

- Sclera
- Orbital fat
- Optic nerve sheath complex
- Peripheral nerve
- Tendon
- High-flow blood vessels

48. Which ocular and orbital tissues *do* normally enhance on postcontrast magnetic resonance imaging studies?

- Choroid
- Ciliary body
- Extraocular muscles
- Lacrimal gland
- Nasal: sinus mucosa
- Cavernous sinus
- Low-blood-flow vessels

49. What is the strategy for ordering imaging studies in a child with leukocoria and total retinal detachment?

First perform B-scan ultrasonography. It is cheap and easy to perform in the office without sedation. The goal is to identify calcification, which favors the diagnosis of retinoblastoma. If calcification is documented by ultrasonography, magnetic resonance imaging (MRI) is the second imaging step, to assess the optic nerve and orbital structures and to rule out extraocular retinoblastoma. MRI is also helpful in evaluating the pineal gland and parasellar region, particularly in patients with bilateral and/or familial retinoblastoma. If calcification is not visualized by ultrasonography, orbital CT should be the second imaging step because MRI cannot easily detect minor calcification.

50. What is the strategy for ordering imaging studies in an adult with the diagnosis of intraocular neoplasm?

A- and B-scan ultrasonography is the first imaging step in evaluating an adult presenting with an intraocular tumor. If ultrasonography, fluorescein angiography, and indocyanine green angiography do not help in the differential diagnosis, pre- and postcontrast-enhanced MRI studies with fat-suppression techniques are most helpful in detecting and diagnosing intraocular lesions.

51. In what clinical situation are contrast-enhanced magnetic resonance imaging studies most helpful in the evaluation of a child with leukocoria?

Contrast-enhanced MRI distinguishes between retinoblastoma and Coats disease.

52. What are the indications for ordering computed tomography orbital studies as a first choice?

- Ocular trauma to rule out foreign body
- Orbital trauma to evaluate suspected fractures
- Detection of calcification (i.e., retinoblastoma)
- Lacrimal gland lesions
- Infectious or noninfectious orbital inflammation
- Bone lesions (i.e., osteoma, fibrous dysplasia, etc.) or to evaluate for bony erosion
- Cases with contraindication for MRI

53. What size computed tomography scan slices should be ordered to evaluate for suspected foreign body or traumatic optic neuropathy?

CT scan slices of 1.0 mm should be ordered.

54. What are the indications for ordering magnetic resonance imaging orbital studies as a first choice?

- Optic neuritis (obtain MRI of the brain)
- CN-III palsy—if pupil involving, obtain urgent MRI and MRA of the head
- Central nervous system pathology (pituitary lesions, occipital lobe lesions, aneurysms)
- Cavernous sinus or orbital apex pathology.
- Suspected papilledema (obtain urgent MRI and MRV of the brain)

- To differentiate cystic and/or hemorrhagic lesions from solid tumors. *Note*: Imaging should not delay the prompt clinical diagnosis and management of an orbital compartment syndrome.
- Optic disc swelling or atrophy (to differentiate optic nerve from optic nerve sheath lesions)
- Intraocular tumor with extraocu lar extension
- Detection of wooden foreign body
- Cases with contraindication for CT scan

55. What features of ocular and orbital structures on magnetic resonance imaging differentiate between T1- and T2-weighted images?

- Vitreous is dark in T1 and bright in T2
- Orbital fat is bright in T1 and dark in T2
- With fat suppression (T1), vitreous and orbital fat will appear dark but extraocular muscles will appear bright
- The majority of orbital tumors will be dark in T1 and bright postcontrast

56. What ocular and orbital lesions appear bright in T1 (without contrast)?

- Lesions containing fat (e.g., dermoids)
- Subacute hemorrhage (3 to 10 days); acute blood (<3 days) is dark in T1
- Lesions containing mucus (e.g., mucocele)
- Tumors containing melanin (e.g., melanoma)

KEY POINTS: SUMMARY OF MODALITIES FOR OPHTHALMIC IMAGING

1. Evaluation of ocular structure
   - ultrasound—A-scan, B-scan, UBM
   - optical coherence tomography
   - CT scan
   - MRI
   - corneal topography
2. Evaluation of function
   - angiography (fluorescein, indocyanine green)
   - Doppler blood flow

57. Name the most common orbital lesions showing a well-circumscribed and sharply delineated appearance on computed tomography and magnetic resonance imaging.

Children	*Adults*
1. Dermoid cyst	1. Cavernous hemangioma
2. Lymphangioma	2. Neurofibroma
3. Rhabdomyosarcoma	3. Neurilemoma
4. Optic nerve glioma	4. Fibrous histiocytoma
5. Hemangiopericytoma	
6. Lymphoma	

58. Name the most common orbital lesions showing an ill-defined appearance on computed tomography and magnetic resonance imaging.

Children	*Adults*
1. Capillary hemangioma	1. Idiopathic orbital inflammation
2. Idiopathic orbital inflammation	2. Metastasis
3. Plexiform neurofibroma	3. Leukemic infiltrate
4. Leukemic infiltrate	4. Primary malignant tumor
5. Eosinophilic granuloma	5. Lymphoproliferative disorders

59. In which clinical situations are contrast-enhanced magnetic resonance imaging studies most helpful in the evaluation of a patient with proptosis?

Pre- and postcontrast MRI studies are very helpful in patients diagnosed with a well-circumscribed lesion because they can differentiate a solid (enhancing) tumor from a cystic (nonenhancing) tumor. In a young patient with acute proptosis, MRI studies can differentiate a hemorrhagic lymphangioma from a growing rhabdomyosarcoma. In suspected orbital inflammation, MRI characteristics of the ill-defined inflammatory tissues may predict the therapeutic response to steroids. Lesions showing high signal on T2-weighted images and marked contrast enhancement respond better to steroids than lesions presenting with lower signal intensity on T2-weighted images and/or with minimal or no contrast enhancement.

60. What are the indications for orbital ultrasonography in imaging orbital lesions?

Orbital ultrasonography is of little help because of its poor histologic specificity and the rapid sound attenuation in the retro-ocular structures. It may be useful to evaluate extraocular extension of an intraocular tumor, the proximal portion of the optic nerve, and extraocular muscles adjacent to the sclera.

61. How can you differentiate optic nerve lesions from optic nerve sheath lesions with computed tomography and magnetic resonance imaging studies?

Differentiation is almost impossible with CT except that optic nerve sheath meningioma may sometimes show linear calcifications best seen on CT. On MRI, the localization of the enhancement (best seen on T1-weighted images with fat-suppression techniques) helps to differentiate a true optic nerve lesion (neoplastic or inflammatory) from an optic nerve sheath process. An optic nerve tumor or inflammation demonstrates enhancement with the core of the optic nerve, whereas an optic nerve sheath neoplasm or inflammation demonstrates peripheral and/or eccentric enhancement. A cystic or hemorrhagic lesion does not enhance.

62. Summarize the magnetic resonance imaging features of normal ocular and orbital tissues.

See Table 5-4.

63. What does OCT stand for?

OCT stands for optical coherence tomography.

64. Explain the basic principles of optical coherence tomography.

OCT is a noninvasive, noncontact imaging technique that measures variations in optical reflectivity across different tissue interfaces. It is analogous to ultrasound, which measures the reflectivity

Table 5-4. MRI Features of Normal Ocular and Orbital Tissues

LOCATION	SIGNAL INTENSITY T1-WEIGHTED IMAGES	SIGNAL INTENSITY T2-WEIGHTED IMAGES	ENHANCEMENT AFTER GADOLINIUM–DTPA INJECTION
Lens	High	Low	–
Vitreous	Low	High	–
Choroid	High	High	+++
Retina	Not detected	Not detected	–
Sclera	Low	Low	–
Optic nerve	Low	Low	–
Orbital fat	High	Low	–
Extraocular muscle	Low	Low	+++
Lacrimal gland	Low	Low	+++
Cortical bone	Low	Low	–

+++, Significant enhancement with gadolinium; –, no enhancement with gadolinium.

of sound waves. OCT provides high-resolution, micrometer-range, cross-sectional images of the retinal layers, choroid, and optic nerve. It is a vital tool for management of a variety of retinal disorders.[1]

65. What is the difference between time-domain and spectral (or Fourier)-domain optical coherence tomography?

Time-domain OCT uses a moving reference mirror, whereas spectral-domain OCT uses a fixed reference mirror. Spectral-domain technology allows for faster image acquisition, better resolution, and fewer movement artifacts.

66. Describe the retinal layers as seen on optical coherence tomography.[2]

See Figure 5-11.

67. Name common indications for optical coherence tomography.[3]

OCT can be useful for diagnosis, monitoring response to therapy, and determining pathogenesis of a variety of macular and optic nerve disorders including the following:

a. Vitreoretinal interface disease such as vitreomacular traction (Fig. 5-12, ***A***) and epiretinal membrane (Fig. 5-12, ***B***).
b. Diagnosis of macular hole and differentiation of full-thickness macular hole (Fig. 5-12, ***C***) from lamellar hole and pseudohole.
c. Surgical planning for macular hole or epiretinal membrane surgery.
d. Assessment for the presence, location (intraretinal, subretinal, or subretinal pigment epithelium), and amount of fluid in diseases such as age-related macular degeneration (AMD, Fig. 5-12, ***D***), retinal vein occlusion, and diabetic macular edema.
e. Evaluate for the presence and stability of nerve fiber layer defects in glaucoma.
f. Monitor treatment response. For example, OCT imaging is used evaluate response to anti-VEGF (vascular endothelial growth factor) agents (Fig. 5-13, ***A*** and ***B***).

68. What structure does enhanced depth imaging optical coherence tomography help visualize?

The choroid is external to both the retina and the retinal pigment epithelium. Enhanced depth imaging OCT improves visualization of the choroid and may play a role in diagnosing certain disorders including central serous chorioretinopathy, idiopathic polypoidal vasculopathy, and choroidal melanoma.[3]

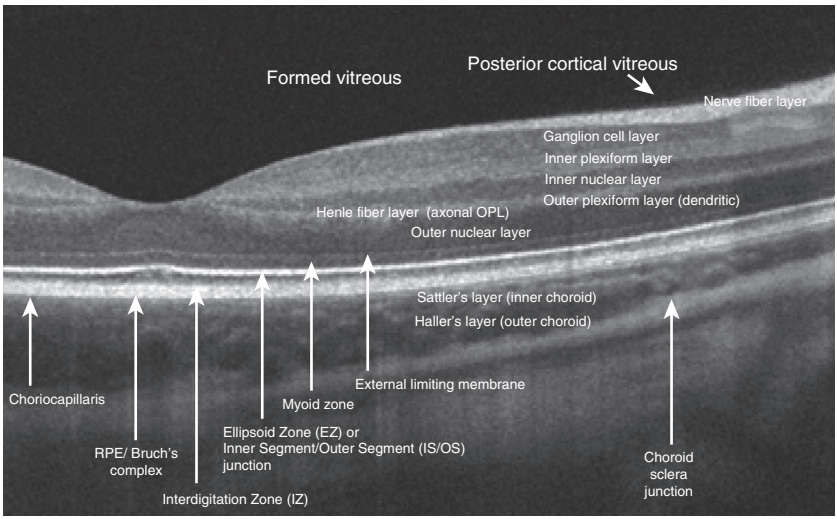

Figure 5-11. Spectral-domain OCT. The macular spectral-domain OCT image is labeled according to the international consensus definition.

69. Describe the technique of fluorescein angiography.

Commercially available sodium fluorescein dye is injected intravenously at a dose of either 2.5 mL of a 25% concentration or 5 mL of a 10% concentration. Although the majority of fluorescein is protein bound, approximately 20% of this dye circulates freely in the vasculature, including the vessels of the retina and choroid. Fluorescein dye fluoresces at a wavelength of 520 to 535 nm (green) after excitation by a light of 485 to 500 nm (blue). White light from a camera flash is passed through a blue filter, exciting unbound fluorescein molecules in the retinal and choroidal circulation and any that have leaked from the vasculature owing to ocular pathology. The blue light stimulates the fluorescein molecule to emit longer-wavelength yellow-green light. The emitted fluorescence and reflected blue light return to the camera, where a yellow-green filter blocks the reflected blue light and allows only the yellow-green fluorescence to enter the camera, by which it is captured onto film or a digital surface.

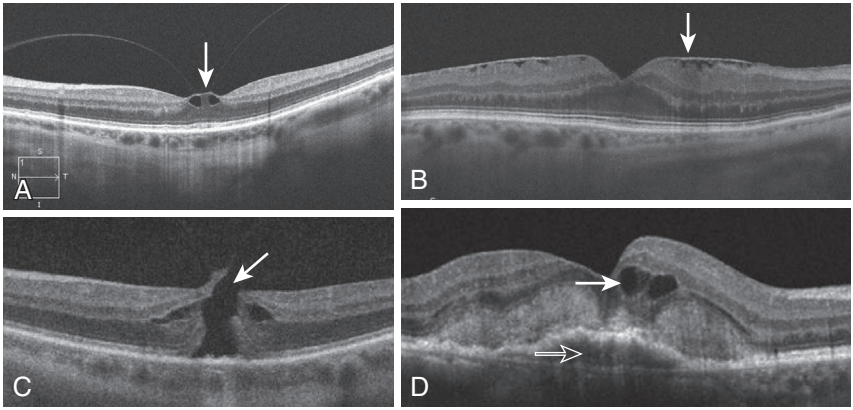

Figure 5-12. Spectrum of retinal pathology demonstrated on OCT. **A,** Vitreomacular traction with distortion of the foveal architecture *(arrow)* and an intraretinal cyst. **B,** Epiretinal membrane *(arrow)* with minimal distortion of the foveal contour. **C,** Full-thickness macular hole *(arrow)*. **D,** Intraretinal fluid *(solid arrow),* subfoveal pigment epithelial detachment *(hollow arrow),* and subretinal fibrosis in a patient with age-related macular degeneration.

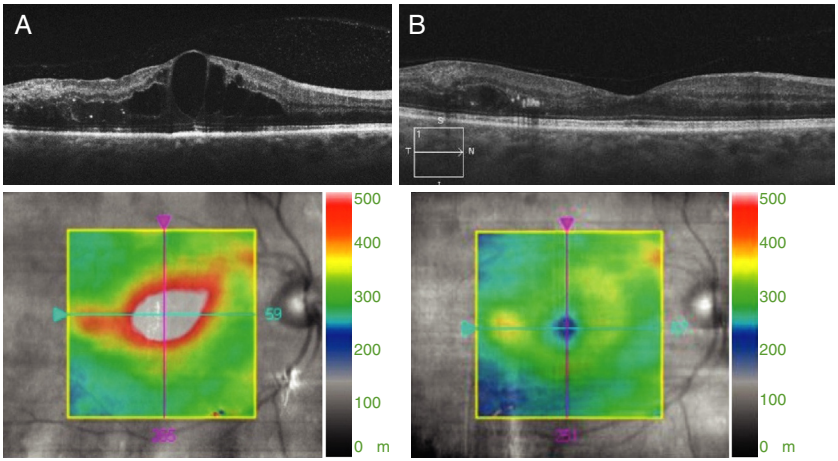

Figure 5-13. Optical coherence tomography demonstrating reduction of diabetic macular edema in response to intravitreal ranibizumab. **A,** Macular OCT and thickness map demonstrating macular edema secondary to diabetic retinopathy prior to treatment. **B,** Macular OCT and thickness map with marked reduction in macular edema 4 weeks after intravitreal ranibizumab. The assessment of macular fluid and response to therapy is one of the most important uses of OCT.

70. What are the normal phases of a fluorescein angiogram?

a. Choroidal filling: This commences 10 to 20 seconds after intravenous fluorescein dye injection. The choroid fills within 5 seconds of dye appearance.
b. Arterial phase: This begins 1 to 2 seconds after choroidal filling.
c. Arteriovenous phase: Laminar venous flow is present.
d. Venous phase: The retinal veins are completely filled with fluorescein dye.
e. Recirculation phase: This begins 45 to 60 seconds after arterial phase

71. Describe fluorescence patterns visible with fluorescein angiography.

Fluorescein angiograms are interpreted based on the pattern, timing, and location of the fluorescence[4] (Fig. 5-14).

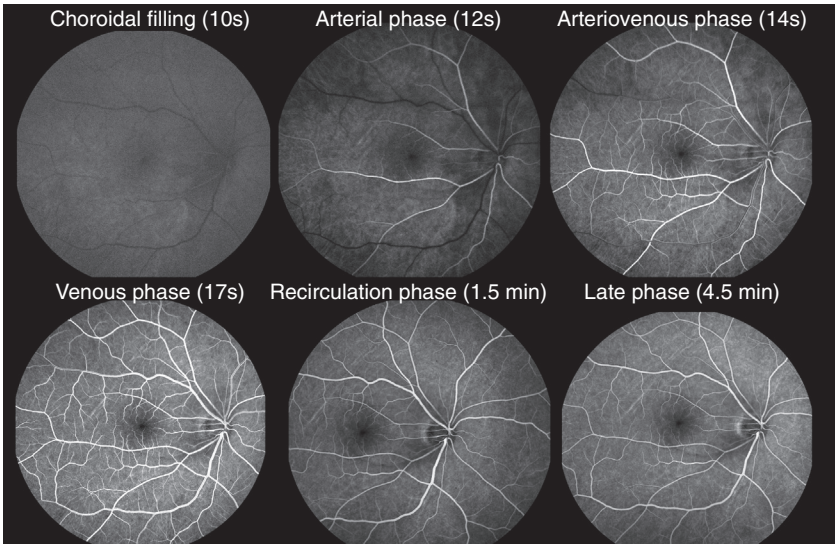

Figure 5-14. Fluorescein angiography. The phases of a normal fluorescein angiogram are labeled, with the times after injection of fluorescein dye into a peripheral vein of the patient noted.

KEY POINTS: PATTERNS OF FLUORESCENCE ON FLUORESCEIN ANGIOGRAPHY

1. Hypofluorescence occurs when the fluorescence signal is blocked by overlying pigment, blood, or fibrous tissue or if the blood vessels do not fill properly, resulting in a vascular filling defect.
2. Hyperfluorescence can be seen in several major patterns, including leakage, staining, pooling, and transmission or window defects.
3. Leakage describes the gradual, marked increase in fluorescence throughout the angiogram as the fluorescein molecules diffuse through the retinal pigment epithelium (RPE) into the subretinal space, out of blood vessels, or from retinal neovascularization into the vitreous.
4. Staining denotes a pattern of fluorescence when fluorescein enters a solid tissue such as a scar or drusen. The fluorescence pattern of staining demonstrates a gradual increase in intensity into the late views with fixed borders that do not expand.
5. Pooling describes the accumulation of fluorescein in a fluid-filled space in the retina or choroid as in a detachment of the RPE.
6. Transmission or window defect refers to a view of the normal choroidal fluorescence through a defect in the pigment or loss of the RPE.

72. What structures are permeable to fluorescein?

The choriocapillaris and Bruch's membrane are freely permeable to fluorescein. In contrast, the retinal pigment epithelium and the retinal capillaries are impermeable to fluorescein.

73. Why is the fovea dark on a fluorescein angiogram?

The fovea is dark for two reasons. One, the xanthophyll pigment in the outer plexiform layer blocks. Secondly, the retinal pigment epithelial cells in the fovea are taller and contain an increased concentration of melanin and lipofuscin.

74. What is the gold standard for the diagnosis of neovascularization?

The gold standard is fluorescein angiography. This study demonstrates progressive leakage of dye in areas of neovascularization. This is useful for imaging retinal neovascularization as in diabetic retinopathy (Fig. 5-15, *A* and *B*) and choroidal neovascularization as in age-related macular degeneration (Fig. 5-15, *C* and D).

75. What are the typical fluorescein angiographic findings in central serous chorioretinopathy?

The classic pattern of central serous chorioretinopathy is a focal, expanding area of hyperfluorescence due to leakage of fluorescein dye from the choroid through the RPE with late pooling in the subretinal space. Some patients may demonstrate a "smokestack" pattern with an expanding area of

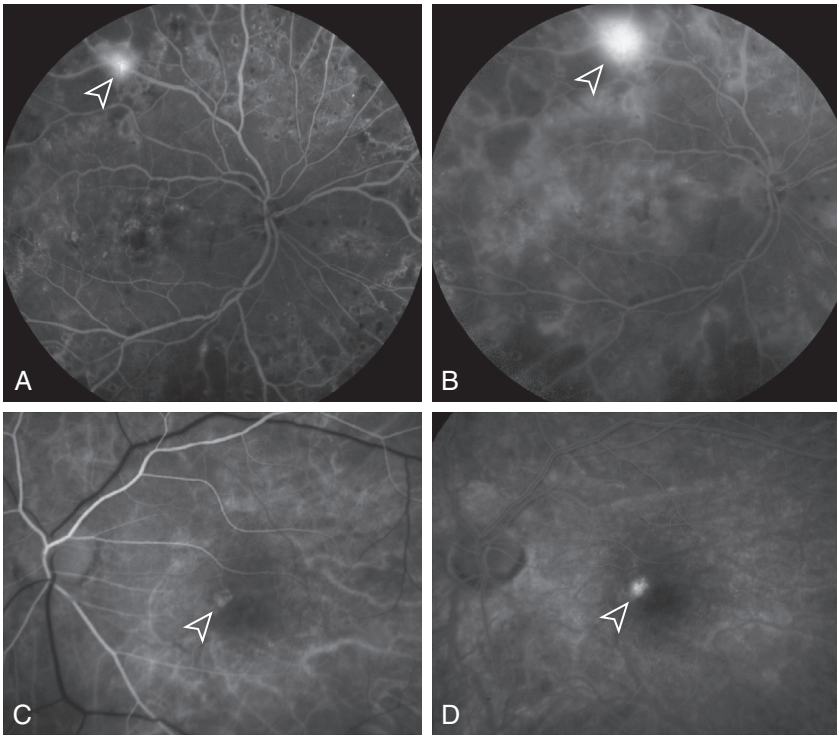

Figure 5-15. Patterns of neovascularization on fluorescein angiography. **A,** Early leakage of the retinal neovascularization is demonstrated (arrow), with hyperfluorescence with ill-defined borders, in this patient with proliferative diabetic retinopathy. **B,** The area of hyperfluorescence expands in the late-phase angiogram, indicating leakage. **C,** The arterial-phase angiogram demonstrates early parafoveal hyperfluorescence *(arrow)* indicative of a classic choroidal neovascular membrane in a patient with age-related macular degeneration. **D,** The late-phase angiogram demonstrates a small but expanding area of hyperfluorescence indicative of leakage from a CNVM *(arrow)*.

hyperfluorescence that rises like smoke from a chimney. In more than 75% of patients, the leakage of fluorescein occurs within one disc diameter of the fovea.

76. What is indocyanine green dye?

Indocyanine green (ICG) is a water-soluble, high-molecular-weight dye that fluoresces with a peak absorption of 805 nm and peak emission of 835 nm.[4] The dye is almost completely protein bound, which limits its diffusion through the small fenestrations of the choriocapillaris. Thus, it remains in the choroidal circulation.

77. What is the theoretical advantage of ICG dye compared to fluorescein dye for retinal angiography?

ICG dye excitation and emission occur at longer infrared wavelengths compared to fluorescein dye. ICG fluoresces through opacities such as pigment, fluid, lipid, and blood, which may produce hypofluorescence on fluorescein angiography.

78. What are clinical uses of indocyanine green angiography?

ICG is most useful to demonstrate vascular polyps in idiopathic polypoidal choroidal vasculopathy (Fig. 5-16) and to differentiate this entity from age-related macular degeneration. ICG angiography may assist in the diagnosis of choroidal neovascularization, central serous chorioretinopathy, and choroidal inflammatory disorders.

79. What are the indications for obtaining an ICG in a patient with suspected age-related macular degeneration to differentiate from idiopathic polypoidal choroidal vasculopathy?

1. Racially pigmented patients
2. Serosanguineous macular detachment in the peripapillary area
3. Serosanguineous macular detachment in the absence of drusen
4. A large vascularized pigment epithelial detachment, particularly with extensive blood or lipid or minimal cystoid macular edema
5 A vascularized pigment epithelial detachment that has proven resistant or minimally responsive to multiple anti-VEGF injections.[4]

80. What cell layer does fundus autofluorescence evaluate?

Fundus autofluorescence (AF) assesses the RPE (Fig. 5-17). AF is the intrinsic fluorescence emitted by a substance after stimulation with excitation energy. The clinical use of fundus AF is based on the autofluorescence of lipofuscin, which accumulates as an oxidative by-product within RPE cells. RPE that is dead or atrophic is hypoautofluorescent, whereas RPE that is metabolically active, but sick, is hyperautofluorescent. Fundus AF is used to evaluate the area of geographic atrophy in AMD and to assess inflammatory diseases of the RPE. It is also used to evaluate for Plaquenil toxicity.

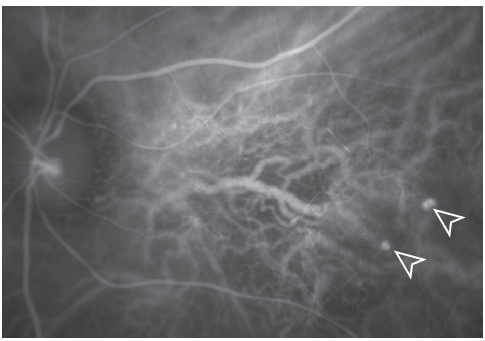

Figure 5-16. Indocyanine green angiography demonstrating the discrete hyperfluorescence of vascular polyps *(arrows)* in a patient with polypoidal choroidal vasculopathy.

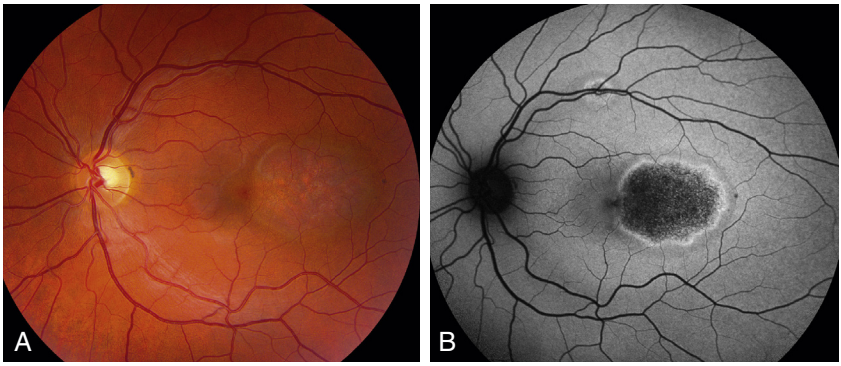

Figure 5-17. A, Color fundus photography and **B,** fundus autofluorescence demonstrating a central area of hypoautofluorescence with a surrounding border of hyperautofluorescence in a patient with a presumed hereditary macular dystrophy of unknown etiology (other eye with similar findings).

KEY POINTS: SUMMARY OF KEY MODALITIES FOR RETINAL IMAGING

1. Optical coherence tomography: provides high-resolution cross-sectional images of the retina, retinal pigment epithelium, and choroid and is vital for management of many retinal disorders
2. Fluorescein angiography: provides an assessment of the retinal vasculature using an intravenous dye and is the gold standard for evaluating for the presence of neovascularization in conditions such as diabetic retinopathy, vein occlusion, and age-related macular degeneration
3. Indocyanine green angiography: provides the best assessment of the choroidal vasculature and is helpful in evaluating diseases of the choroid including central serous chorioretinopathy and polypoidal choroidal vasculopathy
4. Fundus autofluorescence: allows for an assessment of the health of the RPE by imaging the intrinsic autofluorescence of the retina

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CHAPTER 6

VISUAL FIELDS

Janice A. Gault

1. **What are the main types of visual-field tests?**
   - Confrontation visual fields
   - Kinetic perimetry
   - Static perimetry
   - Amsler grids

2. **How are confrontation fields used in practice?**
   Confrontation fields are used as a screening tool because they are a simple, quick, qualitative method for finding gross defects in the peripheral field. The test is performed with the examiner facing the patient and asking if the patient can see fingers in all four quadrants while looking directly at the examiner, testing one eye at a time. In clinical practice, this is more of a screening test. A defect picked up by confrontation fields can be described more definitively with formal field testing.

3. **What is the normal field of vision?**
   From the fixation point, the visual field is 60 degrees nasally, 110 degrees temporally, 75 degrees inferiorly, and 60 degrees superiorly.

4. **What is the difference between kinetic and static perimetry?**
   With kinetic perimetry, a stimulus of a particular size and intensity is moved throughout the visual field. The area within which a given target is perceived is known as that target's isopter. These are marked with different colors to easily differentiate the multiple stimuli used. Central vision is mapped with dimmer, smaller stimuli. Larger, more intense stimuli are used for peripheral vision. The Goldmann perimeter and tangent screen are examples of kinetic techniques. With static perimetry, a test site is chosen and the stimulus intensity or size is changed until it is large enough or bright enough for the patient to see it. The Humphrey and Octopus machines are examples of static perimetry.

5. **When is kinetic perimetry used?**
   The test can be helpful in patients who require significant supervision to complete visual-field testing, i.e., children, stroke victims, and patients with dementia and other mental challenges. Patients with low vision due to central vision loss are another indication.
   Highly trained personnel are needed to administer these tests.

6. **What is full-threshold testing?**
   Full-threshold testing refers to static visual-field testing in which the exact threshold of the eye is measured at every point tested. This technique differs from suprathreshold testing in which test objects are presented at a fixed intensity. Suprathreshold testing is used mainly in screening programs and may miss early defects. Also, a shallow defect will appear the same as an extremely deep defect.

7. **You order a Goldmann visual field, and the isopters are labeled with notations such as I2e and V4e. What do these notations mean?**
   The target size and intensity are indicated by a Roman numeral (I to V), an Arabic numeral (1 to 4), and a lowercase letter (a to e). The Roman numeral represents the size of the target in square millimeters. Each successive number is an increase by a factor of 4. The Arabic numeral represents the relative intensity of the light presented. Each successive number is 3.15 times brighter than the previous one. The lowercase letter indicates a minor filter. The "a" is the darkest, and each progressive letter is an increase of 0.1 log unit.

8. **How is an Amsler grid used to test visual field?**
   The grids can be used to detect central and paracentral scotomas. If held at one-third of a meter, each square subtends 1 degree of visual field.

9. **Where is the physiologic blind spot located?**
   It is in the temporal visual field. The fovea is the center of the visual field. The blind spot is 15 degrees temporal and just below the horizontal plane. On the Humphrey visual field, it is marked by a triangle.

10. When looking at a visual field, how do you differentiate the right eye from the left eye?

The right and left eyes are differentiated by noting where the blind spot is located. The right eye has the blind spot on the right side in its temporal field, and the left eye has the blind spot on the left in its temporal field. If the field loss is so great that the blind spot cannot be identified, the top of the printout should say which eye was tested.

11. What are causes of fixation errors? What can be done to decrease them?

- Poor patient fixation
- "Trigger-happy" patient
- Mistake in locating the blind spot

Try replotting the blind spot, reinstructing the patient, or changing the fixation diamond to one that does not require central vision in patients with macular disease or central scotoma. If the fixation loss is greater than 20%, the test is not reliable. Small defects may be missed and the depth of large defects can be underestimated. A kinetic field may be more helpful clinically.

12. What are false-negative errors?

False negatives occur when a stimulus brighter than threshold is presented in an area where sensitivity has already been determined and the patient does not respond. The patient is usually inattentive and the field will appear worse than it actually is. They may also occur in patients with extremely dense defects.

13. What are false-positive errors?

Most projection perimeters are fairly noisy, and there is an audible click or whirring while the machine moves from one position to another in the field. False positives occur when the projector moves as if to present a stimulus but does not and the patient responds. The patient is "trigger-happy," and the field will look better than it actually is.

14. On a Humphrey visual field, what is the difference between total deviation and pattern deviation?

The total deviation is the point-by-point difference from expected values for normal patients that are in the same age range. It cannot confirm a scotoma, but shows only generalized depression. The pattern deviation adjusts for the generalized depression or elevation and confirms the presence of a scotoma.

15. What is a scotoma?

A scotoma is an area of lost or depressed vision within the visual field surrounded by an area of less depressed or normal visual field. On the pattern deviation plot, three or more nonedge points, clustered in an arcuate area, are suspicious for a scotoma.

16. On a Humphrey printout, what do MD, PSD, SF, and CPSD mean? Are they important?

Mean deviation (MD) is similar to the total deviation plot, i.e., generalized depression. Pattern standard deviation (PSD) is a measure of the degree to which the numbers are different from each other, i.e., local irregularity. This shows more information regarding potential scotomas. Short-term fluctuation (SF) is a measure of intratest error in determining thresholds. Ten predetermined points are each tested twice. Corrected pattern standard deviation (CPSD) is the PSD corrected for the SF. If the SF shows unreliability, the CPSD is better. If the SF is due to true pathology, the PSD is better. If the CPSD or PSD is depressed with $p < 5\%$, it is likely the patient has scotoma.

17. What are false field defects? What are some of their causes?

False field defects occur when the interpreter overlooks physical factors and interprets them as true field defects:

- Ptosis and dermatochalasis can cause loss in the upper parts of the field. Taping the lid up will clear these defects.
- A tilted optic disc can cause local variations in retinal topography, giving the impression of a field defect for refractive reasons alone. When a patient has bilateral tilted discs, the effect can mimic a bitemporal visual field loss.
- A small pupil may give a false impression of true field loss. Dilation of the pupil will clear these defects. This is especially important in patients on miotic therapy (Fig. 6-1).
- The rim of the trial lens will give a defect in the periphery of the central visual field. This will be noted if the patient pulls the head back from the machine while taking the test (Fig. 6-2).

- Media opacities: cornea, lens, and vitreous opacities may cause routine test objects to be invisible. Using larger, brighter test objects may help clarify this problem. This generalized decreased sensitivity can be noted on the total deviation on a Humphrey visual field, but the pattern deviation may show no defects.

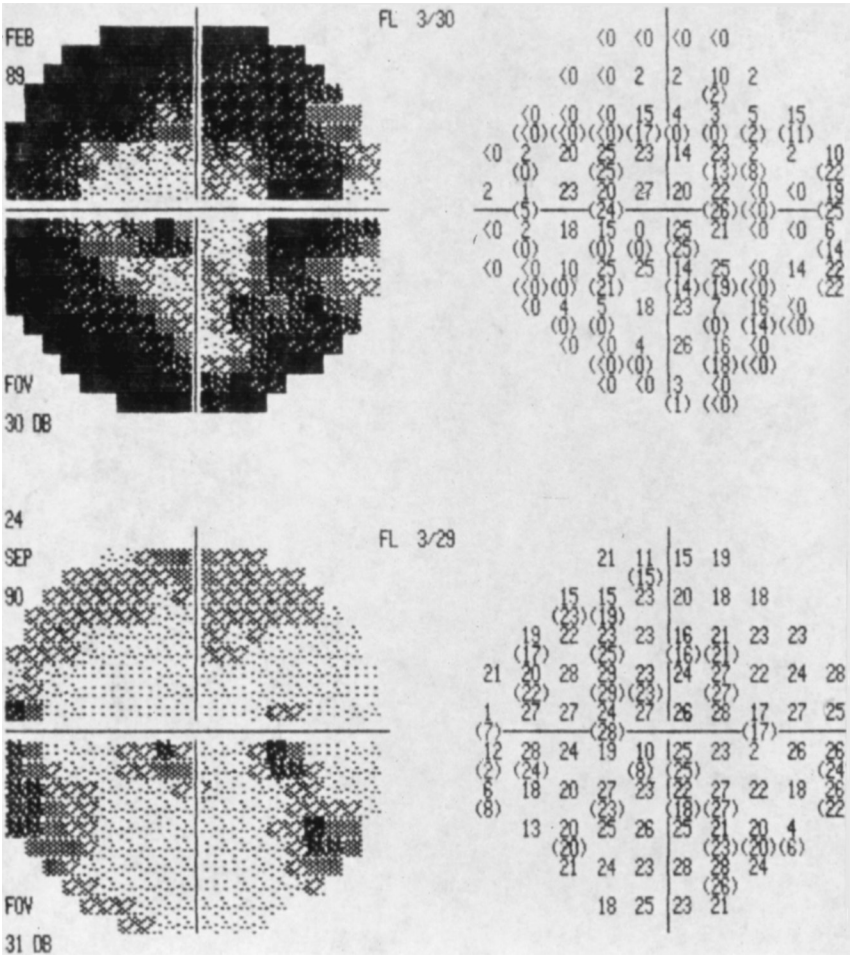

Figure 6-1. A small pupil can create a false impression of visual-field defects. Note that a majority of the defects disappear or lessen when the pupil is dilated from 2 to 8 mm. *(From Gross R: Clinical glaucoma management, Philadelphia, 2001, W.B. Saunders.)*

KEY POINTS: CAUSES OF FALSE-POSITIVE FIELD DEFECTS

1. Ptosis
2. Tilted optic disc
3. Small pupil
4. Rim defect
5. Media opacities

18. What is hemianopia?

Hemianopia is defective vision or blindness in half of the visual field of one or both eyes.

19. Define the terms homonymous and congruous in relation to visual-field defects.

- Homonymous: Pertaining to the corresponding vertical halves of the visual field of both eyes. In plain language, the term is used for defects that occur after neurologic insults that cause loss of a portion of the visual field subsumed by both eyes.
- Congruous: Matched visual-field defects. The more congruous the defect, the more posterior the lesion.

20. How do you describe a visual-field defect?

1. **Position:** Central (defined as the central 30 degrees), peripheral, or a combination of both. Note if the defects are unilateral or bilateral.
2. **Shape:** Very helpful diagnostically. Visual-field defects can be monocular or binocular. The most common form of monocular sector defect is found in glaucoma. The shape is determined by physiologic interruption of nerve fiber bundles. The typical binocular sector defect is a hemianopia.
3. **Intensity:** This refers to the depth of the defect.
4. **Uniformity:** This refers to the depth of the defect throughout the defect.
5. **Onset and course**: This is determined by serial visual fields.

21. What are the different types of hemianopia?

- **Homonymous, total:** Loss of temporal field in one eye and nasal field of the other eye. The vertical midline is respected. The fixation point may be included or spared. This defect implies total destruction of the visual pathway beyond the chiasm unilaterally, anywhere from the optic tract to the occipital lobe. A complete homonymous hemianopia is nonlocalizing.

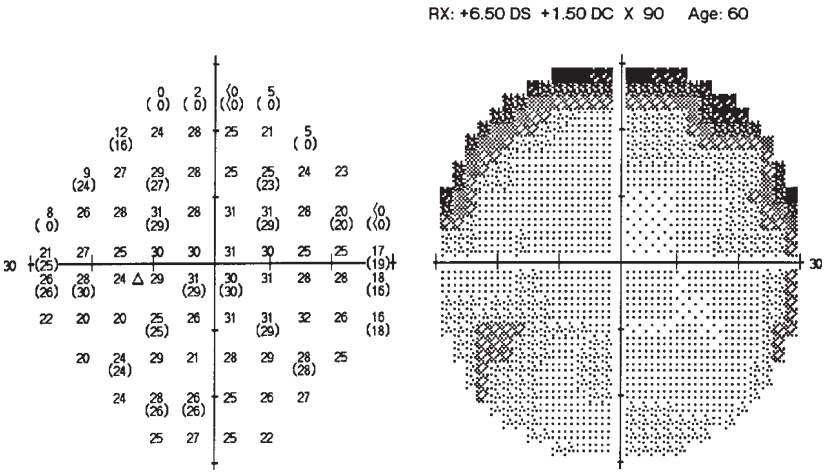

Figure 6-2. Rim artifact caused by the lens and lens carrier. This is most commonly seen in patients on whom a hyperopic correction is being used. A clue to the presence of a rim artifact is the abrupt change from a fairly normal reading to a sensitivity of 0 dB. *(From Alward WLM: Glaucoma: the requisites in ophthalmology, St. Louis, 2000, Mosby.)*

- **Homonymous, partial:** The most common visual-field defect. It may be caused by injury to postchiasmal pathways. Again, it can result from damage at any point from the optic tract to the occipital lobe (Fig. 6-3).
- **Homonymous quadrantanopia:** This is a form of partial homonymous hemianopia.
- **Bitemporal:** May vary from a loss of a small amount of the temporal field to complete temporal hemifield loss. This defect signifies damage in the optic chiasm.
- **Binasal:** This defect signifies an interruption of the uncrossed fibers in both lateral aspects of the chiasm, both optic nerves, or both retinas.
- **Crossed quadrantanopia:** A rare defect in which the upper quadrant of one field is lost along with the lower quadrant of the opposite visual field. It can occur as part of the chiasmal compression syndrome in which the chiasm is compressed from beneath against a contiguous arterial structure. This produces pressure simultaneously from above and below.
- **Altitudinal:** This defect can be unilateral or bilateral. A unilateral defect is prechiasmal such as that found in an ischemic optic neuropathy. Bilateral lesions may be produced by lesions that press the chiasm up, wedging the optic nerve, such as an olfactory groove meningioma (Fig. 6-4).
- **Double homonymous hemianopia:** A result of lesions of the occipital area. There is a loss of all peripheral vision with a remaining small area of central vision representing the spared macula of both eyes. Most are vascular in origin, but they can result from trauma, anoxia, carbon monoxide poisoning, cardiac arrest, and exsanguination (Fig. 6-5).
- **Macula sparing:** This is the rule in occipital damage. The central visual acuity can remain normal.
- **Macula splitting:** Uncommon and difficult to detect because patient will refixate often during the test. This defect occurs with homonymous hemianopia, caused by lesions in the anterior portion of the postchiasmal pathway.

22. Describe the visual pathway.

The first-order neuron is the photoreceptor, a rod or a cone. They synapse with the second-order neurons, the bipolar cells. These synapse with the third-order neurons, the ganglion cells. Axons from these cells cross the retina as the nerve-fiber layer and become the optic nerve. The arrangement of these fibers determines the visual-field defects seen in glaucoma and other optic nerve lesions.

At the chiasm, the temporal fibers are uncrossed, but the nasal fibers cross. The optic tracts begin posterior to the chiasm and connect to the lateral geniculate body on the posterior of the thalamus. Crossed fibers go to laminae 1, 4, and 6. Uncrossed fibers terminate in laminae 2, 3, and 5. The retinal ganglion cell fibers synapse to cells that then connect to the occipital cortex (area 17) via optic radiations in the temporal and parietal lobes.

23. What visual-field defects are characteristically seen in neuro-ophthalmologic disorders?

The pattern of visual-field loss in these patients can often be used to locate very precisely the area of the visual system involved (Fig. 6-6 and Table 6-1).

24. Describe the visual-field defect in Figure 6-7. What are its major causes?

This is a bitemporal hemianopia. Lesions of the chiasm cause bitemporal hemianopia because they damage the crossing nasal nerve fibers. Masses in this area include pituitary tumors, pituitary apoplexy, meningiomas, aneurysms, infection, craniopharyngiomas, gliomas, and other less common tumors. In addition, the chiasm may be damaged by trauma (typically causing a complete bitemporal hemianopia), demyelinating disease, and inflammatory diseases such as sarcoidosis and, rarely, ischemia.

25. What causes binasal hemianopia?

Most nasal field defects are due to bilateral arcuate scotomas from glaucoma. True binasal hemianopias are rare, but they are never a result of chiasmal compression. They may be due to pressure upon the temporal aspect of the optic nerve and the anterior angle of the chiasm or near the optic canal. Causes include aneurysm, tumors such as pituitary adenomas, and vascular infarction.

26. Where would you expect the lesion causing a homonymous hemianopia without optic atrophy to be located?

It should be posterior to the lateral geniculate body. Any lesion anterior to the lateral geniculate body would cause the ganglion axon cells to degenerate.

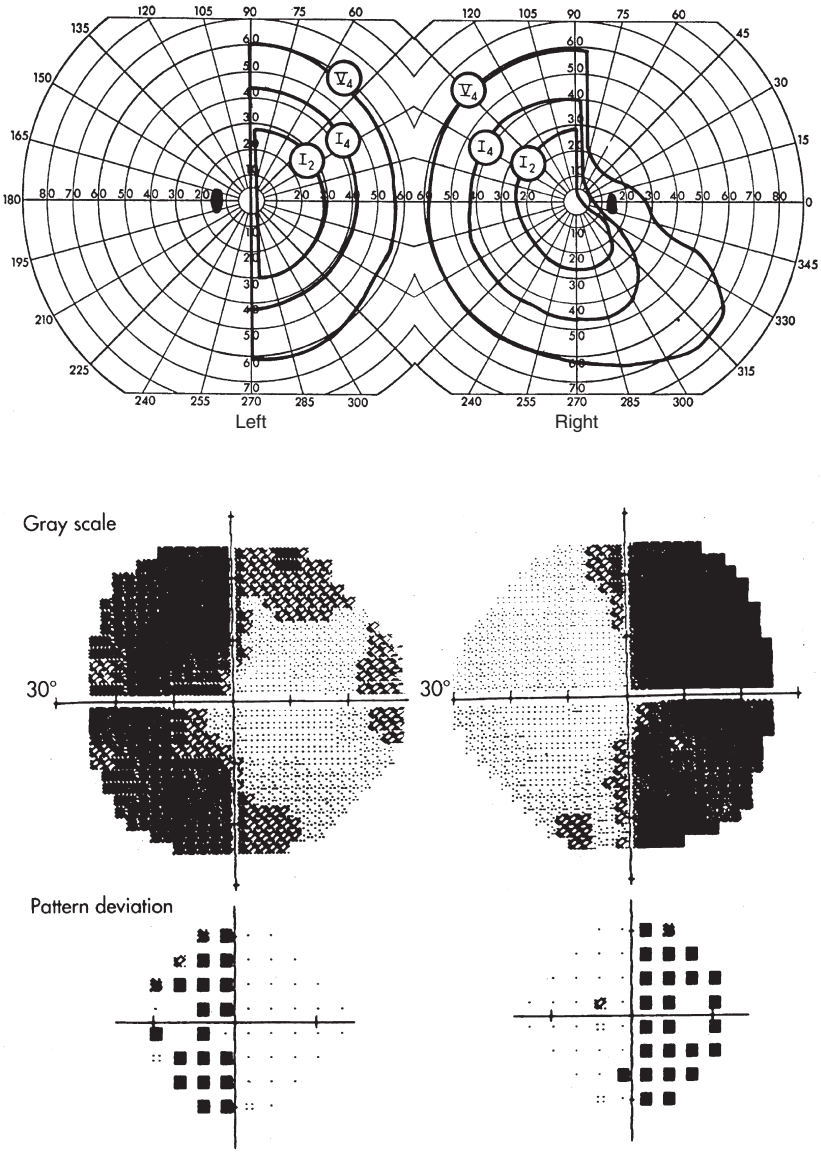

Figure 6-3. Bitemporal hemianopia: incongruous noted on both the Goldmann perimeter (above) and the Humphrey perimeter (below). *(From Burde RM, Savino PJ, Trobe JD: Clinical decisions in neuro-ophthalmology, ed 2, St. Louis, 1992, Mosby.)*

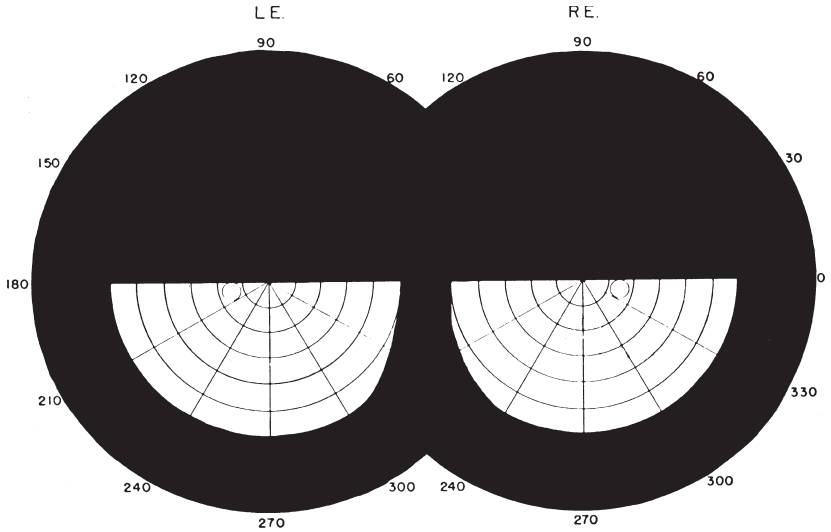

Figure 6-4. Bilateral altitudinal hemianopia. *(From Harrington DO, Drake MV: The visual fields: text and Atlas of clinical perimetry, ed 6, St. Louis, 1990, Mosby.)*

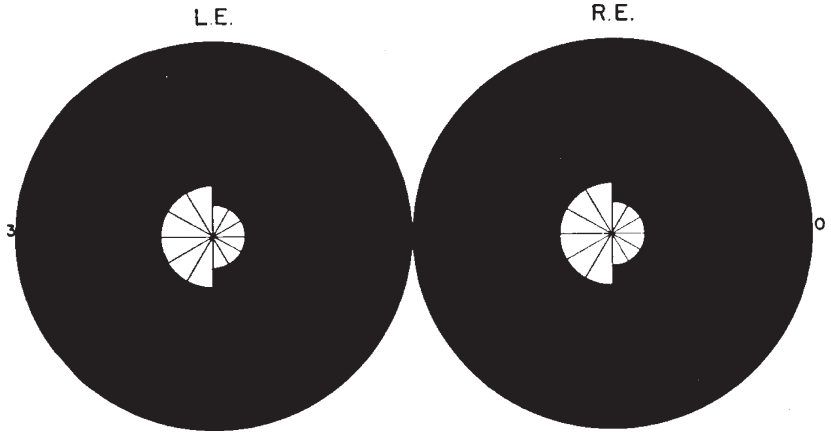

Figure 6-5. Double homonymous hemianopia. *(From Harrington DO, Drake MV: The visual fields: text and Atlas of clinical perimetry, ed 6, St. Louis, 1990, Mosby.)*

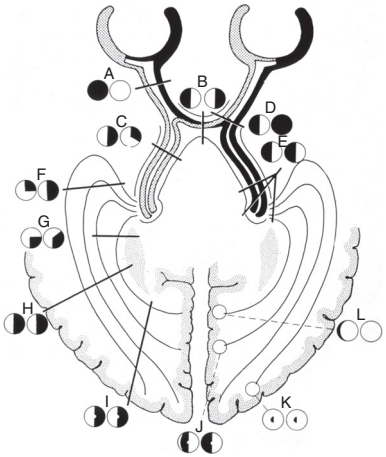

Figure 6-6. Diagram of the visual pathway with sites of nerve fiber damage and corresponding visual fields produced by this damage. **A,** Optic nerve: blindness on involved side with normal contralateral field. **B,** Chiasm: bitemporal hemianopia. **C,** Optic tract: contralateral incongruous homonymous hemianopia. **D,** Optic nerve–chiasm junction: junctional scotoma. **E,** Posterior optic tract, external geniculate ganglion, posterior limb of internal capsule: contralateral homonymous hemianopia, complete or incomplete incongruous. **F,** Optic radiation, anterior loop in temporal lobe: incongruous contralateral homonymous hemianopia or superior quadrantanopia. **G,** Medial fibers of optic radiation: contralateral incongruous inferior homonymous quadrantanopia. **H,** Optic radiation in parietal lobe: contralateral homonymous hemianopia, may be mildly incongruous, minimal macular sparing. **I,** Optic radiation in posterior parietal lobe and occipital lobe: contralateral congruous homonymous hemianopia with macular sparing. **J,** Midportion of calcarine cortex: contralateral congruous homonymous hemianopia with wide macular sparing and sparing of contralateral temporal crescent. **K,** Tip of occipital lobe: contralateral congruous homonymous hemianoptic scotomas. **L,** Anterior tip of calcarine fissure: contralateral loss of temporal crescent with otherwise normal visual fields. *(Adapted from Harrington DO, Drake MV: The visual fields: text and Atlas of clinical perimetry, ed 6, St. Louis, 1990, Mosby.)*

Table 6-1. Summary of Neuro-Ophthalmologic Visual-Field Defects

LESION	VISUAL FIELD
Optic nerve	Central and cecocentral scotomas (i.e., optic neuritis, compressive lesions) Altitudinal defects (i.e., optic nerve drusen, chronic papilledema, ischemic optic neuropathy, optic nerve colobomas)
Optic chiasm	Anterior chiasm or posterior optic nerve: junctional scotoma Body and posterior chiasm: bitemporal hemianopia
Optic tract	Incongruous homonymous hemianopia with or without central scotoma
Optic radiations	Internal capsule: congruous homonymous hemianopia Temporal lobe: superior quadrantanopia Parietal lobe: inferior quadrantanopia
Occipital lobe	Posterior: highly congruous homonymous hemianopia Anterior: monocular contralateral temporal defect Macular or extreme temporal fields may be spared

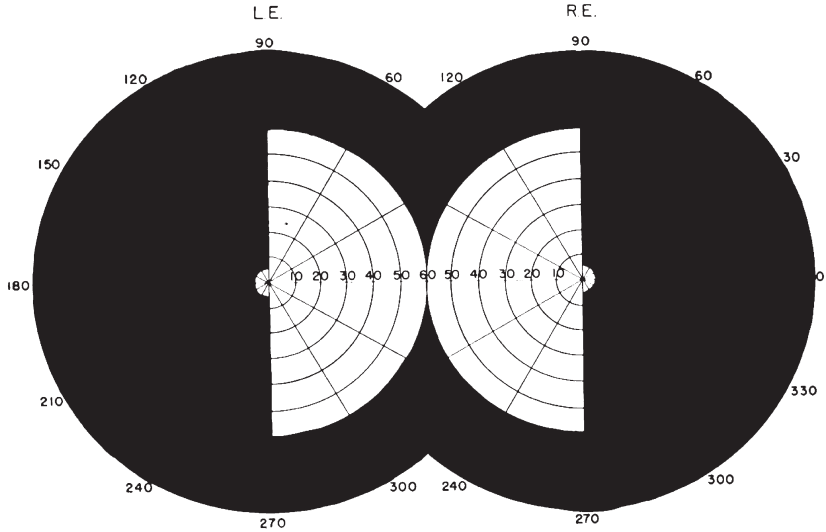

Figure 6-7. Bitemporal hemianopia. *(From Harrington DO, Drake MV: The visual fields: text and Atlas of clinical perimetry, ed 6, St. Louis, 1990, Mosby)*

27. Does visual acuity help to locate the cause of a visual-field defect?

Patients with isolated retrochiasmatic lesions do not have decreased visual acuity unless the lesions are bilateral; then the visual acuity color plates are abnormal and the patient would have a relative afferent pupillary defect. Also examine the patient for optic disc abnormalities such as pallor, cupping, and drusen.

28. Describe the visual-field defect in Figure 6-8. What causes this?

This is a cecocentral lesion defined as a lesion involving both the blind spot and the macular area (to the 25-degree circle). Four primary causes are typically cited: dominant optic atrophy, Leber's optic atrophy, toxic/nutritional optic neuropathy (i.e., tobacco, alcohol, lead, multiple medications), and congenital pit of the optic nerve with a serous retinal detachment. Optic neuritis also may cause cecocentral lesions.

29. Describe the visual-field defect in Figure 6-9. Where is the lesion? Are there any coexistent symptoms?

A "pie-in-the-sky" lesion is a homonymous quadrantanopia involving the superior quadrant. The term indicates a lesion in the optic radiations through the temporal lobe, but similar defects can be seen with occipital lobe lesions as well. These patients often have coexistent seizures and visual hallucinations.

30. Describe the visual-field defect in Figure 6-10. Where is the lesion? Are there any coexistent symptoms?

A "pie-on-the-floor" lesion is a homonymous quadrantanopia involving the inferior quadrant. The term indicates a lesion in the parietal lobe. These patients often have coexistent spasticity of conjugate gaze (tonic deviation of eyes opposite to the side of the lesion when attempting the Bell's phenomenon) and optokinetic asymmetry (diminished or absent response with rotation of optokinetic objects toward the side of the lesion).

31. Describe the visual-field defect seen in Figure 6-11

A junctional scotoma is a unilateral central scotoma associated with a contralateral superior temporal field defect. Thus, in a patient that comes in with poor vision in one eye, it is very important to check the contralateral visual field for superior temporal field loss.

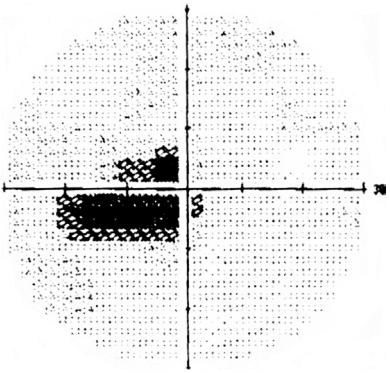

Figure 6-8. Cecocentral scotoma. *(From Burde RM, Savino PJ, Trobe JD: Unexplained visual loss. In Burde RM, Savino PJ, Trobe JD [eds]: Clinical decisions in neuro-ophthalmology, ed 3, St. Louis, 2002, Mosby, pp 1–26.)*

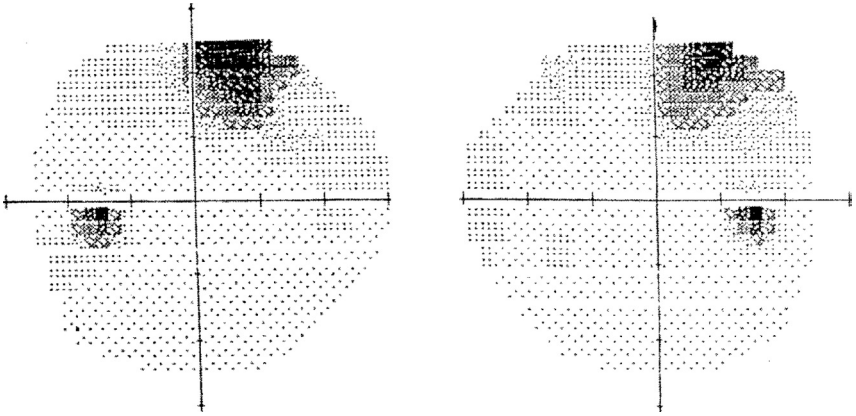

Figure 6-9. Congruous right superior homonymous quadrantanopia following left temporal lobectomy for epilepsy. *(From Burde RM, Savino PJ, Trobe JD: Clinical decisions in neuro-ophthalmology, ed 3, St. Louis, 2002, Mosby.)*

32. What is the anatomic explanation for a junctional scotoma?

Inferonasal retina fibers cross in the chiasm, passing into the contralateral optic nerve (Willebrand's knee). The contralateral optic nerve is compressed near the chiasm. These patients have decreased visual acuity and a relative afferent visual defect.

33. What is an optic-tract syndrome?

Mass lesions of the optic tract are usually large enough to compromise the optic nerve and chiasm as well. Patients have an incongruous homonymous hemianopia (Fig. 6-12), bilateral optic disc atrophy, often in a "bow-tie" pattern, and a relative afferent defect on the side opposite the lesion (i.e., the eye with temporal field loss).

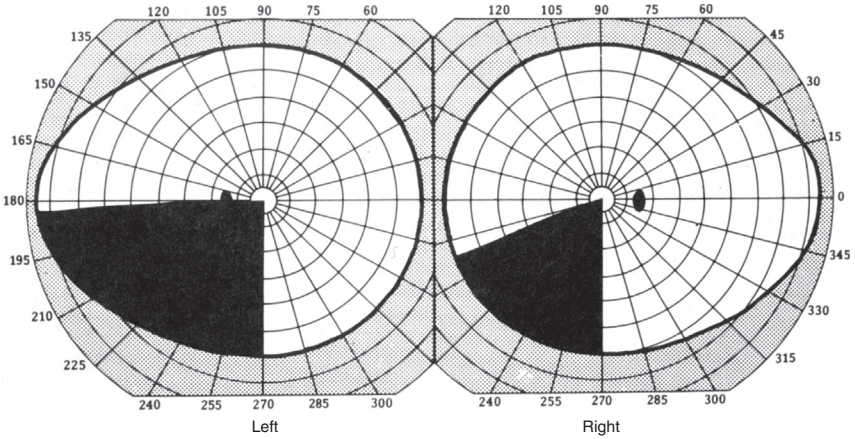

Figure 6-10. Left inferior quadrantanopia in a patient with a right parietal lobe lesion. *(From Kline LB, Bajandas FJ: Neuro-ophthalmology review manual, ed 4, Thorofare, NJ, 1996, Slack.)*

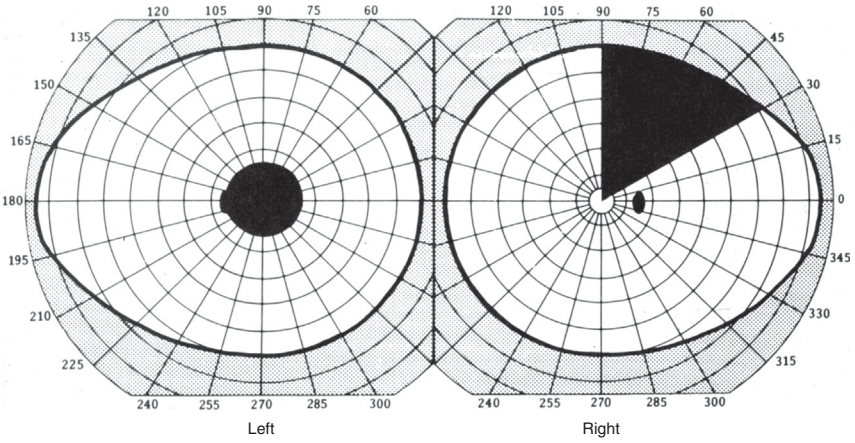

Figure 6-11. Junctional scotoma from a lesion at the left optic nerve and anterior chiasm. *(From Kline LB, Bajandas FJ: Neuro-ophthalmology review manual, ed 4, Thorofare, NJ, 1996, Slack.)*

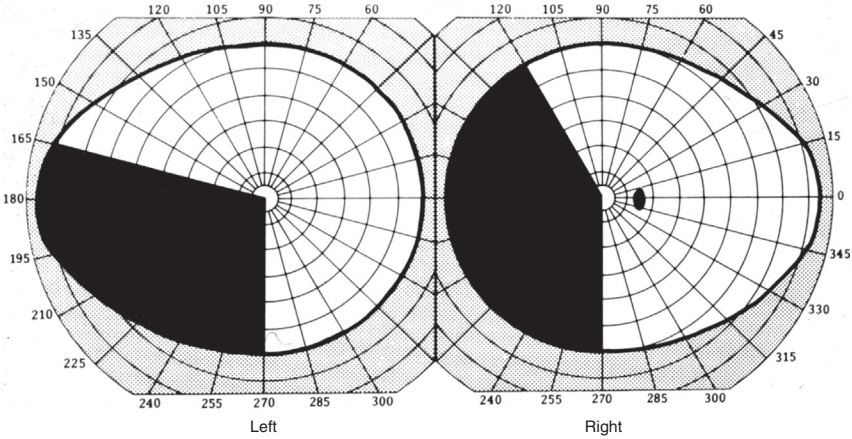

Figure 6-12. Incongruous left homonymous hemianopia from a right optic-tract lesion. *(From Kline LB, Bajandas FJ: Neuro-ophthalmology review manual, ed 4, Thorofare, NJ, 1996, Slack.)*

34. What are the most common visual-field findings in glaucoma?

Glaucoma is a disease of loss of retinal ganglion cells with characteristic optic nerve findings. The classic defects are determined by the anatomy of retinal ganglion cells as they travel to the optic nerve. The axons circle around the fovea in an arc. With damage to the nerve bundles, the classic findings include a nasal step, an arcuate defect within 15 degrees of fixation (also known as a Bjerrum defect), or a Siedel scotoma (a comma-shaped extension of the blind spot; Fig. 6-13). The defect obeys the horizontal midline (in contrast to neurologic field defects, which obey the vertical midline). An exam of the optic nerve is helpful in making the diagnosis in less clear cases. Defects in the optic nerve will predict the visual field loss (e.g., a superior notch of the nerve will be manifested by an inferior arcuate field defect). Usually, the central field is retained until a late stage of the disease. When the central field is lost, a small temporal island may remain.

35. When has the visual field of a person with glaucoma progressed?

The answer remains controversial. First, do not base a diagnosis of glaucoma on one field. If the patient has clear optic nerve damage and corresponding visual field defects, one can make the diagnosis, but the baseline field needs to be repeated because patient performance will improve with practice. A first field with significant defects not corresponding to the clinical optic nerve exam may be full on a second attempt. Improved fixation can also cause field defects to appear more clearly. Persons with glaucoma tend to have more variable visual fields than normal subjects; thus, a single visual field showing worsening should be confirmed with a repeat field. One study concluded that to be certain of progression, one needs a minimum of 5 years of annual visual fields. However, use of clinical correlation can help (Fig. 6-14). Ongoing research is trying to improve our ability to determine which patients are progressing. Newer imaging with ocular coherence tomography, Heidelberg retinal tomography, and scanning laser polarimetry can help determine clinical correlation on visual field testing.

36. Describe the visual field in Figure 6-15. What is your differential diagnosis?

This is a ring scotoma. Severe glaucoma, retinitis pigmentosa, panretinal photocoagulation, vitamin A deficiency, and other retinal and/or choroidal diseases affect the peripheral retina selectively. Aphakic patients may have a prominent ring scotoma from lens-induced magnification of the central field. Clinical exam should differentiate the above easily. Functional visual loss from hysteria or malingering may reveal a ring scotoma on visual-field testing. A Goldmann visual field may be helpful in this situation, as spiraling where an isopter of greater luminance overlaps one that is dimmer can rule out organic disease (Fig. 6-16).

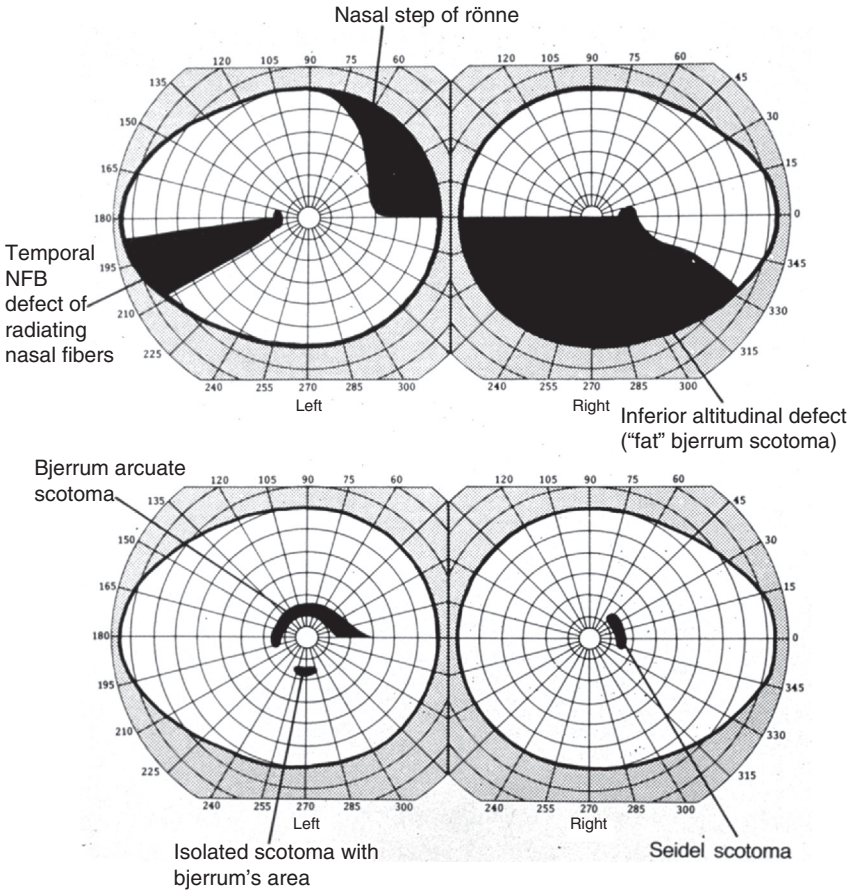

Figure 6-13. Common visual-field findings in glaucoma. *(From Kline LB, Bajandas FJ: Neuro-ophthalmology review manual, ed 4, Thorofare, NJ, 1996, Slack.)*

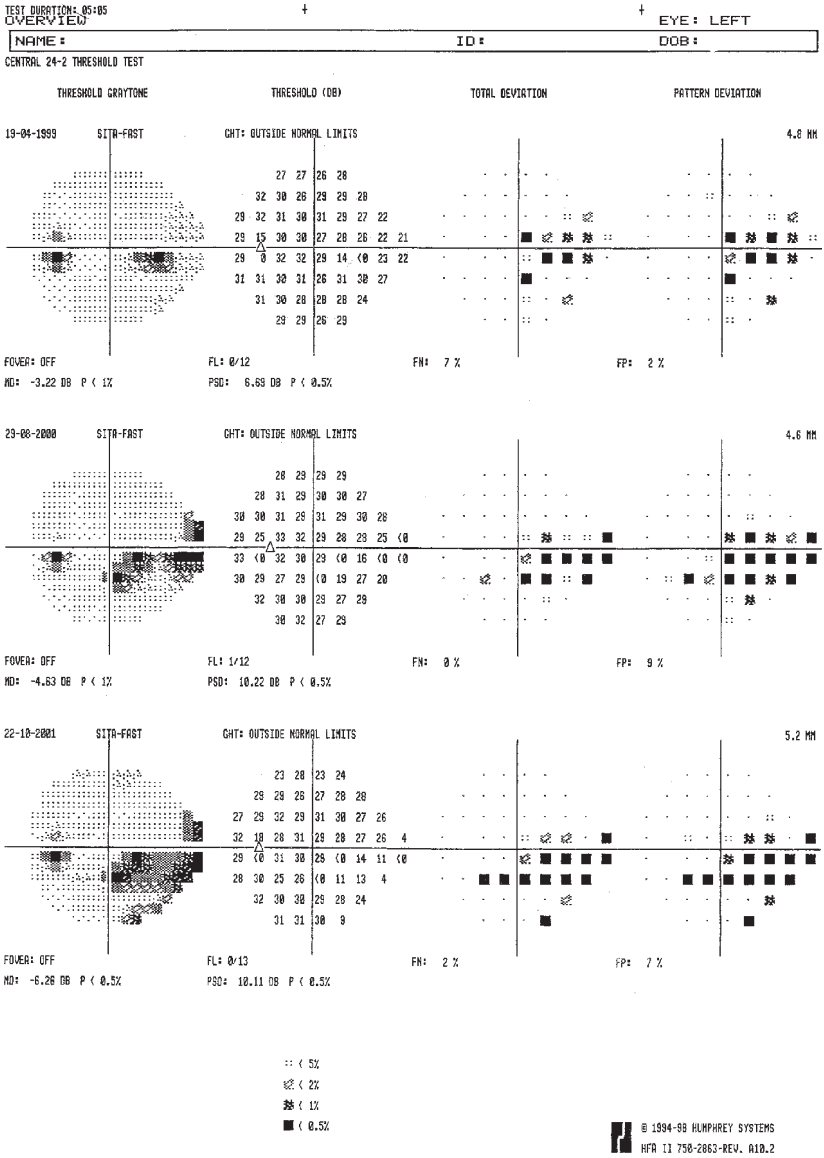

Figure 6-14. Progression of visual-field defects over 3 years. *(From Kanski JJ: Clinical ophthalmology: a systematic approach, ed 5, New York, 2003, Butterworth-Heinemann.)*

37. What is the differential diagnosis of general depression of the field without localized field defects?

This is a general sign without diagnostic value, but can be an indication of glaucoma, media opacities, small pupils, refractive error, and/or an inexperienced or inattentive patient.

38. What clinical findings might mimic a neurologic defect?

An altitudinal defect can be seen with a hemibranch artery or vein occlusion. Peripapillary atrophy will reveal an enlarged blind spot. A disciform macular scar will show a central scotoma (Fig. 6-17). Retinal detachment will show a correlating visual-field defect, even after it has been repaired.

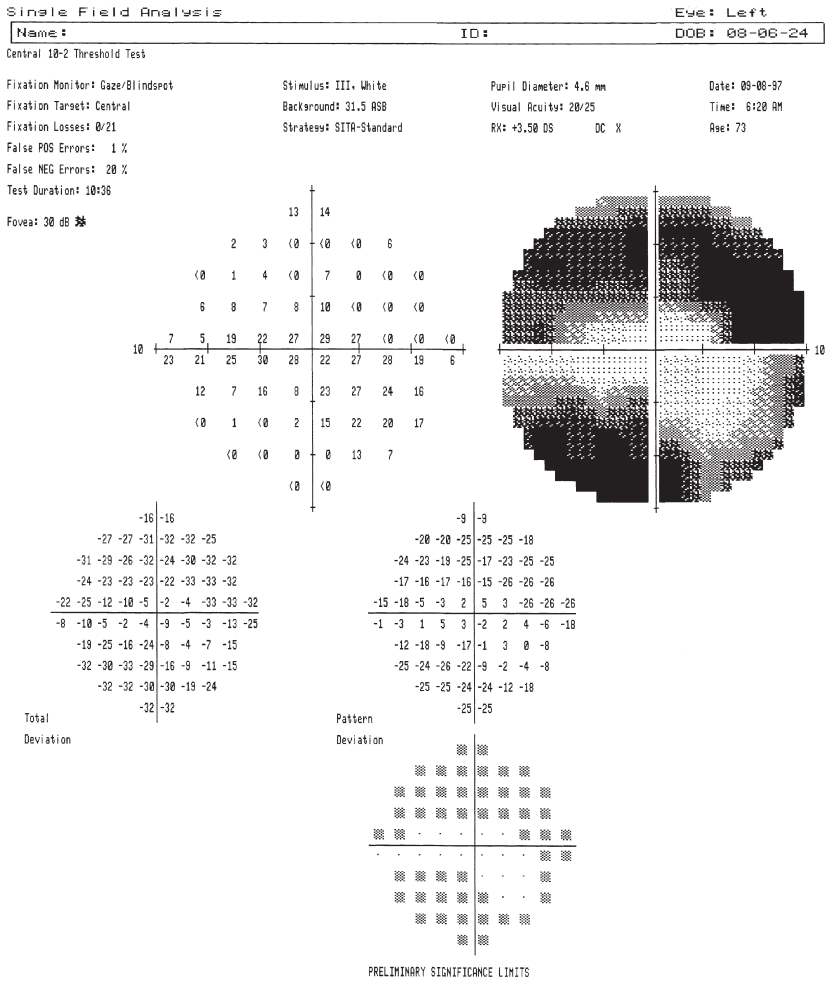

Figure 6-15. Ring scotoma. *(From Gross R: Clinical glaucoma management, Philadelphia, 2001, W.B. Saunders.)*

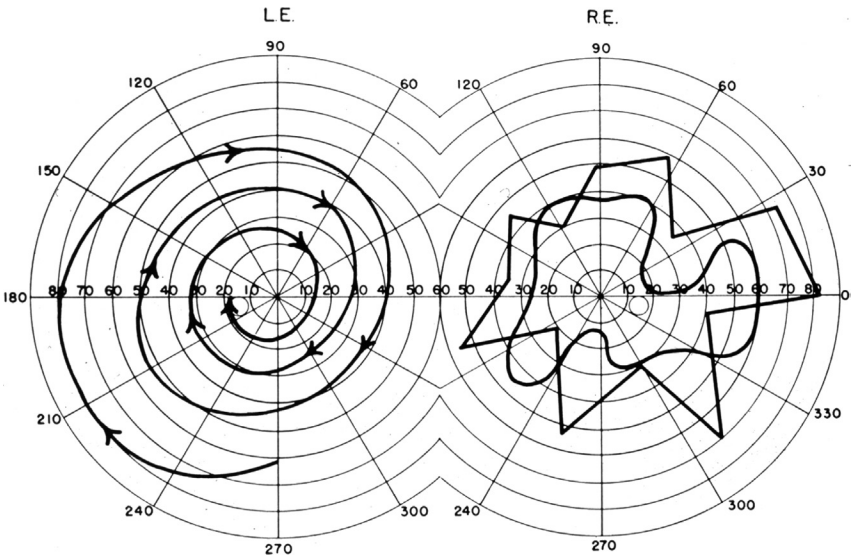

Figure 6-16. Visual fields in a hysterical patient. The left eye shows spiraling. The right eye shows a fatigue field in which a star-shaped interlacing field results from testing opposite ends of the various meridians. *(From Harrington DO, Drake MV: The visual fields: text and Atlas of clinical perimetry, ed 6, St. Louis, 1990, Mosby.)*

KEY POINTS: USING VISUAL FIELDS TO DETERMINE CAUSE

1. Monocular defects are prechiasmal except that the far temporal visual field is seen only by one eye. Watch this in an anterior occipital infarct, which can produce a monocular temporal defect.
2. Lesions posterior to the chiasm do not cross the vertical meridian by more then 15 degrees.
3. Patients with postchiasmal defects typically have normal visual acuity, normal pupils, and a normal exam of the ocular fundus. Papilledema, however, may be seen in patients with space-occupying lesions.
4. Use clinical correlation to interpret fields.

39. What does the future hold for visual-field testing?

Most visual field testing done today is standard automated perimetry. The three important advances in visual-field testing are faster algorithms that decrease test time, short-wavelength automated perimetry (SWAP), and frequency-doubling perimetry. The new algorithm uses previous patient responses to help choose the testing threshold and thus takes less time. Test times are approximately 5 minutes per eye, as opposed to 15 minutes with the older algorithms. SWAP may detect field loss earlier than traditional white-on-white perimetry. SWAP uses standard static threshold-testing strategies with a blue test object on a yellow background. Early results indicate that visual-field defects may be detected several years earlier with SWAP than with standard static testing. Finally, frequency-doubling perimetry is in the early stages of development but may be extremely useful as a screening tool in the future.

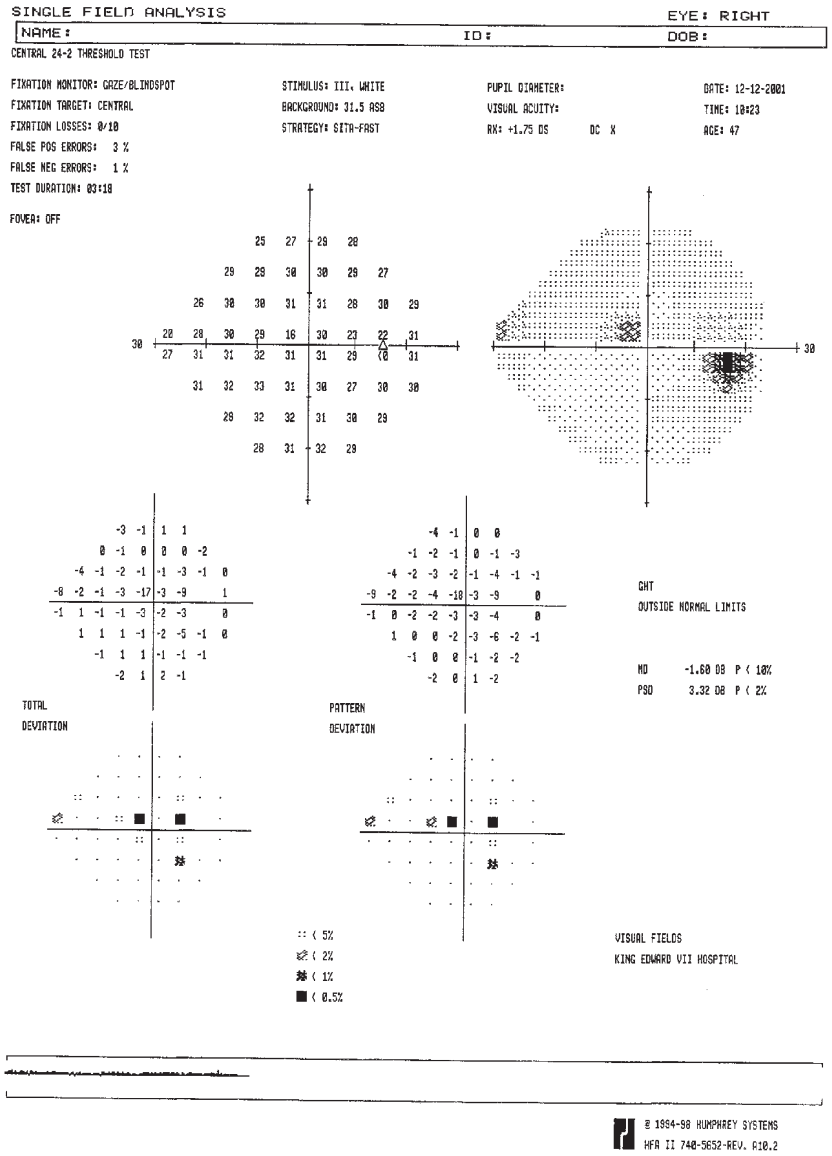

Figure 6-17. Paracentral scotoma. *(From Kanski JJ: Clinical ophthalmology: a systematic approach, ed 5, New York, 2003, Butterworth-Heinemann.)*

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CHAPTER 7

THE RED EYE

Janice A. Gault

II. CORNEA AND EXTERNAL DISEASES

1. Name the main causes of a red eye.

- Conjunctivitis
- Episcleritis
- Subconjunctival hemorrhage
- Scleritis
- Corneal disease and trauma
- Dry eye
- Anterior uveitis
- Acute glaucoma
- Blepharitis

2. A 40-year-old woman complains of watery, itchy eyes with swollen lids. How should you proceed?

In the differential diagnosis of a red eye, the history is often helpful. By asking more questions, you find that she has been mowing the grass; subsequently, her hay fever worsened and her eyes flared. Examination reveals red, edematous lids, chemosis, conjunctival papillae, and mucous strands in the cul-de-sac. A preauricular node is not palpable. She is on loratadine (Claritin), but despite improvement in her rhinitis, her eyes are still uncomfortable. Systemic antiallergy medications rarely affect ocular symptoms. Topical treatment is much more effective. Options for topical medications include:

- Mast cell inhibitors
  - Lodoxamide (Alomide)
  - Nedocromil sodium (Alocril)
  - Cromolyn sodium (Crolom, Opticrom, generic)
  - Pemirolast (Alamast)
- H_1 receptor antagonists
  - Direct: Epinastine (Elestat)
  - Selective: Emedastine (Emadine)
- Combination H_1 antagonists/mast cell inhibitors
  - Ketotifen (Zaditor, Alaway, Claritin, generics) now over the counter (OTC)
  - Olopatadine (Patanol, Pataday)
  - Azelastine hydrochloride (Optivar, generics)
  - Nedocromil (Alocril)
  - Bepotastine (Bepreve)
  - Alcaftadine (Lastacaft)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Diclofenac (Voltaren)
  - Ketorolac (Acular)
- Low-dose steroid (only for short-term use or under close supervision)
- Loteprednol (Alrex, Lotemax)
- Antihistamines/decongestants—OTC
  - Naphazoline/pheniramine (Opcon-A, Naphcon A, Visine A)
  - Naphazoline/antazoline (Vasocon A)

3. The next patient has a similar clinical exam, but was seen by her primary care doctor with "pink eye." Since she started her gentamicin drops, she feels her eyes have gotten worse. Her eyelid skin is erythematous and scaly.

A patient who is allergic to a medication used in or around the eyes presents in a fashion similar to other allergy sufferers although the lid changes may be more severe. Typical offenders include

aminoglycosides, sulfa medications, atropine, epinephrine agents, apraclonidine, trifluridine (Viroptic), pilocarpine, and any ophthalmic medication with preservatives. Immediate cessation of the offending agent, as well as cool compresses and preservative-free artificial tears or a topical antiallergy medication, is appropriate. Impress on the patient that lid rubbing will worsen the condition. If the lid reaction is severe, an ophthalmic steroid cream may be prescribed. Some patients are affected severely enough to develop an ectropion of their lower lids.

4. **The next patient has no seasonal allergies and is not on any topical medications around her eye, but again, the clinical picture looks the same, with lots of itching.**
Ask about exposures to items such as creams, lotions, detergents, fabric softener, hair dyes, cosmetics, nail lacquer, and glues. It can also be an old product, with new formulations or fragrances. A new cat or dog can cause a similar picture. The possibilities are nearly endless. Referral to an allergist for patch testing to determine the cause may be helpful. Cool compresses, preservative-free artificial tears, and topical antiallergy medicines can give symptomatic relief.

5. **What might you expect to see in a patient with epidemic keratoconjunctivitis, or pink eye?**
Examination may reveal tarsal conjunctival follicles as well as a preauricular node. In more severe cases, the patient may have membranes or pseudomembranes. Often, the condition begins in one eye and spreads to the other. Viral conjunctivitis may precede, accompany, or follow an upper respiratory infection. This condition is contagious, and patients need to be warned not to leave any contaminated material in a place where others may touch it. Frequent hand washing is crucial. The physician's exam room needs to be washed down thoroughly with an appropriate disinfectant, because an epidemic may occur among other patients as well as staff. Patients should not return to work or school until the eyes stop weeping, often as long as 2 weeks. The condition typically worsens in the first week before improving over the course of 2 to 3 weeks. Adults may have systemic symptoms of an upper respiratory infection with fevers and muscle pain. Children are less systemically affected. Ophthalmic treatment is supportive, with artificial tears and cool compresses. Steroids should be used only in select cases such as those with subepithelial infiltrates that reduce vision and membranes or pseudomembranes. Steroids decrease symptoms in the short term, but often increase the duration of the disease. Topical NSAIDs and antiallergy medications may alleviate discomfort without prolonging the disease course.

6. **A 25-year-old man states that his eyes have been dripping with discharge over the past 8 hours. You notice significant purulent discharge, a preauricular node, and marked chemosis. What is the next step?**
This condition is an emergency. The most likely diagnosis is gonococcal conjunctivitis. An immediate Gram stain and conjunctival scrapings for culture and sensitivities are imperative. Cultures should be done on blood agar, on chocolate agar at 37° C and 10% CO_2, and a Thayer–Martin plate. If they cannot be done at your office, send the patient to an emergency room that can perform and interpret them urgently.

7. **What are you looking for on the Gram stain?**
A positive Gram stain would show gram-negative intracellular diplococci.

8. **How should the patient be treated?**
    1. Ceftriaxone, 1 gm intramuscularly in a single dose. However, if corneal involvement exists or you are unable to visualize the cornea because of chemosis and lid swelling, the patient should be hospitalized and treated with ceftriaxone, 1 gm intravenously every 12 to 24 hours. *Neisseria gonorrhoeae* can perforate an intact cornea quickly. Penicillin-allergic patients can be treated orally with 500 mg of ciprofloxacin or 400 mg of ofloxacin, both as single doses. However, there is increasing fluoroquinolone resistance in certain areas. Consider an infectious disease consult.
    2. Topical bacitracin or erythromycin ointment four times/day or ciprofloxacin drops every 2 hours. Consider fluoroquinolones every hour if the cornea is involved.
    3. Eye irrigation with saline four times/day until the discharge is gone.
    4. Doxycycline, 100 mg twice a day for 7 days, or azithromycin, 1 gm orally as a single dose for chlamydial infection, which often coexists. Use erythromycin or clarithromycin in a patient who is pregnant or breast-feeding because of the risk of teeth staining in children.
    5. Referral of the patient and sexual partners to family doctors for evaluation of other sexually transmitted diseases.

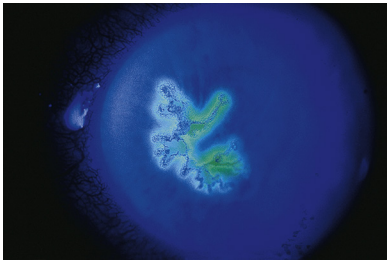

Figure 7-1. A dendrite typical of herpes simplex keratitis with epithelial ulceration, raised edges, and terminal bulbs. *(From Kanski JJ: Clinical ophthalmology: a synopsis. New York, 2004, Butterworth-Heinemann.)*

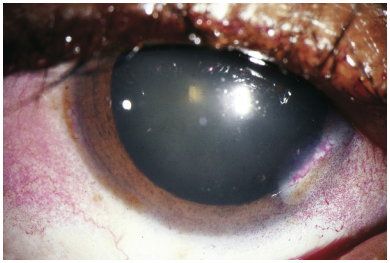

Figure 7-2. Dry eye syndrome with rose bengal staining. *(From Tu EY, Rheinstrom S: Dry eye. In Yanoff M, Duker JS [eds]: Ophthalmology, ed 2, St. Louis, Mosby, pp 520–524.)*

9. A 35-year-old man complains of pain in his left eye for several days, watery discharge, and blurred vision. He thinks he has had the same symptoms before. He admits to stress on the job as well as a recent cold sore. What do you expect to see?

Herpes simplex virus (HSV) would be expected. With fluorescein staining of the eye, you can see a dendritic ulcer with terminal bulbs (Fig. 7-1). It is placed centrally, accounting for the decrease in vision. The patient may also have some anterior chamber cell and flare. He needs a topical antiviral such as ganciclovir (Zirgan), trifluridine (Viroptic), or vidarabine (Vira-A). Debridement of infected epithelium can speed recovery. Add a cycloplegic drop if photophobia and anterior chamber reaction are significant. Topical steroids should be tapered. Oral antivirals such as acyclovir (400 mg five times a day for 7 to 10 days) may be used if topical toxicity or compliance with the drops is a problem. However, they have not been shown to prevent stromal disease or iritis in HSV infection, but they are beneficial if iritis is already present. Once the patient has healed from the acute episode, long-term, oral antiviral prophylaxis such as acyclovir 400 mg twice a day may be indicated if the patient has had multiple episodes of herpetic epithelial or stromal disease.

10. An 80-year-old woman complains of red eyes that constantly tear and burn. They worsen as the day goes on. She also feels foreign-body sensation and reports that her vision is not as clear as before. The vision varies with tear blink. She has noticed this condition over the past several years. What may you find?

On exam, you may find a poor tear film filled with debris, a low tear meniscus, superficial punctate keratopathy inferiorly or throughout the cornea, and, if severe, mucous filaments adherent to the cornea. A normal meniscus is 1 mm in height in a convex shape. A Schirmer's test can quantify her tear production. Figure 7-2 shows the areas of rose bengal interpalpebral staining. Make sure that she can close her eyes completely, because lagophthalmos may cause similar symptoms. The condition may be due to an eyelid deformity from scarring, tumor, or Bell's palsy. Patients may have trouble closing their eyes completely after ptosis surgery.

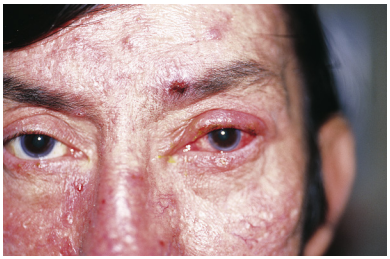

Figure 7-3. Blepharitis. *(From Kanski JJ: Clinical ophthalmology: a test yourself Atlas, ed 2, New York, 2002, Butterworth-Heinemann.)*

11. What may cause superficial punctate keratopathy?

Blepharitis, dry eye, Sjogren syndrome, trauma from eye rubbing, exposure, topical drug toxicity, ultraviolet burns (welder's flash, snow blindness), foreign body under the upper lid, mild chemical injury, trichiasis, floppy-lid syndrome, entropion, and ectropion may cause bilateral superficial punctate keratopathy (SPK). Treatment consists of increasing lubrication and eliminating the cause.

12. What is Thygeson's superficial punctate keratopathy?

Thygeson's SPK consists of bilateral stellate, whitish-gray corneal opacities that are slightly elevated with minimal to no staining. Tears are usually the only required treatment, with occasional topical steroids for severe cases. Thygeson's SPK has a chronic course with remissions and exacerbations.

13. An 83-year-old man has crusty lids and red eyes and complains of "sand in my eyes." What is your diagnosis?

This is a common scenario indeed. Blepharitis may present with crusty, red, thickened eyelid margins with prominent blood vessels (Fig. 7-3). Inspissated oil glands at the lid margins cause meibomianitis. Patients often have both and complain of red, tearing eyes. The lids may be significantly swollen. Patients often have trouble opening their eyes in the morning because of the amount of crusting. SPK is common. If severe and untreated, cornea scarring can develop.

Blepharitis can be divided into anterior and posterior blepharitis. Anterior blepharitis affects the eyelid follicles, base of the eyelash, and eyelid skin. Anterior blepharitis is staphylococcal, seborrheic, or a combination or both. Staphylococcal blepharitis has scaling, crusting, and redness of the lid margin with collarettes at the base of the eyelashes. *Staphylococcus aureus* is more common in these patients. Some think the antigens or toxins from these bacteria may be a factor in the pathophysiology of the disease. Dandruff-like material is seen in patients with seborrheic blepharitis; they may have seborrheic dermatitis of the eyebrows and scalp.

Posterior blepharitis affects the meibomian gland and its orifices. Some have proposed calling this meibomian gland dysfunction (MGD) instead. Foam at the eyelid margin and plugged, swollen meibomian glands and a decreased tear film breakup time are noted in slit lamp exam. Expression of the meibomian glands produces thick toothpaste-like meibomian gland secretions. Eventually, the glands atrophy and cicatrize. Acne rosacea frequently coexists.

14. How do you treat blepharitis?

This chronic condition may require treatment indefinitely or only during flares. Warm compresses two times a day for 5 minutes at a time, baby shampoo on a washcloth or commercial lid scrubs to scrub the eyelid margins twice a day, and artificial tears as needed will help. It may take a week or two of compliance before improvement. Once the condition is under better control, the regimen can be reduced to once a day or as needed. However, when the condition flares, the regimen needs to be increased. Add bacitracin or erythromycin ointment at night. In severe cases, a topical antibiotic/steroid combination may be helpful in the short term, but make sure that the patient understands the risks of long-term use of steroids (e.g., cataracts, glaucoma, increased risk of infection). Topical azithromycin (Azasite) scrubbed into the lashes at night and topical cyclosporine (Restasis) may be helpful for some patients, especially those with MGD. If the patient does not respond, epilating a lash

and looking at it under the microscope may reveal *Demodex*. Infestation has been reported in patients with MGD and collarettes. Treatment with dilute tea tree oil or oral ivermectin has been reported to be of some benefit. MGD has been treated in the office with meibomian gland probing or devices using thermal pulsation (i.e., LipiFlow) to open the blocked orifices. There are no randomized clinical trials on the effectiveness of these procedures yet.

15. If a patient with chronic blepharoconjunctivitis does not improve with multiple therapies, what should be in your differential?

The patient may have sebaceous cell carcinoma. It can be multicentric. Do a biopsy and stain with oil red O. Other tumors such as basal cell, squamous cell, and melanoma are less likely.

16. What other ocular issues are commonly seen in patients with blepharitis?

Patients may have trichiasis or misdirected lashes that scratch the cornea and conjunctiva. If so, the lashes should be epilated. If they are a recurring problem, electrolysis or cryotherapy may provide a more permanent solution. Hordeolum and chalazion are frequently seen in patients with MGD.

KEY POINTS: RED EYE PATIENTS

1. History is important in diagnosis.
2. Itching usually points to allergy. Be suspicious of a diagnosis of allergy without itching.
3. Dry eye symptoms worsen as the day goes on.
4. Blepharitis symptoms may be worse from the beginning of the day.
5. Watery discharge points to a viral cause.
6. Purulent discharge points to a bacterial cause.

17. A 45-year-old man with red, weepy eyes complains of foreign-body sensation for several months. You note he has a bulbous nose and telangiectasias on both cheeks. What is your diagnosis? How do you treat?

Acne rosacea is a disease of the eyes and the skin. Pustules, papules, telangiectasias, and erythema develop on the nose, cheeks, and forehead. Rhinophyma occurs in the later stages of the disease. Telangiectasias of the eyelid margin and chalazia are common, as are blepharitis and meibomianitis. Dry eye, SPK, phlyctenules, and staphylococcal hypersensitivity may occur. In severe cases, the cornea may develop opacification, vascularization, and even perforation.

Treatment for blepharitis and meibomianitis with warm compresses and lid scrubs may be all that is necessary. If the patient does not respond, thinning of the abnormally thick meibomian gland secretions with tetracycline or doxycycline for several weeks may relieve the symptoms, but some patients require a low dose indefinitely. Erythromycin should be substituted in pregnant or nursing women and children because of the risk of teeth staining. A low-dose antibiotic/steroid combination may be useful if SPK or staphylococcal hypersensitivity is a problem; staphylococcal exotoxins may be the cause. Patients can develop infected corneal ulcers; thus, scrapings for smears and cultures may be necessary in patients with "sterile" corneal ulcers before steroids are used.

18. An 18-year-old contact lens wearer presents with her hand over her right eye. She noticed that her eye was somewhat red and irritated 2 days ago but believes that it has gotten worse even though she took out her lens at that time. What are you concerned about?

Whenever a contact lens wearer complains of a red, irritated eye that does not improve over a few hours, a corneal ulcer is high on the differential. After a corneal anesthetic such as proparacaine is instilled, the patient feels some relief and can tolerate examination. You notice a corneal infiltrate with an overlying epithelial defect and anterior chamber cell and flare. See the chapter on corneal infections for the necessary workup and treatment.

19. What else is in the differential diagnosis of a red eye in a contact lens wearer?

- Hypersensitivity reactions to preservatives in solution. The patient may develop an allergy or may not be rinsing the enzyme off completely before placing the lens in the eye.
- Giant papillary conjunctivitis (Fig. 7-4). Patients have large conjunctival papillae on upper lid eversion. Patients may need to discontinue lens wear for several weeks, change their disposable lenses

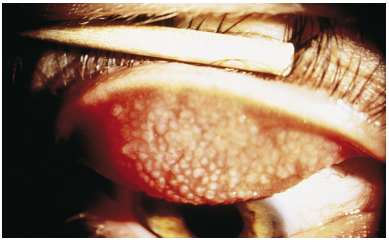

Figure 7-4. A typical case of giant papillary conjunctivitis in a contact lens wearer. *(From Rubenstein JB, Jick SL: Disorders of the conjunctiva and limbus. In Yanoff M, Duker JS [eds]: Ophthalmology, ed 2, St. Louis, 2004, Mosby, pp 397–412.)*

more frequently (even daily), and/or use topical medications such as nonsteroidal anti-inflammatory medications, mast cell inhibitors, or antihistamines. Increased enzyme use and discontinuation of overnight wear also help.

- Contact lens deposits. Old lenses should be replaced.
- Tight lens syndrome. Lenses shrink with age. On exam, the patient may have significant chemosis around the lens, and the lens will not move with a blink. In severe cases, a sterile hypopyon can develop.
- Corneal abrasion.

20. A young mother enters with her infant child. Her left eye is tearing profusely, and she has trouble keeping it open. She states that she was changing the child's diaper when he scratched her eye with his fingernail. What treatment do you recommend?

At the slit lamp, you see a fairly large, central corneal abrasion with no sign of an infiltrate. The upper lid is everted, and no foreign body is seen. The abrasion will heal fairly quickly regardless of treatment; the goals are comfort and prevention of infection. Some patients desire a pressure patch for comfort, but they should not be used in patients who wear contact lenses or who have had trauma from a fingernail or vegetable matter (e.g., a dirty nail or tree branch). Such injuries have a higher chance of contamination and need to be observed for the development of a corneal ulcer. Patching may increase the rate of infection in these patients. A cycloplegic drop, such as cyclopentolate 2%, may relieve the discomfort of ciliary spasm. Prophylactic antibiotics are controversial as they may increase the risk of resistant bacteria if an infected ulcer does develop. If the infection is considered "dirty," tobramycin or ciprofloxacin is a good choice for *Pseudomonas* sp. prophylaxis. A topical anti-inflammatory decreases pain, and some evidence suggests that it may promote healing. However, long-term use of NSAIDs has been associated with corneal melts. The best choice is frequent lubrication with tears and/or ointments to promote healing.

21. Does it make a difference where the abrasion is located?

If the abrasion is large, central, or in a contact lens wearer, the patient should return the next day to make sure that no infection is developing and that the lesion is healing. A bandage contact lens can help with pain and reepithelialization in large defects. A contact lens wearer can resume his or her usual lenses after the defect has healed and the eye feels normal for 3 or 4 days. After the abrasion is healed, examine the patient while he or she is wearing the lenses to ensure that they fit well. Make sure that the lens does not have a tear or significant deposits, which may have contributed to the abrasion.

KEY POINTS: CAUSES OF RED EYE IN A CONTACT LENS WEARER

1. Corneal ulcer
2. Allergy to contact lens solutions
3. Giant papillary conjunctivitis
4. Old lenses
5. Corneal abrasion

22. The same woman as in question 20 returns 3 months later complaining that she awoke in the morning with severe pain, redness, and tearing in the left eye. It feels like the original scratch. She denies rubbing her eye or any other trauma. What may have happened?

Patients who have had a corneal abrasion from a sharp object such as a paper edge or a fingernail may develop recurrent corneal erosions. Recurrent erosions also may be seen in patients who have corneal dystrophy, such as Meesmann's, map-dot-fingerprint, Reis-Buckler, lattice, macular, or granular corneal dystrophy. Typically, patients awaken with severe pain and tearing, or symptoms develop after eye rubbing. On examination, an abrasion may be seen in the area of previous injury, or the epithelium may have healed the defect but appear irregular. Sometimes no abnormalities can be seen, and the diagnosis must be made from the history. Look carefully for any signs of dystrophy, especially in the other eye. Treat with frequent lubrication to heal the epithelial defect. If the corneal epithelium is loose and heaped upon itself, debridement of the loose edges may be necessary first to allow the epithelial defect to heal.

23. Do you treat if the exam is normal in this patient?

After healing, lubrication is crucial. If the eye is dry and the lid becomes stuck to the abnormal epithelium, the cycle will begin again. Artificial tears during the day and lubricating ointment at night will help. A hypertonic solution of 5% sodium chloride theoretically draws out the water from the cornea and promotes epithelial adhesion to its basement membrane. If such treatment does not prevent further erosions, an extended-wear bandage soft contact lens may help. Some patients require anterior stromal puncture or phototherapeutic keratectomy with an excimer laser, which causes small permanent corneal scars that prevent further erosions.

24. A car mechanic complains of a painful red eye. He was fixing a muffler at the time of the onset of pain. What are your concerns?

Most likely, he has a foreign body in his cornea or conjunctiva. It is important to find out what he was doing at the time of the injury. He states that he was hammering metal without safety glasses. This report increases your concern that he may have a ruptured globe. A metal piece that breaks off would travel at a high rate of speed.

On exam, he has 20/20 vision in both eyes. You see no foreign bodies in the conjunctiva or the cornea. You evert the upper lid and find nothing. The intraocular pressure is 2 mm Hg. The other eye has a pressure of 15 mm Hg. Slit lamp exam reveals a conjunctival defect with subconjunctival hemorrhage. It is impossible to determine whether a scleral laceration is present because of the blood blocking the view.

25. What do you do now?

First, put a shield over the eye to prevent further damage to the globe. It is best to examine and treat in the controlled setting of the operating room. The pupil should be dilated to determine whether the foreign body can be seen with the indirect ophthalmoscope. The patient should have nothing else by mouth. A computed tomography scan of the orbits and brain (axial and coronal) is necessary to screen for foreign bodies in the eye, orbit, and brain. Always evaluate the patient systemically to make sure no other injuries are missed. Begin intravenous antibiotics such as cefazolin and ciprofloxacin. Give a tetanus toxoid booster.

26. How do you proceed if, instead of a potential ruptured globe, you find a superficial metallic foreign body at four o'clock on the cornea?

Document visual acuity. Sometimes an infiltrate may be found around the foreign body, especially if it is over 24 hours old. Usually, the infiltrate is sterile. Apply a topical anesthetic (proparacaine), and remove the foreign body with a 25-gauge needle or a foreign-body spud at the slit lamp. A rust ring may have formed, depending on how long the metal has been present. Often it can be removed with the same instruments. It is sometimes safer to leave a rust ring if it is deep or in the center of the visual axis. The rust ring will eventually migrate to the corneal surface, where it is easier and safer to remove. Dilate the pupil, and make sure that the vitreous and retina are normal. The history of hammering makes a dilated exam imperative.

Treat with an antibiotic ointment or drop and a cycloplegic if the patient is severely photophobic and in pain. Large or central defects need follow-up to make sure that healing occurs without infection. An antibiotic such as erythromycin, trimethoprim/polymyxin, or a fluoroquinolone is appropriate.

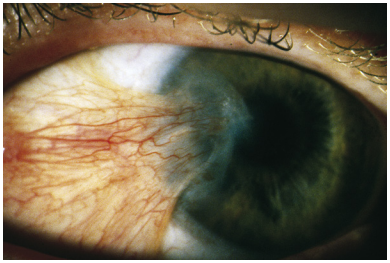

Figure 7-5. An early pterygium with triangular, fibrovascular growth from the conjunctiva (tail) onto the cornea (head). A deposit of iron in the corneal epithelium (Stocker line) may be seen anterior to the head. *(From Kanski JJ: Clinical ophthalmology: a synopsis, ed 5, New York, 2004, Butterworth-Heinemann.)*

27. A lifeguard states that his eye has been red for a long time. He has a wing-shaped fold of fibrovascular tissue nasally in both eyes that extends onto the cornea. Should he be worried?

The lesion is a pterygium (Fig. 7-5). A similar lesion called a pinguecula involves the conjunctiva but not the cornea. Both are usually bilateral. They are thought to result from damage due to chronic ultraviolet exposure or chronic irritation from wind and dust. They may be associated with dellen, an area of corneal thinning secondary to drying because the area adjacent to raised areas may not receive adequate lubrication during blinks. It is necessary to rule out conjunctival intraepithelial neoplasia, which is unilateral, often elevated, and not in a wing-shaped configuration.

Counsel the lifeguard to wear ultraviolet blocking sunglasses and to use artificial tears frequently, especially on sunny, windy days. Surgical removal of a pterygium is indicated if it interferes with contact lens wear, causes significant irritation, or involves the visual axis. Newer surgical techniques are decreasing recurrences, such as using antimetabolites such as mitomycin C.

28. An unfortunate victim of domestic abuse had lye thrown in his face. What should you do?

Even before you check vision, quickly check pH and then begin copious irrigation with saline or Ringer's lactated solution for at least 30 minutes. An eyelid speculum and a topical anesthetic will help. Make sure to irrigate the fornices. Stop irrigation only when pH of 7.0 is reached. If it is not reached after a significant time, check for particulate matter that may be trapping the chemical.

29. What is his prognosis?

Acids tend to have a better outcome than alkalis. Acids precipitate proteins, which limit penetration. Alkalis (lye, cement, plaster) penetrate more deeply. A mild burn may have only SPK or sloughing of part or all of the epithelium. No perilimbal ischemia is seen. Patients need a cycloplegic, antibiotic ointment and rarely pressure patching. Check intraocular pressure, which may be elevated by damage to the trabecular meshwork.

A moderate-to-severe burn has perilimbal blanching and corneal edema or opacification with a poor view of the anterior chamber. A significant anterior chamber reaction may be seen. The intraocular pressure may be elevated and the retina may be necrotic at the point where the alkali penetrated the sclera. The patient may need hospital admission to monitor intraocular pressure and corneal status. A topical antibiotic, cycloplegic, and pressure patching are used. Steroids may be used if the anterior chamber reaction or corneal inflammation is severe. However, they cannot be used for more than 7 days because they promote corneal melting. Collagenase inhibitors such as acetylcysteine (Mucomyst) may help in a melt. Cyanoacrylate tissue adhesive and an emergency patch graft or transplant may be necessary if perforation occurs. Patients require long-term care.

30. A young boy presents with purulent discharge over the past few days. His mother thinks that he needs antibiotics. Do you agree?

Yes. Purulent discharge signals bacterial conjunctivitis as opposed to the watery discharge of viral conjunctivitis. Patients usually have a conjunctival papillary reaction and no preauricular node. Gram stain and conjunctival swab for culture and sensitivities should be done if the conjunctivitis is severe.

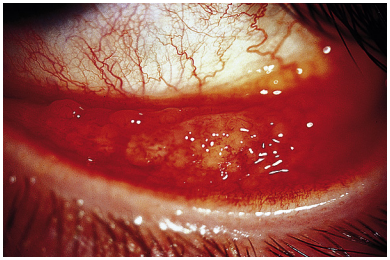

Figure 7-6. Chronic follicular conjunctivitis with large conjunctival follicles, most prominent in the inferior forniceal conjunctiva, and scant mucopurulent discharge. Lymphadenopathy is also present. *(From Kanski JJ: Clinical ophthalmology: a synopsis, ed 5, New York, 2004, Butterworth Heinemann.)*

31. What are the common organisms responsible for bacterial conjunctivitis in children? How should you treat?

Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, and *Haemophilus influenzae* are common; *H. influenzae* is especially common in children. Topical antibiotics such as trimethoprim/polymyxin (Polytrim), ciprofloxacin, or erythromycin four times/day for 5 to 7 days is appropriate. *H. influenzae* should be treated with oral amoxicillin/clavulanate because of the possibility of systemic involvement, such as otitis media, pneumonia, or meningitis. Associated dacryocystitis also warrants oral antibiotics.

32. A 27-year-old woman complains of red, irritated eyes with watery discharge over the past 6 weeks. A follicular conjunctivitis and palpable preauricular node are present. What is the differential diagnosis?

Conjunctivitis lasting longer than 4 weeks is considered chronic (Fig. 7-6). The differential for chronic conjunctivitis includes chlamydial inclusion conjunctivitis, ocular toxicity, Parinaud's oculoglandular conjunctivitis, trachoma, molluscum contagiosum, and silent dacryocystitis.

33. How do you proceed?

History is important. On questioning, the patient reports a recent vaginal discharge. Chlamydial infection becomes high on the list. Such patients also may have white peripheral subepithelial infiltrates and a superior corneal pannus. Stringy, mucous discharge is common. Obtain a chlamydial immunofluorescence test and/or a chlamydial culture of the conjunctiva. Giemsa stain will show basophilic intracytoplasmic inclusion bodies in epithelial cells as well as polymorphonuclear leukocytes. Tetracycline, doxycycline, or erythromycin should be taken orally for 3 weeks by the patient and her sexual partners. Topical ocular erythromycin, tetracycline, or sulfacetamide ointment is used at the same time. Counseling and evaluation for other sexually transmitted diseases should be done by the family physician.

34. How do you diagnose the other causes of chronic conjunctivitis?

1. **Toxic conjunctivitis** is common with many drops (see question 2 for offending agents). These patients may also have allergic dermatitis around the eyes. Treat with preservative-free artificial tears.
2. **Parinaud's oculoglandular conjunctivitis** presents with a mucopurulent discharge and foreign-body sensation. Granulomatous nodules on the palpebral conjunctiva and swollen lymph nodes are necessary for the diagnosis. Fever and rash also may occur. The etiology includes cat-scratch disease (most common), tularemia (contact with rabbits or ticks), tuberculosis, and syphilis.
3. **Trachoma** is seen in underprivileged countries with poor sanitation. It is also caused by chlamydial infection. Patients develop superior tarsal follicles and severe corneal pannus, which, if untreated, lead to significant dry eye, trichiasis, and scarring. Patients may become functionally blind. Diagnosis and treatment are the same as for chlamydial inclusion conjunctivitis.
4. **Molluscum contagiosum** develops a chronic follicular conjunctivitis from a reaction to toxic viral products. On the lid or lid margin, multiple dome-shaped, umbilicated nodules are present. These lesions must be removed by excision, incision and curettage, or cryosurgery to resolve the conjunctivitis.
5. **Dacryocystitis** is an inflammation of the lacrimal sac. Patients usually present with pain, erythema, and swelling over the inner aspect of the lower lid. They also may have a fever. However, a red eye may be the only sign. Pressure over the lacrimal sac may elicit discharge and a complaint of tenderness. Treatment is systemic antibiotics, warm compresses with massage over the inner canthus, and topical antibiotics. Watch patients closely because cellulitis can occasionally develop.

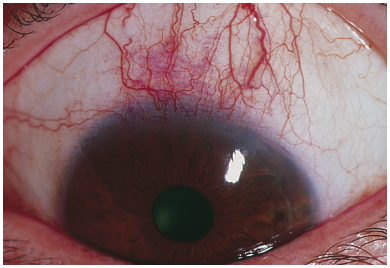

Figure 7-7. Superior limbic keratoconjunctivitis. Slit lamp appearance of focal superior bulbar conjunctival injection is shown with rose bengal staining. *(From Bouchard CS: Noninfectious keratitis. In Yanoff M, Duker JS [eds]: Ophthalmology, ed 2, St. Louis, Mosby.)*

35. A 40-year-old woman presents with a bright red eye that she noticed on awakening in the morning. On examination, she has a subconjunctival hemorrhage. What questions are important to ask?

You need to know whether this is her first episode. Does she have a history of easy bruising or poor clotting? Is she taking any medications or supplements that may increase bleeding time, such as warfarin, aspirin, vitamin E, or garlic? Has she been rubbing her eye or had any injury to her eye? Has she done any heavy lifting or straining? Has she been sneezing or vomiting—anything that may cause a Valsalva maneuver?

36. She answers no to the above questions and states that this is her first episode. Should she be worried?

No. Reassure her that the symptoms will resolve within 2 weeks. Artificial tears will make her more comfortable. Tell her to return if she has further episodes.

37. With further thought, she remembers two other hemorrhages in her left eye and reports that her menses have been much heavier recently. What now?

At this point, referral to an internist for a complete blood count with differential, blood pressure check, prothrombin time, partial thromboplastin time, and bleeding time is appropriate.

38. A 60-year-old woman complains that her eyes have been red and burning over the past several weeks. She also has some tearing and photophobia. On exam, you notice mild conjunctival injection and a slightly low tear meniscus. Should you think of anything else?

Make sure to elevate the upper eyelid. Superior limbic keratoconjunctivitis (Fig. 7-7) is a thickening and inflammation of the superior bulbar conjunctiva. Sometimes a superior corneal micropannus, superior palpebral papillae, and corneal filaments can be found. Fifty percent of patients have associated dysthyroid disease. Artificial tears and ointments are all that are necessary for mild disease. Silver nitrate solution (*not* cautery sticks) may be applied to the superior tarsal and bulbar conjunctiva; mechanical scraping, cryotherapy, cautery, or surgical resection or recession of the superior bulbar conjunctiva may be necessary for more severe disease.

39. A 22-year-old woman presents with mild redness in the temporal quadrant of her left eye for about 1 week. She notices no discomfort. On exam, she has normal vision. Large episcleral vessels beneath the conjunctiva are engorged in the area. They can be easily moved with a cotton swab, and no tenderness is present. The cornea and anterior chamber are clear. The sclera appears to be uninvolved. What is the diagnosis?

You must distinguish between episcleritis (Fig. 7-8) and scleritis. A drop of 2.5% phenylephrine blanches the episcleral vessels but leaves any injected vessels of the sclera untouched. Look for any discharge or conjunctival follicles and papillae to rule out conjunctivitis.

Episcleritis is usually idiopathic. It may be diffuse or sectoral, unilateral or bilateral. Sometimes a nodule may be seen. Rarely, it is associated with collagen-vascular disease, gout, herpes zoster or simplex, syphilis, Lyme disease, rosacea, or atopy. Usually artificial tears and/or a topical vasoconstrictor/antihistamine drop, such as naphazoline/pheniramine, will suffice. If the patient is unresponsive, a mild steroid drop should help. Rarely, oral nonsteroidal anti-inflammatory drugs are necessary. Warn the patient that episcleritis may recur.

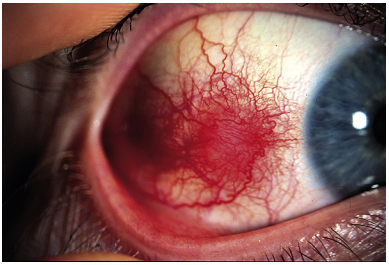

Figure 7-8. A slightly tender and mobile elevated nodule with epithelial injection is typical for nodular episcleritis. *(From Kanski JJ: Clinical ophthalmology: a synopsis, ed 5, New York, 2004, Butterworth-Heinemann.)*

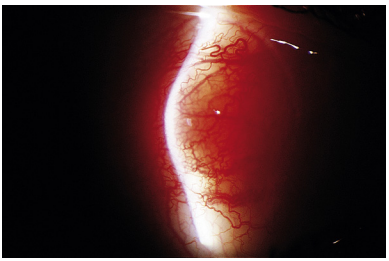

Figure 7-9. Nodular scleritis is painful with a nonmobile nodule associated with swelling of the episclera and sclera. *(From Kanski JJ: Clinical ophthalmology: a synopsis, ed 5, New York, 2004, Butterworth-Heinemann.)*

40. The same patient returns 2 months later. Her left eye is still red, but it is now diffuse. She denies arthritis, rash, venereal disease, tick exposure, or other medical problems. She has been using a vasoconstrictor/antihistamine drop since her last visit. She began using it four times/day, then increased the frequency because her eye continued to be red unless she used it. She now applies drops every 1 to 2 hours. Does this make a difference?

Counsel patients not to use a vasoconstrictor for longer than 2 weeks and no more than four times/day. Just as patients can remain congested if using a vasoconstrictor nose spray frequently, vasoconstrictor eye drops can cause the eyes to stay red. She should stop the drop immediately. Her left eye will be very red for a time until the dependence resolves.

41. A 65-year-old woman with rheumatoid arthritis states that her left eye has been red and painful for a couple of weeks. The pain is severe and radiates to her forehead and jaw and has awakened her at night. It has worsened slowly. Her vision is decreasing. She thinks that she has had a similar condition before. On exam, the conjunctival, episcleral, and scleral vessels are injected temporally. The scleral vessels do not move, and the area is very tender. A scleral nodule is present. The sclera appears bluish in this area, adjacent to which is a peripheral keratitis with a mild anterior chamber reaction. The intraocular pressure is 24 mm Hg in the affected eye and 16 mm Hg in the unaffected eye. What may she have?

She may have nodular anterior scleritis (Fig. 7-9). The inflamed blood vessels are much deeper than those seen in conjunctivitis or episcleritis and do not blanch with 2.5% phenylephrine. In addition, the cornea and anterior chamber are involved. The deep, boring pain is typical with scleritis.

42. How else may scleritis present?

- Diffuse anterior scleritis.
- Necrotizing anterior scleritis with inflammation. The pain is severe, and the choroid is visible through the transparent sclera. The mortality rate is high owing to systemic disease.

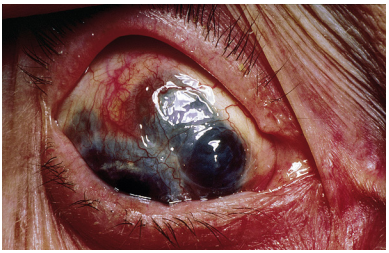

Figure 7-10. Scleromalacia perforans is a noninflammatory form of necrotizing scleritis. *(From Kanski JJ: Clinical ophthalmology: a test yourself Atlas, ed 2, New York, 2002, Butterworth-Heinemann.)*

- Necrotizing anterior scleritis without inflammation (scleromalacia perforans; Fig. 7-10). Such patients have almost a complete lack of symptoms, and most have rheumatoid arthritis.
- Posterior scleritis. It may mimic an amelanotic choroidal mass. An exudative retinal detachment, retinal hemorrhages, choroidal folds, and/or choroidal detachments may be seen. Restricted extraocular movements, proptosis, pain, and tenderness may also occur. Rarely is it related to a systemic disease.

43. What percentage of patients with scleritis have systemic disease? What diseases are associated with scleritis?

Fifty percent of patients with scleritis have systemic disease. The connective tissue diseases, such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, polyarteritis nodosa, and Wegener's granulomatosis, are common associations. Herpes zoster ophthalmicus, Lyme disease, syphilis, and gout also may cause scleritis. Less frequently, scleritis may be associated with tuberculosis, sarcoidosis, or a foreign body.

44. What workup is appropriate for a patient with scleritis?

Any avascular areas of the scleritis must be identified. The red-free filter on the slit lamp is helpful for this purpose. The thinner the sclera, the more severe the disease. The risk of a melt is much higher. A dilated exam is necessary to check for posterior segment involvement. Patients should be referred to an internist or a rheumatologist for a complete physical exam; complete blood count; erythrocyte sedimentation rate; uric acid level; rapid plasma reagin test; fluorescent treponemal antibody, absorbed test; Lyme titer; rheumatoid factor; antinuclear antibody tests; fasting blood sugar; angiotensin-converting enzyme; CH50; C3; C4; and serum antineutrophilic cytoplasmic antibody. If history or symptoms warrant, a purified protein derivative test with anergy panel, a chest radiograph, sacroiliac radiograph, and/or B-scan ultrasonography to detect posterior scleritis should be ordered.

45. How should you treat the patient?

An oral NSAID, such as ibuprofen, 400 to 600 mg four times/day, or indomethacin, 25 mg three times/day, coupled with an antacid or H_2 blocker such as ranitidine is a good initial choice. If the patient is nonresponsive, oral steroids are the next step. In diseases such as systemic vasculitis, polyarteritis nodosa, and Wegener's granulomatosis, an immunosuppressive agent such as cyclophosphamide, methotrexate, cyclosporine, or azathioprine may be necessary. They may be used in combination. Biologics such as the anti-tumor necrosis factor agents infliximab (Remicade) and adalimumab (Humira) are showing promise in some patients. Decreased pain is an indication of successful treatment, although the clinical picture may not show a significant difference for a while.

Scleromalacia perforans does not have an ocular treatment except for lubrication. Patch grafts are used if perforation is a significant risk. Immunosuppression for the underlying systemic disease may be needed.

46. What about topical steroids or a subconjunctival steroid injection?

Topical steroids are not usually effective. Subconjunctival steroids are contraindicated because they may lead to scleral thinning and perforation.

47. A 35-year-old man presents with severe photophobia, pain, and decreased vision in his right eye for 2 days. This condition has occurred several times before. He says that drops have helped. On examination, his vision is 20/50 in the right eye and 20/20 in the left eye. His pupil is poorly reactive on the right and miotic. The left eye is normal, and no afferent pupillary defect is present. The right eye is diffusely injected, especially around the limbus. The anterior chamber is deep, but 2+ cell and flare are present with a few fine keratic precipitates. The left eye is clear. The right eye has an intraocular pressure of 5 mm Hg; the left is 15 mm Hg. Dilated exam is normal. What are the diagnosis and treatment?

The diagnosis is acute, nongranulomatous anterior uveitis. A cycloplegic drop such as cyclopentolate, 1% to 2% three times/day, for mild inflammation, and scopolamine 0.25% or atropine 1% three times/day for more severe inflammation will relax the ciliary spasm, making the patient more comfortable as well as preventing formation of synechiae in the angle and on the pupillary margin. Formation of synechiae increases the long-term risk of angle-closure glaucoma. A steroid drop every 1 to 6 hours, depending on the severity of the anterior chamber inflammation, is started. If no response occurs, a sub-Tenon's injection or oral steroids may be necessary. Rarely, systemic immunosuppressive agents are necessary.

48. A 68-year-old Asian American woman presents with an acutely painful red left eye that developed after a recent anxiety attack. She has blurred vision and sees halos around lights. She has vomited twice. On exam, she has a fixed, middilated pupil and conjunctival injection. The cornea is cloudy. What are you concerned about?

She may have acute angle-closure glaucoma. When the pressure rises quickly in the eye, severe pain and nausea with decreased vision develop. Asian Americans are at increased risk because of their shallow anterior chambers. Examination of the angle of the affected eye may be facilitated by glycerin to clear the corneal edema. If the shallow angle cannot be visualized, the other eye may reveal a narrow angle. For further information about diagnosis and treatment, see Chapter 16.

KEY POINTS: DISEASES THAT MAY MIMIC UVEITIS

1. Rhegmatogenous retinal detachment
2. Posterior segment tumors and lymphoma
3. Intraocular foreign body
4. Endophthalmitis

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CORNEAL INFECTIONS

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CHAPTER 8

1. What is a corneal ulcer?

Infections of the cornea involve the epithelium and/or stroma. Some infections may occur strictly within the epithelium (i.e., herpes simplex epithelial keratitis), whereas others manifest as an infiltrate in the corneal stroma. The term "corneal ulcer" refers to the loss of stroma associated with an overlying epithelial defect (that stains with fluorescein) (Fig. 8-1). A corneal ulcer is usually considered infectious when accompanied by a stromal infiltrate, but may also have a noninfectious (or sterile) etiology.

2. What clinical features distinguish an infectious corneal ulcer?

Infectious corneal ulcers may be caused by bacterial, fungal, viral, or parasitic microorganisms. They classically present with rapid onset of pain, conjunctival injection, photophobia (light sensitivity), and decreased vision. On slit lamp exam, a visible corneal infiltrate is surrounded by corneal edema. If the corneal inflammation is severe, then anterior chamber cell and flare, keratic precipitates, and/or a hypopyon may also develop. Bacterial corneal ulcers may also be associated with a mucopurulent discharge. Some corneal ulcers may be caused by slow-growing organisms, such as anaerobes or mycobacteria; These ulcers may present with a nonsuppurative infiltrate and intact epithelium.

3. What clinical features distinguish a sterile corneal ulcer?

Sterile corneal ulcers are not due to infection with microorganisms. They may be caused by a large variety of etiologies, including dry eye, exposure, neurotrophic keratopathy (e.g., from previous corneal herpetic infections), autoimmune disorders (e.g., rheumatoid arthritis), a secondary immunologic response elicited by staphylococcal hypersensitivity, or hypoxia (e.g., from contact lens wear). These ulcers often present with mild conjunctival reaction, minimal or absent corneal infiltrate, and/or epithelial defect and a quiet anterior chamber (Fig. 8-2). Patients may notice decreased vision but often do not complain of significant redness, pain, photophobia, or discharge.

4. What conditions predispose to corneal infections?

Any condition that disrupts the corneal epithelial integrity may predispose to corneal infection, including:

- Contact lens wear (No. 1 risk factor, responsible for 19% to 42% of cases!)
- Trauma (e.g., corneal abrasion)
- Structural eyelid abnormalities (e.g., ectropion/entropion, trichiasis)
- Dry eye

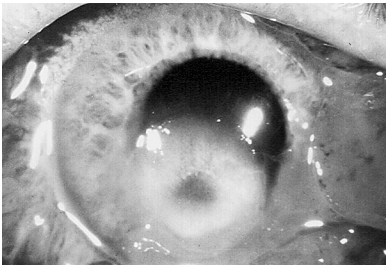

Figure 8-1. Central *Pseudomonas* corneal ulcer.

- Chronic epithelial disease (e.g., recurrent erosions, bullous keratopathy)
- Topical medication toxicity
- Local or systemic immunosuppression (e.g., steroids, diabetes, HIV)
- Contaminated ocular medications

5. How can a contact lens wearer reduce the risk of infection?

Contact lens wear is associated with at least 30% of microbial keratitis cases (ranging from 19% to 42% in different studies), most commonly caused by *Pseudomonas aeruginosa*. The major risk factor identified for corneal infection with contact lens use is sleeping overnight in contact lenses, even if they are approved for extended wear. Patients need to know that disposable contact lenses are not any safer than conventional contact lenses and that lenses with higher oxygen permeability ("high DK" lenses) also increase the risk for infection. Proper contact lens cleaning and disinfection prior to reinsertion, in addition to proper cleaning of contact lens cases, are also of crucial importance in reducing the incidence of contact lens-related corneal infections.[1–3]

6. Describe classic presentations and associations of various types of corneal infections (e.g., bacterial, viral, fungal).

- **History of trauma with any vegetable matter**: Fungal keratitis
- **Oral and eyelid vesicles or repeated problems in only one eye**: Herpetic keratitis
- **Contact lens wear**: *Pseudomonas* or *Acanthamoeba* infection
- **Gram-positive organisms**: Focal, discrete infiltrate
- **Gram-negative organisms**: Spreading diffuse infiltrate
- ***Pseudomonas* infections**: Suppurative infection, stromal necrosis, anterior chamber (AC) reaction with hypopyon
- **Herpes simplex keratitis**: Epithelial dendrite
- ***Acanthamoeba* keratitis**: Ring infiltrate, pain out of proportion to exam
- **Infectious crystalline keratopathy**: dense white, branching infiltrate with minimal inflammatory response (due to α-hemolytic *Streptococcus* species)
- **Fungal keratitis**: Feathery, irregular borders with satellite lesions (Fig. 8-3)

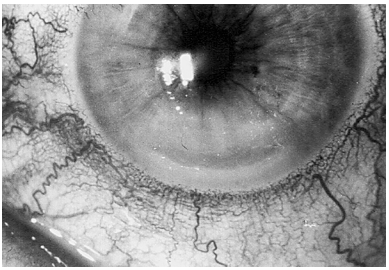

Figure 8-2. Sterile corneal ulcer caused by rheumatoid arthritis.

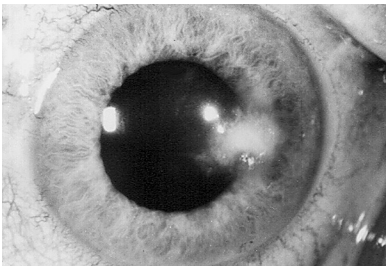

Figure 8-3. Infectious ulcer caused by filamentous fungus. Note the indistinct, feathery borders.

7. When should smears and cultures be performed?

Corneal scrapings for smears and cultures should be obtained on most corneal ulcers suspected of being infectious. Small, peripheral corneal infiltrates (less than 1 mm in diameter) do not necessarily have to undergo scraping prior to the initiation of intensive empiric broad-spectrum antibiotic therapy. However, corneal smears and cultures should be performed in all sight-threatening ulcers (>1 mm), in any case in which an atypical organism is suspected or in any corneal ulcer that is unresponsive to antimicrobial therapy. Of particular importance, corneal infections that do not improve on therapy should undergo scraping or rescraping, and documentation of current antibiotic medication should be given to the laboratory.[4]

8. How should smears and cultures be performed?

Corneal smears and cultures should be performed at the slit lamp after the patient has been given topical anesthetic drops. Corneal scrapings should be obtained using a sterile Kimura spatula, resterilized over a flame between each scraping, or with sterile calcium alginate swabs. Of note, a sterile needle or surgical blade can also be used to scrape corneal ulcers. Separate slides should be used for each smear (e.g., Gram's stain, potassium hydroxide (KOH)). Separate plates should be used for each culture and for Giemsa or calcofluor white stains. For viral cultures, Dacron swabs can be used to obtain viral-infected cells from the cornea. Of note, calcium alginate and cotton swabs should be avoided when obtaining viral cultures, as both can inhibit viral growth.

9. What smears and cultures should be obtained? What culture plates should be used?

See Table 8-1.

Table 8-1. Smears and Cultures for Infectious Keratitis

ROUTINE TEST	TESTS FOR
Gram stain (smear)	Bacteria
KOH or Giemsa stain (smear)	Fungi/yeasts
Sabaroud's dextrose agar culture plate (without cycloheximide)	Fungi
Chocolate agar culture plate	*Hemophilus* and *Neisseria* species
Thioglycolate culture broth	Aerobic and anaerobic bacteria
Optional Test (as needed based on clinical suspicion)	Tests for
Gomori methenamine silver stain (smear)	*Acanthamoeba*, fungi
Acid fast stain (smear)	Mycobacteria
Calcofluor white stain (smear)	*Acanthamoeba*, fungi
Löwenstein-Jensen agar culture plate	Mycobacteria, *Nocardia* spp.
Nonnutrient agar culture plate with *Escherichia coli* overlay	*Acanthamoeba*

10. What is the diagnostic yield for smears and cultures performed prior to the initiation of therapy?

Although Gram's stain smears may provide early insight into the causative organism, they may be negative (with a highly variable positivity range of 0% to 57%). Smears must not be relied on too heavily because their correlation with culture results is low as a result of contamination by normal flora and improper staining/processing technique. On the other hand, cultures grow organisms in approximately 50% to 75% of suspected infectious ulcers. Though cultures performed prior to starting antibiotics have higher yield, clinical evidence suggests that the yield is not significantly diminished by antibiotic treatment if the infection is not responding.

11. What are the most common organisms that cause bacterial keratitis?

The most common organisms that cause bacterial keratitis are *P. aeruginosa* (most common organism in contact lens wearers), *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumonia*, *Proteus*, *Enterobacter*, and *Serratia*.

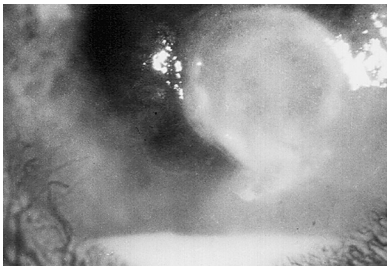

Figure 8-4. Hypopyon associated with infectious corneal ulcer.

12. What is the recommended initial therapy for suspected infectious ulcers? How does one determine whether single-agent, broad-spectrum antibiotics or combination-fortified antibiotics should be used?

In general, initial therapy for corneal ulcers must cover a broad range of gram-positive and gram-negative bacteria and be administered frequently (every 15 to 30 minutes). Previous multicenter studies have shown that monotherapy with topical fluoroquinolones may be as effective as fortified antibiotics in many cases. It is our practice to treat small, peripheral ulcers with a single, fourth-generation fluoroquinolone antibiotic, such as besifloxacin, gatifloxacin, or moxifloxacin, which has shown improved coverage of gram-positive organisms such as streptococcal and staphylococcal species. We reserve combination-fortified antibiotics for more severe, sight-threatening infections. For ulcers that are >1 mm or sight-threatening, it is recommended to start initial broad-spectrum therapy. Once culture results are available, antibiotic therapy tailored to the offending microorganism should be initiated.[5,6]

13. How does the presence of a hypopyon affect the management of infectious keratitis?

The presence of a hypopyon (Fig. 8-4) is indicative of corneal inflammation severe enough to cause a marked anterior chamber response. Therefore, the treatment should be intense, including frequent combined fortified antibiotics in most cases as well as cycloplegic agents to help stabilize the blood–aqueous barrier. For the most part, hypopyons associated with infectious corneal ulcers are sterile and do not require evaluation and treatment for endophthalmitis.

14. When should an anterior chamber and/or vitreous tap be performed?

An anterior chamber and/or vitreous tap should be done whenever endophthalmitis is suspected. Endophthalmitis must be considered when there is severe inflammation after intraocular surgery or perforating trauma, especially when vitreous inflammatory cells are present. Once diagnosed, topical antibiotics are inadequate and intravenous antibiotics are unnecessary; antibiotics must be injected directly into the vitreous cavity after taking samples for culture (with vitrectomy indicated in severe cases). Endophthalmitis secondary to infectious keratitis in the absence of perforation is uncommon, and a sterile inflammatory response in the vitreous that resolves with the clearing of the corneal infection may be present.

15. When should patients with corneal ulcers be hospitalized?

- If the patient lacks the ability or support to administer drops as frequently as every 30 minutes around the clock
- If the patient lives too far away to be followed on a daily basis
- For any condition requiring intravenous antibiotics or possible surgery (e.g., *Neisseria* infections involving the cornea and perforated corneal ulcers)

16. When are systemic medications indicated?

Systemic antibiotics are seldom indicated in bacterial corneal ulcers. However, oral antibiotics are used with impending or existing scleral involvement. Parenteral antibiotics play an important role in the treatment of aggressive infections from *Neisseria* and *Hemophilus* species with corneal involvement and impending perforation.

Systemic antifungal agents are used in some cases of fungal keratitis in which the infiltrate involves deep corneal stroma or in cases that worsen on topical therapy alone. Oral acyclovir is the primary mode of therapy for patients with ocular herpes zoster and is also used by some physicians to treat primary herpes simplex infection.

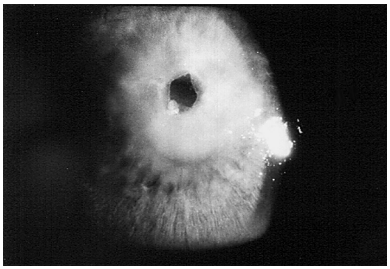

Figure 8-5. Perforated corneal ulcer.

17. Other than antibiotics, what adjunctive therapy may be necessary in the treatment of corneal ulcers?

Topical cycloplegic agents are often indicated to help relieve photophobia and pain from ciliary spasm and to help prevent posterior synechiae.

Severe anterior chamber inflammation may cause the intraocular pressure to increase, often necessitating the use of antiglaucoma medications. Pilocarpine should be avoided because of the phenomenon of blood–aqueous breakdown with subsequent increase in anterior chamber inflammation. In the case of impending or frank perforated corneal ulcer, cyanoacrylate tissue glue can be useful in temporarily and sometimes permanently sealing the open wound.

The role of topical corticosteroids in the management of bacterial keratitis is controversial, but they may be used as well (see below).

18. How should the smear and culture results be used to modify treatment?

Smears may provide a quick means of telling the clinician the general type of infection (e.g., bacterial, fungal, protozoan) and can help start the appropriate empiric therapy. However, we recommend that broad-spectrum antibiotics be continued until culture results are available.

Culture results identify the organism, help to target therapy, and eliminate extraneous medication. Sensitivities can be useful for guiding treatment, but must be interpreted with caution as they are based on drug levels attainable in the serum and not on drug concentrations in the cornea.

19. What are the important immediate and delayed sequelae of corneal ulcers?

The immediate concern with corneal ulcers is progressive thinning and perforation. Management and prognosis change considerably with perforation, and the concern for intraocular infection (i.e., endophthalmitis) rises dramatically. Perforated corneal ulcers can result in the loss of the eye. The delayed sequelae of corneal ulcers deal mainly with corneal scarring, which can severely limit visual acuity and function.

20. How should impending and frank corneal perforations be managed?

Corneal infections can be associated with corneal perforation. One study showed that outdoor occupation, trauma with vegetative matter, a central location of corneal ulcer, monotherapy with fluoroquinolone, and lack of corneal neovascularization, as well as delay in starting management with antimicrobial therapy in infectious keratitis, led to an increased risk of corneal perforation. In this study, *S. epidermidis* was the most commonly isolated organism in cases of perforated corneal ulcers.

Any corneal infection associated with marked thinning or perforation (Fig. 8-5) should be protected with an eye shield without a patch. When the cornea becomes thinned to the point of imminent or existent corneal perforation, certain steps need to be taken. If the affected area is small, cyanoacrylate glue can be used to help seal the defect. However, most cases of perforation will eventually need patch grafting or therapeutic corneal transplantation if the eye has visual potential.[7]

21. What steps should be taken when a corneal ulcer does not respond to empirical therapy?

Reassess the situation. Is compliance a problem? Hospitalization eliminates this issue. If a culture has not been performed, this should be done so that therapy may be culture directed. If the empiric therapy is a fluoroquinolone, fortified antibiotics may be indicated. Consider toxicity from the antibiotics themselves, which may prevent the healing of an ulcer. Think also of the possibility of unusual organisms that would not be covered by broad-spectrum antibiotics: a fungal or mixed bacterial/fungal infection, a viral process with bacterial superinfection, or a protozoan such as *Acanthamoeba*.

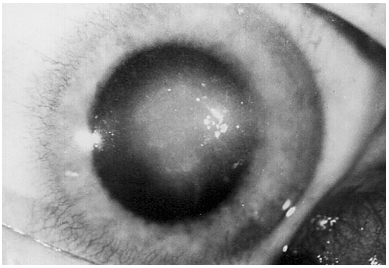

Figure 8-6. Central *Acanthamoeba* ulcer.

If a culture has been performed and appropriate therapy has been initiated, but a corneal ulcer still shows inadequate response, the ulcer should be recultured.

22. What are the current data regarding antibiotic resistance in ocular infections, and how do they relate to the treatment of bacterial keratitis?

Bacterial resistance is a growing worldwide phenomenon, largely due to the widespread use of broad-spectrum antibiotics along with inadequate compliance to antibiotic treatment regimens. The Ocular Tracking Resistance in the United States Today (TRUST) program reported a 12.1% increase in the incidence of methicillin-resistant *S. aureus* strains from January 2000 to December 2005, with greater than 80% resistance of these strains to fluoroquinolones.

The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study demonstrated a high level of bacterial resistance among common ocular pathogens, with 46.5% of *S. aureus*, 58.3% of coagulase-negative staphylococci, 9.0% of *P. aeruginosa*, and 9.3% of pneumococcal isolates showing nonsusceptibility to two or more antibacterial drug classes.

These data have highlighted the importance of culturing corneal ulcers prior to antimicrobial treatment.[8,9]

23. When should a corneal biopsy be considered?

Corneal biopsy should be considered whenever an ulcer is failing intensive antibiotic therapy and the etiology remains unclear owing to negative cultures. *Acanthamoeba* (Fig. 8-6) is particularly difficult to grow in culture, and the infection may be deep in the cornea. If this organism is suspected, a corneal biopsy is the best opportunity to identify cysts (more commonly) or trophozoites in the tissue.

A corneal biopsy may also be considered for deep corneal infiltrates that are not accessible with superficial scraping. Alternatively, a 6-0 or 7-0 silk suture can be passed through these stromal infiltrates and then placed in various culture media.

Corneal biopsies can significantly contribute to the diagnosis and management of infectious keratitis due to unknown etiology. In one study, a microorganism was successfully isolated in 82% of corneal biopsies conducted for infectious keratitis; these biopsies ultimately led to a change in antimicrobial therapy in 89% of patients.[10]

24. What is the role of topical corticosteroids in the treatment of corneal ulcers?

The role of topical corticosteroids as an adjunctive therapy for corneal ulcers is controversial. Some advocate that corticosteroids help to reduce inflammation and decrease corneal scarring, whereas others fear that corticosteroids predispose to recrudescent infection and progressive thinning leading to perforation. Corticosteroids should not be used in the initial treatment of corneal ulcers and can be used in conjunction with antibiotics with extreme caution only after clinical improvement has been demonstrated with appropriate antibiotics.

Although animal models have shown that topical corticosteroid use does not have an impact on the bactericidal effects of antibiotics, case reports have demonstrated worsening of bacterial keratitis after initiation of steroids. Currently, it is recommended that corticosteroids are not used in the initial stage of treatment of bacterial keratitis. Once a specific organism is identified and an appropriate antibiotic is initiated, it is recommended to start corticosteroids only if a patient has a favorable clinical response to antibiotic therapy and is able to return for frequent follow-up examinations.

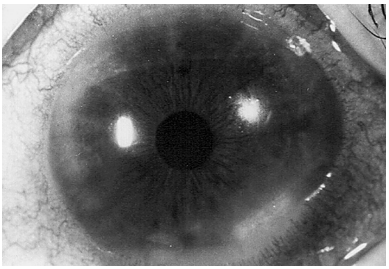

Figure 8-7. Staphylococcal hypersensitivity infiltrate located in the inferior peripheral cornea. Note its marginal location and clear separation from the limbus.

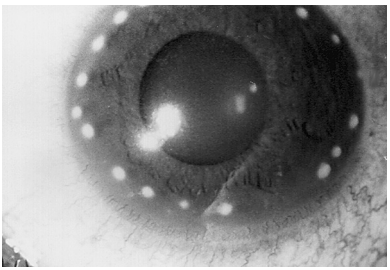

Figure 8-8. Small peripheral infiltrates caused by a sterile reaction to contact lens solution.

25. How are staphylococcal hypersensitivity infiltrates diagnosed and managed?

Staphylococcal marginal keratitis is mostly a bilateral condition that involves the peripheral cornea adjacent to the limbus in the lower half of the area. Corneal infiltrates due to staphylococcal hypersensitivity may be multiple, may stain minimally or not at all with fluorescein, are located in the peripheral cornea separated from the limbus by a clear area (Fig. 8-7), and are not associated with anterior chamber inflammation. They accompany staphylococcal blepharitis and meibomitis and represent an immunologic reaction to staphylococcal antigens. Some patients with staphylococcal marginal keratitis may also have acne rosacea. Mild cases of staphylococcal hypersensitivity should be treated with lid hygiene and antibiotic ointment. In more severe cases, combined antibiotic–steroid drops or ointments can be added. If concerned about an infectious etiology, treat the infiltrate(s) initially with intensive antibiotics.[11]

26. What is appropriate therapy for small peripheral infiltrates in a contact lens wearer?

Remember that small infiltrates in a contact lens wearer may be sterile or infectious. Sterile infiltrates are usually located in the peripheral subepithelium with an overlying intact epithelium and have minimal pain (Fig. 8-8). When in doubt, presume infection.

Patients with infiltrates should first stop all contact lens wear. One can forego scraping and treat presumed infectious infiltrates frequently (every 30 to 60 minutes) with a single broad-spectrum antibiotic (i.e., besifloxacin, gatifloxacin, or moxifloxacin) after a loading dose (i.e., one drop every 15 minutes for an hour) and then an antibiotic ointment (i.e., ciprofloxacin) at bedtime. Patients should be followed closely and undergo scraping if the epithelial defect and infiltrate do not improve.

27. When should a gonococcal infection be suspected? What additional workup and treatment should be initiated?

A gonococcal infection should be suspected when an acute onset of marked conjunctival injection is associated with severe mucopurulent discharge, marked chemosis, and preauricular adenopathy, particularly in neonates (Fig. 8-9). Corneal infiltrates can progress rapidly and perforate within 48 hours. Workup should include conjunctival scrapings for immediate Gram's stain and culture using chocolate

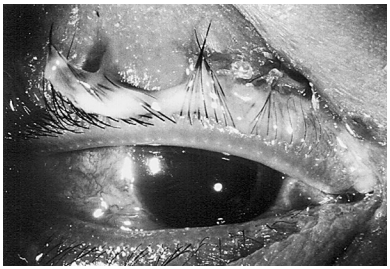

Figure 8-9. Gonococcal conjunctivitis with marked conjunctival injection and copious mucopurulent discharge on the eyelid margins.

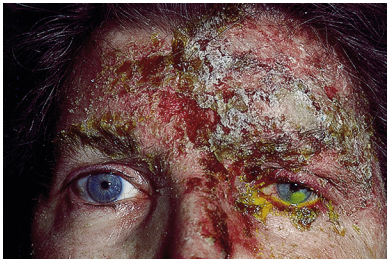

Figure 8-10. Herpes zoster ophthalmicus with crusting and ulceration of skin innervated by the first division of the trigeminal nerve. *(From Kanski JJ: Clinical ophthalmology: a synopsis. New York, 2004, Butterworth-Heinemann.)*

agar medium. Treatment should include frequent irrigation with saline, a 1-gm intramuscular dose of ceftriaxone, and frequent topical fluoroquinolone drops. If the cornea is involved or if compliance is problematic, the patient should be hospitalized for parenteral ceftriaxone therapy and close follow-up.

In patients with gonococcal keratitis, urethral symptoms most often precede ocular symptoms by several weeks. It is important to advise that these patients be screened for other sexually transmitted diseases, especially *Chlamydia*.[12]

KEY POINTS: CORNEAL ULCERS

1. A corneal ulcer is infectious until proven otherwise.
2. You are never wrong to culture an ulcer.
3. Some small, peripheral ulcers can be treated empirically and closely followed.
4. Any ulcer not responding to therapy should be recultured.

28. Why do herpetic infections occur?

Herpes simplex virus (HSV) keratitis is usually caused by the type 1 virus, often spread by an oral "cold sore." The type 2 virus causes neonatal ocular infection after a newborn passes through an infected birth canal. Follicular conjunctivitis, corneal dendritic ulcers, cutaneous vesicles, and preauricular adenopathy may be seen. Of note, follicular conjunctivitis is not seen in neonates, as their immune system is not yet robust enough to respond strongly.

Herpes zoster ophthalmicus (shingles of the eye) represents reactivation of the varicella zoster virus (VZV) in the first division of cranial nerve V (Fig. 8-10). Nerve damage in a dermatomal distribution may lead to severe and chronic pain. Associated keratitis, uveitis, and glaucoma may be severe, chronic, and difficult to treat.

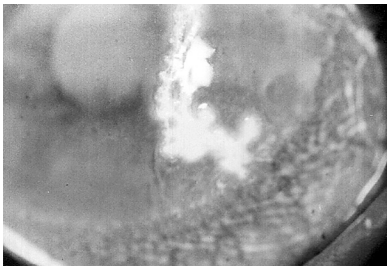

Figure 8-11. Classic herpes simplex dendrite staining brightly with fluorescein.

29. Why is herpes a recurrent disease?

After primary contact with the herpes virus (HSV or VZV), the virus gains access to the central nervous system. The virus becomes latent in the trigeminal ganglia (HSV type 1 or VZV) or in the spinal ganglia (HSV type 2). Recurrent attacks occur when the virus travels peripherally via sensory nerves to infect target tissues such as the eye. These attacks may be triggered by any of the following stressors: fever, ultraviolet light exposure, trauma, stress, menses, and immunosuppression. The most impressive example of this pathway of recrudescence is the dermatomal involvement of the zoster virus.

30. Give some nonocular signs suggestive of a herpetic corneal infection.

Some nonspecific signs of primary herpetic corneal infection include fever, malaise, and lymphadenopathy (especially preauricular adenopathy on the involved side). The vesicular skin rash of herpes zoster infections characteristically involves the dermatome of the first division of cranial nerve V on one side, does not cross the midline, and progresses to scarring. The presence of this rash on the tip of the nose (referred to as the Hutchinson's sign) is a useful sign indicating probable ocular involvement, because both areas are innervated by the nasociliary nerve, a branch of cranial nerve V_1. Patients with herpes simplex can present with vesicular lesions in the perioral and periocular region that resolve without scarring.

31. Are there differences between corneal infections caused by herpes simplex and herpes zoster viruses?

Although corneal infections from herpes simplex and herpes zoster can present in similar clinical fashions, there are subtle features that can help differentiate between the two. Herpes simplex keratitis is an episodic condition, whereas herpes zoster ophthalmicus results in chronic disease. The corneal dendrites of herpes simplex infections are epithelial ulcers whose edges stain brightly with fluorescein and have terminal bulbs (Fig. 8-11). Herpes zoster dendrites are raised lesions, do not have terminal bulbs, and do not stain well with fluorescein.

Herpetic infections can also produce iris atrophy and the pattern of iris atrophy can often distinguish herpes simplex from herpes zoster infection. In herpes simplex, patchy iris atrophy predominates; in herpes zoster infection, sectoral iris atrophy is seen.

32. What are the noninfectious manifestations of a herpetic keratitis?

Some ophthalmic findings of herpetic keratitis are not directly caused by the viral infection itself but instead relate to the immunologic response to the infection. Examples of this phenomenon include chronic keratouveitis (in which large keratic precipitates are associated with corneal edema) and disciform and necrotizing keratitis (in which stromal infiltration with leukocytes and neovascularization can occur with an intact epithelium).

Corneal scarring and neurotrophic ulcers are signs of previous herpetic keratitis that can be visually debilitating and potentially necessitate surgical intervention with penetrating keratoplasty or tarsorrhaphy.

33. How should these infections be treated?

Herpes simplex epithelial keratitis and conjunctivitis have traditionally been treated with frequent topical trifluorothymidine (Viroptic) drops. A new topical ganciclovir ophthalmic gel (Zirgan) specifically developed for the treatment of acute herpes simplex keratitis is now available, and it is dosed much less frequently (i.e., five times/day for 1 week, three times/day for 1 week) and is much less toxic to the ocular surface compared to previous agents. Topical acyclovir (Zovirax) ointment can be added for

skin involvement but cannot be used in or near the eye. Disciform stromal keratitis should be managed with topical corticosteroids and prophylactic antiviral agents.

All herpes zoster infections, regardless of ocular involvement, are treated primarily with oral acyclovir (800 mg per oral five times/day for 7 to 10 days) or the newer equivalent oral agents (i.e., valacyclovir, famciclovir). Skin lesions should receive antibiotic ointment and warm compresses. Topical medications should be added as needed according to other ocular involvement (e.g., conjunctivitis, uveitis, glaucoma).

34. What is the role of topical corticosteroids in herpes simplex keratitis?

Although topical corticosteroids are contraindicated in the presence of active epithelial disease, such as in dendritic keratitis, their use in treating herpes simplex stromal keratitis with an intact epithelium is beneficial. The Herpetic Eye Disease Study has documented that topical steroids and prophylactic antivirals are safe and effective in the treatment of stromal keratitis.[13]

35. When should oral acyclovir be used in herpes simplex keratitis?

The Herpetic Eye Disease Study reported:

- Oral acyclovir (400 mg orally twice daily for 1 year) reduced the recurrence of ocular herpes simplex in patients who had one or more recurrent episodes.
- Oral acyclovir (400 mg orally five times/day for 10 weeks) may be helpful for treating herpes simplex iridocyclitis, but the results did not reach statistical significance.
- Oral acyclovir did not benefit patients with active stromal keratitis and did not prevent the development of stromal keratitis or uveitis in patients with active epithelial disease. Acyclovir is contraindicated during pregnancy and in patients with renal disease.[14]

KEY POINTS: HERPETIC KERATITIS

1. Herpes simplex typically causes episodic keratitis.
2. Herpes zoster causes a dermatomal rash and chronic ulcers and pain.
3. Topical ganciclovir gel is now available for the treatment of epithelial HSV keratitis.
4. Topical steroids are used for herpetic stromal keratitis.
5. All patients with VZV eye disease should receive oral acyclovir (or equivalent).
6. Oral acyclovir is beneficial only in certain types of HSV eye disease.

36. Are corneal infections common after refractive surgical procedures such as laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK)?

Corneal infection is a potentially vision-threatening complication after LASIK but is fortunately uncommon. The incidence is estimated to be between 1 in 5000 and 1 in 10,000. Although the epithelium is usually left intact in this procedure, the corneal flap created in LASIK produces a potential space in the corneal stroma for endogenous and exogenous flora to proliferate and result in an infection.

Even though the corneal epithelium is removed in PRK, fortunately there is a low rate of microbial keratitis after this procedure as well. Two large case series on microbial keratitis after PRK revealed an incidence of 0.02% after PRK. Another large case series demonstrated an incidence of microbial keratitis at 0.2% after PRK.

The most commonly reported causative organisms of microbial keratitis after LASIK include gram-positive bacteria and atypical mycobacteria. Typically, early postoperative infections are associated with gram-positive bacteria, whereas late postoperative infections are associated with atypical mycobacteria and other unusual organisms.[15,16]

37. What other conditions can be mistaken for a corneal infection after LASIK?

Although microbial infection should always be considered, the more common condition that manifests with an infiltrate under the flap is diffuse lamellar keratitis (DLK; Fig. 8-12). DLK is an inflammatory condition of unclear etiology that usually presents within 1 to 3 days after LASIK and has the appearance of sandy debris in the stromal interface (hence the term “sands of the Sahara syndrome”).[17]

38. What clinical features help to distinguish DLK from an infectious process after LASIK?

DLK initially presents with a diffuse sandy infiltrate located in the periphery of the stromal interface. Patients are typically asymptomatic with a quiet eye. As the condition progresses, the infiltrate moves toward the center of the cornea and may begin to aggregate in clumps. Advanced cases of DLK can

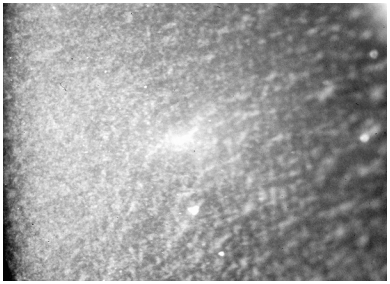

Figure 8-12. Advanced case of diffuse lamellar keratitis.

cause decreased vision and melting of the flap. Early treatment consists of frequent topical corticosteroids, and advanced cases may require systemic corticosteroids, lifting of the flap, and irrigation of the stromal interface. The lack of a distinct corneal infiltrate, conjunctival injection, cell and flare, and keratic precipitates favors the presence of DLK rather than infection.

39. How should corneal infections after LASIK be prevented and managed?

Blepharitis should be treated preoperatively. Sterile technique, including hand scrubbing, sterile gloves, prepping solution (i.e., povidone iodine 10%), and draping of eyelashes, should be used. Postoperative treatment with a single-agent, broad-spectrum topical antibiotic also helps to reduce the incidence of infectious keratitis.

Whenever an infection is suspected, the patient should be taken to an operating room where the flap can be lifted under a microscope for diagnostic smears and cultures. Depending on the severity of the infection, topical therapy with either a single-agent, broad-spectrum antibiotic or combination-fortified antibiotics should be initiated.[18]

KEY POINTS: LASIK INFECTIONS

1. Infections after LASIK are uncommon.
2. DLK is an inflammatory and not an infectious condition.
3. A suspicious infiltrate after LASIK should always be cultured.

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OPHTHALMIA NEONATORUM

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CHAPTER 9

1. **How does ophthalmia neonatorum typically present?**
   Inflammation of the conjunctiva within the first month of life is classified as ophthalmia neonatorum (neonatal conjunctivitis). A purulent or mucoid discharge from one or both eyes is present. In addition to conjunctival injection, edema and erythema of the lids are often present.

2. **What is the usual means of transmission for neonatal conjunctivitis?**
   Conjunctivitis is usually transmitted to the newborn by passage through the mother's infected cervix at the time of delivery and reflects the sexually transmitted infections prevalent in the community. The organisms can ascend into the uterus as well, and so may cause conjunctivitis even in the setting of cesarean section. It may also be spread by people handling the baby soon after birth.

3. **What is the most common cause of neonatal conjunctivitis in the United States?**
   Neonatal conjunctivitis is the most common ocular disease of newborns. It is most often caused by *Chlamydia trachomatis* (6.2/1000 live births). One hundred years ago *Neisseria gonorrhoeae* was the leading cause of blindness in infants. Today gonococcal conjunctivitis is seen less in industrialized nations (3/1000 live births) because of neonatal ocular prophylaxis and better prenatal screening.

4. **List the common causes of ophthalmia neonatorum, their usual clinical presentations, and their approximate times of onset after birth.**
   See Table 9-1.

Table 9-1. Common Causes of Ophthalmia Neonatorum with Time of Onset and Typical Characteristics

TYPE	TIME OF ONSET	TYPICAL CHARACTERISTICS
Chemical (e.g., silver nitrate drops)	Within hours of instillation	Self-limiting, mild, serous discharge (occasionally purulent) Lasts 24-36 h
Chlamydia trachomatis	5-14 days	Mild-to-moderate, thick, purulent discharge (severity is variable) Erythematous conjunctiva, with palpebral more than bulbar involvement
Neisseria gonorrhoeae	24-48 h	Hyperacute, copious, purulent discharge Lid swelling and chemosis common
Bacterial (nongonococcal)*	After 5 days	Variable presentation, depending on organism
Herpetic	Within 2 weeks	Conjunctiva only mildly injected Serosanguineous discharge Vesicular rash on lids sometimes seen Most have concomitant systemic herpetic disease

**Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus viridans, Haemophilus influenzae, Escherichia coli, Pseudomonas aeruginosa.*

5. **What type of neonatal conjunctivitis is associated with the most severe complications to the eye?**
   N. gonorrhoeae has the ability to penetrate intact epithelial cells and divide within them. Its onset is rapid and can quickly lead to corneal perforation and endophthalmitis.

KEY POINTS: MOST COMMON CAUSES OF NEONATAL CONJUNCTIVITIS

1. Chemical
2. Chlamydial
3. Gonococcal
4. Bacterial
5. Herpetic

6. What other diagnostic tool is used to differentiate the various causes of neonatal conjunctivitis?

In most cases one cannot rely solely on clinical characteristics and time of onset for accurate diagnosis; therefore, initial therapy is also based on the results of Gram and Giemsa stains performed immediately on conjunctival swabs and scrapings. Their classic characteristics are listed in Table 9-2. However, classic findings are not seen in all cases. Specimens are also sent for culture and sensitivity testing and antigen detection tests. Treatment regimens are adjusted accordingly once the results are known, and clinical response is observed. Polymerase chain reaction is likely to play an increasing role in the identification of pathogens causing conjunctivitis because of its high sensitivity and specificity.

Table 9-2. Gram and Giemsa Stain Findings with Various Causes of Neonatal Conjunctivitis

CAUSE	STAIN	FINDINGS
Chemical	Gram	Polymorphonuclear neutrophils (PMNs)
Chlamydial	Giemsa	Basophilic intracytoplasmic inclusion bodies in conjunctival epithelial cells
Gonococcal	Gram	Gram-negative intracellular diplococci in PMNs
Bacteria	Gram	Gram-positive or gram-negative organisms
Herpes simplex	Giemsa	Multinucleated giant cells, lymphocytes, plasma cells

7. In a neonate, is a follicular reaction in the conjunctiva more indicative of a chlamydial or a gonococcal infection?

Neither. Follicular reactions are not seen in the neonate because of the immaturity of the immune system.

8. Why is Crede prophylaxis (2% silver nitrate drops) no longer the standard agent of choice for routine neonatal conjunctivitis prevention?

Crede prophylaxis is no longer the favored agent because of its high incidence of associated chemical conjunctivitis.

9. What is currently used for neonatal prophylaxis?

The American Academy of Pediatrics endorses the use of 1% tetracycline or 0.5% erythromycin ointment for neonatal prophylaxis. This is aimed primarily at preventing gonococcal conjunctivitis, which can have devastating ocular consequences. It is also effective for chlamydial infection.

10. What is the differential diagnosis of neonatal conjunctivitis?

- **Birth trauma:** Usually evident by history.
- **Foreign body/corneal abrasion:** Usually diagnosed by a combination of history and exam with fluorescein.
- **Congenital glaucoma:** Accompanying early signs are tearing, photophobia, blepharospasm, and fussiness. Later signs include corneal edema and corneal enlargement. Intraocular pressure is elevated.
- **Nasolacrimal duct obstruction:** Occurs in 6% of neonates and is usually associated with edema of the inner canthus and matting of the eyelids. Tearing is common, and the conjunctiva is usually not affected.
- **Dacryocystitis:** Infection of the lacrimal sac, with erythema and swelling of the inner canthus and nasal conjunctival injection. Purulent drainage can often be expressed from the punctum.

11. When is systemic treatment indicated for neonatal conjunctivitis? Why?
Systemic treatment is necessary for all cases of chlamydial, gonococcal, and herpetic conjunctivitis because of the potential for serious disseminated disease. A complete systemic examination is performed at the time of diagnosis to determine the extent of disease.

12. List the potential ocular and systemic sequelae of untreated neonatal conjunctivitis.
See Table 9-3.

Table 9-3. Ocular and Systemic Sequelae of Untreated Neonatal Conjunctivitis

TYPE	OCULAR	SYSTEMIC
Chemical	None (a self-limited entity)	None
Chlamydial	Chronic infection may cause corneal scarring and symblepharon (adhesion of eyelid to eye)	Pneumonitis and otitis media
Gonococcal	Corneal ulceration, perforation, and endophthalmitis (may occur within 24 h of onset)	Meningitis, arthritis, sepsis, and death
Bacterial	*Pseudomonas* sp. may cause corneal ulcer, perforation, and endophthalmitis	Usually none
Herpetic	Recurrences throughout life may cause corneal scarring and profound amblyopia. Chorioretinitis and cataracts also may develop.	Meningitis and disseminated CNS disease (mortality rate can be as high as 85%)

CNS, Central nervous system.

13. What is the treatment for chlamydial conjunctivitis?
Oral erythromycin syrup is given for 2 to 3 weeks (50 mg/kg/day in four divided doses) Topical erythromycin or sulfa ointment may be used four times/day, though there is not clear evidence that this is effective. The mother and her sexual partner also are treated with oral tetracycline, 250 to 500 mg four times/day, or doxycycline, 100 mg two times/day, for 7 days for presumed systemic disease, even if asymptomatic. Tetracycline cannot be used in children, pregnant women, or breast-feeding mothers because it will stain developing teeth.

KEY POINTS: POTENTIAL SYSTEMIC COMPLICATIONS OF NEONATAL CONJUNCTIVITIS

1. Pneumonitis
2. Meningitis
3. Otitis
4. Arthritis
5. Sepsis/death

14. What is the treatment for gonococcal conjunctivitis?
As a result of the high incidence of penicillin-resistant organisms, the Centers for Disease Control and Prevention recommend treatment with penicillinase-resistant antibiotics. Intravenous ceftriaxone (a third-generation cephalosporin) is started immediately and is given for 7 days at a dose of 25 to 50 mg/kg/day. The intravenous form can be changed to an oral equivalent, after significant improvement is noted, to complete a 7-day course. A single 125-mg intramuscular dose of ceftriaxone or a 100 mg/kg intramuscular dose of cefotaxime given immediately after diagnosis is an accepted alternative treatment. This single parenteral dosing is also indicated for infants born to mothers with known gonococcal infections, even without the diagnosis of conjunctivitis.

Bacitracin ointment is administered topically four times/day, and saline lavage is hourly until the discharge is eliminated. Patients are generally hospitalized and evaluated for evidence of dissemination.

Because of the high incidence of concomitant chlamydial infection in women who contract gonorrhea, the infant, the mother, and her sexual partner are also treated systemically for *Chlamydia* as outlined above. It is reasonable to test for other sexually transmitted diseases.

15. What is the treatment for bacterial conjunctivitis?

Bacterial conjunctivitis is treated with erythromycin or gentamicin ointment applied four times/day for 2 weeks for gram-positive or gram-negative conjunctival swab results, respectively. The antibiotic choice may be altered later once culture and sensitivity results are known. In cases of corneal involvement, as seen with virulent organisms such as *Pseudomonas* sp., fortified topical antibiotics are administered and are often supplemented with systemic treatment.

KEY POINTS: POTENTIAL OCULAR COMPLICATIONS OF NEONATAL CONJUNCTIVITIS

1. Corneal scarring
2. Symblepharon
3. Corneal perforation
4. Endophthalmitis

16. What is the treatment for herpes simplex viral conjunctivitis?

Intravenous acyclovir, 10 mg/kg, is given every 8 hours for 10 days, along with vidarabine 3% ointment (Vira-A), five times/day, or trifluorothymidine 1% (Viroptic), every 2 hours, for 1 week.

17. How can the incidence of ophthalmia neonatorum be reduced in future generations?

The population most at risk for contracting neonatal conjunctivitis is infants born to mothers without adequate prenatal care or mothers involved with substance abuse. Because of its high association with serious systemic disease, neonatal conjunctivitis is still an important public health issue worldwide. Although not universally accepted, some countries (e.g., Sweden and England) have abandoned the use of routine prophylaxis after birth in favor of careful screening for sexually transmitted diseases and better prenatal care.

WEBSITE

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TOPICAL ANTIBIOTICS AND STEROIDS

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CHAPTER 10

1. You are an antibiotic or steroid eyedrop just placed in the conjunctival fornix. Discuss the barriers to your journey into the eye.

Many eyedrop dispensers deliver a 50-μL eyedrop. However, only 20% of this volume is retained by the conjunctival cul-de-sac, and the excess immediately flows over the eyelids. Of the portion that remains, approximately 80% drains through the lacrimal system. In addition, because of the 15%/min tear turnover rate, almost all of the topically applied medication disappears from the conjunctival cul-de-sac in about 5 minutes. Irritating drugs produce reflex tearing and may be cleared even more quickly.

During this critical 5 minutes, the topically applied drug faces numerous tissue obstacles. Absorption by the conjunctiva quickly disperses the medication systemically via the conjunctival vasculature. The small portion that penetrates the episclera faces the relative impermeability of the sclera and the tight junctions of the retinal pigment epithelium. The cornea poses three different barriers to entry. The corneal epithelium and the endothelium possess tight junctions that force the drugs to pass through the cellular membranes and limit passage of hydrophilic drugs. The corneal stroma is water-rich and limits movement of lipophilic drugs. Even after entry into the anterior chamber, the lens effectively limits most drug penetration, and very little enters the posterior segment of the eye through topical administration.

Such formidable barriers seem insurmountable, but inflammation and infection render these barriers less effective, and modifications of the drug and/or its vehicle can facilitate entry into the eye. In addition, the desired site of action may be the ocular surface and not inside the eye.

2. Given the above barriers, how would you increase delivery of topical antibiotics or steroids to the desired site of action?

The patient can perform punctal occlusion to decrease the amount of drainage through the lacrimal system by 65% and leave more drug for intraocular absorption. Of course, frequent instillation also increases drug absorption, but the practical limit is probably every 5 minutes because the subsequent eyedrop can wash out the previous eyedrop before intraocular absorption.

Changing the characteristics of the drug and/or its vehicle can also improve delivery. Increasing the concentration of the drug may be limited by the solubility of the drug in the vehicle, and the high tonicity of higher concentrations triggers reflex tearing that quickly clears the drug from the ocular surface. Also, increasing lipid solubility of the drug appears to promote corneal passage despite the dual barrier characteristic of the cornea. In addition, adding surfactants that disturb the corneal epithelium dramatically increases drug entry.

3. Name the four different formulations of topical medications and the advantages and the disadvantages of each.

- **Solutions** are easily instilled, but contact time is minimal, requiring frequent administration. In addition, the "pulse" nature of absorption invites transient overdose and toxicity.
- **Suspensions** allow longer contact time, but the particulate nature of the preparation may be irritating and trigger reflex tearing. Suspensions settle to the bottom of the bottle and need to be shaken before the eyedrops are instilled. Patients also may complain of accumulation of the precipitates or forget to shake the bottle before administering the eyedrops.
- **Gels** are more viscous than solutions and suspensions and they are retained on the eye longer, allowing for better penetration of the active ingredients. In contrast to the suspensions, in which the active ingredient may precipitate, the gels allow for a more uniform distribution.
- **Ointments** increase the contact time further, requiring the least frequent instillation, but leave a film over the eye that blurs vision. In addition, water-soluble drugs do not dissolve in the ointment vehicle and are present as crystals. Crystals are trapped in the ointment vehicle until the crystals on the

surface of the ointment contact the ocular surface after the ointment vehicle melts with exposure to body temperature. This type of absorption allows entry of constant but low amounts of the drug. Other methods of delivery include soft contact lenses, soluble ocular inserts, or implantable devices. Medications inserted into punctal plugs are also being studied.

KEY POINTS: STRATEGIES TO INCREASE THE PENETRATION OF TOPICAL MEDICATIONS

1. Punctal occlusion.
2. Increase the frequency.
3. Increase the concentration of drug in the drop.
4. Increase the lipid solubility of the drug.
5. Use surfactants to disturb the corneal epithelium.

4. What are some of the indications for using topical antibiotics?

Topical antibiotics are used to treat conjunctivitis, conjunctival ulceration, corneal ulceration, and canaliculitis. They are also used as prophylaxes against infection before and after ocular surgeries such as cataract, glaucoma, retina, corneal transplant, refractive surgery, and ocular surface surgeries. Topical antibiotics are also used as prophylaxes in patients with corneal epithelial defects and in some cases patients who wear therapeutic contact lenses. Prophylaxis with antibiotics is becoming more controversial as it may select for more resistant bacteria should an infection occur.

5. A 60-year-old man complains of crusting of the eyelids in the morning and chronic foreign-body sensation. Examination reveals moderate blepharitis with numerous collarettes around the eyelashes. What would you recommend?

Blepharitis often responds well to just warm compresses and eyelid scrubs, but supplemental antibiotic gels or ointments applied to the eyelash base or conjunctiva may be helpful, especially when numerous collarettes are seen around the eyelashes. Frequently used antibiotic ointments include erythromycin, bacitracin, and Polysporin. Azithromycin comes as an ophthalmic gel drop. Erythromycin and azithromycin are macrolide antibiotics that inhibit bacterial protein synthesis by binding to the 50S ribosomal unit. They have a broad spectrum of coverage but suffer from relatively poor intraocular absorption. They are most appropriate for blepharitis and conjunctivitis. Bacitracin is composed of numerous polypeptides that inhibit bacterial cell wall synthesis. Polysporin combines bacitracin and polymyxin B, which are peptides that act like detergents to lyse bacterial cell membranes, and offers better coverage of gram-negative bacteria.

6. A 30-year-old woman with "cold" symptoms presents with redness and mucus discharge in both eyes. The ocular symptoms began in the right eye 1 week ago but now involve both eyes despite treatment of the right eye with sulfacetamide four times/day, as prescribed by her family physician. Examination reveals bilateral follicular conjunctivitis with preauricular adenopathy. What would you recommend?

History and examination are consistent with viral conjunctivitis. Artificial tears and cool compresses may provide comfort. Follow-up in 1 to 2 weeks is advisable to look for potential membranous conjunctivitis which may require topical steroids. Sulfacetamide is a bacteriostatic structural analog of *p*-aminobenzoic acid and inhibits synthesis of folic acid. It has a broad spectrum of coverage and good corneal penetration and becomes more effective when combined with trimethoprim, which blocks a successive step in bacterial folate metabolism. It appears to be used often by nonophthalmologists for initial treatment of red eyes; it is fine for mild bacterial conjunctivitis but is not helpful for viral conjunctivitis.

7. A 55-year-old woman complains of discharge and redness of her right eye for 4 weeks. Her family physician told her that she had "pink eye" and prescribed erythromycin ointment, then sulfacetamide, and then ciprofloxacin, but the symptoms have not improved. Examination reveals diffuse papillary conjunctivitis with purulent discharge. There is no preauricular adenopathy or previous history of "cold" symptoms. What should you do?

The patient has chronic conjunctivitis, possibly bacterial. Topical therapy usually brings prompt relief, and you should make sure that she uses the medications properly. Assuming that she is getting

the medications into the eye in a proper dosing regimen, conjunctival cultures can be performed to look for resistant or unusual bacteria. Testing for ocular *Chlamydia* may also be helpful. Chronic dacryocystitis should be investigated by applying firm pressure below the medial canthal tendon in an attempt to produce a diagnostic purulent discharge through the lacrimal punctum. An abscess in the nasolacrimal sac may provide a source of bacteria resistant to topical antibiotics.

8. A 25-year-old man holding a towel over his right eye complains of copious discharge that began in the morning. Examination reveals diffuse conjunctival hyperemia and chemosis with thick, purulent discharge. A prominent preauricular adenopathy is also present. What should you do?

Hyperacute bacterial conjunctivitis in sexually active patients should prompt urgent conjunctival smears and cultures to look for gonococcal conjunctivitis. Although rare, gonococcal conjunctivitis requires immediate systemic antibiotics, with topical antibiotics as an adjunctive treatment only.

9. A 26-year-old physician in a general surgery residency with a doctorate in pharmacology presents with foreign-body sensation and photophobia in both eyes after sleeping with soft contact lenses during his call night. A midperipheral 2-mm corneal ulcer with surrounding corneal stromal edema is present with scant anterior chamber reaction. What should you do?

The chances of developing a corneal ulcer increase by a factor of 10 when the patient sleeps with contact lenses. Corneal cultures are recommended, although some ophthalmologists may manage small corneal ulcers without cultures.

Initial therapy should cover a broad spectrum of bacteria. Traditionally, fortified cephalosporin and aminoglycoside have been used, but many believe that fluoroquinolones offer similar efficacy (especially for small ulcers) with less toxicity. In addition, fortified topical antibiotics are not universally available and need to be refrigerated.

Fluoroquinolones inhibit bacterial DNA synthesis by binding to DNA gyrase and inhibiting the supercoiling of bacterial DNA. They offer a superb spectrum of coverage in in vitro studies, although there is increasing resistance from methicillin-resistant *Staphylococcus aureus* and methicillin-resistant coagulation-negative *Staphylococcus*. Even so, they appear to be highly effective for most corneal ulcers, especially contact lens-induced corneal ulcers, but large clinical series with attention to resistance and treatment failure have not been completed.

Aminoglycosides bind to bacterial ribosomal subunits and interfere with protein synthesis. They offer a broad spectrum of coverage but require transport into the bacteria, which may be reduced in anaerobic environments of an abscess. Coadministration of antibiotics that alter bacterial cell-wall structure improves aminoglycoside penetration into bacteria and produces a synergistic effect.

Cephalosporins are β-lactam antibiotics synthesized or derived from compounds isolated from the fungus *Cephalosporium acremonium*. They inhibit bacterial transpeptidase, which is critical for bacterial cell-wall synthesis. In general, later generations provide broader coverage with better gram-negative but poorer gram-positive activity. Cefazolin is a first-generation cephalosporin that is traditionally combined with an aminoglycoside for the initial treatment of more severe or centrally located corneal ulcers. It covers gram-positive and some gram-negative organisms but misses *Pseudomonas* sp. and, therefore, requires the addition of an aminoglycoside or fluoroquinolone for initial broad-spectrum coverage.

10. After corneal cultures are done, the patient is instructed to take ciprofloxacin drops every hour around the clock. Next day, he is in worse pain, and the corneal ulcer has enlarged to 3 mm with tenacious purulent discharge. What is your next step?

Make sure the eyedrops are getting into the eye. Ask the patient to demonstrate eyedrop administration. Several eyedrops fall on the floor, then on his cheeks, and finally he announces success when the eyedrops fall on his closed eyelids. Often, antibiotic failure is due to improper administration. Patients should be observed taking their eyedrops. A friend or family member may need to administer the eyedrops to be sure that the medications are getting to the source of infection, especially when frequent instillation is required. Indeed, some patients require hospitalization to receive intensive eyedrop administration.

In addition, the patient should have taken the drug more often. The manufacturer's recommended dose of ciprofloxacin for corneal ulcers is two drops every 15 minutes for the first 6 hours, followed by two drops every half-hour for the remainder of the first day. Then, two drops every hour for the second day, decreasing to two drops every 4 hours for days 3 to 14, are suggested. However, this regimen may be altered in response to clinical exam and culture results. Frequent dosing of ciprofloxacin may

produce a white precipitate over the ulcer, but this precipitate does not appear to impede the bactericidal activity and usually resolves when the dose is tapered.

Ofloxacin is also used but has different manufacturer's recommendations:

- **Days 1 and 2:** One to two drops every 30 minutes while awake
- **Awaken at 4 and 6 hours after retiring:** Give one to two drops
- **Days 3 to 7 or 9:** One to two drops hourly while awake
- **Days 7–9 to completion:** One to two drops four times/day

Fourth-generation fluoroquinolones, gatifloxacin, moxifloxacin, and besifloxacin, are also available with better gram-positive coverage and comparable gram-negative coverage. These medications have not been FDA approved for the treatment of corneal ulcers but they are frequently used off-label for this condition.

11. The patient now prefers a "proven" treatment regimen with a long history and requests topical fortified antibiotics. However, he recalls that minimal bactericidal concentration for most pathogenic bacteria is far below that provided by the fortified antibiotics and accuses you of wasting money and drugs. Is he right?

No. In vitro and in vivo results in other sites of the body may not be applicable to the eye. Indeed, in the vitreous, the dose–response relationship has been demonstrated up to 100 times the in vitro minimal bactericidal concentration.

12. The patient reminds you that he is penicillin-allergic and does not enjoy anaphylaxis. What antibiotics should you choose? How do you begin therapy?

Penicillin is not often used in ophthalmology because of poor penetration into the eye and active transport out of the eye by the organic acid transport system of the ciliary body. However, inflammation improves ocular penetration. Penicillin inhibits bacterial transpeptidase and prevents bacterial cell-wall synthesis. Varieties of modification of the original compound have produced varying spectra of activity. Penicillin G and V are still highly effective for many gram-positive and gram-negative bacteria, but many strains of *S. aureus* and *S. epidermidis* are now resistant. Penicillinase-resistant penicillins such as methicillin are useful for penicillinase-producing staphylococci. Broad-spectrum penicillins, ampicillin and amoxicillin, have better gram-negative coverage, and semisynthetic penicillins such as carbenicillin, piperacillin, and ticarcillin extend coverage to *Pseudomonas, Enterobacter*, and *Proteus* spp.

Immediate allergic response to penicillin, such as hives or anaphylaxis, is a strong contraindication for its use, and there is 10% cross-reactivity with cephalosporins. Therefore, for patients with penicillin allergy, cefazolin should be replaced with vancomycin. Vancomycin is a complex glycopeptide that inhibits bacterial cell-wall synthesis with principally gram-positive coverage, including methicillin-resistant *S. aureus* and *Streptococcus faecalis*, which is a frequent bacterial pathogen in infections of filtering blebs.

As mentioned above, an aminoglycoside is synergistic with cell-wall–inhibiting antibiotics, and the patient should be started on fortified vancomycin and tobramycin. Give the patient four doses—an alternating dose every 5 minutes—followed by alternation every half-hour to 1 hour. Actual dosing may vary in different institutions.

13. The next morning the ulcer looks worse with 4-mm corneal infiltrate and purulent material overlying the ulcer. The corneal culture confirms *Pseudomonas aeruginosa.* Why did the patient not improve?

Pseudomonas corneal ulcers sometimes require double coverage. Fortified piperacillin or ticarcillin could be added in a non-penicillin-allergic patient. Frequent ciprofloxacin (or another fluoroquinolone) could also be resumed, especially in this case.

14. The next day, the ulcer looks stable, but the patient complains of persistent and perhaps worsening pain. Examination reveals diffuse punctate corneal epithelial defects, inferior conjunctival erythema, and swollen lower eyelids. What should you do?

Toxicity is often less severe with topical administration; indeed, some common topical antibiotics such as neomycin and polymyxin cannot be given intravenously because of systemic toxicity. However, intensive regimens of potent antibiotics often produce surface toxicity with prominent involvement of lower more than upper conjunctiva. The toxicity is related to several factors, including the pH of the antibiotic drop and the presence of preservative in the solution. Fortified antibiotic drops, which are prepared by diluting intravenous antibiotics with preservative-free artificial tears and topical moxifloxacin, are preservative free. Occasionally, only analgesics and cool compresses can be offered if the infection is not under control. Fortified vancomycin should be decreased or discontinued because tobramycin and ciprofloxacin are more important for *Pseudomonas* ulcer, and the ulcer appears to be stabilizing.

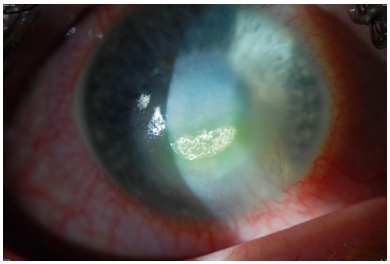

Figure 10-1. Anterior segment of right eye demonstrates refractile superficial crystalline deposits overlying an area of epithelial defect in a patient who was treated with a prolonged course of topical ciprofloxacin.

15. One week later the patient presents to you complaining of a dense white infiltrate in his cornea. Examination reveals superficial dense white material with gritty appearance in the area of the healing ulcer (Fig. 10-1). What is going on?

Prolonged use of ciprofloxacin drops/ointments causes characteristic macroscopic deposits in up to 20% of patients through a compromised corneal epithelium. These eventually disappear after discontinuation of the ciprofloxacin eye medication.

16. The patient slowly improves, but significant corneal opacity remains. He would like binocular vision for his surgical career and asks you to get rid of his corneal haze. How do you respond?

Read on to learn about topical steroids. Often, inflammatory opacities fade well with topical steroids. When, how much, and how long to use topical steroids are controversial, but a trial of topical steroids is often warranted before considering surgical options. The infection should be under control first before applying any topical steroids.

KEY POINTS: CORNEAL ULCERS

1. Small, noncentral ulcers can be managed without cultures.
2. Fluoroquinolones every half-hour to 1 hour initially may offer similar efficacy with less toxicity than fortified topical antibiotics.
3. *Pseudomonas* ulcers may require double coverage.
4. The use of topical steroids after the infection is under control can decrease the size and density of the scar.

17. Review the currently available topical antibiotics in generic and brand names.

See Table 10-1.

18. How do topical steroids work?

The specific mechanisms of action of steroids are not completely understood. At a molecular level, inhibition of arachidonic acid release from phospholipids may be the most important effect. Arachidonic acid is converted to prostaglandins and related compounds that are potent mediators of inflammation. At a cellular level, steroids must be carried to the cytoplasm, where they bind to soluble receptors and then enter the nucleus to alter transcription of various proteins involved in immune regulation and inflammation. At the tissue level, steroids suppress the cardinal signs of inflammation such as edema, heat, pain, and redness through a variety of mechanisms. They cause vasoconstriction and decrease vascular permeability to inflammatory cells. Cellular and intracellular membranes are stabilized to inhibit release of inflammatory mediators such as histamine. Neutrophilic leukocytosis is inhibited, and macrophage recruitment and migration are also decreased. Overall, steroids are potent anti-inflammatory and immunosuppressive agents with wide-ranging ophthalmic applications, but their adverse effects as well as their benefits should be understood before use.

Table 10-1. Currently Available Topical Antibiotics

GENERIC	BRAND NAME	CLASS	PREPARATION
Gentamicin Tobramycin	Genoptic S.O.P. Garamycin Gentacidin Gentak Tobrex	Aminoglycosides	0.3% ointment or solution 0.3% ointment or solution
Besifloxacin Ciprofloxacin Ofloxacin Norfloxacin Moxifloxacin Gatifloxacin Levofloxacin	Besivance Ciloxan Ocuflox Chibroxin Vigamox Zymar Quixin	Fluoroquinolones	0.6% suspension 0.3% solution or ointment 0.3% solution 0.3% solution 0.5% solution 0.3% solution 0.5% solution
Azithromycin Erythromycin	Azasite AK-Mycin Ilotycin	Macrolides	1% gel drop solution 0.5% ointment
Sulfacetamide	Bleph-10 AK-Sulf Sodium Sulamyd	Sulfonamides	10% ointment or solution 10% ointment or solution 10% ointment or solution
Polymyxin B	Neomycin Gramicidin (Neosporin)	Polymyxins	10,000 units, 1.75 mg, 0.025 mg/mL solution
Tetracycline		Tetracycline	1% solution or ointment
Bacitracin	AK-Tracin		500 units/g ointment
Chloramphenicol	Chloromycetin Ocu-Chlor Chloroptic		0.5% ointment, 1.0% solution
Polymyxin B/trimethoprim Polymyxin B/bacitracin Polymyxin B/bacitracin/neomycin Polymyxin/neomycin/gramicidin	Polytrim Polysporin ointment Neosporin ointment Neosporin drop	Combination antibiotic medications	0.1%/10,000 units/mL solution 10,000 units/g, 500 units/g ointment 10,000 units, 3.5 mg, 400 units/g ointment 10,000 units, 1.75 mg, 0.025 mg

19. Because steroids are not cures, what general categories of disorders warrant ophthalmic use of topical steroids?

Abelson and Butrus identify three broad categories of disorders that warrant steroid use: postsurgical, immune hyperreactivity, and combined immune and infectious processes. Remarkably, postoperative use of steroids has not been evaluated in a well-controlled, double-blinded study. Although their use in this setting is almost universal, some ophthalmologists report adequate control of postoperative inflammation with topical nonsteroidals for various ophthalmic procedures. The second category includes various uveitides, allergic and vernal conjunctivitis, corneal graft rejections, and other processes in which the immune system activity is harmful to the host tissue. The last category includes viral and bacterial corneal ulcers, especially herpes simplex and herpes zoster, in which control of infectious processes must be balanced with control of inflammation that may scar delicate ocular tissue.

20. The physician with the residual corneal opacity wants to minimize his corneal opacity but is concerned about potential side effects of topical steroids. How do you advise him?

Exacerbation of the existing infection with reactivation of dormant organisms or inhibition of wound healing is the most immediate concern. Other well-known adverse effects include glaucoma and

cataracts, but numerous other side effects have been observed, including blepharoptosis, eyelid skin or scleral atrophy, and mydriasis.

In a randomized, multicenter clinical trial, investigators compared the effects of topical prednisolone sodium phosphate 1% to placebo in culture-positive bacterial corneal ulcers that were treated with topical moxifloxacin for at least 48 hours prior to randomization. No improvement in the overall best spectacle-corrected visual acuity at 3 months was observed in the group treated with corticosteroids compared to placebo. In addition there were no differences in the scar/infiltrate size, time to reepithelialization, and rate of corneal perforation between the groups. However, subgroup analysis demonstrated that ulcers with central location and presenting vision of counting fingers (CF) or worse did better in the steroid-treated group. At 1 year, a small amount of visual improvement (one line) was noted in eyes treated with steroids whose ulcer was not caused by *Nocardia*, especially if the steroids were begun 2–3 days after the antibiotics were started, as opposed to 4 days or longer.

Systemic absorption may be significant with frequent use, and in such cases punctal occlusion should be encouraged. A 6-week regimen of topical 0.1% dexamethasone sodium phosphate has been shown to suppress the adrenal cortex, and some patients with systemic hay fever improve with topical ocular steroids. Of course, all of these effects are more frequent with intensive and chronic use of steroids.

21. After a lengthy discussion, the patient agrees to try topical steroids. However, given his interest in pharmacology, he requests a brief discussion of the pharmacokinetics of a few of the available topical steroids

Topical steroids may be prepared as solutions, suspensions, or ointments. Phosphate preparations may be prepared as solutions because they are highly water-soluble in the aqueous vehicles but penetrate less well into intact corneal epithelium than acetate or alcohol suspensions, which have biphasic solubility. Nevertheless, 1% prednisolone phosphate achieves a significant corneal level of 10 μg/g within 30 minutes of instillation, which improves to 235 μg/g when the corneal epithelium is removed. Dexamethasone phosphate enters the cornea and anterior chamber within 10 minutes, reaches a maximum in 30 to 60 minutes, and slowly disappears over the next few to 24 hours.

22. The patient also requests that the most potent steroid be used with rapid taper so that the overall course may be shortened. Which steroid do you choose?

Anti-inflammatory effects of topical steroids differ depending on the clinical setting and method of measurement. However, certain generalizations can be made:

- Higher concentrations and more frequent instillations, up to every 5 minutes, increase concentrations of steroids in the cornea and aqueous.
- With corneal epithelium intact, prednisolone acetate suspension > dexamethasone alcohol solution > prednisolone sodium phosphate solution > dexamethasone phosphate ointment.
- With corneal epithelial defects, prednisolone sodium phosphate solution > dexamethasone phosphate solution > prednisolone acetate suspension.

23. The patient is started on 1% prednisolone acetate four times/day. His opacity is beginning to recede, but he returns 2 days later with complaints of a white precipitate that forms on his conjunctiva and insists on a change of medication to prevent this annoying buildup. Which steroid do you choose now?

Suspensions leave a milky precipitate that some patients find unpleasant. In addition, despite shaking the bottles before instillation, a variable amount of the suspension may be delivered if particles are not evenly distributed. Therefore, some ophthalmologists prefer phosphate solutions despite lower potency with intact epithelium. A change to 1% prednisolone phosphate is reasonable if patient compliance is improved.

24. On day 10 of steroid therapy, the corneal opacity is receding rapidly, but the patient complains of foreign-body sensation. Examination reveals large corneal epithelial dendrites. What should you do?

Steroids do not cause herpetic keratitis but may promote herpetic keratitis when viral shedding is timed with the presence of steroids on the ocular surface. Often the dendrites are large and numerous in the presence of steroids, and steroids should be rapidly tapered or stopped. Of course, start full dosing of a topical antiviral (e.g., ganciclovir or trifluridine) or an oral antiviral (e.g., acyclovir, valacyclovir, or famciclovir).

25. Fortunately, the dendrite heals rapidly and the previous corneal opacity has faded significantly with return to 20/20 vision in that eye. Four years have passed, and the patient is now seeking employment. Opportunities are scarce, and his only job offer is from a large organized health company that hopes to use him as a pharmacist as well as a physician as a cost-saving measure. Understandably, he is stressed. Now he notices extreme photophobia and redness of his eye. Examination reveals corneal stromal edema and focal keratic precipitates consistent with herpes simplex keratouveitis. What should you do?

Many stimuli, including stress, may promote recurrence of herpetic keratitis. Other stimuli include menses, sun exposure, and fever. If the inflammation is severe or central vision is threatened, steroids should be given with antiviral coverage to decrease corneal scarring and intraocular inflammation. One regimen may be acyclovir 400 mg two times/day and 1% prednisolone acetate four times/day. Other regimens may be acceptable. Antiviral coverage is probably unnecessary below one drop/day of 1% prednisolone acetate.

26. Two days later, only marginal improvement is noted, but intraocular pressure is 35 mmHg. What happened?

Significant steroid-induced rises in intraocular pressure have been demonstrated in up to 6% of patients after 6 weeks of topical dexamethasone, and patients with glaucoma or family history of glaucoma are particularly susceptible. The mechanism appears to be decreased aqueous outflow, perhaps as a result of deposition of mucopolysaccharides in the trabecular meshwork. The extent of intraocular pressure rise varies with type and dose of steroids. Usually, steroids with greater anti-inflammatory potency elicit greater elevation of intraocular pressure. For example, steroids with low intraocular bioavailability and potency, such as fluorometholone, cause lower rises in intraocular pressure after a greater duration of therapy than more potent steroids such as dexamethasone. Loteprednol appears to be an exception. It appears to have similar suppression of anterior chamber cell and flare compared to 1% prednisolone acetate, with intraocular pressure elevation similar to that of fluorometholone. Regardless, the elevated intraocular pressure subsides, usually within 2 weeks, by decreasing or discontinuing steroid therapy, but topical aqueous suppressants may be needed in some patients.

However, steroid-induced rises in intraocular pressure rarely occur in less than 2 weeks and certainly not after 2 days of steroid therapy. Patients with intraocular inflammations, especially in herpetic keratouveitis, may have increased intraocular pressure as a result of intraocular inflammation. Therefore, in the present patient, the topical steroids should be increased and not decreased.

27. The frequency of prednisolone acetate administration was increased to every 3 hours while awake, and timolol, two times/day, was added. One week later the intraocular pressure is normal, and intraocular inflammation has subsided. Prednisolone acetate is tapered to two times/day. The patient returns 2 days later with recurrence of pain and photophobia and return of intraocular inflammation. What happened?

You tapered the steroids too quickly. A useful rule is to decrease steroids by no more than half of the previous dose every week to many weeks, especially in herpetic keratouveitis, in which rebound inflammation is frequent. Make sure that the patient is still taking the eyedrops. Sometimes patients abruptly stop the eyedrops when they feel better and then suffer rebound inflammation.

28. Review the commonly available topical steroids and their generic and brand names.

See Table 10-2.

29. What are some of the topical antibiotic/steroid combinations and when is it appropriate to use them?

There are many antibiotic/steroid combination drops and ointments available on the market. See Table 10-3.

These medications are often used in eyes with mild superficial infections associated with some inflammation, such as staphylococcal marginal hypersensitivity. Combination medications should be used cautiously as steroids can cause a rapid progression and worsening of corneal ulcer. Also, long-term use of these medications can lead to formation of cataract and elevated intraocular pressure and/or glaucoma.

Table 10-2. Commonly Available Topical Steroids

GENERIC NAME	BRAND NAME	PREPARATION
Difluprednate	Durezol	0.05% emulsion
Dexamethasone sodium phosphate	AK-Dex, Decadron	0.05% ointment
Dexamethasone sodium phosphate	AK-Dex, Decadron	0.1% solution
Fluorometholone	FML Forte	0.25% suspension
Fluorometholone	FML Liquifilm, Fluor-Op	0.1% suspension
Fluorometholone	FML S.O.P.	0.1% ointment
Fluorometholone acetate	Flarex	0.1% suspension
Prednisolone acetate	Pred Forte, Econopred Plus	1% suspension
	Pred Mild, Econopred	0.125% suspension
Prednisolone sodium phosphate	Inflamase Forte, AK-Pred 1%	1% solution
	Inflamase Mild, AK-Pred 0.125%	0.125% solution
Rimexolone	Vexol	1% suspension
Loteprednol	Lotemax	0.5% suspension

Table 10-3. Topical Steroid/Antibiotic Combinations

GENERIC	BRAND NAME
Dexamethasone (0.1%)/neomycin(0.35%), polymyxin B (10,000 units)	Maxitrol
Dexamethasone (0.1%)/tobramycin(0.3%)	Tobradex
Hydrocortisone (1%)/neomycin (0.35%)/polymyxin B ointment (10,000 units)	—
Hydrocortisone (1%)/neomycin (0.35%)/bacitracin (400 units)/ polymyxin B ointment (10,000 units)	—
Loteprednol (0.5%)/tobramycin (0.3%)	Zylet
Prednisolone (1%)/gentamicin suspension (0.3%)	Pred-G
Prednisolone (0.6%)/gentamicin ointment (0.3%)	Pred-G S.O.P.
Prednisolone (0.5%)/neomycin (0.35%/polymyxin B solution (10000 units)	Poly-Pred
Prednisolone (0.20%)/sulfacetamide sln(10%)	Blephamide
Prednisolone (0.2%)/sulfacetamide ointment (10%)	Blephamide S.O.P.

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DRY EYES

Janice A. Gault

CHAPTER 11

1. **What is the definition of dry eye?**
   A dry eye, or keratoconjunctivitis sicca, is a condition in which the tear film is abnormal and cannot lubricate the anterior surface of the cornea adequately. The resulting changes in the ocular surface can cause ocular discomfort, scarring, and, in severe cases, loss of vision and perforation.

2. **Describe the normal tear film**
   The normal tear film is a 1.0-mm convex band with a regular upper margin.

3. **What are the components of the tear film?**
   The normal tear film is made of three components. The outer layer is a thin lipid layer produced by the meibomian glands, which open along the upper and lower lid margins. The middle layer, the thickest, is composed of aqueous produced from the main and accessory lacrimal glands. The innermost layer is a mucin layer produced by conjunctival goblet cells.

4. **What is the function of the outer lipid layer?**
   It retards evaporation of the aqueous middle layer. If it is dysfunctional, evaporative dry eye will result.

5. **What causes dysfunction of the outer lipid layer?**
   It could be caused by oil deficiency, as in meibomian gland dysfunction (i.e., blepharitis). Also, an abnormal lid contour, as in ectropion or lid tumor, or poor blinking, found in Bell's palsy, can cause outer lipid layer dysfunction.

6. **What is the function of the aqueous middle layer?**
   It supplies oxygen from the atmosphere to the corneal epithelium, washes away debris, and has antibacterial properties due to IgA, lysozyme, and lactoferrin present within it. If deficient, hyposecretive dry eye results, as found in Sjögren's syndrome.

7. **What is the function of the inner mucin layer?**
   It covers the villus surface of the corneal epithelium, converting it from a hydrophobic surface to a hydrophilic one, thus allowing the aqueous layer to lubricate the cornea.

8. **What diseases of the conjunctiva can cause dry eye?**
   Conjunctival scarring can injure the goblet cells. Patients with cicatricial ocular pemphigoid, Stevens-Johnson syndrome, chemical burns (especially alkali), and graft-versus-host disease in bone marrow transplantation may have dry eye. Patients with other conjunctival disorders that accompany conditions such as aniridia may also have dry eyes. Vitamin A deficiency can result in the loss of goblet cells. This is becoming more common with the increase in gastric bypass procedures.

9. **What is necessary for the normal resurfacing of the tear film?**
   A normal blink reflex, normal lid anatomy and contour, and a normal corneal epithelium. Of course, a normal tear film makeup is essential.

10. **What are the types of dry eye?**
    Basically, there are three main types:
    - **Hyposecretive (i.e., Sjögren or non-Sjögren syndrome):** The aqueous component is low. Ten percent of severe dry eye patients have Sjögren syndrome. Lacrimal deficiency or obstruction and systemic drugs are other causes.
    - Evaporative
      1. Extrinsic causes are vitamin A deficiency, topical drugs and their preservatives, contact lens wear, and environmental factors such as low humidity or allergens.
      2. Intrinsic factors are meibomian gland dysfunction, eyelid abnormalities (i.e., Bell's palsy, ectropion) or corneal surface changes such as dellen, and poor blink.
    - **Mixed:** This combines features of the other two.

11. What are the symptoms of dry eye?

Burning, irritation, foreign body sensation, light sensitivity, and blurred vision. Usually, the symptoms are worse in the afternoon and evening and better on awakening. A dry or dusty environment may cause more difficulties in patients with dry eye than in others. Cigarette smoke can be extremely irritating. Symptoms are worse in low-humidity environments, such as those with central air and in an airplane, during prolonged reading or driving with a decreased blink rate owing to increased concentration, and windy conditions.

12. What are the most common signs of dry eye?

In the early stages, ocular symptoms may be more impressive than what is found on the examination. Signs of dry eye include a decreased tear meniscus, debris in the tear film, conjunctival injection, and superficial punctate keratitis and conjunctivitis. Abnormal fluorescein or rose bengal staining of the corneal and conjunctival epithelium in the exposed interpalpebral fissure (at 3 and 9 o'clock) of the lower third of the cornea is often present. The upper half of the cornea is usually spared. In more severe disease, filamentary keratitis can develop as well as corneal scarring. Blepharitis with a frothy tear film may be seen in tandem with dry eye.

13. What is Sjögren's syndrome?

Sjögren's syndrome is a triad of dry eye, dry mouth (xerostomia), and a collagen vascular disease. Rheumatoid arthritis is the most common, but systemic lupus erythematosus, Wegener's granulomatosis, scleroderma, systemic sclerosis, and primary biliary cirrhosis may also be associated. The lacrimal gland acini and ducts are damaged in the autoimmune disease. Ten percent of severe dry eye patients have Sjögren's syndrome.

14. How do you determine if a patient has Sjögren's syndrome?

Order anti-Sjögren syndrome A antibody (SSA or anti-Ro), anti-Sjögren syndrome B antibody (SSB or anti-La), rheumatoid factor, and antinuclear antibody. A biopsy of the lacrimal gland may be necessary. Then, refer to a rheumatologist.

15. Who gets dry eye?

Women are more likely to develop this than men, probably in relation to changes in hormone levels. It is also associated with birth control use. Contact lens wearers frequently have problems with dry eye, especially with long histories of contact lens use.

It may be seen in all age groups, but it is most common after 60 years of age. It can occur in patients in their 20s and 30s, but may be overlooked unless patients are specifically questioned about symptoms. LASIK and blepharoplasty can exacerbate underlying dry eye. Radiation treatments can also cause dry eye. Many systemic medications have a side effect of dry eye.

16. What medications may be a cause of dry eye?

Topical eye drops such as those used in glaucoma can cause or worsen dry eye. The medication or the preservative may cause toxicity to the epithelial cells. Aminoglycoside antibiotics (i.e., Neosporin and gentamicin), β-blockers, and pilocarpine are common offenders.

Systemic medications that can decrease tear production include antimuscarinics (scopolamine, Detrol), antihistamines, lithium, diuretics, estrogens (including birth control pills), antihypertensives (β-blockers, α-agonists), antidepressants, chemotherapy agents, antipsychotics, marijuana, and morphine.

17. What stains are used in dry eye diagnosis?

Fluorescein stains corneal and conjunctival epithelial defects. Rose bengal stains mucin and epithelial cells that are dead or devitalized, but still in place, as well as breaks in the tear film on the cornea or conjunctiva. Thus, rose bengal will show earlier, more subtle abnormalities in comparison to fluorescein. Lissamine green stains damaged or devitalized cells, but does not stain healthy cells in contrast to the other two dyes.

18. How do you measure a tear breakup time (TBUT)?

Instill fluorescein into the lower fornix. Ask the patient to blink several times and then stop. The TBUT is the time from the last blink to the development of a dry spot noted by black spots in the fluorescein film. Normal is 10 or more seconds. It decreases with age, but less than 5 seconds is good evidence for dry eye. Meibomian gland dysfunction may show a TBUT of zero.

19. What is Schirmer's test?

A Schirmer's test filter strip is placed with the notched edge over the lid margin. The tear film in the lacrimal lake is absorbed over 5 minutes and measured. A normal Schirmer's test wets the strip 10 mm. Usually, it is done with topical anesthesia so as to not cause reflex tearing.

20. What other tests are done in dry eye patients?

Tear film osmolarity is elevated in patients with dry eye disease as well as other disease states such as bacterial conjunctivitis and meibomitis. Tear lactoferrin levels are low in dry eye disease. MMP-9 is a marker of inflammation and elevated in tears in dry eye disease. Quick and simple in-office tests are available for all of these. Tear meniscus height can be measured with optical coherence tomography. It remains to be seen if the community at large will adopt any of these. They all give evidence to make a diagnosis of dry eye disease as well as objective markers to observe treatment effectiveness or failure.

21. What are the treatments for dry eye patients?

The Management and Therapy Subcommittee of the International Dry Eye Workshop has recommended that treatments be based on disease severity. Dry eye severity is graded from 1 to 4 (see Table 11-1). Even if a patient has a normal exam, but describes typical dry eye (level 1), treatment should be instituted. Begin with environmental modifications, stopping any topical and/or systemic medications that might be worsening the symptoms, warm compresses, and blepharitis treatment. Start tear replacement therapy. They are used as needed depending on the patient's symptoms. Once or twice a day may be fine for some; others may need nearly every hour. Lacrisert is a solid form of artificial tear placed in the lower cul-de-sac that melts over a period of 12 hours. It is seldom used but can be very effective in a small number of patients. Lubricating ointments can be used at night. It will blur vision, but may be necessary during the day if exposure is a significant problem, as in Bell's palsy.

Patients should also be counseled to avoid conditions with low humidity such as central air heating, to prevent air from blowing into their eyes as from an air conditioner vent at home or in the car, and to

Table 11-1. Levels of Dry Eye Severity

DRY EYE SEVERITY LEVEL	1	2	3	4+
Discomfort, severity, and frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe, frequent, or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic, and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/–	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian gland	MGD variable present	MGD variable present	Frequent	Trichasis, keratinization, symblepharon
TBUT (s)	Variable	≤10	≤5	Immediate
Schirmer score (mm/5 min)	Variable	≤10	≤5	≤2

From Behrens, A, Doyle, J, Stern, L, et al: Dysfunctional tear syndrome: A delphi approach to treatment recommendations. *Cornea* 25:900-907, 2006.

TBUT, Fluorescein tear breakup time; *MGD*, meibomian gland disease.

*Must have signs *and* symptoms.

use a humidifier while sleeping and at work if possible. Increased lubrication is often necessary during plane travel, as airplane cabins have very low humidity, and while reading or studying or driving, as the blink reflex is decreased during concentration.

Dry eye patients may better tolerate newer contact lenses with a high-DK and high water content. Daily disposable lenses are a good choice.

22. What if the patient uses tears six to eight times a day and returns with red, painful eyes and more superficial punctate keratitis?

The patient may be sensitive to the preservatives in the tears. In these patients, preservative-free tears may be necessary.

23. What if this is still not enough or the patient has a clinical exam that is worsening?

Punctal occlusion is an option. Patients who use tears every 2 hours or more may benefit from closing the lower puncta. Placement of a punctal plug can be easily done as an office procedure. Patients may notice local irritation for a short time, but this usually resolves. Occasionally, epiphora may result from overflow tearing and the plug can quickly be removed in the office. If the patient is comfortable with this, but the plug falls out, permanent closure can be done by using cautery. Between 10% and 20% of the tear film is drained through the upper puncta, and these may be closed subsequently if the lower lid punctal closure is not adequate to control symptoms. Of course, any lid contour abnormalities should be addressed as well (e.g., ectropion, lid laxity).

KEY POINTS: SEVERE DRY EYE

1. Frequent tear use may make symptoms worse if the patient is sensitive to the preservatives.
2. Occlude the lower lid puncta first and then proceed to upper lid punctal occlusion.
3. Cyclosporine may increase tear production, but it may take months to see results.

24. A patient with punctal occlusion returns with more irritation and burning since the procedure was done. The tear film meniscus is greatly improved. What happened?

If a patient has significant blepharitis, the symptoms can worsen after punctal occlusion. The debris is trapped and not drained and now has a higher concentration than before. Make sure blepharitis is treated adequately before placing punctal plugs to prevent this.

25. Is there any treatment to increase tear production?

Topical cyclosporine (Restasis) decreases cell-mediated inflammation of the lacrimal tissue and ultimately can increase tear production. Patients need to use it twice a day for 1 to 3 months to get a response and then continue for up to 6 months or more. Some practitioners are using a mild steroid four times a day for the first 2 weeks of Restasis to decrease inflammation and stinging until the cyclosporine begins to work. This is often used in patients with level 2 or 3 severity.

26. What is the role of acetylcysteine?

Acetylcysteine is a mucolytic agent used to break up mucus in patients that have filamentary keratitis and mucous plaques.

27. What other agents are used in a patient with level 4 severity of dry eye?

Other options are systemic cholinergic and anti-inflammatory agents, autologous serum tears, moisture chamber goggles, and a temporary or permanent lateral tarsorrhaphy. Rheumatologic evaluation may help elucidate the cause and coordinate systemic treatments.

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CHAPTER 12

CORNEAL DYSTROPHIES

Sadeer B. Hannush and Lorena Riveroll-Hannush

1. What are corneal dystrophies?

Corneal dystrophies are bilateral, inherited, noninflammatory, commonly progressive alterations of the cornea that are usually not associated with any other systemic condition. Most corneal dystrophies are autosomal dominant disorders occurring after birth. Because each dystrophy may exhibit a spectrum of clinical manifestations, examining multiple family members frequently aids in establishing the diagnosis.

2. How do degenerations differ from dystrophies?

In contrast to dystrophies, degenerations are unilateral or bilateral aging changes that are not inherited. They are also not associated with systemic disease.

3. Discuss the general anatomic classification of corneal dystrophies.

- **Anterior membrane dystrophies** include disorders affecting the corneal epithelium, epithelial basement membrane (Fig. 12-1), and Bowman's layer.
- **Stromal dystrophies** occur anywhere in the stromal layer of the cornea between Bowman's layer and Descemet's membrane.
- **Posterior membrane dystrophies** are primarily abnormalities of the endothelium and Descemet's membrane.

KEY POINTS: DIFFERENCES BETWEEN CORNEAL DYSTROPHIES AND DEGENERATIONS

1. Corneal dystrophies are always bilateral.
2. They are inherited.
3. They may occur shortly after birth.

4. What is the International Committee for Classification of Corneal Dystrophies?

The International Committee for Classification of Corneal Dystrophies (IC3D) was created in 2008 to study what genetic analyses had brought to light and the relations between genetic abnormalities and their phenotypic description available at the time. Members of The Cornea Society assigned a category number from 1 to 4 to each one of the known dystrophies, reflecting the "level of evidence" of its existence. All dystrophies were given a name, alternative names, and eponyms; their Mendelian inheritance in humans, inheritance, genetic locus, and gene; their onset, signs, symptoms, and course; their light microscopy, transmission electron microscopy, immunohistochemistry, and confocal microscopy results; and a category.

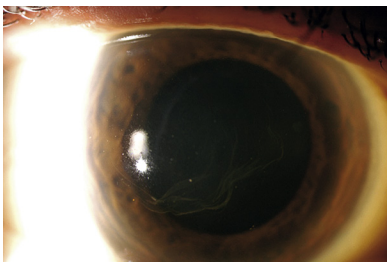

Figure 12-1. Typical mare's tail sign in epithelial basement membrane dystrophy.

All anterior membrane dystrophies are autosomal dominant. Examples are Meesmann's juvenile epithelial dystrophy, epithelial basement membrane dystrophy, and corneal dystrophies of Bowman's layer.

5. Which is the most common anterior membrane dystrophy? Which is strictly epithelial?

Epithelial basement membrane dystrophy is by far the most common anterior membrane dystrophy. In fact, it has the highest prevalence of all of the corneal dystrophies. Areas of extra basement membrane result in maplike and/or fingerprint changes as well as intraepithelial microcysts. Five percent of otherwise normal corneas have been observed to have such changes.

Second in prevalence are the corneal dystrophies of the Bowman's layer (CDBs): Reis-Bücklers (CDB-I) and Thiel-Behnke honeycomb-shaped dystrophy (CDB-II). These disorders consist of gray reticular opacities beneath the epithelium.

Meesmann's dystrophy is the rarest of the three and is strictly epithelial. This disorder, noted in the first few years of life, presents as a bilaterally symmetric pattern of microcysts or vesicles seen strictly in the epithelial layer of the cornea, usually in the interpalpebral fissure.

6. What are the most common presenting symptoms of anterior membrane dystrophies?

First are the symptoms associated with corneal erosions—pain, foreign body sensation, photophobia, and tearing, especially with opening of the lids during sleep or upon awakening in the morning. Erosions are most common in the setting of epithelial basement membrane dystrophy. The second symptom is blurred vision secondary to either irregularity of the surface, seen in epithelial basement membrane dystrophy, or corneal clouding, frequently seen in the dystrophies of the Bowman's layer or Meesmann's dystrophy

7. Discuss treatment options for recurrent corneal erosions associated with anterior membrane dystrophies.

The conservative approach includes the generous use of lubricating eyedrops during the day and ointments at night. Some physicians advocate the use of topical steroids to stabilize the basement membrane, and others advocate hypertonic saline, especially in ointment form at night to dehydrate the epithelium and aid in its attachment to the underlying layers. Patching, either conventional or with collagen or bandage contact lenses, hypothetically decreases the mechanical effect of lid movement on the already weakened corneal epithelium. Recalcitrant cases may require surgical intervention.

KEY POINTS: RECURRENT CORNEAL EROSIONS

1. Recurrent corneal erosions may be associated with anterior membrane and stromal dystrophies.
2. They have common symptoms: pain, blurred vision, and photophobia.
3. Recurrent corneal erosions are frequently amenable to medical therapy with lubrication and hyperosmotic agents.
4. They can be treated surgically with mechanical or laser keratectomy or stromal puncture.

8. Discuss the role of surgery in the treatment of anterior membrane dystrophies.

In the setting of recalcitrant corneal erosions, mechanical debridement of the loose epithelium and basement membrane or anterior stromal puncture, together with the use of a bandage lens, may aid in reepithelialization of the surface and adherence of the epithelium to the underlying layers. Mechanical debridement also may be used to remove an irregular epithelial basement membrane if an associated visual decline is noted. Typically these patients do not have symptoms of corneal erosion but complain of blurred vision. Topography reveals marked irregularity of the Placido rings. Removal of the abnormal epithelium and basement membrane can restore normal anterior corneal anatomy paralleled by improvement in vision. For the Bowman's layer dystrophies a more aggressive superficial or lamellar keratectomy may be required. This may be microkeratome assisted. Lamellar keratoplasty may also be considered.

9. Do lasers have a role?

The yttrium–aluminum–garnet laser has been used instead of a needle to accomplish anterior stromal puncture but does not offer a clear advantage. The excimer laser has been used

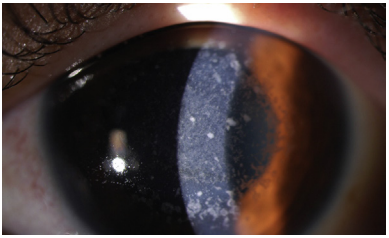

Figure 12-2. Slit lamp appearance of granular dystrophy.

for treatment of recurrent erosions associated with basement membrane dystrophies and for removal of deeper layers in conditions such as Reis-Bücklers and Thiel-Behnke dystrophies (phototherapeutic keratectomy). Although in the first instance the excimer laser may not offer a clear advantage over debridement, in the second it has supplanted manual lamellar keratectomy as the treatment of choice. Microkeratome-assisted lamellar keratectomy may be equally effective.

10. What controversy surrounds the dystrophies affecting the Bowman's layer?

Until recently there has been some confusion over dystrophies affecting the Bowman's layer, because they present with two different sets of characteristics, but historically they have been lumped under Reis-Bücklers dystrophy. The first set was described by Reis in 1917 and later by Bücklers in 1949 and the second by Thiel and Behnke in 1967. Küchle et al. divided the Bowman's membrane dystrophies into two classifications: corneal dystrophy of the Bowman's layer type I and type II. Type I is synonymous with the original Reis-Bücklers dystrophy and equivalent to what also has been described as superficial variant of granular dystrophy. Type II is honeycomb-shaped and is also known as the Thiel-Behnke corneal dystrophy. The two dystrophies have slightly different characteristics on light microscopy. Transmission electron microscopy, on the other hand, differentiates them unequivocally.

11. Describe the inheritance patterns of the stromal dystrophies.

- **Autosomal dominant:** Granular (Groenouw type I; Fig. 12-2), lattice, Avellino granular–lattice, Schnyder's crystalline, fleck, central cloudy dystrophy of François, pre-Descemet, congenital hereditary (stromal), and posterior amorphous dystrophies
- **Autosomal recessive:** Macular (Groenouw type II) and possibly gelatinous droplike dystrophies

12. Match the stromal dystrophy with the histochemical stain for the accumulated substance.

- **Granular:** Masson trichrome stains hyaline
- **Lattice:** Congo red stains amyloid (amyloid deposits exhibit polarized light birefringence and dichroism)
- **Macular:** Alcian blue stains mucopolysaccharides (glycosaminoglycans)
- Lattice and macular dystrophies also stain with periodic acid–Schiff stain.

13. Describe the clinical features of the three major stromal dystrophies.

See Table 12-1.

14. Is lattice dystrophy associated with systemic amyloidosis?

There are three types of lattice dystrophy. Only type II (Meretoja's syndrome or familial amyloid polyneuropathy type IV), which has less corneal involvement than type I or III, is associated with systemic findings, including blepharochalasis, bilateral facial nerve palsies, peripheral neuropathy, and systemic amyloidosis.

15. What is the differential diagnosis of corneal stromal crystals? What systemic findings are associated with Schnyder's crystalline dystrophy?

The differential diagnosis of corneal stromal crystals includes Bietti's peripheral crystalline dystrophy, cystinosis, and dysproteinemias, such as multiple myeloma, Waldenstrom's macroglobulinemia, and benign monoclonal gammopathy.

Table 12-1. Clinical Features of the Three Major Stromal Dystrophies

FEATURE	AGE OF ONSET		
	Granular dystrophy	**Lattice dystrophy**	**Macular dystrophy**
Deposits	First decade	First decade	First decade
Symptoms	Third decade or none	Second decade	First decade
Decreased vision	Fourth or fifth decade	Second or third decade	First or second decade
Erosions	Uncommon	Frequent	Common
Corneal thickness	Normal	Normal	Thinned
Opacities	Discrete with sharp borders and clear intervening stroma early but becoming hazy later, not extending to limbus	Refractile lines and subepithelial spots, diffuse central haze, not extending to limbus except in advanced cases	Indistinct margins with hazy stroma between, extending to limbus; central lesions more anterior and peripheral lesions more posterior

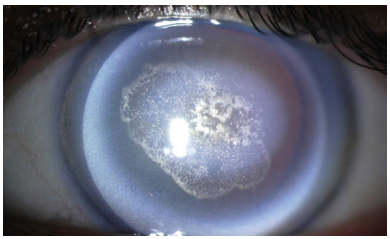

Figure 12-3. Schnyder's crystalline stromal dystrophy.

Schnyder's dystrophy (Fig. 12-3) is strongly associated with hypercholesterolemia with or without hypertriglyceridemia. There is no direct association with primary hyperlipidemias, and serum lipid levels do not correlate with the density of the corneal opacities. The dystrophy more likely represents a localized defect in cholesterol metabolism. Of importance, not all patients with Schnyder's dystrophy have clinical evidence of corneal crystalline deposits.

16. How does central cloudy dystrophy of François differ from posterior crocodile shagreen?

Although some physicians have argued that the location of the lesions differs in the two conditions, the lesions are clinically the same. It is generally accepted that the polygonal "cracked-ice" lesions of the central cloudy dystrophy of François are more central, deeper, and, by definition, bilateral with an inheritance pattern. On the other hand, posterior crocodile shagreen is more commonly peripheral and anterior stromal and is classified as degeneration. Of importance, both conditions are associated with normal corneal thickness and no recurrent erosions or significant visual compromise.

17. What characterizes Avellino dystrophy?

Avellino dystrophy also has been called granular–lattice dystrophy. The granular deposits occur in the anterior stroma early in the progression of the condition, followed later by lattice lesions in the mid- to posterior stroma and finally by anterior stromal haze. More patients with Avellino dystrophy experience recurrent erosions than patients with typical granular dystrophy. The disease-causing genes of lattice dystrophy type I, granular dystrophy, Avellino dystrophy, and Reis-Bücklers dystrophy have been mapped to chromosome 5q, suggesting one of the following possibilities:

1. A corneal gene family exists in this region.
2. These corneal dystrophies represent allelic heterogeneity (i.e., different mutations within the same gene manifest as different phenotypes).
3. They are the same disease.

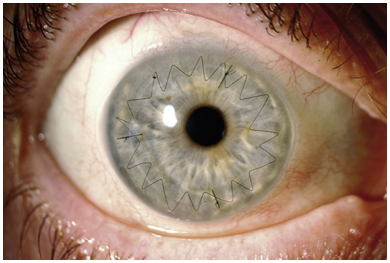

Figure 12-4. Appearance of eye after penetrating keratoplasty.

18. How are stromal dystrophies treated?

To the extent that some dystrophies, such as lattice and Avellino, are associated with recurrent erosions, they are treated as discussed earlier. When the lesions obscure vision and are restricted to the anterior third of the stroma, they are usually amenable to manual lamellar, microkeratome-assisted lamellar, or phototherapeutic keratectomy with the excimer laser. If the lesions are deeper, lamellar or penetrating keratoplasty is necessary.

19. Is keratoplasty a definitive treatment?

Deep anterior lamellar keratoplasty (DALK) offers the advantage of preserving the host Descemet's membrane and endothelium. Penetrating keratoplasty may be considered as well, especially if the surgeon is not comfortable with the DALK technique. Both keratoplasty techniques are associated with recurrence of the pathology in the graft as early as 1 year after surgery. The recurrent pathology is sometimes milder than in the original cornea but may require regrafting not infrequently (Fig. 12-4).

KEY POINTS: KERATOPLASTY

1. Deep anterior lamellar keratoplasty (DALK) is the procedure of choice for stromal dystrophies with deep stromal involvement not amenable to surgical or phototherapeutic keratectomy.
2. Endothelial keratoplasty (Descemet stripping endothelial keratoplasty or Descemet membrane endothelial keratoplasty) is the procedure of choice for posterior membrane dystrophies.
3. Penetrating keratoplasty (PK) may also be considered for stromal or posterior membrane dystrophies, especially when the surgeon is not familiar with anterior and posterior keratoplasty techniques.
4. DALK and PK do not prevent recurrence of stromal dystrophies in the donor graft.

20. Name the three posterior membrane dystrophies.

- Posterior polymorphous dystrophy (PPMD)
- Fuchs' endothelial dystrophy
- Congenital hereditary endothelial dystrophy (CHED)

21. What is their common clinical manifestation?

All three essentially share the pathway of corneal edema and increased thickness, resulting in visual compromise.

22. Describe the inheritance patterns of the three posterior membrane dystrophies.

Posterior polymorphous and Fuchs' dystrophies have an autosomal dominant inheritance pattern. Two forms of congenital hereditary endothelial dystrophy exist. The autosomal dominant form presents in early childhood and is slowly progressive and frequently symptomatic. The autosomal recessive form presents at birth and is nonprogressive, but it is associated with significant visual compromise and nystagmus due to marked corneal edema.

Table 12-2. Main Clinical Characteristics of the Three Posterior Membrane Dystrophies

FEATURE	PPMD	FUCHS' DYSTROPHY	CHED
Onset	Second to third decade, rarely at birth	Fifth to sixth decade	Birth to first decade
Corneal findings	Vesicles, diffuse opacities, and corneal edema	Guttae, stromal thickening, epithelial edema, and subepithelial fibrosis	Endothelium rarely visible with marked corneal thickening and opacification
Other ocular abnormalities	Peripheral synechiae, iris atrophy/corectopia, and glaucoma	Narrow angles and glaucoma	None
Differential diagnosis	ICE syndrome, early-onset CHED	Pseudoguttae, Chandler's syndrome, herpes simplex keratitis, aphakic or pseudophakic bullous keratopathy, and other guttate conditions	Congenital glaucoma, metabolic opacification, Peters' anomaly, forceps injury, early-onset PPMD, and infectious etiologies

ICE, Iridocorneal endothelial.

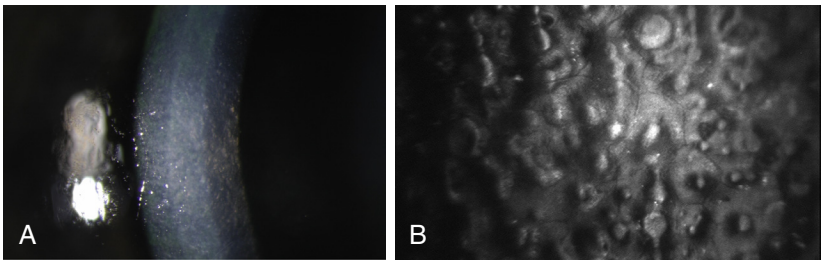

Figure 12-5. A, Slit lamp photo of cornea with advanced Fuchs' dystrophy. **B,** Confocal microscopy of guttate changes in Fuchs' dystrophy.

23. Describe the main clinical characteristics of the three posterior membrane dystrophies.

See Table 12-2.

24. How does Fuchs' dystrophy differ from cornea guttata?

Cornea guttata basically refers to a pattern of corneal guttae that are usually found on the central cornea. They sometimes coalesce, produce a beaten-metal appearance, and are associated with increased pigmentation. This condition does affect vision, although not significantly. In 1910 Fuchs described a more severe form of the condition associated with stromal thickening and epithelial edema with secondary marked visual compromise (Fig. 12-5, *A* and *B*). This represents an advanced stage of the same dystrophy.

25. Describe the workup of a patient with Fuchs' dystrophy

- **History:** Ask about previous intraocular surgery
- **Biomicroscopic examination:** Guttae on the posterior corneal surface, increased stromal thickness, and epithelial edema with possible subepithelial bullae
- Intraocular pressure measurement
- Ultrasound or optical pachymetry
- Specular microscopy to evaluate number, size, and shape of endothelial cells
- Anterior segment optical coherence tomography (OCT)

26. What overlapping features are seen in posterior polymorphous dystrophy and iridocorneal endothelial syndromes?

Overlapping features of PPMD and ICE are abnormal corneal endothelium, peripheral anterior synechiae, corectopia, and glaucoma.

27. What is unique about the congenital hereditary endothelial dystrophy cornea?

The CHED cornea shows markedly increased corneal thickness, unlike any other corneal dystrophy.

28. Discuss the management and prognosis of posterior membrane dystrophies

Conservative management has a role, especially in the earlier stages of Fuchs' dystrophy. Topical hypertonic saline solution, dehydration of the cornea with a blow dryer, and reduction of intraocular pressure may decrease corneal edema and improve vision. Bandage contact lenses may be used in the setting of recurrent erosions or subepithelial bullae. However, when vision is significantly compromised by Fuchs' or other posterior membrane dystrophies, the definitive solution is endothelial keratoplasty (Descemet stripping endothelial keratoplasty (DSEK) or Descemet membrane endothelial keratoplasty (DMEK)). DSEK involves transplantation of a layer of donor posterior stroma with Descemet's membrane (DM) and endothelium (Fig. 12-6, *A–C*). DMEK is a pure anatomic replacement of the host DM and endothelium with healthy donor tissue. This is surgically challenging because of the very thin nature of the donor tissue (15 to 20 μm) (Fig. 12-6, *D–G*). Keratoplasty, endothelial or penetrating, has the best prognosis in Fuchs' dystrophy, especially in the absence of glaucoma; a fairly good prognosis in PPMD in the absence of glaucoma; and a guarded prognosis in CHED, especially in the early pediatric age group.

29. Can PPMD recur in the graft?

Recurrence of PPMD has been reported.

30. Discuss considerations for combined cataract extraction and corneal transplantation in patients with Fuchs' dystrophy.

- **First scenario: Visually significant cataract and borderline corneal function.** The decision whether to perform corneal transplantation at the time of cataract extraction may be based on a number of factors, including appearance of the corneal endothelium by specular microscopy, corneal thickness, visual variation throughout the day, and postoperative visual requirements of the patient. Patients with no evidence of frank stromal edema, including absence of morning blur and a stable central corneal thickness less than 620 μm, are likely to tolerate cataract extraction alone. The risk of corneal decompensation is outweighed by the advantage of rapid visual rehabilitation from cataract surgery alone. On the other hand, in patients with frank stromal edema, central corneal thickness greater than 650 μm, or an increase of more than 10% in corneal thickness in the morning compared with later in the day, the cornea is unlikely to tolerate routine cataract extraction. The patient will benefit from a triple procedure (i.e., cataract extraction with implant combined with keratoplasty, usually DSEK or DMEK). Having said that, most surgeons are opting to offer their patients with early but visually significant Fuchs' dystrophy and cataract the modern triple procedure, which includes endothelial keratoplasty (DSEK or DMEK) combined with cataract extraction and intraocular lens implantation, because of the high success of and the rapid visual rehabilitation after this combined procedure.
- **Second scenario: Corneal edema requiring corneal transplantation and mild-to-moderate cataract.** With the wide acceptance of DSEK and the recent emergence of DMEK as the preferred procedures for the surgical management of visually significant Fuchs' dystrophy, together with the predictability of the refractive outcome when combined with cataract extraction (CE) and intraocular lens (IOL) implantation, more triple corneal procedures (DSEK or DMEK + CE/IOL) are being performed for corneal endothelial disease and even early cataract. Some surgeons, however, especially when treating prepresbyopic patients, prefer to stage the procedures, starting with endothelial keratoplasty followed a few months later, when the cornea is stable physiologically and refractively, with CE/IOL. This may give the patient the best chance for good unaided vision especially with the increased popularity of toric IOLs. The incidence of graft decompensation after secondary CE/IOL is small.

31. List some interesting trivia about corneal dystrophy.

- The apostrophe in Fuchs' dystrophy is after the "s," not before.
- In cornea guttata, guttata is the adjective describing the cornea. The actual excrescences of Descemet's membrane between the endothelial cells are corneal guttae, not corneal guttata.

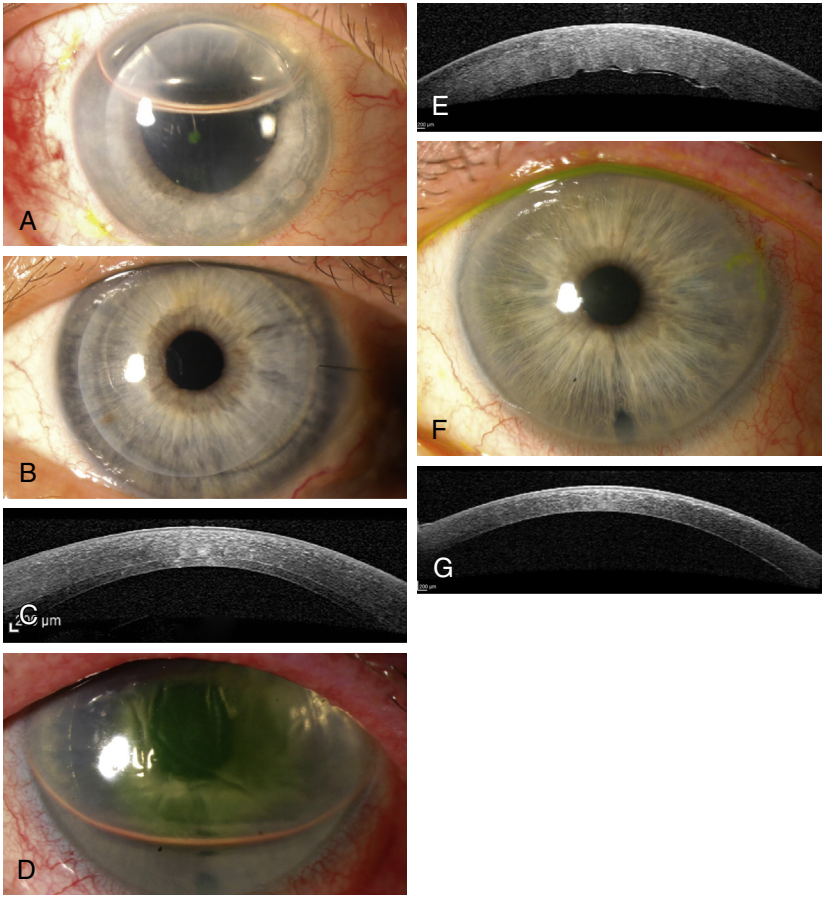

Figure 12-6. A, One day after Descemet stripping endothelial keratoplasty (DSEK). Postoperative bubble allows one to check the border and adherence of the graft. **B,** DSEK 1 week postoperative. The border of the graft is visible. **C,** Anterior segment OCT of cornea after DSEK. **D,** One day after Descemet's membrane endothelial keratoplasty (DMEK). **E,** Anterior segment OCT 1 day after DMEK with Descemet's membrane almost indistinguishable, showing in complete adherence of the graft. **F,** One month after DMEK. **G,** Anterior segment OCT 1 month after DMEK.

- Although keratoconus is usually bilateral and may have an inheritance pattern, it is considered an ectasia, not a dystrophy.
- Dua's layer is a structure in the posterior stroma, 5 to 8 collagen lamellae and 5 to 16 μm thick, devoid of keratocytes, and with a high bursting pressure reaching 750 mm Hg.
- When the Descemet's membrane is stripped off the posterior stroma it always scrolls endothelial side out!

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KERATOCONUS

Irving Raber

CHAPTER 13

1. What is keratoconus?

Keratoconus is a noninflammatory ectatic disorder of the cornea that leads to variable visual impairment. The cornea becomes steepened and thinned, thereby inducing myopia and irregular astigmatism. In advanced stages the cornea assumes a conical shape, hence the term keratoconus. The condition is usually bilateral, although frequently asymmetric.

2. Who gets keratoconus?

It is difficult to estimate the incidence of keratoconus because the diagnosis is easily overlooked, especially in the early stages. The reported incidence varies between 1 and 20 per 100,000 per year with a mean prevalence of 54.4 per 100,000. Some studies report a female predominance, whereas other studies report a male predominance. There is no known racial predilection.

3. What is the cause of keratoconus?

The cause of keratoconus is unknown. The etiology is multifactorial with both genetic and environmental factors playing a role. Various biochemical abnormalities have been documented in keratoconic corneas, including reduced collagen content, decreased or altered keratin sulfate molecules, reduced total protein and increased nonproteinaceous material, and increased collagenolytic and gelatinolytic activity associated with reduced matrix metalloproteinase inhibitor levels. Several studies have shown that the enzyme and proteinase inhibitor abnormalities are most prominent in the epithelial layer of the cornea. This suggests that the basic defect in keratoconus may reside in the epithelium and its interaction with the stroma. Additional studies implicate abnormal processing of free radicals and superoxide within keratoconus corneas leading to buildup of destructive aldehydes and/or peroxynitrites. Eye rubbing has been implicated as a cause of keratoconus. When asked, patients with keratoconus will frequently admit to excessive eye rubbing.

4. What is the relationship between contact lens wear and keratoconus?

The relationship between contact lens wear and keratoconus is controversial. Circumstantial evidence suggests that contact lens wear may lead to the development of keratoconus, especially long-term use of rigid contact lenses. Such patients tend to present at an older age and have a flatter corneal curvature than typical patients with keratoconus. In addition, the so-called contact lens-induced cones tend to be more centrally located in the cornea than the more typical cones, which are characteristically decentered inferiorly.

Contact lens warpage is diagnosed when contact lens wear induces irregular astigmatism without slit lamp features of keratoconus. Discontinuing lens wear for weeks to months eliminates the irregular astigmatism and allows the cornea to resume its normal shape, whereas in the so-called contact lens-induced keratoconus the changes are permanent and do not resolve when contact lens wear is discontinued.

Some contact lens practitioners are of the opinion that contact lenses can be used to flatten the cornea and reverse or at least retard further progression of keratoconus. However, I believe that corneal flattening induced by contact lens wear in patients with keratoconus is temporary and that the cornea ultimately reverts to its pre-contact lens shape once lens wear is discontinued.

5. Is keratoconus hereditary?

The role of heredity in keratoconus has not been clearly defined. The majority of cases occur sporadically with no familial history. However, some cases of keratoconus are transmitted within families. One study used corneal topography to diagnose subclinical cases of keratoconus. Familial transmission was documented in 7 of 12 families (58.3%) of patients with keratoconus and no known family history of corneal or ocular disease. The authors postulate autosomal dominant inheritance with incomplete penetrance as the mode of transmission. Other studies report that 6 to 25% of keratoconus patients have a positive family history, and there are numerous reports of concordance between monozygotic twins and discordance between dizygotic twins. Autorecessive inheritance has been suggested in a few studies with high consanguinity. Numerous genetic loci have been mapped in keratoconus

families but as of today no genetic mutations have been confirmed. It may be that there are multiple genes involved in the development of keratoconus. Genetic heterogeneity may also be involved in keratoconus wherein different gene abnormalities manifest a similar phenotype.

6. What systemic conditions are associated with keratoconus?

There is a definite relationship between atopy and keratoconus. The prevalence of atopic diseases such as asthma, eczema, atopic keratoconjunctivitis, and hay fever is higher in patients with keratoconus than in normal controls. Atopic patients are bothered by ocular itching, and excessive eye rubbing also may contribute to the development of keratoconus.

There is an association between Down syndrome and keratoconus. Approximately 5% of patients with Down syndrome manifest signs of keratoconus. The incidence of acute hydrops in keratoconus patients with Down syndrome is definitely higher than in patients without Down syndrome. As in atopic subjects, keratoconus patients with Down syndrome tend to be vigorous eye rubbers. This may explain, at least in part, the relationship with keratoconus.

Keratoconus is also associated with various connective tissue disorders, such as Ehlers-Danlos syndrome, osteogenesis imperfecta, and Marfan's syndrome. There are conflicting reports of an association between keratoconus, mitral valve prolapse, and joint hypermobility. One study has reported an association between keratoconus and false chordae tendineae in the left ventricle. The relationship between various connective tissue diseases and keratoconus suggests a common defect in the synthesis of connective tissue.

7. What ocular conditions are associated with keratoconus?

Keratoconus has been described in association with various ocular diseases, including retinitis pigmentosa, Leber's congenital amaurosis, vernal conjunctivitis, floppy eyelid syndrome, corneal endothelial dystrophy, and posterior polymorphous corneal dystrophy.

8. What are the symptoms of keratoconus?

The characteristic onset of keratoconus is in the late teens or early twenties, although earlier and later onset has been reported. Symptoms usually begin as blurred vision with shadowing around images. Vision becomes progressively more blurred and distorted with associated glare, halos around lights, light sensitivity, multiple images, and ocular irritation.

9. How is the diagnosis of keratoconus made?

During the early stages of keratoconus, the patient presents with myopic astigmatism, and a normal slit lamp examination. Corneal topography/tomography is helpful in documenting the presence of keratoconus even before keratometric or slit lamp findings become apparent. As the disease progresses an irregular light reflex with scissoring on retinoscopy can be appreciated through the dilated pupil. The cornea steepens and thins with irregularity of the mires on keratometry. Obvious signs of keratoconus become apparent at the slit lamp.

KEY POINTS: DIAGNOSIS OF KERATOCONUS

1. Topographic mapping of the anterior corneal surface.
2. Elevation analysis of the anterior and posterior corneal surfaces.
3. Slit lamp examination of the cornea.
4. Evaluation of the light reflex through a dilated pupil.

10. What are the topographic signs of keratoconus?

With conventional topography, the Placido rings of light are reflected off the cornea, and corneal curvature is derived from the distance between the rings and displayed as a color-coded map. Distortion of the rings is noted early on in the disease.

a. The characteristic sign of keratoconus on topography is inferior midperipheral steepening (Fig. 13-1). Numerous studies have tried to develop quantitative topographic parameters to define keratoconus. In one study, central corneal power >47.20 diopters (D) combined with steepening of the inferior cornea compared with the superior cornea of >1.20 D detected 98% of patients with keratoconus. However, it may be difficult to make a definitive diagnosis of keratoconus based on topographic findings alone. This is of particular importance in patients seeking refractive surgery because the results

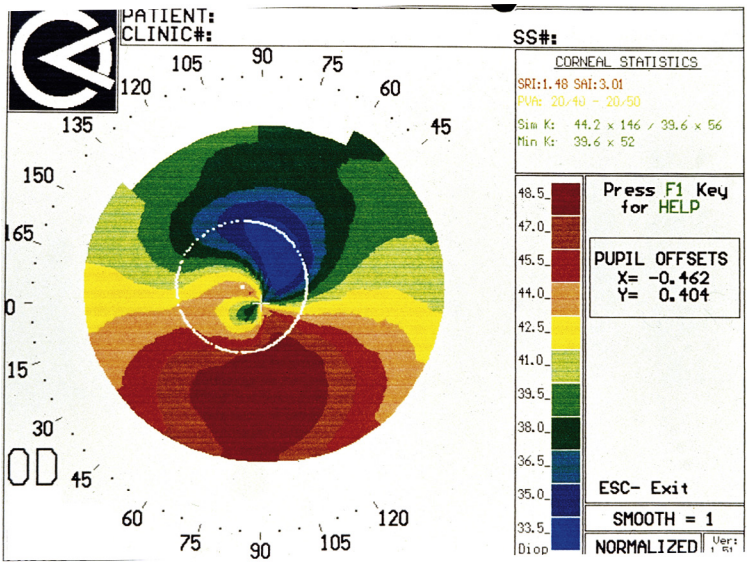

Figure 13-1. Map showing symmetric inferior steepening.

of the surgery are poorly predictable in patients with keratoconus. Patients with apparently normal corneas may have inferior midperipheral steepening >1.20 D but normal central corneal powers in the range of 43 to 45 D. It is difficult to know whether such patients represent a forme fruste of keratoconus and, as such, should be dissuaded from considering refractive surgery, especially LASIK because such surgery can result in cornea ectasia, in effort manifesting characteristic signs and symptoms of keratoconus. However, excimer laser photofractive keratectomy can be a viable option in select patients with borderline findings. Each case must be analyzed on an individual basis.

b. Corneal tomography units utilize scanning slit technology or a Scheimpflug-based imaging system to document corneal shape, corneal thickness measurements across the cornea, and elevation of the front and back corneal surfaces in relation to a computer-generated best-fit sphere. These instruments also present standard Placido disc color maps. The additional information, especially the corneal elevation and corneal thickness profile, is very helpful in differentiating between forme fruste or early keratoconus and nonkeratoconic corneas. Of particular note is when the thinnest area of the cornea corresponds with the area of minimal maximal elevation. Some of the units provide specialized diagnostic software to help with making the diagnosis of keratoconus. In addition, some tomography units, as well as some high-frequency ultrasound biomicroscopy machines, provide corneal epithelial thickness profiles that add to our diagnostic armamentarium. The corneal epithelium tends to be thinner over the area of corneal ectasia, which is usually decentered inferiorly with compensatory epithelial thickening centrally. However, no technology is 100% specific and 100% sensitive, requiring the surgeon's input, especially when evaluating patients presenting for refractive surgery.

11. What are the slit lamp findings of keratoconus?

The earliest slit lamp signs of keratoconus are apical thinning and steepening, usually located inferior to the center of the pupil. As the keratoconus progresses, the thinning and ectasia become more prominent with the development of apical scarring that begins in the anterior stroma and progresses into in the deeper layers of the stroma (Figs. 13-2 to 13-5). Fine linear striae become apparent in the deep stroma just anterior to the Descemet's membrane, usually oriented vertically or obliquely. They are thought to represent stress lines in the posterior stroma and are known as Vogt's striae. They can be made to disappear when the intraocular pressure is transiently raised by applying external pressure to the globe. In some mild cases of keratoconus, the pressure from rigid gas-permeable contact lens wear can induce the formation of such striae, which disappear

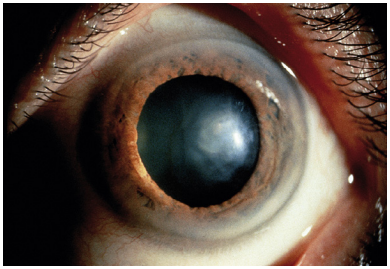

Figure 13-2. Apical scarring.

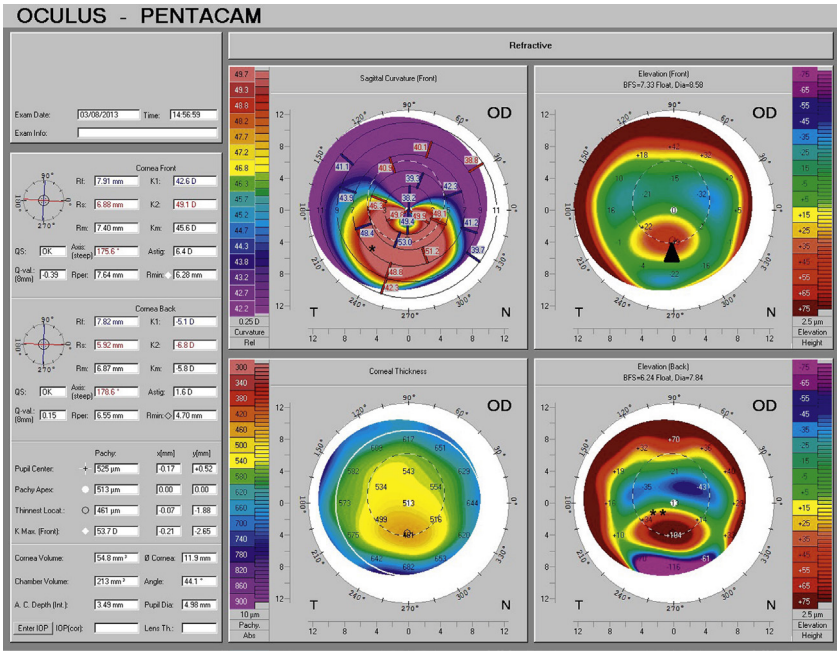

Figure 13-3. Scheimpflug-based tomography demonstrating a corneal curvature map (top left) with inferior steepening, anterior (top right) and posterior (bottom right) with inferocentral elevation posterior greater than anterior, and corneal thickness (bottom left) with thinnest area corresponding to the area of maximal elevation.

when the lens is removed. A Fleischer ring is commonly seen outlining the base of the cone. This is the result of hemosiderin pigment deposition within the deeper layers of the corneal epithelium. A Fleischer ring may only partially outline the cone but, as the ectasia progresses, tends to become a complete circle with more dense accumulation of pigmentation that is best appreciated while viewing with the cobalt blue filter on the slit lamp (Fig. 13-6). Subepithelial fibrillary lines in a concentric circular pattern have been described just inside the Fleischer ring. The source of these fibrils is unknown but has been postulated as epithelial nerve filaments. Anterior clear spaces thought to represent breaks in the Bowman's membrane are sometimes seen within the thin portion of the conical protrusion. Prominent corneal nerves are reportedly more common in keratoconic corneas. In the more advanced stages, when the eye is rotated downward, the corneal ectasia causes protrusion of the lower lid. This is known as Munson's sign.

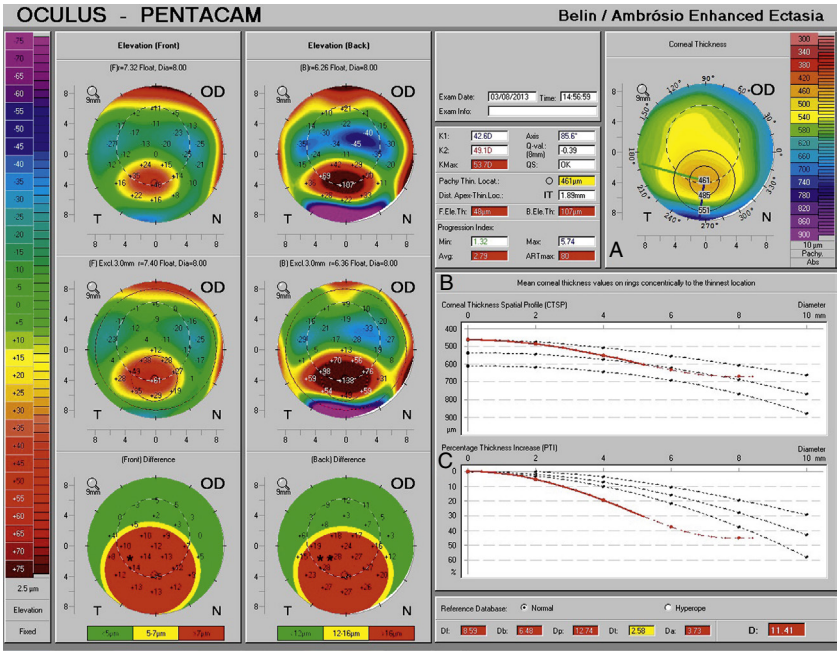

Figure 13-4. Belin/Ambrosio enhanced ectasia map demonstrating enhanced anterior and posterior elevation (bottom left two columns) as well as various corneal thickness profiles (right images **A, B,** and **C**) that further support the diagnosis of keratoconus.

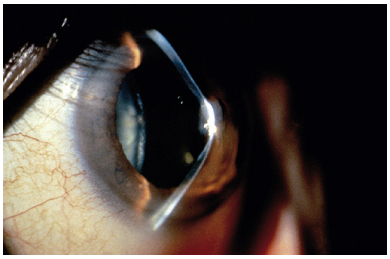

Figure 13-5. Apical thinning and scarring demonstrated in slit beam.

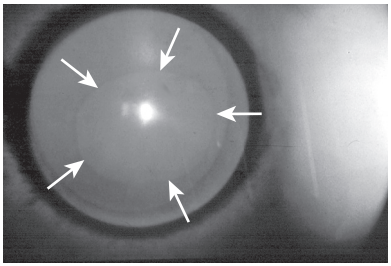

Figure 13-6. Cobalt blue illumination demonstrating Fleischer ring outlining the extent of the cone. *Arrows* point to margins of the ring.

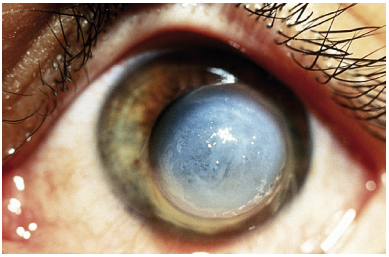

Figure 13-7. Acute hydrops.

12. How does keratoconus progress?

The onset of keratoconus characteristically occurs in the mid to late teens, progressing slowly for several years before stabilizing. However, delayed onset or late progression of keratoconus is not uncommon. As the disease progresses, the corneal thinning and epithelial ectasia become more prominent with increasing apical scarring. Two types of cones have been described: (1) a small round or nipple-shaped cone that tends to be more central in location and (2) an oval or sagging cone that is usually larger and displaced inferiorly, with the thinning extending close to the inferior limbus. Progression of keratoconus tends to manifest as increased thinning and protrusion, although enlargement of the cone also occurs with extension peripherally.

13. What is acute hydrops?

Acute hydrops (Fig. 13-7) occurs in the more advanced cases of keratoconus. Ruptures in the Descemet's membrane allow aqueous to enter into the corneal stroma, resulting in marked thickening and opacification of the cornea that are usually restricted to the cone. The involved stroma becomes massively thickened with large, fluid-filled clefts, overlying epithelial edema, and bulla formation. Rarely, a fistulous tract may develop through the cornea, with resultant leakage of aqueous from the anterior chamber through the fluid-filled stroma and epithelium onto the corneal surface. The corneal edema gradually resolves over weeks to months as endothelial cells adjacent to the rupture in the Descemet's membrane enlarge and migrate across the defect, laying down new Descemet's membrane. With healing, scarring tends to flatten the cornea, thereby facilitating the possibility of subsequent contact lens fitting with significant usual improvement as long as the scarring spares the visual axis. Some corneas with acute hydrops tend to develop stromal neovascularization that increases the potential risk of graft rejection if corneal transplantation ultimately becomes necessary. Acute hydrops is more common in patients with Down syndrome and vernal keratoconjunctivitis, presumably related to the repeated trauma of eye rubbing in these patients.

Most cases of acute hydrops resolve spontaneously, requiring supportive treatment with topical hyperosmotic agents such as 5% sodium chloride drops and/or ointment to promote corneal deturgescence. Some patients with acute hydrops complain of severe photophobia and benefit from the use of topical steroids and/or cycloplegic agents. In addition, topical steroids should be instituted in patients with signs of corneal neovascularization. Recent studies have reported quicker resolution of acute hydrops with injection of air or nonexpansile concentrations of SF_6 and C_3F_8 into the anterior chamber to promote closure of the rupture in Descemet's membrane. However, several injections are sometimes required and many surgeons feel the benefits do not outweigh the risks, such as cataract and pupillary block glaucoma. Once the hydrops has resolved, the resultant scarring tends to result in corneal flattening. The patient can then try to resume contact lens wear if the central cornea has not become excessively scarred. Otherwise, the only alternative is a corneal transplant.

14. What is the histopathology of keratoconus?

Most histopathologic studies of keratoconic corneas are performed on advanced cases that require lamella or penetrating keratoplasty. In addition, most patients were previous long-term contact lens wearers, which also may affect the histopathologic findings, as contact lens wearers may induce more apical scarring.

Changes have been described in every layer of the cornea. The stroma of the cone is thinner than the surrounding cornea. The apical epithelium tends to be flattened and thinned with scattered fragmentation and dehiscence of the epithelial basement membrane. Iron noted in the epithelial cells outlining the cone corresponds to the Fleischer ring.

Among the most characteristic histologic changes of keratoconus are breaks in Bowman's membrane that are sometimes filled in with epithelium and/or stromal collagen. Ultimately, the anterior corneal stroma may become replaced with irregularly arranged connective tissue.

The Descemet's membrane is normal unless acute hydrops has occurred. Depending on the stage of the reparative process, breaks in the Descemet's membrane with curled edges subsequently become covered by adjacent endothelial cells that slide over and lay down new membrane. The corneal endothelial cells tend to be normal, although they may exhibit increased pleomorphism and polymegathism.

15. How is keratoconus treated?

Mild cases of keratoconus can be successfully managed with spectacles. However, as the keratoconus progresses and the amount of irregular astigmatism increases, patients are unable to obtain satisfactory vision with spectacle correction. Contact lenses can then be used to neutralize the irregular astigmatism, thereby offering significant visual improvement over spectacles. As the cornea becomes more distorted, scarred, and ectatic, contact lens fitting becomes more difficult and vision deteriorates, ultimately necessitating surgical intervention.

16. What types of contact lenses are used to treat keratoconus?

Conventional spherical myopic soft contact lenses may be used successfully in mild cases of keratoconus with minimal manifest astigmatism. Toric soft contact lenses also may be used in some patients without excessive amounts of irregular astigmatism. The vast majority of patients with keratoconus are managed with rigid gas-permeable contact lenses. Fitting such lenses over a distorted ectatic cornea is difficult. Numerous lens designs are available for fitting patients with keratoconus, including varying diameters of spherical lenses, aspheric lenses, toric lenses, and lenses with multiple curvatures on the posterior surface, such as the Soper cone and Ross cone lenses. These last two have a steeper central curve to vault the apex of the cone and a flatter peripheral curve to align with the more normal peripheral cornea. Computed topography/tomography can be helpful in fitting these challenging patients.

Large gas-permeable scleral contact lenses that vault the cornea and are filled with a fluid reservoir that bathes the corneal surface are now being used more frequently in managing patients with prominent ectatic cones who cannot be fit with more conventional gas-permeable lenses. A piggyback system is another option available for treating patients with keratoconus: A gas-permeable contact lens is fitted on top of a soft contact lens. This system is a little more expensive and time-consuming for both practitioner and patient but can be helpful in managing select cases that have failed more conventional contact lens fitting. Another specialized lens design incorporates a rigid gas-permeable center with a soft peripheral skirt to reduce the edge awareness of conventional gas-permeable lenses. Such hybrid lenses may actually center better and offer a more stable fit by virtue of their large diameter, which extends beyond the limbus. However, they have a tendency to be tighter over time, sometimes causing corneal neovascularization and hypoxia.

17. Can keratoconus be prevented?

Developed in Germany, collagen crosslinking is a technique to prevent the progression of keratoconus. It involves saturating the corneal stroma with riboflavin drops and then applying ultraviolet light (UV-A) at a wavelength of 365 nm. The riboflavin serves as a photo-sensitizing agent that interacts with the UV-A, leading to crosslinking within collagen and the extracellular matrix of the corneal stroma, resulting in strengthening of the cornea. The riboflavin absorbs the UV-A in the anterior stroma sparing the endothelium of any adverse effects. The procedure is limited to corneas greater than 400 μm in thickness to avoid endothelial toxicity. Thinner corneas can be "thickened up" by using hypotonic riboflavin solution.

The procedure is used all around the world, except in the United States, where it is not yet FDA approved. It has been shown to stabilize the cornea and prevent progression. Numerous studies demonstrate the long-term safety and efficacy of the procedure. Although it must be stressed that the crosslinking prevents progression rather than treating the disease, some patients have been shown to gain 1 to 2 D of corneal flattening, associated with small improvement in visual acuity.

The traditional crosslinking technique requires removal of the corneal epithelium to allow the riboflavin better access to the corneal stroma. Removing the epithelium carries with it the risk of infection as well as stromal haze that usually resolves spontaneously. Several investigators have been studying "epi on" techniques by modifying the riboflavin solution and/or the corneal epithelium to promote transepithelial transport of the riboflavin, eliminating the need for epithelial debridement. To date, the "epi on" technique does not seem to be as efficacious as "epi off." Not only does the transepithelial absorption of riboflavin have to be worked out, there is also the issue of the corneal epithelium blocking UV-A from getting through into the stroma to exert its effect. However, "epi on" is certainly a much simpler procedure with little or no discomfort and little or no risk of infection.

Investigators are also studying the benefits of combining collagen crosslinking with intracorneal ring segments, topographic guided excimer laser surface ablation, and conductive keratoplasty.

18. What are the surgical options for treating keratoconus?

Surgical intervention is reserved for patients with keratoconus who cannot be successfully fit with contact lenses or who fail to obtain satisfactory vision with contact lenses. Atopic patients with keratoconus tend to require surgery much more frequently than nonallergic patients because the allergic diathesis tends to interfere with contact lens tolerance.

- **Penetrating keratoplasty (full-thickness corneal transplantation)** is the most common surgical technique used to rehabilitate patients with keratoconus. The surgical procedure requires excision of the entire cone, frequently determined by the outline of the Fleischer ring using a manual trephine or femtosecond laser. The donor tissue is cut the same size or slightly larger to obtain good wound apposition with sutures, most commonly 10-0 nylon, utilizing various interrupted running or combined suturing techniques. If the cone extends close to the limbus (usually inferiorly), a large corneal graft is needed. Usually the grafted tissue is centered on the pupil, but when the cone is eccentric, an eccentric graft is used to encompass the entire cone, taking care to leave the optical zone free of sutures. Increasing graft size with proximity to the limbal blood vessel reduces the "immune privilege" of the usually avascular cornea, thereby increasing the risk of immunologic reaction.
- **Lamellar (partial thickness) keratoplasty** has become increasingly popular for the treatment of keratoconus. A lamellar graft has the advantage of being an extraocular procedure that avoids the risk of intraoperative positive pressure wherein intraocular contents can be expelled through the trephined opening in the cornea made during penetrating keratoplasty. It also eliminates the risk of endothelial rejection while increasing the donor pool because it does not require a healthy corneal donor endothelium, which is discarded at the time of surgery.

A lamellar procedure is more demanding technically than a full-thickness procedure. It involves replacing as much of the corneal stroma as possible while leaving behind the patient's own endothelial layer and Descemet's membrane. The resultant visual acuity is similar to that from a penetrating keratoplasty when no stroma is left behind. This is best accomplished in deep anterior lamellar keratoplasty (DALK) with the Anwar "Big Bubble" technique. Air is used to cleanly separate Descemet's membrane from the overlying stroma. When some recipient stoma remains during manual lamellar dissection, the resultant interface usually causes some degradation of the usual image, which can limit the visual recovery.

- **Intracorneal rings** are polymethylmethacrylate ring segments of varying thickness and configuration inserted into the midperipheral corneal stroma. They are useful in treating mild keratoconus in patients who are contact lens intolerant. The therapeutic rationale is to support the ectatic area of the cornea, thereby reducing corneal steepening and regularizing the astigmatism associated with keratoconus, with improvement in both uncorrected and best spectacle-corrected visual acuity. However, they do not slow or prevent progression of corneal ectasia. In the United States, Intacs (Addition Technology) are the only ring segments that are FDA approved.
- **Epikeratophakia** is a type of onlay lamellar procedure using a freeze-dried donor cornea that is sewn on top of a deepithelialized host cornea. The purpose is to flatten the cornea with the hope of offering improved spectacle-corrected visual acuity and/or better contact lens fitting. After initial enthusiasm in the late 1980s, the procedure has been abandoned by most surgeons because of complications and poor visual results. However, in select cases in which a full-thickness corneal transplant is contraindicated, such as patients with Down syndrome who may aggressively rub their eyes and dehisce a full-thickness wound or patients at high risk for immune rejection (e.g., multiple graft failures in the other eye), lamellar grafts or epikeratophakia are worthy of consideration.
- **Thermokeratoplasty** is a technique in which heating the cornea from 90° C to 120° C causes shrinkage of corneal collagen fibers with resulting flattening of the cornea. This procedure has been abandoned for the most part because of unpredictable results, induced scarring, and the potential for recurrent corneal erosions because of damage to the epithelial basement membrane complex. However, when the apex of the cone spares the visual axis, thermokeratoplasty may be used to flatten the cornea, thereby allowing more favorable spectacle-corrected visual acuity and/or contact lens fitting. In addition, thermokeratoplasty may be helpful in promoting resolution of acute hydrops.

Additionally, some patients with keratoconus develop an elevated subepithelial scar at the apex of the cone as the result of chronic apical irritation from contact lens wear. Corneal epithelial breakdown may develop over the scar, thereby interfering with contact lens wear. These scars can be removed or smoothed out manually with a blade or with the excimer laser, thereby allowing resumption of contact lens wear and sparing the patient an otherwise needed corneal transplant.

19. What are the results of corneal transplant in patients with keratoconus?

As mentioned previously, most corneal transplantation surgery for keratoconus involves penetrating keratoplasty, although DALK is increasing in popularity. The results of such surgery are excellent, with clear grafts in approximately 90% of patients, most of whom obtain best corrected visual acuity of 20/40 or better. The most frequent problem arising in patients with keratoconus who undergo corneal transplantation is high postkeratoplasty astigmatism. However, the astigmatism following corneal transplant surgery tends to be much more regular than the irregular astigmatism of the original disorder. This difference allows most patients to achieve satisfactory visual results with spectacle correction, even if they have a large amount of astigmatism that most patients without keratoconus would not be able to tolerate in spectacles. If the astigmatism cannot be tolerated in spectacles, contact lens wear or refractive surgery (excimer laser ablation or incisional keratotomy) can be offered. Because keratoconus tends to be asymmetric, many patients undergoing corneal transplantation in one eye manage with a contact lens in the lesser involved eye and thus prefer to wear a contact lens in the operated eye as well. The contact lens tends to neutralize most of the astigmatism in the corneal transplant and frequently offers a little better vision than spectacles especially if there is some degree of irregularity in the astigmatism.

It usually takes up to a full year or more for the corneal transplant wound to heal. If the patient is seeing well with the sutures in place, the sutures are left undisturbed and tend to disintegrate spontaneously over a few years. Sometimes disintegrating sutures erode through the corneal epithelium and cause a foreign body sensation. If they are not removed from the surface of the cornea, they can cause secondary infection. After sutures disintegrate and/or are removed, a significant change in the refractive error may occur. All graft sutures should have disintegrated or have been removed before keratorefractive surgery is contemplated postcorneal transplantation.

Graft rejection occurs in approximately 20% of patients with keratoconus who undergo penetrating keratoplasty. Most immune rejections can be reversed with appropriate local steroid therapy if caught early. Irreversible rejection leads to permanent corneal clouding that requires repeat penetrating keratoplasty. A repeat graft has a reasonably good prognosis, although the success rate is lower than the primary graft and tends to diminish with each successive transplant. If multiple graft failures occur an "artificial cornea," i.e., keratoprosthesis, can always be considered.

WEBSITE

National Keratoconus Foundation
www.NKCF.org

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CHAPTER 14

REFRACTIVE SURGERY

Sebastian P. Lesniak and Brandon D. Ayres

1. What are the refractive components of the eye?

The cornea and the lens refract incident light so that it is focused on the fovea, the center of the retina. The cornea contributes approximately 44 diopters (D) compared with only 18 D from the lens. In addition, the anterior chamber depth and axial length of the eye contribute to the refractive status.

2. What are the various types of refractive errors?

- **Myopia,** or nearsightedness, exists when the refractive elements of the eye place the image in front of the retina.
- **Hyperopia,** or farsightedness, exists when the image is focused behind the retina.
- **Astigmatism** usually refers to corneal irregularity that requires unequal power in different meridians to place a single image on the fovea. Lenticular astigmatism (due to the lens) is less common than corneal astigmatism.
- **Presbyopia** is the natural impairment in accommodation often noted around age 40 years. The power of the corrective "add" or bifocal segment to combat presbyopia increases with age.

3. How is myopia related to age?

Myopia is common among premature infants, less common in full-term infants, and uncommon at 6 months of age, when mild hyperopia is the rule. Myopia becomes most prevalent in adolescence (approximately 25%), peaking by 20 years of age and subsequently leveling off. This information is important for determining the appropriate age to consider refractive surgery.

4. What are the goals of refractive surgery?

Goals vary for each patient. Certain patients desire refractive surgery because of professional or lifestyle issues; examples include athletes and police, fire, and military personnel, who may find glasses or contact lenses hindering or even dangerous. Other patients, such as high myopes, may find spectacle correction inadequate because of image minification or may be intolerant of contact lenses. In general, the goals of refractive surgery are to reduce or eliminate the need for glasses or contact lenses without altering the quality of vision or best-corrected vision.

5. What features characterize a good candidate for refractive surgery? Are there any contraindications?

First, patients considering refractive surgery should be at least 18 to 21 years of age with a stable refraction. Patients with certain ocular conditions (such as severe dry eye or uveitis) or particular systemic diseases (such as autoimmune collagen vascular disease or uncontrolled diabetes) and patients taking medications that impair wound healing are poor candidates. Keratoconus, a condition in which the cornea is irregularly cone-shaped, remains a contraindication for refractive surgery because results are unpredictable. Analysis of corneal curvature with computerized corneal topography should be performed on all patients before surgery because early keratoconus has a prevalence of up to 13% in this population and may be missed by other diagnostic methods.

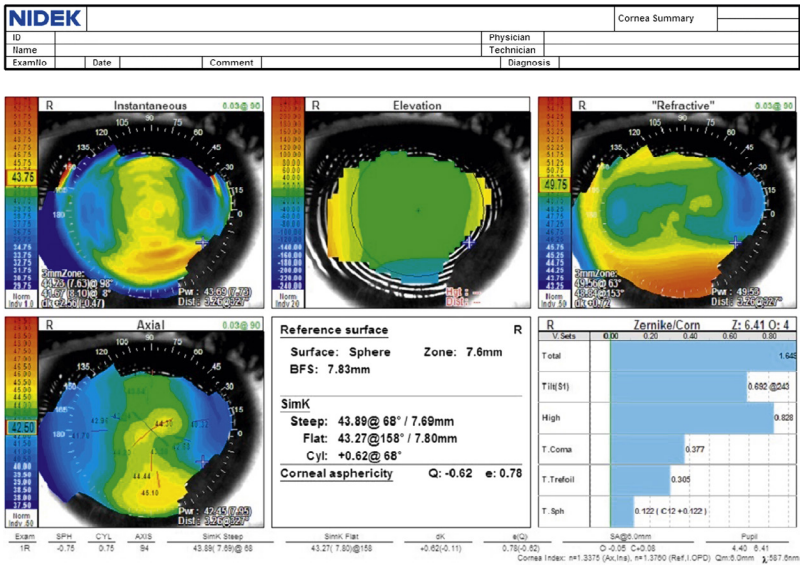
Second, patients' motivations and expectations should be explored thoroughly so that unrealistic hopes may be discovered preoperatively. For example, the patient who is constantly cleaning his or her glasses because of "excruciating glare" from dust on the lenses or who desires perfect uncorrected vision is not a good candidate for refractive surgery. A careful discussion of the risks and benefits of surgery is particularly important. Patients may want to try contact lenses before considering surgery. The concept of presbyopia must also be explained; many patients are prepresbyopic and have no understanding that achieving excellent uncorrected vision at distance will require correction for reading at near within a few years.

6. How is corneal topography used in the evaluation of patients undergoing refractive surgery?

Corneal topography is extremely useful for evaluating patients undergoing refractive surgery because it generates precise images of corneal curvature that correspond to a large area of the cornea. This

information aids in presurgical planning and postsurgical evaluation. Placido disc-based systems detect reflected images of rings projected onto the cornea. A computer generates a topographic "map" of corneal curvature based on the measured distance between the rings reflected from the cornea (Fig. 14-1, *A* and *B*). Optical coherence tomography systems provide high-resolution cross-sectional images of the cornea and are based on the reflection of infrared wavelengths from biological tissues. Scheimpflug-based systems use slit beams and a rotating camera, which maps sections of the cornea (Fig. 14-2). These systems allow for anterior and posterior corneal topography measurement and can also estimate corneal thickness.

Subtle corneal abnormalities, such as early keratoconus (forme fruste) or contact lens-induced corneal warpage, may be detected only by topography. The Oculus Pentacam Scheimpflug system provides the Belin/Ambrósio enhanced ectasia display, which aides in screening of keratoconus and corneal ectasia (Fig. 14-3). In addition, postoperative and preoperative topographic maps may be analyzed to generate "difference" maps that isolate the procedure-induced changes. Computerized corneal topography is also extremely useful for determining the cause of imperfect vision after refractive surgery commonly due to irregular astigmatism.



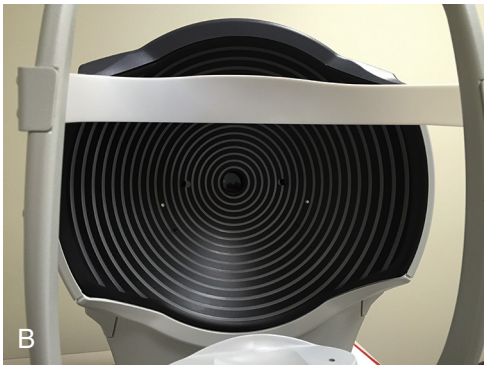


Figure 14-1. A, Corneal diagnostic summary in a post-LASIK patient. **B,** The Nidek OPD Scan III Placido-based corneal analyzer.

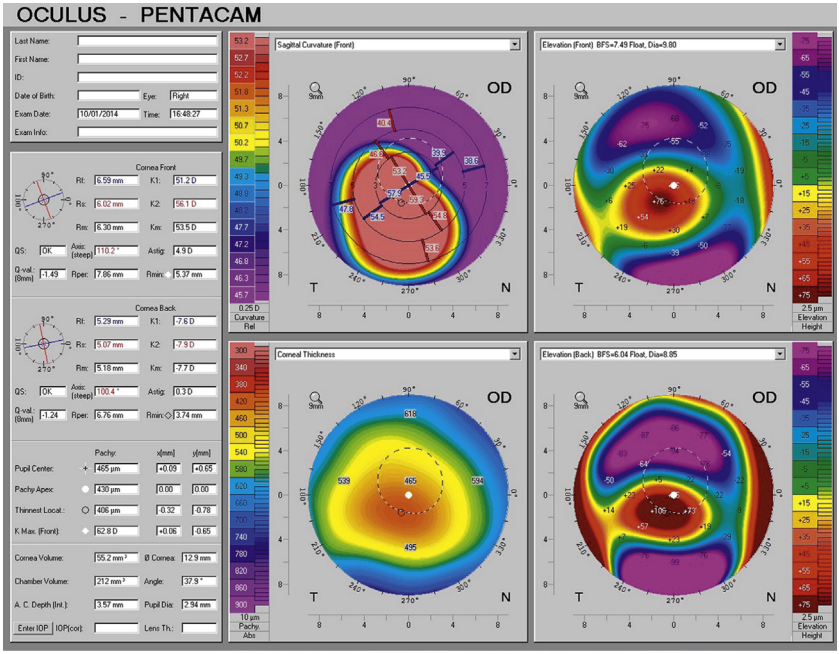


Figure 14-2. Scheimpflug-based corneal topography with corneal changes typically seen in keratoconus.

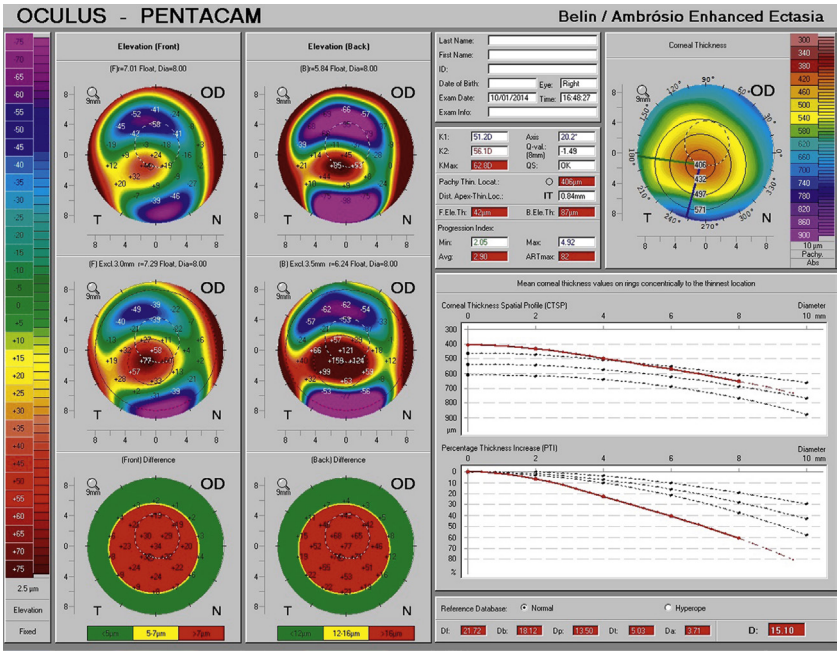


Figure 14-3. Scheimpflug-based corneal topography with Belin/Ambrósio enhanced ectasia display.

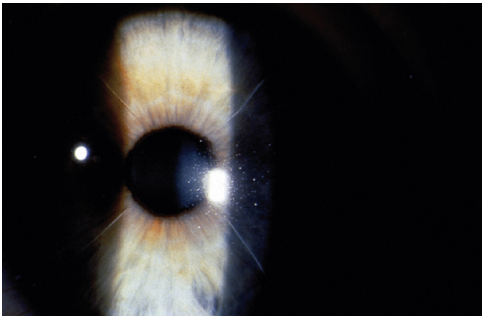


Figure 14-4. Three weeks after four-incision radial keratotomy.

7. What are the major options for the surgical treatment of myopia?

- Radial keratotomy (RK)
- Photorefractive keratectomy (PRK)
- Laser-assisted in situ keratomileusis (LASIK)
- Intracorneal ring segments (Intacs)
- Phakic intraocular lens (IOL) implants
- Clear lens extraction

8. How does RK reduce myopia?

Radial keratotomy is a historical method for treatment of myopia and now has largely been replaced by excimer laser procedures. Deep radial incisions cause steepening of the cornea peripherally, which results in secondary flattening of the central cornea. The number, length, and depth of incisions and the size of the clear, central optical zone along with the patient's age determine the refractive effect. Typically, four incisions are used for low myopia (Fig. 14-4) and eight incisions for moderate myopia. However, some patients had as many as 32 incisions for high myopia.[1,2]

9. What are the various RK techniques?

- The "American" technique involves making centrifugal incisions (from the center toward the limbus) with an angled diamond knife blade.
- The "Russian" technique uses centripetal incisions (from the limbus toward the center) with a straight vertical diamond knife blade. The Russian technique gives deeper incisions and more refractive effect; however, there is greater danger of entering the optical zone.

Based on statistical analysis of previous cases, standardized nomograms are used to determine the number of incisions and optical zone size, depending on the patient's age and desired refractive change.

10. What results have been achieved with RK? What about complications?

Several major investigations have been performed, the most important of which is the Prospective Evaluation of Radial Keratotomy study. This study showed that 60% of treated eyes were within 1 D of emmetropia up to 10 years postoperatively. After 10 years, 53% had at least 20/20 uncorrected vision, and 85% had at least 20/40 vision. However, 43% of eyes had a progressive shift toward hyperopia of at least 1 D after 10 years. This shift was noted to be worse for eyes with the smaller optical zone of 3 mm. Only 3% of patients lost two or more lines of best-corrected visual acuity, and all had 20/30 vision or better. Three of more than 400 patients complained of severe glare or starburst that made night driving impossible. Corneal perforations occurred in 2% of cases; none required a suture for closure. Overall, the best results were achieved in the low-myopia group (−2.00 to −3.00 D). As with any invasive procedure, infection is a small but real risk (Fig. 14-5).[3]

11. How does PRK reduce myopia?

PRK involves direct laser treatment of the central corneal stroma. Specifically, the "excited dimer" (excimer) 193-nm UV laser causes flattening of the central cornea through a photoablative/photodecomposition process whereby more tissue is removed centrally than peripherally. Under topical anesthesia, the central corneal epithelium is removed either with a spatula or with the laser. The laser is then used to ablate a precise quantity of stromal tissue with submicrometer accuracy to achieve the

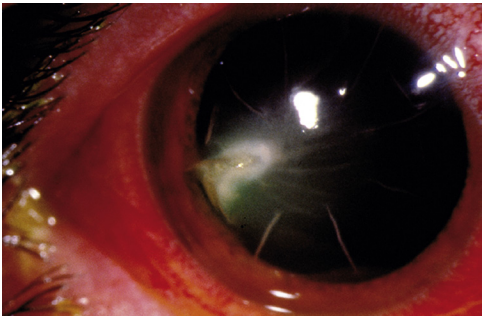


Figure 14-5. Infection at radial keratotomy incision.

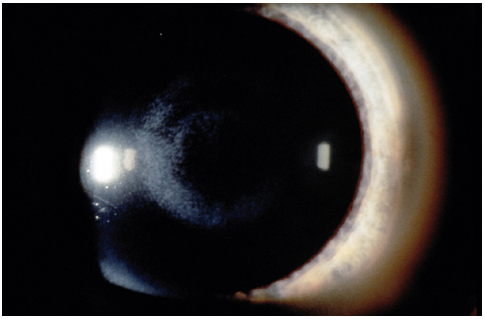


Figure 14-6. Mild stromal haze, 3 months after photorefractive keratectomy.

desired refractive effect. PRK is preferred over LASIK in cases of irregular astigmatism, thin corneas, epithelial basement membrane disease, prior corneal surgery, or LASIK complications. In some cases if the LASIK flap cannot be created safely, the procedure may be converted to PRK.

12. What results have been achieved with PRK? What about complications?

A randomized 20-year prospective clinical trial of PRK found the following:

- Slight but significant increase in myopia (0.54 D) after PRK between 1 and 20 years, particularly in those under 40 at the time of treatment and in female patients.
- Corneal power remained unchanged, but axial length increased.
- The procedure was safe, with no long-term sight-threatening complications and with improvements in corrected distance visual acuity and corneal transparency with time.

Residual corneal haze is a known complication of PRK (Figs. 14-6 and 14-7).[4]

13. What is LASIK?

LASIK stands for laser-assisted in situ keratomileusis. The procedure involves creating a corneal flap to ablate midstromal tissue directly with an excimer laser beam, ultimately flattening the cornea to treat myopia and steepening the cornea to treat hyperopia. Whereas earlier techniques of keratomileusis consisted of removing a corneal cap and resecting stromal tissue manually, technological advancements have revolutionized this procedure into a highly automated process. Contemporary techniques use a femtosecond laser for flap creation and an excimer laser for tissue ablation. After a lid speculum is placed and topical anesthetic is applied, the suction ring is centered on the cornea to stabilize the eye. Historically a mechanical microkeratome blade was used to create the corneal flap, but currently most surgeons have switched to femtosecond laser for creating the LASIK flap. After the flap is created, the vacuum on the ring is released, and the flap is

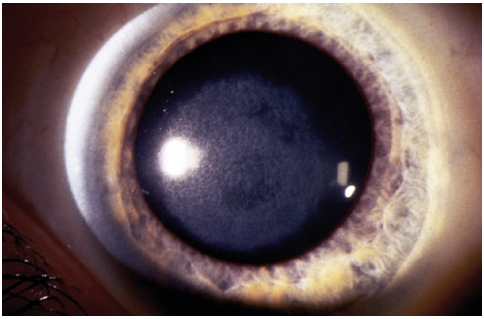


Figure 14-7. Moderate-to-severe stromal haze, 6 months after photorefractive keratectomy.

then lifted, exposing the bare stromal bed. Next, the excimer laser is applied directly to the stromal tissue. Afterward, the corneal flap is replaced to its original position, typically without sutures, and allowed to heal.

14. How has the use of the femtosecond laser in the LASIK procedure helped to improve results versus the microkeratome?

A meta-analysis of multiple studies found that:

- No significant differences were identified between the two groups in regard to a loss of two or more lines of vision or to patients achieving 20/20 vision or better ($P = 0.24$)
- The femtosecond group had more patients who were within ±0.50 D of target refraction
- Flap thickness was more predictable in the femtosecond group
- The microkeratome group had more epithelial defects
- The femtosecond group had more cases of diffuse lamellar keratitis[5]

15. What is the range of myopia recommended for correction with LASIK?

LASIK is generally recommended for myopia as low as 1 D and as high as 10 to 12 D, although it is FDA approved for myopia up to 14 D.

16. What are the advantages and disadvantages of LASIK versus RK and PRK?

LASIK offers the advantage of minimal postoperative pain as well as earlier recovery of vision because the epithelium is left essentially intact. There is less chance of corneal scarring and haze than after RK and PRK. The disadvantages of LASIK include the brief intraoperative period of marked visual loss (due to high intraocular pressures generated by the suction ring); the risk of flap irregularities, subluxation, or dislocation (Fig. 14-5); and the expense of the procedure. Additional problems associated with LASIK include irregular astigmatism and the potential for epithelial ingrowth or infection under the flap.

LASIK offers several advantages to the surgeon. Because the technique involves making a flap in the anterior corneal stroma, the risk of corneal perforation associated with RK is virtually nonexistent. The creation of a uniform smooth flap with preservation of the central Bowman's layer also reduces the subepithelial scarring seen with PRK. The use of the femtosecond laser allows little room for surgeon error. However, its automated aspect also poses disadvantages. The surgeon has limited intraoperative control over creation of the flap and ablation of the stroma. The vacuum ring can be difficult to place on a patient with narrow palpebral fissures or deep orbits. Femtosecond-created flaps can be difficult to lift and tears in the flap can be created. On occasion gas could cause perforation in the flap (vertical gas breakthrough).

17. How do the surgical results of LASIK compare with those of PRK?

Several studies have compared the results of LASIK and PRK in both low-to-moderate and moderate-to-high myopia. Overall, the refractive and visual results are comparable after the first 1 to 3 months. LASIK allows faster visual recovery. Pop and Payette compared the results of LASIK and PRK for the treatment of myopia between −1 and −9 D. They concluded that visual and refractive outcomes were similar at follow-up visits between 1 and 12 months, but LASIK patients were more likely to experience halos. In general, when refractive subgroups are analyzed, less predictable results are

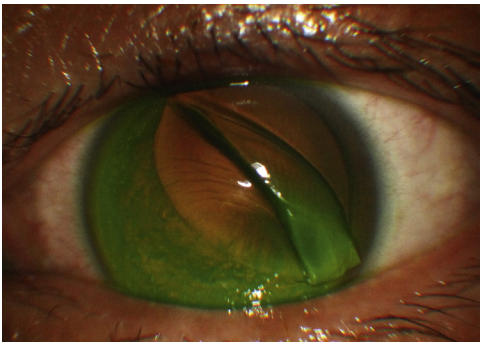


Figure 14-8. Dislocated LASIK flap.

achieved in the higher myopia groups for both procedures. Nevertheless, LASIK may be the best corneal technique available for treating higher degrees of myopia.[6]

18. What is "wavefront?" Are wavefront ablations any better than standard LASIK?

In standard LASIK the spherical and cylindrical aberrations are measured using computerized corneal topography and manifest and cycloplegic refraction. The excimer laser is then programmed based on these data. A wavefront measurement has the ability to measure many more aberrations than just sphere and cylinder. To measure a wavefront an aberrometer shines low-intensity laser light through the pupil. The laser light is then reflected off the retina and through the lens, pupil, and cornea and is distorted by the refractive properties of the eye. This wavefront of light is then used to detect an infinite number of ocular aberrations (evaluated, for example, by Zernike polynomials or Fournier analysis).

In a wavefront ablation the data collected by the aberrometer are converted into a sphere and cylindrical equivalent (usually with room for physician adjustment) and the customized ablation is carried out. Although the hope for wavefront-guided LASIK and PRK is high, there is no significant clinical evidence that it is better than carefully planned standard LASIK. Some studies have shown a reduction in higher order aberrations after wavefront-guided ablations, while others have shown an increase. As surgical techniques and technology improve, perhaps the clinical results of wavefront LASIK will begin to outshine standard LASIK.

19. Name the important potential complications of LASIK.

Complications are uncommon and are not listed in order of frequency:

- Premature release of suction ring
- Intraoperative flap amputation (microkeratome)
- Postoperative flap dislocation/subluxation (may require suturing of flap into place) (Fig. 14-8)
- Epithelialization of flap-bed interface (causes irregular astigmatism, light scattering, and possibly flap damage) (Fig. 14-9)
- Irregular astigmatism
- Infection
- Diffuse lamellar keratitis (DLK)
- Progressive corneal ectasia[7]

KEY POINTS: COMMON POTENTIAL CONTRAINDICATIONS TO LASIK

1. Thin cornea.
2. Irregular astigmatism.
3. Keratoconus.
4. Anterior basement membrane dystrophy.
5. Herpes simplex or zoster keratitis.

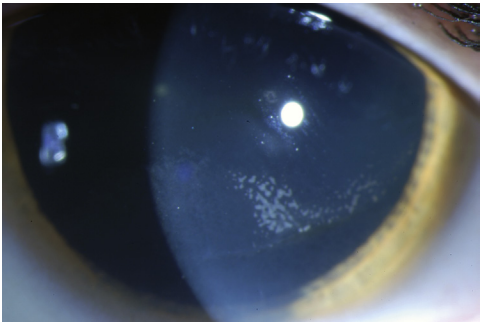


Figure 14-9. Epithelial ingrowth under the LASIK flap.

20. What is diffuse lamellar keratitis? How is it treated?

DLK was originally termed "sands of the Sahara syndrome" because of the clinical appearance of a wavy inflammatory reaction in a LASIK flap interface. It generally appears 1 to 3 days after a primary LASIK procedure or an enhancement. The exact cause is unknown and is most likely multifactorial. Suspected etiologies include bacterial endotoxins, meibomian secretions, oils from the microkeratome, and excessive laser energy from the IntraLase femtosecond laser. Treatment involves high-dose topical steroids. In severe cases, lifting the flap and irrigating the interface may be helpful.[8]

21. What is Epi-LASIK? What are the potential advantages?

Epi-LASIK is a modified surface ablation, which uses a keratome and an epithelial separator that creates a plane between the epithelial basement membrane and the Bowman's membrane. As the "epitheliatome" passes over the eye it creates an epithelial flap on a hinge, very similar to a LASIK flap. The epithelial flap is then reflected, exposing the surface of the Bowman's membrane. The excimer laser is then used to alter the shape of the cornea, after which the epithelial flap is repositioned. The advantage of Epi-LASIK is the safety of a surface procedure but with potentially faster visual recovery, less postoperative discomfort, and less haze than PRK. Epi-LASIK has largely been abandoned in favor of LASIK, or the flap is removed entirely as in PRK.

22. What is the femtosecond laser? What are its potential advantages?

Current femtosecond laser technology systems use neodymium:glass 1053-nm (near-infrared) wavelength light. Laser energy is converted into mechanical energy in a process known as photodisruption. The femtosecond laser uses ultrafast pulses of energy to ablate tissue with extreme precision. The ultrashort pulses prevent heat buildup, thus allowing minimal to no damage to surrounding tissues. In refractive surgery this laser is used to cut a lamellar flap in the cornea. The potential advantages of using the femtosecond laser include greater safety, reproducibility of flap thickness, decreased flap complications, and decreased epithelial defects. Flap striae and interface deposits may also be reduced. Currently available femtosecond lasers for LASIK flap creation include the IntraLase FS and iFS laser systems from Abbott and Femto LDV systems from Ziemer.

In cataract surgery, the femtosecond laser creates a very precise capsulotomy and fragments the lens nucleus. These features may reduce surgical risks associated with traumatic cataracts, zonular instability, and pseudoexfoliation. Primary and secondary corneal cataract incisions can also be created more precisely by the laser. Arcuate incisions that reduce astigmatism can also be created during cataract surgery, taking into account surgically induced astigmatism from cataract incisions. Many of the femtosecond lasers that are used in cataract surgery can also be used to create LASIK flaps.[9-12]

23. What is progressive corneal ectasia?

Corneal ectasia is progressive corneal thinning and steepening with irregular astigmatism that causes poor vision. It is thought to result mainly in eyes with forme fruste keratoconus or from a stromal bed that is too thin after LASIK. Most surgeons believe that the stromal bed (calculated by taking the central corneal thickness minus the flap thickness minus the laser ablation) should be at least 250 μm to prevent corneal ectasia. However, other surgeons believe that the minimal stromal bed thickness

should be greater. Long-term follow-up is required to determine the answer. Corneal collagen cross-linking is a treatment option for corneal ectasia, but it is not yet FDA approved.

24. What are intracorneal ring segments?

Intacs are an FDA-approved procedure for the correction of low myopia and mild to moderate keratoconus. This procedure involves the placement of two 150-degree arc segments of polymethylmethacrylate plastic at two-thirds depth in the peripheral cornea. This "tissue addition" results in flattening of the central cornea.[13]

25. How much myopia do Intacs treat?

Intacs are FDA-approved to treat between −1 and −3 D of nearsightedness in patients with no more than 1 D of astigmatism and who are at least 21 years of age.

26. What are the refractive results of Intacs for myopia?

In U.S. clinical trials at 1 year, 97% of patients had 20/40 vision or better, 74% had 20/20 vision or better, and 53% had 20/16 vision or better without correction.

27. List the potential complications of Intacs.

Complications are not common and are not listed in order of frequency.

- Induced astigmatism
- Fluctuating vision
- Anterior or posterior perforation of the cornea
- Infection
- White deposits along the ring segment
- Extrusion of the ring segment

28. Is the Intacs procedure reversible?

The Intacs can be removed, and most eyes return to their original refractions.

29. What are phakic intraocular lens implants?

These lens implants are placed in the eye without the removal of the patient's own crystalline lens. There are currently three main types: an anterior chamber lens clipped to the iris, an angle-supported anterior chamber lens, and a posterior chamber lens in the ciliary sulcus (just in front of the crystalline lens). The Artisan or Verisyse iris-clip anterior chamber lens is currently FDA approved for −5 to −20 D of myopia with up to 2.5 D of astigmatism. The Visian implantable collamer lens (ICL) implant (Fig. 14-10) sits in the posterior chamber behind the pupil and is approved for −3 to −20 D of myopia. The toric version of this lens is available outside the United States and can be used to correct up to 6.0 D of astigmatism.[14,15]

30. What is the effect of the Verisyse phakic IOL implant on endothelial cell count?

The FDA found no significant loss in endothelial cell counts with the Verisyse iris-claw phakic IOL at 2 years after implantation. In a worst case scenario (by adjusting for measurement inaccuracy), 9% of eyes would have been at risk for 10% loss of endothelial cells at 12 months. Eyes at risk were found to have higher preoperative endothelial cell counts. Several authors have reported that the iris-claw lenses do accelerate endothelial cell loss.[16,17]

31. What are accommodative and multifocal IOLs?

As opposed to the more common single-vision IOLs implanted after cataract surgery, which leave the eye with very little ability to focus, the accommodative IOLs allow the eye to move the implant by various mechanisms to allow a greater range of focus. The only FDA-approved accommodative IOL as of this writing is the Crystalens by Bausch + Lomb. The optic of the Crystalens is on hinges that allow for vitreous pressure to move the IOL anteriorly and posteriorly. This movement changes the refractive power of the IOL and allows patients greater reading ability. In the FDA 1-year trial, 98% of patients with bilateral implants were 20/25 at distance, 96% could read 20/20 at arm's length, and 73% could read at near without any assistance from glasses or contact lenses.

Multifocal IOLs simultaneously focus near and distance light. The ReSTOR lens has apodized diffractive changes on the lens surface. The Tecnis lens has its diffractive steps on the posterior surface.

32. Are there any other surgical options for the treatment of myopia or presbyopia?

Because the crystalline lens adds about 18 D of power to the optical system, clear lens extraction may be used in patients with a comparable level of myopia. However, performing intraocular surgery for a purely refractive goal is controversial. In addition, highly myopic eyes carry a moderate risk of retinal detachment, which is increased after lens extraction.

Figure 14-10. Visian ICL implant.

The SMILE procedure developed by Zeiss utilizes the VisuMax femtosecond laser to create a thin disc of tissue (lenticule) inside the corneal stroma, which is then extracted through a small incision. Unlike LASIK, this procedure does not require a flap. It is intended for treatment of myopia up to −10.00 D. This procedure is not yet FDA approved in the United States.

Kamra and Raindrop are corneal inlays that offer surgical options for presbyopia. The Kamra inlay (Fig. 14-11) works on the same principle as a camera aperture by increasing the depth of focus. The opening in the inlay allows only focused light into the eye, allowing one to see near, far, and everything in-between. The Raindrop inlay (Fig. 14-12) is designed to gently reshape the anterior cornea, providing near and intermediate vision in the nondominant eye. At this time neither the Kamra nor the Raindrop is FDA approved in the United States.

33. What are the treatment options for astigmatism?

The correction of astigmatism is slightly more forgiving than the correction of myopia. A patient with 3.00 D of astigmatism is usually quite pleased with a postoperative residual of 1.25 D of cylinder correction because reasonably good vision results. Each of the procedures for myopia has adaptations to address astigmatism alone or simultaneously with myopia. Astigmatic keratotomy refers to making transverse (straight) or arcuate astigmatic cuts in the midperiphery of the steep corneal meridian. We have learned that crossing of transverse and radial incisions is problematic. Epithelial ingrowth into the stroma, healing difficulties, and significant scarring may result. Excimer laser photo-astigmatic refractive keratotomy uses a cylindrical ablation pattern rather than spherical ablation to remove tissue in a chosen meridian (astigmatic correction). If compound myopic astigmatism is present, a combination of spherical and cylindrical patterns results in correction of both myopia and astigmatism. Similar astigmatic corrections have been achieved with LASIK. Whichever procedure is employed, the axis of the astigmatism should be marked with the patient seated, because it may shift when the patient reclines. Corneal

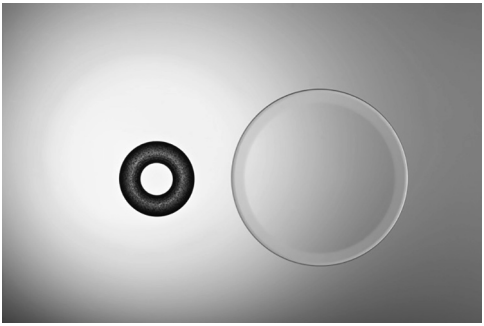


Figure 14-11. Kamra corneal inlay.

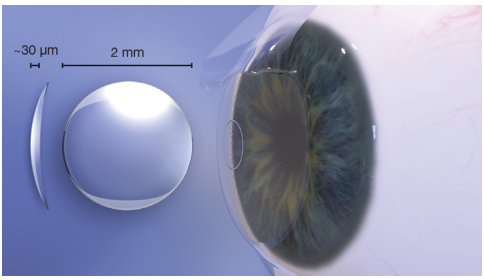


Figure 14-12. Raindrop corneal inlay.

astigmatism can also be addressed during cataract surgery with a toric intraocular lens implanted after crystalline lens extraction.

34. What can be done about astigmatism after a corneal transplant?

There are several options. First, selective removal of sutures in steep meridians may improve astigmatism. A rigid gas-permeable contact lens may be especially effective in alleviating irregular astigmatism. However, many patients do not tolerate or desire contact lenses after corneal transplant surgery. Once all sutures are out and the refraction is stable, arcuate relaxing incisions may be performed in the donor cornea along the steep meridian to reduce astigmatism. An alternative technique involves using a blade to open the wound partially and relax several clock hours of the graft–host junction as opposed to creating incisions in the donor tissue. The femtosecond laser can also be used to create arcuate keratotomy incisions. As described above, the excimer laser also has been used to correct post-corneal transplant astigmatism. Relaxing incisions combined with compression sutures (across the graft–host interface) have been used successfully to correct astigmatism of 5 to 10 D by causing steepening of the cornea in the sutured median (Fig. 14-13). For astigmatism greater than 10 D, a wedge resection (of corneal tissue followed by sutured closure of the wound) may be performed in the flat meridian.

35. A 40-year-old Olympic ski coach desires refractive surgery so that he may see distance clearly. His refraction is –3.00 × –2.00 at 180 in both eyes. The surgeon performs radial incisions for 3.00 D of myopia and transverse incisions to flatten the steep meridian by 2.00 D at 90 degrees. Is the patient happy?

The patient is unhappy because of residual myopia. He now knows more about the "coupling effect" than his surgeon. When one incision causes corneal flattening in one meridian, there is a compensatory steepening of the unincised corneal meridian 90 degrees away. In the case above, the coupling effect of the incised and unincised meridians (90 degrees apart) should have been anticipated. Radial incisions must be used to correct the 3.00 D of spherical myopia as well as the approximate 1.00 D of steepening induced by the transverse incisions. In general, short incisions tend to cause less steepening of the unincised meridian than longer incisions.

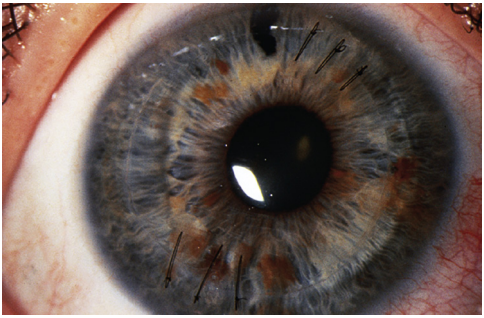


Figure 14-13. Treatment for post-corneal transplant astigmatism. Compression sutures were placed in the flat meridians (1:00 to 3:00 and 6:30 to 8:00), and relaxing incisions were performed in the graft wound 90 degrees away.

36. What about procedures for hyperopia?

Of the available options, none is as effective or reliable as the procedures for myopia.

For low levels of hyperopia, *holmium laser thermokeratoplasty* has been used with some success. This procedure is FDA approved for the "temporary reduction" of hyperopia in patients 40 years of age or older with between +0.75 and +2.50 D of manifest spherical equivalent with −0.75 D of astigmatism. Eight (or 16) peripheral laser spots are placed in a ring (or two), each spot causing shrinkage of the stromal collagen and resulting in steepening of the central cornea. Problems to be resolved include regression of effect and induced astigmatism.

Conductive keratoplasty (CK) involves the use of low-energy radio-frequency energy delivered to the cornea with a guarded needle in a ring pattern around the midperiphery of the cornea. The heat generated causes collagen shrinkage, allowing the central cornea to steepen. CK was FDA approved in 2002 for the treatment of hyperopia in patients 40 years of age and older with a manifest refraction between +0.75 and +3.25 D. The procedure is effective for low to moderate hyperopia, but the trend is for regression over several years. CK has also recently been FDA approved to treat presbyopia in people over 40.

Hyperopic excimer laser PRK also has been approved by the FDA to treat hyperopia between +1 and +6 D. Treatment of hyperopic astigmatism also has been approved by the FDA in patients with +0.5 to +5.0 D of sphere with refractive astigmatism of +0.5 to +4.0 D and a maximal manifest refraction spherical equivalent of +6.0 D at the spectacle plane. The laser is used to create a large, donut-shaped ablation that requires a generous epithelial defect (often 9 mm or more).

Hyperopic LASIK treatments are currently FDA approved to treat up to 6 D of hyperopia with up to 6 D of astigmatism. Performing the laser ablation under a corneal flap has the theoretical advantage of decreased haze (ablation performed deep to the Bowman's layer) and faster healing response (no large epithelial defect).

Phakic intraocular lenses can treat hyperopia as well as myopia; however, they are not currently FDA approved to do so.

Clear lens extraction is a technique already familiar to most surgeons. Phacoemulsification is performed with implantation of one or two IOLs as required by the degree of hyperopia. However, accommodation is completely eliminated by the procedure. Moreover, the risks of intraocular surgery, including endophthalmitis, are difficult to justify in eyes without organic disease.

37. What are the effects of refractive surgical procedures on corneal endothelial cells?

Although endothelial cell loss was an early concern in RK, studies using specular microscopy have demonstrated only a small, nonprogressive loss of endothelial cells. After excimer laser treatment of myopia, studies in animals and humans suggest a small, insignificant loss of endothelial cells that diminishes over time. Certainly it is much more of a concern with intraocular surgery, especially phakic IOLs. Ongoing studies are important. As the treated population grows older, patients eventually will require cataract surgery. There are already case reports of a renewed hyperopic shift in post-RK patients undergoing cataract surgery. Is corneal decompensation in Fuchs' endothelial dystrophy accelerated by previous refractive surgery? Many questions remain unanswered. Effects of the laser itself, the inflammatory response, and the toxicity of topically applied drugs may contribute to endothelial cell loss and require further study.

38. What is the role of drugs in refractive surgery?

The first issue is pain, which is important in all treatment modalities but most significant for PRK. After PRK, increased levels of prostaglandin E-2 have been found, which sensitize the pain response of nerves. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketorolac and diclofenac sodium have been shown to decrease pain by reducing prostaglandin E-2 levels. However, these agents also increase white blood cell response in the cornea and should be used concomitantly with a topical steroid. One study found increased sterile corneal infiltrates when topical NSAIDs were used alone.

Another issue is corneal haze after PRK. The cornea undergoes a wound-healing response to the excimer laser ablation. Activated keratocytes lay down new collagen and proteoglycan matrix (the haze). This is first apparent at 1 month postoperatively, peaks at 3 months, and then decreases as remodeling ensues. Several experimental and retrospective studies have shown that topical steroids reduce corneal haze after PRK. However, a prospective, double-masked study revealed no benefit from topical steroids versus placebo. Still, in a subgroup of patients steroids may be beneficial, and they are typically used postoperatively.

Topical steroids also have been studied in the modulation of corneal curvature. Despite controversy in the literature, topical steroids apparently help to prevent regression of myopic effect after PRK. In fact, cessation of steroids has been associated with myopic regression, which may be reversed on reinstituting therapy in certain patients.

Mitomycin C (MMC) is a cell-cycle-nonspecific alkylating agent that targets rapidly dividing cells. MMC is being used by topical application during PRK for people with moderate to high myopia. The goal is to reduce the proliferation of keratocytes and fibroblasts, thus reducing the haze seen after moderate to deep ablations. MMC has shown great promise in refractive surgery and is felt to be safe for use on the cornea; however, the adverse reactions to MMC when used on the conjunctiva or sclera can be quite severe. Reported complications of MMC include corneal and scleral melts, cataract formation, and corneal edema.

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GLAUCOMA

Mary J. Cox and George L. Spaeth

CHAPTER 15

GLAUCOMA

1. What is glaucoma?

Glaucoma is a highly heterogeneous group of conditions in which tissues of the eye are damaged. Usually the optic nerve is damaged, resulting in a characteristic optic neuropathy with associated visual-field loss. In conditions such as acute angle-closure glaucoma, the lens, cornea, and other structures may be affected as well. The etiology of glaucoma is multifactorial. Elevated intraocular pressure (IOP) is one of the factors responsible for the damage. The role of IOP in glaucoma damage is variable. Increased IOP is the sole cause for the damage in acute angle-closure glaucoma, whereas, in low-tension glaucoma (LTG), IOP may play less of a role in the disease process.

2. How is glaucoma classified?

The broad classifications of glaucoma are somewhat artificial; they tend to blur as we learn more about the disease and its pathogenesis. Traditionally, glaucoma has been classified as open-angle or closed-angle based on the gonioscopic angle appearance. This differentiation plays an important role in treatment. Open- and closed-angle glaucoma have been further classified as primary or secondary. Open-angle glaucoma is classified as primary when no identifiable contributing factor for the increased IOP can be identified. Secondary glaucoma identifies an abnormality to which the pathogenesis of glaucoma can be ascribed. Examples include pseudoexfoliative, uveitic, angle recession, and pigmentary glaucoma.

3. How prevalent is glaucoma?

Glaucoma is the second leading cause of irreversible blindness in the United States and the third leading cause of blindness worldwide. Primary open-angle glaucoma affects approximately 2.5 million Americans. Half are unaware that they have the disease. Population-based studies have shown prevalence among Caucasians 40 years of age and older ranging from 1.1% to 2.1%. The prevalence among African Americans is three to four times higher. Prevalence also increases with age. People over 70 have a prevalence three to eight times higher than people in their forties.[1]

4. Name risk factors for the development of primary open-angle glaucoma.

Known risk factors include elevated intraocular pressure, age, race, and a positive family history of glaucoma. Decreased central corneal thickness also has been shown to contribute to the risk of developing glaucoma. Presumed risk factors for which evidence exists but sometimes appears conflicting include myopia and diabetes mellitus. Potential risk factors for which some association has been found include hypertension, cardiovascular abnormalities, sleep apnea, and vasospastic conditions such as Raynaud's phenomenon or migraine. Disc hemorrhage, increased cup-to-disc ratio, and asymmetric cupping of the optic nerve may represent either risk factors or evidence of early disease.[2]

5. Discuss the genetics of primary open-angle glaucoma.

Primary open-angle glaucoma (POAG) is most likely inherited as a multifactorial or complex trait. A combination of multiple genetic factors or of genetic and environmental factors is required to develop the disease. One specific gene, the TIGR/myocilin gene, has been found to confer susceptibility to POAG. Family history is an important risk factor for the development of glaucoma. The Baltimore Eye Survey found the relative risk of having POAG is increased approximately 3.7 times for individuals having siblings with POAG.[3,4]

6. What is the pathogenesis of glaucoma?

The pathogenesis of glaucoma has been only partially elucidated. In some cases elevated intraocular pressure may cause optic nerve damage by mechanically deforming the optic nerve with posterior bowing of the lamina cribrosa. In other cases a decrease in perfusion of the optic nerve may

cause damage. This may happen from a sudden drop in blood pressure in response to blood loss or medications. Anemia can also result in ischemia of the optic nerve. Focal vasospasm may contribute to decreased perfusion and ischemia in patients with the low-tension forms of glaucoma. In most patients, several different pathogenetic mechanisms probably operate simultaneously.[5]

7. What is the clinical presentation of primary open-angle glaucoma?

Primary open-angle glaucoma is slowly progressive and painless. It is usually bilateral but often asymmetric. Central visual acuity is relatively unaffected until late in the disease; therefore, patients are often asymptomatic. Advanced disease may be present before symptoms are noticed.

8. What is normal intraocular pressure?

The line between normal and abnormal intraocular pressure is not clear. Mean intraocular pressure is around 16 mm Hg, with a standard deviation of 3 mm Hg. It is a non-Gaussian distribution skewed toward higher pressures. Elevated intraocular pressure has been shown to be a risk factor for glaucoma; however, only 5% of people with pressures above 21 mm Hg eventually develop glaucoma. Conversely, patients with glaucoma damage may have intraocular pressures consistently in the normal range.[6,7]

9. True or false: Loss of peripheral vision is a warning sign of early glaucoma.

False. Loss of temporal vision (side vision) is the last to be affected in most types of glaucoma. The first area to be damaged in most people with glaucoma is vision to the nasal side of central vision. This helps explain why patients do not notice loss of vision until the damage is marked. Both eyes provide vision to the nasal side so a blind spot is not noted with both eyes open until vision is lost in both eyes.[1]

KEY POINTS: COMMON VISUAL-FIELD DEFECTS FOUND IN GLAUCOMA

1. Superior/inferior nasal step.
2. Superior/inferior arcuate defect.
3. Generalized depression.
4. Paracentral loss.
5. Temporal or central island with advanced disease.

10. What is a glaucoma suspect?

A glaucoma suspect is an adult who has an open angle on gonioscopy and one of the following findings in at least one eye:

- Optic nerve suspicious for glaucoma
- Visual-field defect consistent with glaucoma
- Elevated intraocular pressure consistently greater than 22 mm Hg

If a patient has two or more of the above findings, then a diagnosis of glaucoma is more likely. The decision to treat a glaucoma suspect takes into account the above findings as well as additional risk factors and the general health of the patient.[5]

11. In examination of the optic nerve, what findings could be consistent with a diagnosis of glaucoma or suspicion of glaucoma?

Diffuse narrowing of the optic nerve rim, focal narrowing or notching of the optic nerve rim, vertical elongation of the optic cup, nerve fiber layer defects, nerve fiber layer hemorrhages, and asymmetric cupping of the optic nerves are all signs of glaucoma or suspicion of glaucoma. An acquired pit of the optic nerve is a pathognomonic sign of glaucoma.[8]

KEY POINTS: COMMON OPTIC NERVE FINDINGS IN GLAUCOMA

1. Diffuse narrowing of the neuroretinal rim.
2. Focal narrowing or notching of the neuroretinal rim.
3. Nerve fiber layer defects.
4. Disc hemorrhages.
5. Asymmetry of optic nerve cupping.

12. A patient presents with optic nerve damage in one eye as pictured in Figure 15-1. The other eye has lower pressures and a healthier optic nerve with a normal visual field. What is the prognosis for the healthier optic nerve?

The optic nerve in Figure 15-1 shows complete loss of the inferotemporal rim. Optic nerve damage in one eye has been associated with a significantly increased risk of future damage in the other eye. Twenty-nine percent of untreated fellow undamaged eyes will show visual-field loss in an average of 5 years.[9]

13. A 74-year-old African American female presents for a routine eye examination. She has not been to an ophthalmologist in 10 years. Her intraocular pressures are 26 mm Hg in the right eye (OD) and 24 mm Hg in the left eye (OS). Her optic nerves are as pictured in Figure 15-2. What information is important to obtain from the patient?

The optic nerves in Figure 15-2 show significant asymmetry with a narrower rim supertemporally in the right eye in comparison to the left eye. She has not been seen by an ophthalmologist for years. The history is a crucial part of the evaluation; it identifies possible secondary causes for glaucoma (e.g., trauma, steroid use) as well as risk factors such as family history, helps determine the visual demands and support system of the patient, and can give an idea of the patient's general health and

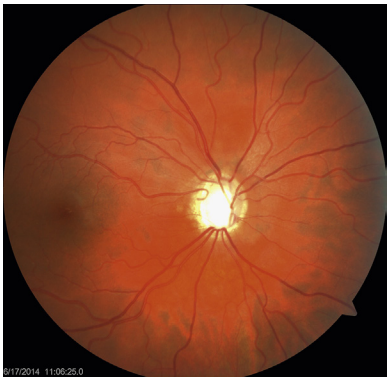

Figure 15-1. Complete loss of the neuroretinal rim is a sign of advanced glaucoma.

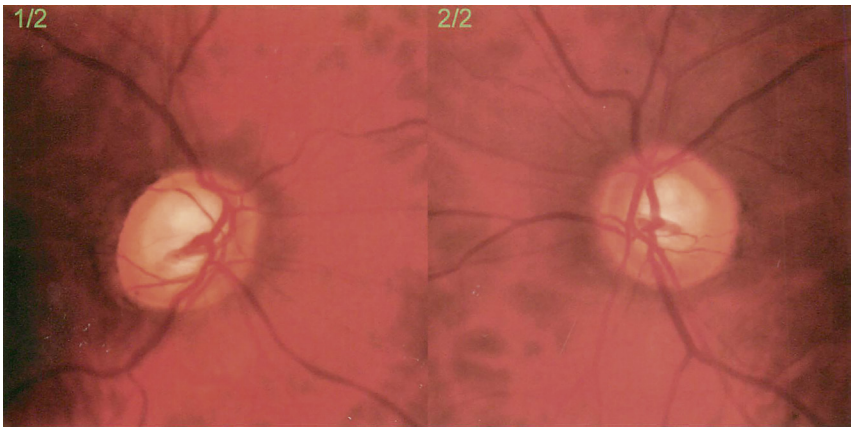

Figure 15-2. Asymmetry of the cup-to-disc ratio can be an early sign of glaucoma.

life expectancy. All of these components help formulate a treatment plan most likely to be agreeable to the patient, least likely to be damaging, and of an appropriate level of aggressiveness for each individual patient.

14. If the patient in question 13 had been to another ophthalmologist several times a year and was presenting for the first time in your office, what information would be important to obtain?

Old records are valuable. Knowing about previous surgeries, lasers, and medicines (both those that worked and those that did not) helps formulate a current treatment plan. Previous intraocular pressure readings, former visual-field tests, and optic nerve evaluations can establish the rate of progression of the disease, a key piece of information in determining the level of aggressiveness needed in treatment.

15. True or false: If the patient in question 13 had a normal visual field, she would be unlikely to have glaucoma.

False. Visual-field defects may not be apparent until as much as 50% of the optic nerve fiber layer has been lost.

16. True or false: If the patient in question 13 had intraocular pressures of 19 mm Hg OD and 18 mm Hg OS, then she would be unlikely to have glaucoma.

False. A single intraocular pressure measurement in the normal range is not enough to eliminate the possibility of glaucoma. Several studies suggest that as many as 30 to 50% of individuals in the general population having glaucomatous optic nerve damage and visual-field defects have an initial IOP measurement of less than 22 mm Hg. Diurnal IOP fluctuation and artificially low measurements due to decreased central corneal thickness or other factors may contribute to the normal IOP. In addition, patients with average-pressure glaucoma have glaucomatous optic neuropathies without ever demonstrating elevated intraocular pressures.[10,11]

17. How does intraocular pressure fluctuate in glaucoma patients?

Individuals without glaucoma may have an IOP fluctuation of 2 to 6 mm Hg over a 24-hour period. IOP in glaucoma patients may vary widely. Untreated glaucoma patients may vary by 15 mm Hg or more. The majority of patients demonstrate the highest pressures in the morning with decrease throughout the day. Other patterns with peak pressures at night or midday as well as flat patterns without variation have been reported.[12]

18. What role does central corneal thickness play in the evaluation of glaucoma?

Corneal thickness is important to consider for two reasons. First, corneal thickness affects the measurement of IOP so that the measured IOP may be inaccurate if the corneal thickness is not average. The actual average central corneal thickness is approximately 544 μm. IOP is about 5 mm Hg lower than measured for each 100 μm that the cornea is thicker than normal. The true IOP is actually higher than measured when the cornea is thinner than average. Second, a thin central cornea, in itself, is associated with more severe glaucoma. The Ocular Hypertension Treatment Study identified reduced central corneal thickness as a risk factor for glaucoma in patients with IOP between 24 and 32 mm Hg.[13,14]

19. Name factors that affect the measurement of intraocular pressure.

Intraocular pressure measurements can be overestimated and underestimated based on several factors (see Table 15-1).

20. What role does imaging play in the evaluation and management of glaucoma?

Significant structural retinal nerve fiber layer (RNFL) loss occurs prior to functional visual-field loss. Periodic stereoscopic optic disc photography remains the gold standard for documentation of the optic nerve appearance and assessment of glaucoma progression over time. However, newer technologies such as optical coherence tomography (OCT) are now available to assess the RNFL, optic nerve head, and ganglion cell complex. This technology may assist in the detection of RNFL loss in situations in which the subtle signs of disease could be overlooked on clinical exam. It can also help confirm the diagnosis or progression of glaucoma in the setting of corresponding RNFL defects and visual-field defects.[15]

21. What parameters on optical coherence tomography are useful in the diagnosis and management of glaucoma?

As pictured in Figure 15-3, OCT measures the RNFL thickness and then compares those data with a normative age-matched database. Green, yellow, and red colors signify the percentage chance that

Table 15-1. Factors Influencing the Measurement of Intraocular Pressure

Overestimation of IOP
Pressing on the globe
Thick tear meniscus (too much fluorescein)
Thick central cornea
Valsalva (breath-holding or straining)
Thick neck/obese patients
Anxiety
Astigmatism
Orbital disease/restrictive ocular myopathy, as with Graves' disease
Corneal scarring and high corneal rigidity
Flat anterior chamber
Underestimation of IOP
Thin tear meniscus (too little fluorescein)
Thin central cornea
Corneal edema
Repeated IOP measurements/prolonged contact with cornea
Low corneal rigidity

the thickness is within the normal range for an age-matched population. OCT also documents optic nerve head parameters including optic rim area, optic disc area, average cup/disc ratio, vertical cup/disc ratio, and optic cup volume.[16]

22. True or false: If the OCT showed no evidence of RNFL thinning, then the patient does not have glaucoma.

False. OCT technology may be limited by signal quality, image artifact, and confounding ocular disease. Serial imaging can be used as an adjunct to standard perimetry and optic disc photography. Clinical decisions should not be made on the basis of a single test or technology.

23. What is the primary goal of treatment of patients with glaucoma?

The primary goal in the treatment of glaucoma is enhancing the patient's health by improving or preserving his or her vision. One way of preserving vision is by lowering the intraocular pressure. It is important not to lose sight of the primary goal in treatment. All treatment options carry side effects and risks. The patient's general health and visual demands always need to be considered.

24. Name the initial treatment options for primary open-angle glaucoma.

Options include observation or lowering the intraocular pressure by using eyedrops, laser trabeculoplasty, or surgery.

25. What factors help determine which option to try?

When deciding on an initial treatment for a patient with glaucoma, several factors need to be considered. First, determine how aggressive the treatment needs to be. The level of aggressiveness takes into consideration the severity of the disease, the rapidity of progression, and the general health of the patient. Second, the toxicity and cost of the various treatment options need to be assessed. This will help predict compliance. For example, a 70-year-old healthy patient with advanced disease and an inability to tolerate medicines would most likely benefit from surgery. A healthy 45-year-old with mild-to-moderate disease may begin with medication or, if unable to be compliant or tolerate medicines, a laser trabeculoplasty. An elderly sick patient with mild-to-moderate disease may benefit from observation alone.

26. Are eyedrops safer than oral medications?

No. Eyedrops are directly absorbed into the blood through the nasal mucosa. This route bypasses the first-pass metabolism of drugs by the liver and can allow increased effects for a given amount of absorption.

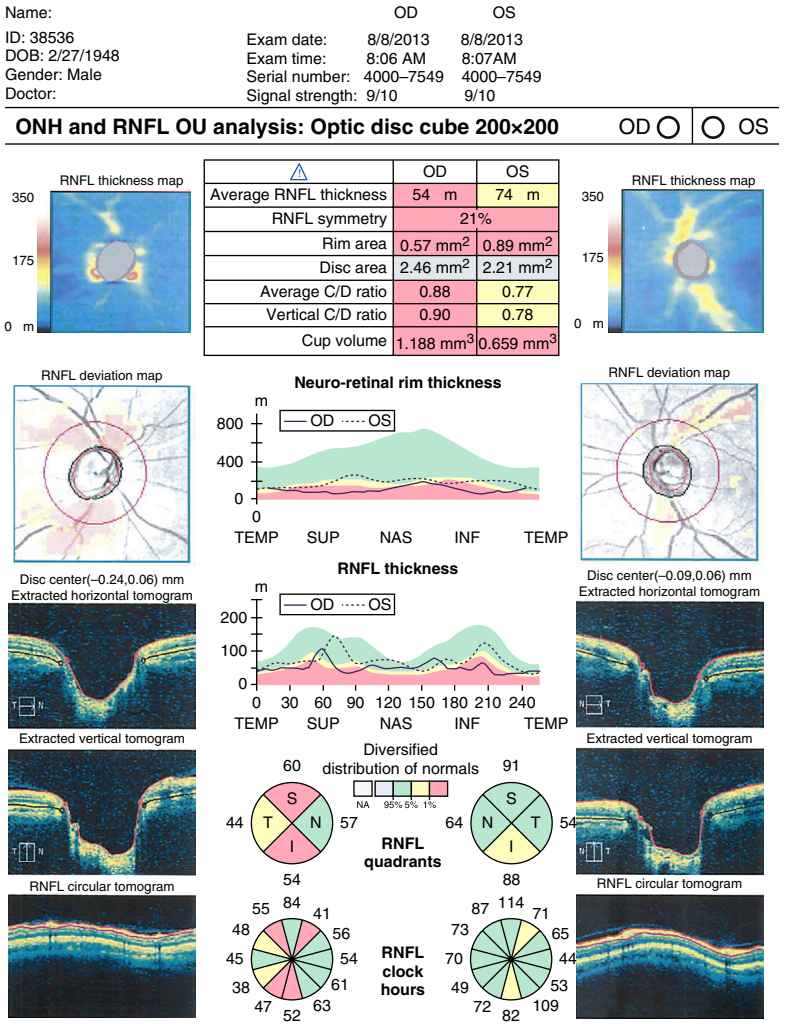

Figure 15-3. OCT shows thinning of the RNFL in the patient from Figure 15-2.

27. Are some optic nerves more resistant to intraocular pressure damage than others?

Yes. Small nerves with no peripapillary atrophy but small central cups in which it is not possible to see laminar dots are less likely to become damaged than eyes with large optic nerves, large cups, peripapillary atrophy, and prominent laminar dots. A large cup does not necessarily correlate with glaucoma if the optic nerve itself is large. It is important to determine the optic nerve size when evaluating neuroretinal rim.

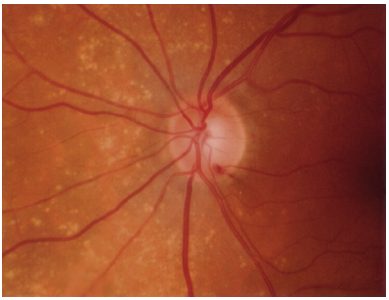

Figure 15-4. Elongation of the optic nerve cup can be an early finding in glaucoma. Splinter disc hemorrhages can be a prognostic indicator for progressive disease.

28. A patient being treated for glaucoma presents for a follow-up examination with an optic nerve appearance as shown in Figure 15-4. Discuss the findings.

Figure 15-4 demonstrates an optic nerve with vertical elongation of the cup. Narrowing at the superior and inferior rim often occurs in glaucoma. A nerve fiber layer hemorrhage is present at the inferotemporal rim of the optic nerve. Disc hemorrhages are commonly found in glaucoma patients. They are important prognostic signs for the development or progression of visual-field loss.[17]

29. Name five potential causes of disc hemorrhages.

- Glaucoma
- Posterior vitreous detachments
- Diabetes mellitus
- Branch retinal vein occlusions
- Anticoagulation

30. What is low-tension glaucoma?

Low-tension glaucoma is one of the traditional labels for a glaucomatous optic neuropathy that occurs without evidence of elevated intraocular pressure. Because "low" is a relative word, and because many people with "low tension" have IOP above the mean, but in the average range, a better term is "average-pressure glaucoma" (APG). There is much controversy over whether APG is part of a spectrum of primary open-angle glaucoma with IOP that is not elevated above the average range or its own disease entity. The optic nerve in patients with APG is susceptible to damage at normal IOP. Ischemia may contribute significantly to the progression of the disease. Studies suggest a higher prevalence of vasospastic disorders such as migraine or Raynaud's phenomenon, coagulopathies, cardiovascular disease, and autoimmune disease in patients with low-tension glaucoma. Nocturnal hypotension and anemia may also result in decreased optic nerve perfusion in patients with low-tension glaucoma.

31. What disease entities can mimic low-tension glaucoma?

Undetected "high-tension glaucoma" can mimic LTG. This could be the result of a missed elevation of IOP that occurs at times when the IOP was not measured, a thin central cornea, or an error in applanation. The patient could have suffered a previous episode of severe intraocular pressure elevation from a secondary glaucoma such as uveitic or steroid-induced glaucoma that had subsequently normalized. He or she could have suffered intermittent spikes from angle closure. The patient may have suffered an episode of optic nerve hypoperfusion due to blood loss from surgery or trauma. Compressive optic nerve lesions, ischemic optic neuropathy, congenital anomalies, and certain retinal disorders can also mimic APG (Table 15-2).[18]

32. What tests should be considered in the workup of a patient with glaucomatous-appearing optic nerves and visual fields without elevated intraocular pressure?

Usually the diagnosis is clear on the basis of the appearance of the optic nerve, the visual field, and the asymmetry of IOP with the higher pressure in the eye with more damage. When not clear, a diurnal curve and central corneal thickness should be checked to be certain the condition is not a "high-tension" glaucoma with low intraocular pressure readings. A computed tomography or magnetic

Table 15-2. Differential Diagnosis of Glaucoma-Like Optic Discs and Visual Fields

1. Missed elevated IOP
   - diurnal variability
   - Incorrect measurement
   - thin central cornea (<500 μm)
2. Previous IOP elevation, no longer present
3. Shock-induced optic neuropathy
4. Compressive optic neuropathy
5. Ischemic optic neuropathy
6. Giant cell arteritis (temporal arteritis)
7. Optic nerve anomalies (pituitary tumors, etc.)
8. Macular degeneration
9. Juxtapapillary choroiditis
10. Myopia
11. Demyelinating disease

resonance imaging scan to evaluate for compressive lesions of the optic nerve or chiasm may be indicated. If history or symptoms suggest, rapid plasma reagin/Venereal Disease Research Laboratory, rheumatoid factor/antinuclear antibody, or erythrocytic sedimentation rate may be checked to look for syphilis, autoimmune diseases, or temporal arteritis (giant cell arteritis) as potential causes. If a patient is on blood pressure medicines or has a history of hypotension, a 24-hour Holter monitor to check for nocturnal hypotension may be indicated.

33. How is average-pressure glaucoma treated?

The Collaborative Normal-Tension Glaucoma Study found that by reducing the intraocular pressure by 30% the rate of progression of visual-field loss was reduced from 35% to 12%. Lowering intraocular pressure is the mainstay of treatment for average-pressure glaucoma, as well as primary open-angle glaucoma.[19]

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CHAPTER 16

ANGLE-CLOSURE GLAUCOMA

Paul Harasymowycz, Jing Wang, and George L. Spaeth

1. What landmarks are seen in the anterior chamber angle?

The structures noted in anterior-to-posterior sequence are as follows (numbered list corresponds to numbers in Fig. 16-1):

1. **Schwalbe's line:** The peripheral or posterior termination of the Descemet's membrane, seen clinically as the apex or termination of the corneal light wedge. May be visible inferiorly as the most anterior nonwavy pigmented line.
2. **Anterior, *nonpigmented,* trabecular meshwork (TM):** Clear whitish band.
3. **Posterior, *pigmented,* TM:** Variably pigmented band of homogeneous width. Usually most pigmented inferiorly (Fig. 16-2).
4. **Schlemm's canal:** Variably visible light gray band at the level of the posterior TM. Elevated episcleral venous pressure or pressure from the edge of the goniolens will cause blood to reflux, making it appear as a faint red band.
5. **Scleral spur:** Narrow, white band of sclera invaginating between the TM and the ciliary body. Marks the insertion site of the longitudinal muscle fibers of the ciliary body to the sclera.
6. **Ciliary body (CB) band:** Pigmented band marking the anterior face of the ciliary body. Variably, iris processes may be seen as lacy projections crossing this band. By definition, iris processes do not cross the scleral spur. Projections that cross the scleral spur to the TM are peripheral anterior synechiae (PAS) and may be focal, pillar-like, or broad sheets.
7. **Iris**

2. Why is a goniolens necessary to visualize the anterior chamber angle?

Light from the anterior chamber (AC) angle undergoes total internal reflection at the cornea (tear)–air interface, preventing direct visualization. A goniolens changes the refractive index at the interface, enabling visualization.

3. What are the different kinds of gonioscopy? How do they differ?

- A Koeppe contact lens is used for direct gonioscopy. This technique is cumbersome, requiring the patient to be supine. A clear, viscous liquid such as methylcellulose is used as a coupling medium. By using a direct viewing system such as a binocular microscope, the anterior chamber angle is visualized.
- Indirect gonioscopy uses a mirrored contact lens. The Goldmann three-mirror lens vaults the central cornea and requires a viscous coupling liquid. The Zeiss (Fig. 16-3), Posner, or Sussman four- or six-mirror lenses directly contact the cornea and thus do not require a coupling agent beyond the patient's normal tear film. These can be used at the slip lamp.

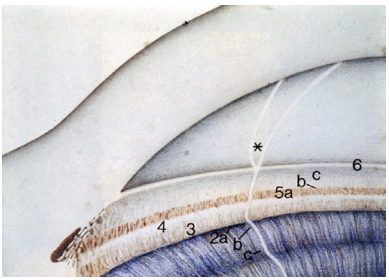

Figure 16-1. Diagram of anterior chamber anatomy.

Figure 16-2. Inferior quadrant of heavily pigmented open angle.

Figure 16-3. Zeiss goniolens.

4. Which goniolens is preferred by most glaucoma specialists and why?

The Zeiss, Posner, and Sussman lenses are preferred by a majority of glaucoma specialists for the following reasons:

- Speed and ease of use (they do not require a viscous coupling liquid and, because of their four or six mirrors, they do not need to be rotated to see all 360 degrees of the angle).
- The ability to perform indentation gonioscopy and the absence of a suction effect on the eye. Indentation cannot be performed with the Goldmann lens because of its larger diameter. The suction effect of the Goldmann lens can sometimes artificially widen narrow angles. These two qualities can be critically important when evaluating eyes with narrow angles.
- Elimination of the transient degradation of corneal clarity that is a consequence of the viscous liquid and Goldmann lens manipulation, which can make subsequent fundus examination difficult.

Warning: When first mastering gonioscopy, the Zeiss lens can be more difficult than the Goldmann lens. In inexperienced hands, excessive indentation can easily occur, which will make the angle appear wider than it really is. Zeiss gonioscopy demands a light touch. One way to make sure you are not pressing is for the contact to be so light that you occasionally lose part of the contact meniscus. If you see any corneal striae or if your view is not crystal clear, you are probably indenting.

5. How is gonioscopy performed?

1. Topical anesthesia is essential for patient comfort and cooperation.
2. Rest your elbow on the slit lamp platform and your ring and/or small fingers on the side bar or on the patient's cheek to help stabilize your hand.
3. Examination can be facilitated by asking the patient to stare straight ahead with the fellow eye without blinking.
4. To facilitate viewing a particular quadrant of the angle with indirect gonioscopy, either tilt the mirror toward the quadrant or have the patient look toward that mirror. For example, when viewing the

Table 16-1. The Scheie and Schaffer Classification Systems

	GRADE 0	GRADE I	GRADE II	GRADE III	GRADE IV
Scheie		Wide open	Scleral spur visible, CB band not seen	Can see only to anterior TM	Closed
Schaffer*	Closed	10°	20°	30°	40°

*The angle is graded as a slit when it is between grades 0 and I.

superior angle, either tilt the inferior mirror upward, toward the superior angle, or have the patient look down slightly, toward the inferior mirror.

5. The superior–inferior relationships in the nasal and temporal mirrors and the nasal–temporal (right–left) relationships in the superior and inferior mirrors are preserved, not inverted as in indirect ophthalmoscopy. For example, when viewing the superior angle through the inferior mirror, an area of PAS seen at five o'clock in the mirror is actually at one o'clock, not eleven o'clock.

6. How can I determine which patients may have narrow angles and need gonioscopy?

The van Herick technique uses a thin slit beam focused at the limbus to approximate angle depth by comparing the peripheral AC depth to corneal thickness. Grade I has a peripheral AC depth less than one-quarter of the corneal thickness; grade II is one-quarter of the corneal thickness; grade III is one-half of the thickness; and grade IV is one corneal thickness or more. Patients who are grade I or II certainly have narrow angles and should have gonioscopy. This technique, however, should never replace gonioscopy in eyes with clear media as part of a glaucoma evaluation. It falsely gives the appearance of an open angle in some eyes with plateau iris or anterior rotation of the ciliary body (see classification below).

7. What are the different gonioscopic anterior chamber angle classification systems?

Table 16-1 summarizes the *Scheie* system, which is rarely used, and the *Schaffer* system, which is the most commonly used.

The *Spaeth system,* however, is the most descriptive. The first element is a capital letter (A to E), for the level of iris insertion:

- **A** = Anterior to TM
- **B** = Behind the Schwalbe's line, or at the TM
- **C** = At scleral spur
- **D** = Deep angle, CB band visible
- **E** = Extremely deep

If during indentation gonioscopy, the true iris insertion is noted to be more posterior than originally apparent, the original impression is put in parentheses, followed by the true iris insertion outside parentheses.

The second element is a number that denotes the iridocorneal angle width in degrees at the level of the trabecular meshwork, usually from 5 to 45 degrees.

The third element is a lower-case letter describing the peripheral iris configuration:

- **f** = Flat
- **b** = Bowed or convex
- **c** = Concave
- **p** = Plateau configuration

In addition, the pigmentation of the posterior TM is graded on a scale of 0 (none) to 4 (maximal). For example, (A)C10b, 2+PTM refers to an appositionally closed 10-degree angle that, with indentation, opened to the scleral spur and revealed moderate pigmentation of the posterior TM.

8. How do I know if I can safely dilate a patient, with or without a slit lamp?

If no slit lamp is available, use a penlight and shine it from the temporal side perpendicular to the central visual axis. In an eye with a normal or "safe" anterior chamber depth, the entire nasal half of the iris will be illuminated as well as the temporal half. In an eye with a shallow or questionable anterior chamber depth, none or only part of the nasal half of the iris will be illuminated. This technique does not hold true in eyes with plateau iris.

If a slit lamp is available, angles that are less than or equal to 15 degrees are at risk for closure and probably should not be dilated. An eye with a 20 degree angle should be watched closely, as it may narrow further with time, and should be reevaluated with tonometry and gonioscopy after dilation. An exception to these general guidelines is plateau iris (discussed later), in which the angle may be wider than 20 degrees and still at risk for closure. Thus, the peripheral iris configuration is also very important.

9. What are other methods of evaluating anterior chamber angles besides gonioscopy?

There are several imaging devices that can display the anterior chamber angles. Ultrasound biomicroscopy (UBM) uses ultrasound to visualize the angles. The ultrasound waves are not blocked (absorbed) by the iris pigmented epithelium. Therefore, it has the advantage of visualizing the ciliary body. UBM is particularly useful to identify a plateau iris configuration. Anterior-segment optical coherence tomography (OCT) uses a diode laser to obtain anterior segment imaging. Limbus-to-limbus images are possible in a single scan with the Visante OCT. OCTs designed for retinal imaging can perform anterior segment imaging if used with adaptive lenses. However, because the diode laser can be blocked by the iris pigmented epithelium (especially in dark irises), OCT cannot visualize the CB as clearly as UBM in individuals with dark irises. In addition to UBM and OCT, Scheimpflug cameras (Pentacam) use a specific optical principle to image angles. Classification of angles by UBM and OCT is different from that by gonioscopy. Gonioscopy is still the gold standard of angle classification. Gonioscopy also gives valuable information such as pigmentation or presence of abnormal vessels that cannot be demonstrated by imaging devices.

10. How is angle closure classified?

I. By clinical presentation
   A. Acute
   B. Subacute or intermittent
   C. Chronic

II. By mechanism
   A. Posterior pushing mechanism
      1. Pupillary block (can occur in phakic, pseudophakic, or aphakic eyes)
         a. Relative Idiopathic (i.e., primary angle closure) Miotic induced
         b. Absolute or true: By posterior synechiae from any inflammatory etiology
      2. Lens induced
         a. Phacomorphic (due to an intumescent cataractous lens or a swollen lens in a diabetic)
         b. Lens subluxation
            i. Trauma
            ii. Pseudoexfoliation syndrome
            iii. Hereditary/metabolic disorder (e.g., Marfan's syndrome, homocystinuria)
         c. Lens pushed forward
            i. Aqueous misdirection syndrome (malignant or ciliary-block glaucoma)
            ii. Mass (e.g., tumor, retinopathy of prematurity, persistent hyperplastic primary vitreous)
      3. Plateau iris
         a. True plateau iris
         b. Pseudoplateau—iris and ciliary body cysts
      4. Swelling/anterior rotation of the ciliary body (some overlap within this)
         a. Inflammatory (e.g., scleritis, uveitis, after panretinal photocoagulation)
         b. Congestive (e.g., after scleral buckling surgery, nanophthalmos)
         c. Choroidal effusion—secondary to medications (e.g., topiramate), hypotony after trauma or surgery, uveal effusion, etc.
         d. Suprachoroidal hemorrhage (SCH)—intraoperative or postoperative. Risk factors for SCH include previous intraocular pressure (IOP) elevation followed by hypotony, high myopia, advanced age, aphakia, previous vitrectomy, systemic hypertension or atherosclerotic vascular disease, and postoperative Valsalva maneuver
   B. Anterior pulling mechanism—synechial angle closure
      1. Chronic appositional closure from any of the above
      2. Intraocular inflammation (uveitis)—forming synechial membrane
      3. Neovascular glaucoma
         a. Central retinal vein occlusion (CRVO), accounts for one-third of cases
         b. Diabetes mellitus, accounts for another one-third of cases

c. Carotid occlusive disease, comprises approximately 10% of cases
d. Miscellaneous (e.g., central retinal artery occlusion (CRAO), tumors, chronic retinal detachment)

4. Iridocorneal endothelial syndrome
   a. Progressive iris atrophy
   b. Chandler's syndrome
   c. Cogan-Reese syndrome

11. What do the terms PACS, PAC, APAC, and PACG signify? How are they related to acute, subacute, and intermittent angle closure?

PACS stands for primary angle closure suspect
PAC stands for primary angle closure
PACG stands for primary angle closure glaucoma
APAC stands for acute primary angle closure

The terms refer to a new classification system of angle closure, which is currently used in most clinical and epidemiological studies. This system was developed by the International Society of Geographical and Epidemiological Ophthalmology between 1998 and 2005. PACS refers to patients with narrow angle on *gonioscopy* but without elevated IOP or presence of PAS. PAC refers to patients with narrow angle and elevated IOP or PAS. PACG refers to patients with narrow angle and glaucomatous optic neuropathy and/or visual field defects (Table 16-2).

The purpose of this new classification system is to unify the definition of glaucoma. It reserves the term *glaucoma* for the presence of optic neuropathy. For example, a patient presenting with acute elevated IOP secondary to angle closure will be referred to as APAC instead of acute angle closure glaucoma, as the patient may not have developed (yet) glaucoma optic neuropathy at the episode of acute angle closure.

The new classification system relates to the traditional classification of angle-closure glaucoma to some degree. Acute angle-closure glaucoma is referred to as acute primary angle closure; chronic angle-closure glaucoma can be either PAC or PACG depending on the status of the optic nerve and visual field. Subacute or intermittent angle-closure glaucoma can be PACS, PAC, or PACG with self-limited symptoms. The status of the angle and optic nerve dictates the classification of angle closure instead of the patient's symptomatology and probably has better prognostic value than the previous system.

The new classification intends to describe the natural history of angle closure. Anatomically narrow angles (i.e., PACS) are common; about 4 to 10% of the population above the age of 40 have some degree of narrow angle. Angles narrow with age as the lens thickens throughout life. *Some* (not all) PACS will progress to PAC and eventually to PACG. Some PACS will develop APAC. We are still trying to identify which subgroup of PACS will progress to PACG and evaluating effective preventive treatments.

PRIMARY ANGLE CLOSURE (RELATIVE PUPILLARY BLOCK AND OTHER MECHANISMS)

12. What is the epidemiology of primary angle-closure glaucoma?

Inuit or Eskimos have the highest incidence of APAC, followed by Asians and then Caucasians and those of African descent. It is more common in Northern European Caucasians than in Mediterranean Caucasians. The peak incidence is between the ages of 55 and 65. In both Asians and

Table 16-2. The International Society of Geographic and Epidemiological Ophthalmology Classification of Angle Closure

	NARROW ANGLES	ELEVATED IOP OR PAS	GLAUCOMATOUS OPTIC NEUROPATHY
Primary angle closure suspect (PACS)	+	–	–
Primary angle closure (PAC)	+	+	–
Primary angle closure glaucoma (PACG)	+	+/–	+

Caucasians, women are three to four times more likely to develop angle closure than men. In those of African descent, the incidence is equal between men and women. There is a greater incidence in hyperopes. The inheritance appears to be polygenic. However, the asymptomatic form of angle closure glaucoma (PACG) is the most common form of angle-closure glaucoma across all ethnicities.

13. Which is more common: chronic angle-closure glaucoma or symptomatic acute angle closure?

The chronic, asymptomatic form of PACG is much more common across all ethnicities. Most of the angle-closure diseases are asymptomatic. This highlights the importance of gonioscopy in *every patient* presenting with elevated IOP and/or glaucoma optic neuropathy. In fact, patients with PACG are often misdiagnosed as having primary open-angle glaucoma (POAG) because gonioscopy is omitted during clinical examination. It is very important to differentiate PACG from POAG, as the treatments are different for the two. The treatment of PACG starts with addressing the mechanism of angle closure—performing laser peripheral iridotomy (PI) or removing the lens. The treatment of POAG starts with aqueous suppression or enhancing outflow by medication or laser.

14. What are the symptoms of acute primary angle closure?

Patients may complain of ocular pain, redness, blurred or foggy vision, halos around lights, nausea, and vomiting. The visual symptoms are partly caused by the corneal edema that occurs from the sudden severe rise in IOP. This, the most common presentation, is most often induced by stress, low ambient light levels, and, occasionally, various medications. If the IOP exceeds the pressure in the ophthalmic or central retinal artery, visual loss occurs as a result of ischemia of the optic nerve or retina. Most APAC progresses into chronic angle closure with elevated IOP (i.e., PAC) and the development of glaucomatous optic neuropathy (i.e., PACG).

15. Describe the signs or exam findings seen in acute primary angle closure.

- **IOP:** Typically greater than 45 mm Hg.
- **Conjunctiva and episclera:** Dilated vessels.
- **Cornea:** Epithelial and stromal edema.
- **Anterior chamber:** Shallow; cells or flare variably present.
- **Iris:** Dilated vessels (as distinguished from neovascularization of the iris), middilated nonreactive or sluggish pupil, and sector atrophy from ischemia (only if previous episodes have occurred).
- **Lens:** Glaukomflecken (not seen acutely, but if present initially, may indicate previous episodes of angle closure).
- **Gonioscopy:** With narrow angle or closed angle, one may be unable to view structures owing to corneal edema (glycerin may be used to clear the cornea); superior angle is usually the narrowest and the first to develop PAS.
- **Optic nerve:** Occasional swelling and hyperemia from vascular congestion; may mimic papilledema.
- **Retina:** May be normal or may show signs of vascular occlusion.
- **Fellow eye:** Examination of the fellow eye is *very important* in making the diagnosis. It usually also has a shallow anterior chamber and narrow angle. If the fellow eye has a normal AC depth and a normal angle width, the diagnosis of primary angle closure should be reevaluated and secondary causes need to be addressed.

KEY POINTS: COMMON SIGNS OF ACUTE PRIMARY ANGLE CLOSURE

1. Dilated conjunctival and episcleral vessels.
2. Corneal edema.
3. Shallow anterior chamber with or without cells or flare.
4. Middilated, sluggish, or unreactive pupil.
5. Lens glaukomflecken.
6. Shallow anterior chamber and narrow angle in fellow eye.

16. How does subacute or intermittent angle closure present clinically?

The symptoms are similar to an acute attack but usually less severe, tend to recur over days to weeks, and may be confused for headaches. They resolve on their own, often when the individual goes to sleep or enters a well-lit area (both induce miosis). These episodes can result in chronic angle closure.

Between episodes, the IOP is normal and the ocular exam is usually normal, except for the presence of narrow angles and, sometimes, glaukomflecken, cataracts, and PAS on gonioscopy.

17. How does chronic angle closure present clinically?

It is usually asymptomatic, unless marked visual-field loss has occurred. Gradual closure of the angle, by simple apposition and/or PAS, leads to a more gradual rise in IOP. The IOP is more variable but can be as high as 60 mm Hg without any symptoms. The cornea is usually clear, because the IOP rises gradually, resulting in a lack of pain, redness, decreased vision, or other symptoms. This is the most dangerous form of angle closure. Because of the lack of symptoms and very high IOP, patients tend to present late with very advanced disease.

18. What are the anatomic characteristics of eyes with primary angle closure?

Anatomically, the eyes have short axial length, hyperopia, anterior segment crowding, including a thicker lens, and/or peripheral iris.

19. What is the pathophysiologic mechanism of relative pupillary block?

The crystalline lens grows thicker throughout life. In eyes that are predisposed, apposition between the posterior iris surface and the anterior lens capsule gradually increases. As the iridolenticular touch increases, the resistance to aqueous flow from the posterior to the anterior chamber increases, gradually increasing posterior chamber pressure. Under conditions in which the pupil is in a middilated position (e.g., from stress, low ambient light levels, sympathomimetic or anticholinergic medications), the elevated posterior chamber pressure causes the lax or floppy iris to bow anteriorly and occlude the trabecular meshwork. It is hypothesized that thinner or lighter-colored irises are more likely to cause an acute rise in IOP because they are thinner and floppier, causing acute angle closure. Less floppy, thicker irises are pushed anteriorly more gradually, especially peripherally. This leads to creeping chronic angle closure, with or without PAS, and a more gradual IOP rise (Fig. 16-4).

20. What nonmedical maneuver may help to lower intraocular pressure even before medicating the patient?

Even before starting medical treatment, indentation gonioscopy can sometimes help to lower IOP by pushing aqueous from the central AC peripherally, opening the angle if it is not sealed with PAS. This must be done carefully to avoid abrading the corneal epithelium, which is swollen and may abrade more easily than normal. An anterior chamber paracentesis with a blade or needle may more rapidly decompress the eye, and medications would further lower the IOP.

21. How would you treat the involved eye medically?

The "kitchen sink" approach is generally preferred, using some combination of the drugs listed below (Table 16-3). The use of miotics such as pilocarpine in narrow, potentially occludable, angles is a subject of some debate, even among glaucoma specialists. The rationale for miotic use is to pull the peripheral iris away from the TM, which opens the angle and prevents appositional closure. It may, however, make the angle narrower and potentially induce angle closure by causing the lens–iris diaphragm to move anteriorly with contraction of the ciliary muscle, which relaxes zonular tension and makes the pupillary block worse. If pilocarpine is used in such a patient, repeat gonioscopy should be performed 30 to 60 minutes after the initial drop. If the angle is not any wider, some would argue that a laser PI should be performed right away. If this is not feasible, consider adding a β-blocker to decrease aqueous secretion until the PI is performed.

- **Topical inhibitors of aqueous secretion:** β-Blockers, carbonic anhydrase inhibitors (CAIs), and α2-adrenergic agonists.
- **Uveoscleral outflow enhancers:** The prostaglandin analogs, as well as the α2-agonist brimonidine, increase uveoscleral outflow. Their use in angle closure has not been studied as extensively as some of the other agents, but they can also help lower the IOP. There is some theoretical concern that prostaglandin analogs could increase ocular inflammation. It should be remembered that miotics cause ciliary muscle contraction and decrease uveoscleral outflow.
- **Carbonic anhydrase inhibitors:** In patients who are not nauseated, an oral CAI is administered. If intravenous (IV) medications are available and the patient is unable to tolerate oral medications, IV acetazolamide is preferred as an adjunct to topical therapy because of its faster onset of action.
- **Hyperosmotic agents:** Hyperosmotic therapy reduces vitreous volume and can be a very powerful weapon in lowering IOP and breaking an attack. Glycerin and isosorbide can be given orally. Intravenous mannitol is the most potent agent for lowering IOP, but it also increases blood volume and should be used with caution, especially in patients with systemic medical issues such as congestive heart failure or kidney failure.

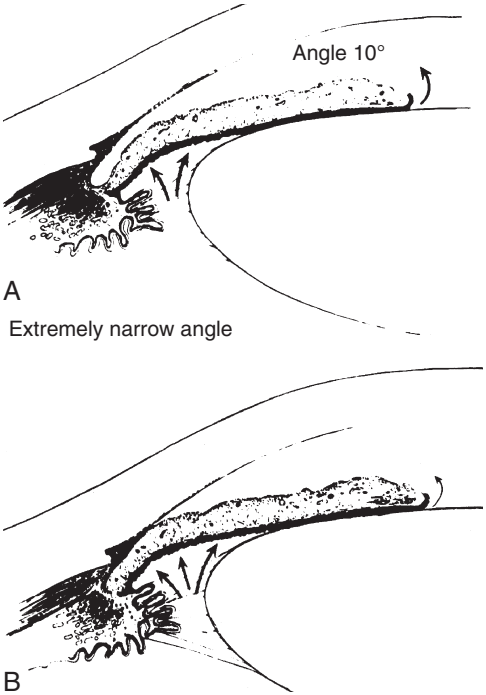

Figure 16-4. Mechanism of relative pupillary block closure. **A,** Extremely narrow angle with resistance to aqueous flow between the iris and the lens, leading to increased posterior chamber pressure. **B,** Closed angle.

- **Topical steroids:** Topical steroids (e.g., prednisolone 1% q.i.d.) are a useful adjunct to control the usually concurrent intraocular inflammation that may or may not be clinically apparent.
- **Miotics:** Pilocarpine helps to break the attack by pulling the peripheral iris away from the TM and increasing trabecular outflow. However, the pupillary sphincter (but not the ciliary muscle) usually becomes ischemic at IOPs above 40 to 50 mm Hg and therefore unresponsive to miotics until the IOP is lowered with other medications. The duration of IOP elevation and sphincter ischemia ultimately determines whether the sphincter will respond to miotics even after the IOP is lowered. The usual concentration used is 1% or 2%. Pilocarpine should be used with caution to avoid cholinergic toxicity. Also keep in mind that it may make some cases of angle closure worse, as noted above. Some believe it should not be used in aphakic or pseudophakic pupillary block.
- **Topical glycerin:** Topical glycerin can be quite helpful to clear the cornea, which facilitates detailed examination of the eye and also laser treatment.
- **Others:** The α2-agonist brimonidine increases uveoscleral outflow, as do the prostaglandin analogs.

KEY POINTS: BASIC TREATMENT OF ACUTE PRIMARY ANGLE CLOSURE

1. "Kitchen sink" approach of maximal medical topical therapy plus oral acetazolamide if patient not nauseated.
2. Oral hyperosmotics if above not effective and patient not nauseated, otherwise IV mannitol.
3. Laser peripheral iridotomy.

22. How would you treat the involved eye with laser?

Laser PI is the definitive procedure of choice to relieve pupillary block (Fig. 16-5). Angle closure from any etiology other than pupillary block will not respond to iridotomy. The argon or Q-switched YAG

Table 16-3. Treatment of Angle-Closure Glaucoma

FIRST DAY OF PRESENTATION	IOP <40 mm Hg	IOP 40-60 mm Hg	IOP >60 OR >40 mm Hg WITH CUPPING
	• Topical pilocarpine 1%	• Topical pilocarpine 2%	• Topical α-agonist and β-blocker
	• Topical β-blocker and α-agonist (possible topical carbonic anhydrase inhibitor)	• Topical β-blocker and α-agonist	• Topical prednisolone 1%
		• Topical prednisolone 1%	• IV acetazolamide 500 mg
	• Recheck at 1 hour	• IV acetazolamide 500 mg	• Analgesics and antiemetics as needed
1 hour after presentation	IOP < IOP of other eye	IOP reduced 50% but > IOP of other eye	IOP not reduced >50%
	• Topical β-blocker and α-agonist 2 times/day	• Topical pilocarpine 2%	• Topical pilocarpine 2%
	• Topical prednisolone 1% as needed	• Oral acetazolamide 500 mg	• Topical β-blocker and α-agonist
	• Recheck at 1 hour	• Recheck at 1 hour	• Oral glycerol 50% 1 mg/kg (or mannitol if vomiting)
2 hours after presentation	IOP < IOP of other eye	IOP reduced 50% but > IOP of other eye	IOP still not reduced 50%
	• Home on topical pilocarpine 1% 2 times/day and topical prednisolone 1% 4 times/day	• Topical pilocarpine 2% • Topical β-blocker and α-agonist • Oral glycerol 50% 1 mg/kg (or mannitol if vomiting) • Recheck at 1 hour	• Refer to specialist • Admit for IV mannitol • Maintain on oral acetazolamide 500 mg 2 times/day
	• Return next day		• Topical agents, α-agonists, β-blockers 2 times/day
			• Keep NPO in preparation for surgery next day
			• If possible, have specialist see patient on same day
			• Do iridotomy or have specialist do iridoplasty (see "IOP elevated even after repeat mannitol"). In unlikely event that cornea is clear, do iridotomy

Continued on following page

Table 16-3. Treatment of Angle-Closure Glaucoma* *(Continued)*

SECOND DAY	IOP < IOP OF OTHER EYE	IOP ELEVATED EVEN AFTER REPEAT MANNITOL
	• If eye uninflamed and cornea clear, do Nd:YAG peripheral iridotomy in affected eye	• Clear cornea with glycerin
	• If eye inflamed and cornea not clear, defer peripheral iridotomy in affected eye and do peripheral iridotomy on fellow eye	• Gonioscope again • Check disc
		• If peripheral iridotomy not already done, try to do if able to see adequately
		• If laser iridotomy already done and angle still closed, consider iridoplasty
		• If IOP falls >50% below presentation level, continue topical and oral medications and adjust therapy, depending on amount of cupping and future course of glaucoma
		• If IOP does not fall >50% below level at presentation, patient probably needs guarded filtration procedure
		• If IOP falls >50% below presentation level, continue topical and oral medications and adjust therapy, depending on amount of cupping and future course of IOP
Third day	• Do Nd:YAG peripheral iridotomy on fellow eye if not already done	
	• Arrange follow-up	
	• Plan to do Nd:YAG laser iridotomy on affected eye as soon as cornea is clear and eye quiet	

Note: All topical medications apply to the affected eye. No therapy in the form of drops is to be used in the unaffected eye unless that eye also has glaucoma or other ocular problems. Specifically, pilocarpine is *not* to be used in the unaffected eye.

*Glaucoma Service, Wills Eye Hospital/Jefferson Medical College.

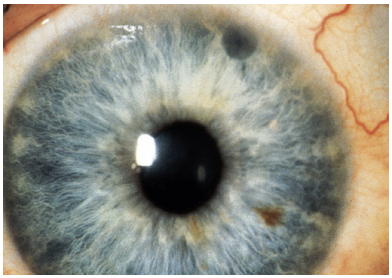

Figure 16-5. Patent laser peripheral iridotomy.

lasers are used. The Nd:YAG laser is preferred because it is faster, is easier, requires fewer bursts with less energy (causes less inflammation), is not dependent on iris color, and is less likely to cause complications such as posterior synechiae. The argon laser's thermal effect can help prevent bleeding and facilitate penetration of thick irides.

There is also some difference of opinion regarding the timing of the laser peripheral iridotomy in acute angle closure. If the IOP cannot be reasonably controlled medically, then the PI must be performed immediately. If the pressure can be reasonably controlled medically, it may be better to defer the iridotomy for a few days for the following reasons:

- Corneal edema, from high pressure, and Descemet's folds, from the abrupt lowering of pressure, can both make visualization and performing the iridotomy more difficult. In addition, because the anterior chamber is usually shallow, the corneal endothelium is closer to the point of laser energy focus and is more likely to be damaged from the concussion.
- The iris is usually somewhat congested, edematous, and inflamed during an attack. This can make the iridotomy more difficult to perform. More power may be required to successfully penetrate the iris, and this can be more uncomfortable for the patient than when the eye is not inflamed.

23. What are the most common complications of laser peripheral iridotomy?

The most troublesome problem is a ghost image resulting from light that has entered through the PI.

- **Argon:** Posterior synechiae and localized cataracts. Argon laser PIs are more likely to close than are Nd:YAG PIs.
- **Nd:YAG:** A hemorrhage may occur in up to 50% of eyes. It is usually small and localized to the area of the PI, but sometimes can form a significant hyphema. The bleeding may be controlled by applying gentle pressure on the eye with the contact lens. Even relatively large hyphemas are almost always gone the next day.

Transient IOP spikes of more than 6 mm Hg do occur in up to 40% of patients, most often within the first 1 to 2 hours. Perioperative treatment with apraclonidine decreases the incidence and severity of postlaser IOP spikes. β-Blockers and CAIs have been used, but with less success. The incidence and severity of postoperative IOP elevation are similar with argon and Nd:YAG lasers.

24. What if a peripheral iridotomy is unsuccessful? What other options are available for acute primary angle closure?

I. Other laser treatments for APAC
   A. Laser iridoplasty: Using a goniolens, spots of argon or diode laser aimed at the peripheral iris pull the iris away from the angle.
   B. Cyclophotocoagulation (CPC): mild cyclophotocoagulation using diode laser can abort cases of APAC refractory to medical and laser treatments (iridotomy and iridoplasty). It is not considered the first-line treatment for APAC but can be successful at aborting an episode of APAC when all options have failed before proceeding to surgery.

In most cases of APAC, the IOP can be brought down successfully with medical treatment (usually requiring systemic medication) and laser treatment; surgery is rarely indicated in resolving IOP in the acute phase of APAC. It is not infrequent, however, that after a crisis of APAC, the IOP is elevated chronically (i.e., APAC progresses into PAC/PACG). Studies from recent years have demonstrated the benefit of removing the lens in the treatment of APAC, PAC, and PACG even when there is an absence of significant cataract.

II. Surgical options for APAC
   A. Clear corneal peripheral iridectomy: This procedure was the treatment of choice for angle-closure glaucoma (acute or chronic) prior to the introduction of laser iridotomy. It is rarely performed today. However, if laser is not available or unable to be performed successfully, surgical iridectomy can be an option.
   B. Early cataract extraction for APAC: recent studies demonstrated the benefit of lens extraction in patients with APAC, PAC, and PACG. Unlike in POAG, the IOP-lowering effect of cataract extraction alone is significant in all primary angle closure cases (APAC, PAC, or PACG).
   C. Cataract extraction combined with goniosynechialysis: Mechanical pulling of PAS from the angle is performed at the end of cataract extraction surgery using a goniolens and a forceps of the surgeon's choice. The goal is to relieve the blockage of the trabecular meshwork from PAS and restore the outflow of aqueous humor. Some studies suggest that goniosynechialysis is more effective when the PAS are recent.
   D. Cataract extraction combined with endocyclophotocoagulation (ECP): Laser treatment of the ciliary body is performed at the time of cataract extraction using an endoscope equipped with

a diode laser. Similar to CPC (which refers to external laser application on the ciliary body), ECP coagulates the ciliary body and reduces IOP. In addition, laser application shrinks the ciliary body and opens the angle further, sometimes referred to as endocycloplasty. Currently, there is no evidence that cataract extraction combined with ECP or goniosynechialysis is superior to cataract extraction alone in the treatment of angle-closure diseases.

E. Trabeculectomy or tube shunts: Close to half the cases of APAC will progress into chronic PAC or PACG. In cases in which the IOP is consistently elevated despite laser iridotomy and medical treatment, lens extraction should be performed prior to filtering or tube shunt surgery, as the former carries fewer long-term complications and is often effective in reducing IOP. In advanced cases of PACG requiring very low IOP, combined lens extraction and filtering or tube surgery may be the best option.

When operating on these eyes, it is important to remember that they already have shallow chambers and are more likely to develop flat chambers and aqueous misdirection (malignant or ciliary block glaucoma). The use of miotics can also increase the chances of aqueous misdirection.

25. When can you consider an attack to be completely "broken"?

An attack can be considered "broken" when the intraocular pressure in the involved eye is lowered significantly and the patient's symptoms are resolved. However, many of these eyes will have chronically elevated IOP and require further medical and surgical treatment over the long term.

26. What are the chances of the same thing happening to the fellow eye?

There is a 40 to 80% chance of an acute attack in the fellow eye over the next 5 to 10 years.

27. What would you recommend for the fellow eye?

Prophylactic laser PI would be recommended, if a gonioscopic evaluation reveals a potentially occludable angle. It may be appropriate to treat the fellow eye first (if the angle is occludable), while waiting for the involved eye to quiet down and for the cornea to clear. The use of pilocarpine in the fellow eye to try to prevent angle closure by pulling the peripheral iris away from the TM until PI is performed is not without risk, as discussed in question 21.

28. Describe the short- and long-term sequelae to the various structures of the eye after an acute angle-closure attack

- **Cornea:** Shortly after the IOP is lowered, the epithelial microcystic edema will resolve, and Descemet's folds may be seen from the acute reduction in IOP (Fig. 16-6). The stromal edema takes longer to resolve. In most cases, significant endothelial damage occurs. If the attack has caused enough endothelial injury, epithelial and stromal edema may persist. Endothelial pigment may result from the pigment released during iridotomy or from any ischemic atrophic regions of the iris.
- **Anterior chamber:** Even after successful PI, the AC is usually still shallower than normal. Cataract extraction is the definitive treatment to deepen the anterior chamber.
- **Iris:** One may see a middilated, nonreactive, or sluggish pupil and sector atrophy and stromal necrosis from ischemia. Posterior synechiae may eventually develop long after a PI is performed owing to the alternate route available for aqueous humor flow. The pupil is often vertically oval.
- **Lens:** Glaukomflecken are small whitish anterior subcapsular opacities representing areas of necrotic lens epithelium with adjacent subcapsular cortical degeneration (see Fig. 16-6). Cataracts

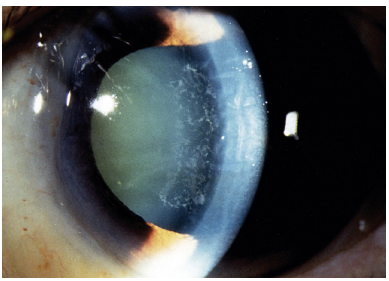

Figure 16-6. Photograph of an eye after resolution of an acute angle-closure attack. Note the corneal Descemet's folds, the PI at twelve o'clock at the upper edge of the photograph, and the lacy pattern of glaukomflecken under the anterior lens capsule.

may develop or progress after an attack. Cataract extraction can be beneficial for IOP control in primary angle-closure glaucoma.

- **Zonules:** Zonular weakness may not manifest until much later, i.e., during cataract extraction or spontaneous subluxation or dislocation.
- **Gonioscopy:** PAS.
- **Optic nerve:** Disc congestion and swelling, if present, may take several days to resolve. Acute attacks typically produce more pallor than cupping. Chronic angle closure usually produces more cupping than pallor, similar to open-angle glaucoma. OCT may show a loss of ganglion cells and thinning of the retinal nerve fiber layer.
- **Retina:** "Decompression retinopathy" may be seen after rapid lowering of the IOP as scattered intraretinal hemorrhages concentrated more around the posterior pole and optic nerve. Peripapillary atrophy can also develop over time, along with focal nerve-fiber bundle defects, diffuse thinning of the retina, etc.

29. What types of medications are contraindicated in narrow-angle glaucoma?

Topical and systemic sympathomimetic and anticholinergic medications should be avoided by people with eyes that have narrow and potentially occludable angles until a prophylactic laser iridotomy is performed. These are found in many over-the-counter antihistamine and cold remedies, antispasmodics for overactive bladder, and some antiparkinsonian agents. These medications are not contraindicated in patients with eyes that have narrow but not occludable angles, or eyes with a patent iridotomy, or in patients with open-angle glaucoma.

Use *miotics* with caution in patients with narrow angles, regardless of occludability, because of the risk of causing further narrowing by anterior displacement of the lens–iris diaphragm. These patients should at least have repeat gonioscopy after commencing miotic therapy to rule out this possibility. If the angles do become significantly narrower, one must consider discontinuation of miotic therapy or performing a prophylactic PI, if there is a compelling reason for continuing miotic therapy.

KEY POINTS: LONG-TERM SEQUELAE OF AN ACUTE PRIMARY ANGLE-CLOSURE ATTACK

1. Corneal endothelial cell loss, endothelial pigment.
2. Permanently middilated and unreactive pupil.
3. Iris sector atrophy, posterior synechiae.
4. Peripheral anterior synechiae in the angle.
5. Glaukomflecken, other cataractous changes.
6. Occasionally, lens zonular weakness (may be causative).
7. Optic nerve pallor out of proportion to cupping.

30. List some possible causes for persistent or recurrent intraocular pressure elevation after a successful peripheral iridotomy.

- PAS formation and/or undetected injury to the TM during the period of angle closure
- Nonpupillary block angle closure (see question 10, classification, II.A.1 to 4.)
- Incomplete iridotomy will result in persistent IOP elevation. Occlusion of the iridotomy with debris or a membrane may cause a recurrent episode of pupillary block angle closure. Remember that transillumination does not equal patency.
- Underlying or residual trabecular meshwork dysfunction—chronic apposition of iris to trabecular meshwork can induce trabecular dysfunction even in the absence of PAS.

PLATEAU IRIS

31. What is plateau iris configuration?

Anteriorly positioned (and sometimes larger than normal) ciliary processes push the peripheral iris more anteriorly than normal (Fig. 16-7). The central AC is usually slightly shallow or normal depth, but the angle recess is narrower than the depth of the AC would suggest. The iris has a relatively flat contour, with a sharp peripheral drop-off at the angle approach. This finding is designated "p" in our

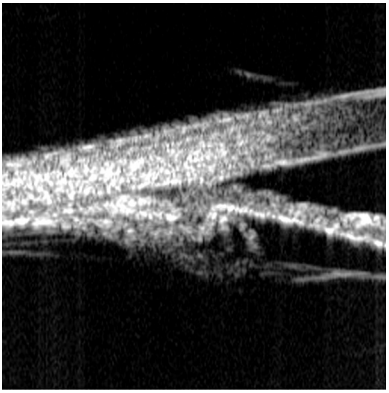

Figure 16-7. Ultrasound biomicroscopy image of the anterior segment of an eye with plateau iris. Note the large ciliary processes causing anterior displacement of the peripheral iris and angle closure, whereas the central iris remains flat.

gonioscopic system. A component of pupillary block is frequently present. With dilation, the peripheral iris folds into the angle and occludes the TM.

32. How does plateau iris present clinically?

It may be noted on routine examination or present as an acute or chronic angle-closure glaucoma.

33. Describe the epidemiology of plateau iris.

Traditional teachings describe patients with plateau iris configuration (PIC) as usually younger (typically fourth and fifth decades) and less hyperopic than patients with primary angle closure; they may even be myopic. With the advent of anterior segment imaging devices such as UBM, it has been found that plateau iris configuration is quite common in both Asians and Caucasians—about 20 to 30% of the population has PIC. PIC refers to a narrow angle with steep iris on gonioscopy despite a patent iridotomy; however, the IOP is normal in the plateau iris configuration. Eyes with PIC can develop elevated IOP acutely (APAC) or chronically (PAC). Traditionally, PIC eyes with elevated IOP, either acutely or chronically, are referred to as having plateau iris syndrome. It is unclear how many PIC eyes will progress to APAC or PAC. We suspect that only a small percentage of PIC patients will develop elevated IOP. However, we are still unable to identify which subset of PIC will progress to APAC or PAC.

34. How can plateau iris be distinguished from relative pupillary block (primary) angle closure on slit lamp examination?

Primary angle closure normally presents with a shallow central AC and moderate to significant iris convexity, which is in contrast to the appearance of PIC noted above. With indentation gonioscopy, the angle is much harder to open and does not open as widely as a typical narrow angle. A "hills and valleys" profile may be seen when looking at the angle. In addition, indentation gonioscopy reveals the almost pathognomonic "double hump sign," characterized by posterior displacement of the midperipheral iris but a persistently anterior position of the peripheral iris. Persistence of the plateau iris appearance despite a patent iridotomy confirms the diagnosis clinically. High-resolution UBM can also confirm the diagnosis.

35. What is plateau iris syndrome?

Plateau iris syndrome is an acute or chronic angle closure that develops with dilation, or even spontaneously, in an eye with plateau iris configuration and a patent PI.

36. How is plateau iris syndrome treated?

PIC is a subset of PACS. Plateau iris syndrome (PIS) is APAC or PAC secondary to plateau iris configuration. The treatment of PIC or PIS is similar to the treatment of PACS, PAC, or APAC.

The primary procedure of choice in an eye with (or at risk for) angle closure is laser peripheral iridotomy, to eliminate any component of pupillary block that may be present. In general, the older the patient, the more the pupillary block contributes, as a percentage, to the mechanism of angle closure. However, laser iridotomy is *not* adequate treatment in these cases; it is merely the necessary

first step. Eyes with PIC often require other treatments to open the angle, especially if the patient has symptoms of intermittent angle closure or a positive prone darkroom test. It is essential to perform gonioscopy after the iridotomy to verify the angle status.

Laser peripheral iridoplasty may be necessary in patients whose angle approach remains very narrow despite a patent PI. This technique uses the argon laser to apply burns circumferentially to the peripheral iris, which cause it to contract and pull away from the angle. Although the green wavelength is usually used, use of the yellow-green wavelength may improve absorption of laser energy in more lightly colored irides. One important potential complication that should always be discussed with the patient is the risk of a permanently larger pupil size postoperatively and its attendant potential to increase problems with glare. Avoiding vessels is also important to prevent anterior ischemia.

Chronic miotic therapy can also be a useful alternative or adjunct to iridoplasty in eyes with a narrow approach despite a patent PI. With either method of therapy, the angle should be examined with gonioscopy after instillation of pilocarpine and at regular 6- to 12-month intervals afterward, to document the effect on angle configuration.

37. Are angles always open after a successful laser peripheral iridotomy?

No. About 20 to 40% of PACS eyes still have narrow angle even after a successful laser peripheral iridotomy. To reiterate, PACS eyes do not have elevated IOP. Angles can remain narrow after a successful laser PI with normal IOP. The possible mechanisms of narrow angle after laser PI are plateau iris configuration, thick peripheral iris (often found in Chinese PACS eyes), and lens-related mechanisms. Other secondary causes of angle narrowing should be sought as well. See question 10.

AQUEOUS MISDIRECTION SYNDROME (MALIGNANT/CILIARY BLOCK GLAUCOMA)

38. What is aqueous misdirection syndrome?

Posterior misdirection of aqueous into the vitreous cavity causes an anterior displacement of the lens–iris diaphragm. It most commonly occurs in eyes with narrow angles after ocular (typically glaucoma-filtering as well as cataract) surgery, but can occur after laser procedures or, rarely, spontaneously. Miotic use and previous angle-closure glaucoma increase the risk of occurrence. It typically presents within the first postoperative week with a shallow to flat anterior chamber and a high IOP, but the IOP may be normal in an eye with a functioning filter. Serous choroidal effusion/detachment, pupillary block, and suprachoroidal hemorrhage should be ruled out.

39. Why does aqueous misdirection occur? How does it present clinically?

It is still unclear why aqueous misdirection occurs. It is not an uncommon entity in glaucoma patients who undergo cataract or glaucoma surgery, especially in those with angle-closure glaucoma. It is hypothesized that a spontaneous or induced choroidal effusion in an eye with an impermeable vitreous can cause anterior chamber shallowing from a posterior pushing mechanism (the vitreous pushing the lens–iris diaphragm). This hypothesis makes clinical sense as aqueous misdirection often occurs during the surgery when the anterior chamber volume is not maintained, leading to a transient hypotony.

Aqueous misdirection can occur during surgery or postoperatively. Patients will present with blurred vision with myopic shift (forward movement of lens). On slit lamp examination, the anterior chamber is diffusely shallow, both centrally and peripherally, in contrast to pupillary block, in which the anterior chamber is more shallow peripherally than centrally. The IOP is usually high to normal.

40. How is aqueous misdirection treated medically?

- Cycloplegics relax the ciliary muscle, which increases zonular tension and pulls the lens–iris diaphragm posteriorly. Cycloplegics are also essential in the management of angle closure due to anterior rotation of the ciliary body. They may be required indefinitely.
- Aqueous suppressants.
- Hyperosmotic agents.
- Miotics are contraindicated.

41. How can aqueous misdirection be treated with laser if it is unresponsive to medication?

The goal of therapy is to reestablish aqueous flow from the posterior chamber to the anterior chamber and to try to create a channel for aqueous flow from the posterior segment to the anterior segment.

- **Nd:YAG laser hyaloidotomy:** In pseudophakes and aphakes, using the Nd:YAG laser to disrupt the anterior vitreous face can be successful in resolving aqueous misdirection.
- **Argon laser treatment of ciliary processes:** Regardless of the lens status, this procedure can be done only if a surgical iridectomy or a relatively large laser iridotomy is present.

42. How can aqueous misdirection be treated surgically if it is refractory to medical therapy and/or laser?

The timing and mode of intervention depend on the following factors:

- Duration of misdirection without resolution.
- Degree and duration of shallowness or flatness of the anterior chamber. When there is contact between the corneal endothelium and the crystalline lens or an intraocular lens, surgical correction is urgent.
- IOP and optic nerve status.

The treatment options are as follows:

- **Anterior chamber reformation:** Occasionally this can be performed at the slit lamp by injecting a small amount of air followed by viscoelastic through a peripheral corneal paracentesis wound. The initial air helps to confirm complete penetration of the needle through the cornea into the AC before injecting any viscoelastic. Because the IOP is almost always elevated with the aqueous misdirection syndrome, this is rarely an option.
- **Pars plana anterior or posterior vitrectomy (PPV):** Removing the vitreous is often the curative surgery for aqueous misdirection. Aqueous misdirection can occasionally persist or recur even after PPV, especially in phakic eyes.
- **Lens extraction:** This may be combined with vitrectomy. The posterior capsule and anterior hyaloid are usually incised to allow aqueous passage to the anterior chamber.
- **Iridozonulohyalovitrectomy:** This can be performed in phakic, pseudophakic, or aphakic eyes and consists of rendering the eye unicameral, by passing a vitrector either from the pars plana forward or from the anterior chamber posteriorly.

NEOVASCULAR GLAUCOMA

43. What typically causes neovascular glaucoma?

Posterior segment (retinal) ischemia results in the production of angiogenic factors that stimulate the formation of a neovascular membrane on the iris (NVI). Vascular endothelial growth factor (VEGF) has been shown to be the primary angiogenic factor. As the membrane first grows into the angle and across the scleral spur to the TM, the angle appears anatomically open. Later, the membrane contracts, pulling the peripheral iris up to the TM and peripheral cornea, creating PAS. This process can occur over significant areas of the angle very quickly (often in a few days), producing an acute angle-closure glaucoma (through an anterior pulling mechanism). Common causes of neovascular glaucoma (NVG) are CRVO (one-third), proliferative diabetic retinopathy (one-third), and carotid occlusive disease (approximately 10%). Occasionally, CRAO, chronic uveitis, and intraocular tumor can cause NVG.

44. How is neovascular glaucoma treated?

1. The underlying etiology of the neovascularization must be diagnosed and treated, usually with panretinal photocoagulation (PRP) or, if the lack of clear visualization of the retina precludes PRP, peripheral retinal cryotherapy for posterior segment ischemic processes. Anti-VEGF compounds injected into the vitreous or AC can produce a dramatic regression of NVI within 1 to 2 weeks. Patients should have repeat gonioscopy after anti-VEGF injection, as the rapid contraction of the neovascular membrane may lead to further angle closure.
2. **Medical treatment**. The percentage of angle that is closed with PAS as well as the outflow resistance of the TM still open will determine the potential for successfully treating the glaucoma medically. Even if the angle is completely closed, maximal tolerated aqueous suppressant and, if necessary, hyperosmotic therapy should be used in an attempt to temporize until surgery is performed. Miotics should not be used, because they decrease uveoscleral outflow and increase inflammation.
3. **Surgical treatment**. One of the most important principles to remember when operating on these eyes, especially eyes with florid NVI, is to try to avoid rapid decompression of the eye. The fragile new vessels may rupture, creating a spontaneous hyphema that can significantly complicate subsequent management.

- **The guarded filtering procedure (trabeculectomy)** has been used to control the IOP in these eyes with poor results. The success rate is somewhat better if an adjunctive antimetabolite such as mitomycin C is used. The risk of filtration failure due to fibrosis is higher, presumably owing to the presence of angiogenic factors in the aqueous.
- **Aqueous tube shunts** have become the procedure of choice for many glaucoma surgeons, but still have success rates of only approximately 70%, owing to the often poor prognosis of the underlying pathologic process.

4. **Laser cyclophotocoagulation**. This may be a viable option in eyes with minimal visual potential, as an attempt to control IOP for long-term comfort and to prevent the need for enucleation for pain owing to high IOP. The diode laser is the preferred method of cyclophotocoagulation. Cyclophotocoagulation by cryotherapy is seldom used nowadays because of the risk of phthisis bulb and postoperative pain and inflammation.

MISCELLANEOUS

45. What are the various mechanisms of producing angle closure secondary to ocular inflammation?

- PAS formation from any etiology
- Complete pupillary block (secluded pupil) from posterior synechiae resulting in iris bombé
- Uveal effusion causing anterior rotation of the ciliary body (uncommon)
- Exudative retinal detachment pushing the lens–iris diaphragm forward (rare)

N.B. Intraocular inflammation leads to elevated IOP mostly through open-angle mechanisms: blockage of the trabecular meshwork by debris or pigment and steroid-induced ocular hypertension.

46. Describe nanophthalmos.

Nanophthalmos is a bilateral condition in which the globes are significantly shorter than normal, with an axial length less than 20 mm (mean 18.8 mm), with a corresponding hyperopia. In addition, the corneal diameter is smaller (mean 10.5 mm versus 12 mm for a normal adult) and the sclera is much thicker (often at least twice as thick) than normal. The unusually thick sclera creates an impediment to uveoscleral outflow that predisposes to choroidal effusions, either spontaneously or after surgery, and angle closure. Angle-closure glaucoma can also occur as a result of anterior-segment crowding without uveal effusions.

47. List one systemic medication that can cause angle closure by producing ciliochoroidal effusions and the principles for management of this type of angle closure.

Topiramate, a sulfa-derived antiepileptic medication whose indications have expanded to include the treatment of migraine headaches and obesity, has been reported to cause idiosyncratic ciliochoroidal effusions with acute onset myopia and angle-closure glaucoma. Thus, a careful and thorough history can be crucial in making the diagnosis. These changes do gradually resolve with discontinuation of the medication. Pupillary block is usually not present and thus laser peripheral iridotomy is not helpful. Miotics will make the problem worse, as they cause anterior movement of the lens–iris diaphragm. The treatment includes topical and systemic aqueous suppressants, systemic hyperosmotics if necessary for IOP control, steroids, and cycloplegics to help pull the lens–iris diaphragm posteriorly.

WEBSITES

1. The Glaucoma Foundation:
www.glaucomafoundation.org
{link accessed successfully by Maria on 9.18}
2. Glaucoma Research Foundation:
www.glaucoma.org
{link accessed successfully by Maria on 9.18}
3. www.gonioscopy.org
{link accessed successfully by Maria on 9.18}

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CHAPTER 17

SECONDARY OPEN-ANGLE GLAUCOMA

Janice A. Gault

1. **A 72-year-old man presents for a routine exam. He states that vision in the left eye is getting bad. On exam, he has vision of 20/30 in the right and counts fingers at 3 feet in the left. The intraocular pressure in the right eye is 25 mmHg, in the left eye, 42 mmHg. The optic nerve appears somewhat cupped on the right, severely so on the left. Visual fields reveal a significant nasal step in the right eye and a temporal island on the left. He does not have pseudoexfoliation syndrome or a Krukenberg spindle in either eye. His angles are deep. What do you suspect?**
   A history of trauma. The patient had been a boxer, and he was often hit in his eyes. Angle-recession glaucoma can be asymptomatic until many years later when visual loss occurs. On gonioscopy, the angle recession is determined by torn iris processes and posteriorly recessed iris, revealing a widened ciliary body band. Comparison with the other eye may help to identify this condition. Any patient with traumatic iritis or hyphema needs to be warned of this complication, which may occur many years later. Treatment is the same as with open-angle glaucoma except that miotic agents are ineffective and may even increase the intraocular pressure. Argon laser trabeculoplasty (ALT) is rarely effective.

2. **What should you look for to make a diagnosis of pseudoexfoliation glaucoma?**
   Fibrillar, "dandruff-like" material is deposited on the anterior lens capsule in a characteristic bull's eye pattern, most easily seen after pupillary dilation. This material is also seen clinically in the angle and on the iris. Gonioscopy reveals a heavily pigmented trabecular meshwork and a Sampaolesi's line, which is pigment deposited anterior to the Schwalbe's line (Fig. 17-1).

   Pseudoexfoliation syndrome is thought to be part of generalized basement membrane disorder, because it can be found histologically in other parts of the body. It may be unilateral or bilateral with

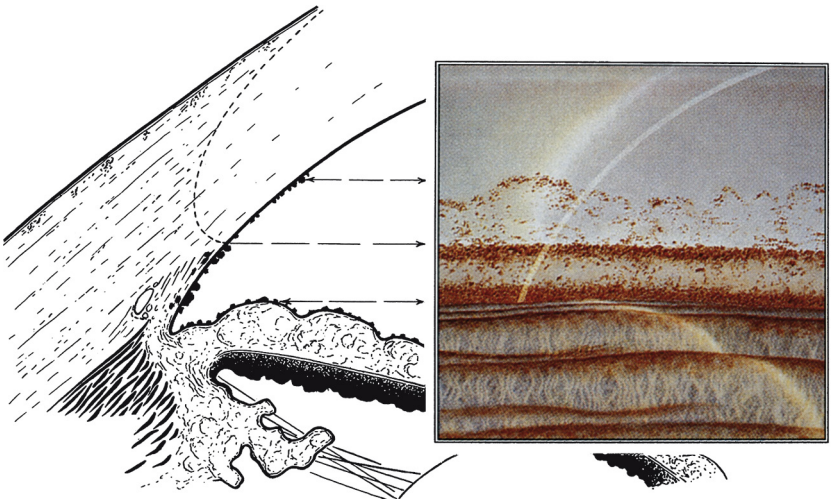

Figure 17-1. The Sampaolesi's line is a scalloped band of pigmentation anterior to the Schwalbe's line. *(From Alward WLM: Color Atlas of Gonioscopy. St. Louis, Mosby, 1994.)*

asymmetry. Although pseudoexfoliation is infrequent in the United States, it accounts for more than 50% of open-angle glaucoma in Scandinavia. The condition is often more resistant to medical therapy than primary open-angle glaucoma and may require ALT, selective laser trabeculoplasty (SLT), or surgical therapy.

3. Is the condition cured after cataract extraction?

No. The deposits continue, and cataract surgery has a higher risk in such patients. The zonules are weak, and synechiae are often present between the iris and the anterior lens capsule. There is an increased risk of posterior capsular rupture and zonular dialysis.

4. What is true exfoliative glaucoma?

True exfoliative glaucoma is a capsular delamination caused typically by exposure to intense heat, as seen in glassblowers.

KEY POINTS: PSEUDOEXFOLIATION GLAUCOMA

1. Bull's-eye deposits on anterior lens capsule.
2. Sampaolesi's line on gonioscopy.
3. Less responsive to medical therapy.
4. Higher risk for complications in cataract surgery.

5. A 24-year-old man with sarcoidosis presents with an intraocular pressure of 35 mmHg in the right eye and 32 mmHg in the left eye. He notes mild pain and some decreased vision but is otherwise asymptomatic. On examination, you notice 2+ cell and flare in both eyes as well as significant posterior synechiae and mutton-fat keratic precipitates. Gonioscopy reveals an open angle with no peripheral anterior synechiae. A dilated exam reveals no significant cupping of either optic nerve. What do you do?

Most likely, the inflammatory cells have clogged the trabecular meshwork. Intensive topical steroids and a cycloplegic should decrease the inflammatory load and break the synechiae to prevent angle closure from becoming an issue in the future. Antiglaucoma medications are also appropriate until the pressure decreases. However, miotics are contraindicated because they may cause further synechiae and precipitate angle closure. They also increase the permeability of blood vessels and may contribute to an increase in inflammation. Prostaglandin agonists or analogs may also increase inflammation and should be avoided. The aggressiveness with which the pressure is lowered depends a great deal on optic nerve cupping.

6. The same patient returns 14 days later with pressures of 40 and 45 mmHg in the right and left eye, respectively. Exam reveals minimal cell and flare in each eye as well as a significant decrease in the keratic precipitates. He has been using prednisolone acetate 1% every hour and atropine 1% three times/day. What should you do?

A gonioscopy should be performed. The differential of increased intraocular pressure in this situation includes:

- Steroid response. Decreasing steroids lowers the pressure if this is the cause.
- Cellular blockage of the trabecular meshwork from the inflammatory cells. Increasing the steroids lowers the pressure if this is the cause.
- Synechiae formation causing an element of secondary angle closure or blocking of the meshwork. Gonioscopy determines whether the angle is open. Increased steroids may melt the synechiae.

Provided the angle is open and without neovascularization, the most likely cause is response to steroids. The increased intraocular pressure may occur anywhere from a few days to years after initiating therapy. Raised intraocular pressure has been seen with topical steroids in or around the eye, after oral and intravenous administration of steroids, and even with inhalers. Patients with Cushing's syndrome with excessive levels of endogenous steroids are also at risk. Optic nerve evaluation is crucial to determine the risks of damage. Decrease the steroid concentration or dosage and start antiglaucoma therapy. A topical nonsteroidal agent may help decrease inflammation without increasing intraocular pressure. Fluorometholone and loteprednol (Alrex, Lotemax) are also less likely to increase intraocular pressure than other formulations of steroids; however, they have less potency to decrease inflammation.

7. What does a Krukenberg spindle look like? What does it mean?

A Krukenberg spindle is a vertical pigment band on the corneal endothelium (Fig. 17-2). It is typically found in patients with pigmentary dispersion syndrome. The iris is often bowed posteriorly and rubs against the lens zonules. This process causes midperipheral spokelike iris transillumination defects. Gonioscopy reveals a densely pigmented trabecular meshwork for 360 degrees. The patient is often asymptomatic but may notice blurred vision, eye pain, and halos around lights after exercise or pupillary dilation. Pigmentary dispersion syndrome is more common in young adults and white, myopic males. It is usually bilateral.

8. How is pigmentary dispersion treated?

If no optic disc damage is noted and the visual fields are normal, the patient may be observed. Treatment for intraocular pressure over 28 mmHg is usually indicated, although this point is controversial. Once damage is noted, miotics may be the first line of therapy because they minimize contact between the zonules and the iris. However, miotics also cause myopic fluctuation and may not be practical in young patients, especially in myopes with lattice degeneration because of their increased risk of retinal detachment. Laser peripheral iridectomy has been recommended; it treats the posterior bowing of the iris and may theoretically cure the disorder. The pressures may still be elevated until the residual pigment in the trabecular meshwork is cleared. This treatment is controversial and seems to have fallen out of favor. Patients also respond well to ALT or SLT because of the increased pigment of the trabecular meshwork.

9. A 95-year-old woman presents with a markedly red, painful right eye of 2 days' duration. Her vision is hand motions at 1 foot and 20/400 in the right and left eye, respectively. Exam of the right eye reveals a steamy cornea with a pressure of 60 mmHg and no view of the anterior chamber. The left eye has a brunescent cataract but appears to be deep and quiet with a pressure of 18 mmHg. With topical glycerin, the cornea clears in the right eye to reveal iridescent particles floating in the anterior chamber with a morgagnian cataract. Gonioscopy reveals bilateral open angles. No view is obtained of either posterior chamber. What do you do now?

The patient denies a history of uveitis. A B-scan of both eyes reveals only significant cataract without retinal detachment or intraocular tumor. The leakage of lens material through an intact lens capsule is obstructing the trabecular meshwork. If the diagnosis is in question, paracentesis may be done to examine the anterior chamber reaction microscopically. Macrophages are filled with lens cortical material (phacolytic glaucoma). Typically, the lens is hypermature, as in this patient. The intraocular pressure must be reduced and the inflammation controlled before surgical therapy is attempted. A steroid such as prednisolone acetate 1% every hour, a cycloplegic such as scopolamine 0.25% three times/day, and antiglaucoma medications are started immediately. Cataract extraction is performed in the next day or two once the eye is less inflamed.

10. A 64-year-old woman who had cataract surgery in the left eye 1 week ago presents to the emergency department complaining that the eye is red and painful with decreasing vision. What is your concern?

First, you must think of endophthalmitis. Any patient presenting after surgery with a red, painful eye with decreased vision must be presumed to have endophthalmitis until it is ruled out. The exam

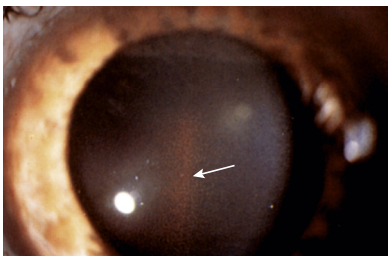

Figure 17-2. A Krukenberg spindle *(arrow)* is made of pigment deposited on the endothelium in pigmentary dispersion syndrome. *(From Alward WLM: Color Atlas of Gonioscopy. St. Louis, Mosby, 1994.)*

reveals vision of hand motions at 2 feet, a severely injected eye with corneal edema, 4+ cell and flare, and an intraocular pressure of 47 mmHg. The anterior chamber is filled with lens cortical material, and a rupture in the posterior capsule is seen. A large chunk of nuclear material is in the vitreous. The optic nerve is mildly cupped.

Because the lens material is seen in the anterior chamber, treatment with steroids and antiglaucoma medications is appropriate, along with close observation. The diagnosis is most likely lens-particle glaucoma. The patient is started on prednisolone acetate 1% every 2 hours, scopolamine 0.25% three times/day, latanoprost once daily, a β-blocker twice daily, apraclonidine twice daily, and acetazolamide sequels twice daily. In addition, because her pressure is so high, mannitol is given. When the pressure improves to 25 mmHg, she is sent home. The next day, she counts fingers at 5 feet, her intraocular inflammation is subsiding, and the pressure is 23 mmHg. Once her eye is less inflamed and the pressure well controlled, she is scheduled for removal of the remaining lens material. If the retained lens material is minimal, patients sometimes can be maintained on medical therapy until the eye clears without surgery.

11. What other type of open-angle glaucoma can be caused by the lens?

Phacoanaphylactic glaucoma, which occurs after penetrating trauma or surgery. The patient is sensitized to the lens protein during a latent period and develops a granulomatous uveitis. This feature distinguishes it from lens-particle glaucoma. Patients are treated medically and may need surgery to remove the lens if they do not respond adequately.

12. What is Posner-Schlossman syndrome? Who gets it?

Patients are young to middle-aged. They notice unilateral attacks of mild pain, decreased vision, and halos around lights. Episodes tend to recur. Also known as glaucomatocyclitic crisis, this disorder is idiopathic. On exam, intraocular pressure is high, usually between 40 and 60 mmHg. The angle is open on gonioscopy without synechiae, and the eye is minimally injected. Anterior chamber reaction is minimal. The corneal epithelium may be edematous because of the acute rise in pressure. A few fine keratic precipitates may be present on the corneal endothelium, often inferiorly. Treatment includes steroids and antiglaucoma medications to reduce aqueous production. A cycloplegic agent is necessary only if the patient is symptomatic. The attacks usually resolve in a few hours to a few weeks. No therapy is needed between attacks. However, the risk of chronic open-angle glaucoma is increased in both eyes.

13. What is the classic triad of Fuchs' heterochromic iridocyclitis?

This consists of heterochromia, cataract, and low-grade iritis. The iritis is mild and does not cause synechiae. Characteristic stellate, colorless keratic precipitates are seen over the inferior endothelium. Fine new vessels may be seen in the angle but do not cause closure. The glaucoma is difficult to control and often does not correspond to the degree of inflammation. Steroids are not often helpful.

14. A patient reports for postoperative check-up 1 day after cataract surgery. The pressure in the operated eye is 40 mmHg, and the patient complains of nausea. What is the most likely cause?

Retained viscoelastic from surgery. The pressure usually increases 6 or 7 hours after surgery and normalizes within 24 to 48 hours, depending on the type of viscoelastic. Most eyes tolerate short-term pressures up to 30 mmHg; of course, tolerance depends on preexisting optic nerve status. Medical treatment and paracentesis to remove the viscoelastic are indicated to decrease pressure quickly and relieve nausea. Paracentesis is somewhat controversial because of the small increased risk of endophthalmitis.

15. What else can cause postoperative glaucoma?

Hyphema, pigment dispersion, generalized inflammation, aphakic or pseudophakic pupillary block, malignant glaucoma (aqueous misdirection syndrome), and steroid-response glaucoma. In patients who have undergone an intracapsular cataract extraction, α-chymotrypsin is injected into the anterior chamber to dissolve the zonules. The zonular debris may block the trabecular meshwork postoperatively. Epithelial ingrowth may occur many months to years after surgery or trauma and block outflow.

16. A patient had cataract surgery 1 year ago but continues to have episodes of anterior chamber cell and flare with increased intraocular pressure. Some of the cells are red blood cells. What is the diagnosis?

The diagnosis is uveitis–glaucoma–hyphema syndrome. The cells may layer out to produce a hyphema, usually as a result of irritation from an anterior chamber intraocular lens, although a

posterior chamber lens may be involved. Gonioscopy may reveal where the irritation is occurring, such as from a lens in the sulcus or a haptic causing iris chafing. Treatment consists of atropine, topical steroids, and antiglaucoma medications until the pressure is reduced. Argon laser of the bleeding site, if it can be identified, may be curative. However, exchange or removal of the intraocular lens is often necessary.

17. How can raised episcleral venous pressure cause glaucoma?

Aqueous drains from the anterior chamber through the trabecular meshwork, Schlemm's canal, and intrascleral channels to the episcleral and conjunctival veins. Normal drainage depends on an episcleral venous pressure that is lower than the pressure of the eye. Usually, it ranges from 8 to 12 mmHg. However, if it is higher than intraocular pressure, drainage does not occur. Blood will be seen in the Schlemm's canal on gonioscopy. Drugs that reduce aqueous humor formation are obviously the most effective medical treatment.

KEY POINTS: CAUSES OF RAISED EPISCLERAL VENOUS PRESSURE

1. Thyroid ophthalmopathy.
2. Carotid and dural fistulas.
3. Superior vena cava syndrome.
4. Retrobulbar tumors.
5. Orbital varices.
6. Sturge-Weber syndrome.

18. A patient with long-standing diabetes has had recurrent vitreous hemorrhage. While you are observing him, waiting for the condition to clear, intraocular pressure increases to 35 mmHg. What should you suspect?

When intraocular hemorrhages clear, hemolytic or ghost-cell glaucoma may develop. Hemolytic glaucoma occurs because macrophages full of hemoglobin block the trabecular meshwork. Reddish cells can be seen in the anterior chamber. In ghost-cell glaucoma, degenerating red blood cells block the aqueous outflow. Khaki cells in the anterior chamber may layer out to form a pseudohypopyon. Both conditions can be treated medically until the hemorrhage clears. However, because the intraocular pressure may become markedly raised, washout of the anterior chamber and/or vitrectomy often becomes necessary. In addition, the patient may be developing neovascular glaucoma; thus it is important to check the angles for new vessels and angle narrowing.

19. What other conditions may cause open-angle glaucoma?

1. Intraocular tumor may cause secondary open-angle glaucoma by invasion of the chamber angle or blockage of the trabecular meshwork by tumor debris.
2. Siderosis or chalcosis from a retained metallic foreign body.
3. Chemical injuries from acid or alkali can shrink the scleral collagen or cause direct damage to the trabecular meshwork.
4. Posterior polymorphous dystrophy is a bilateral and autosomal dominant disease. Vesicles are seen at the Descemet's membrane. Corneal edema occurs in severe cases. Iridocorneal adhesions may occur. Glaucoma is associated in 15% of cases.
5. Iridocorneal endothelial syndrome

20. What is iridocorneal endothelial syndrome?

It is a spectrum of three entities that overlap considerably:

- **Essential iris atrophy:** Iris thinning leads to iris holes and pupillary distortion
- **Chandler's syndrome:** Mild iris thinning and distortion with hammered metal appearance of corneal endothelium
- **Cogan-Reese syndrome:** Pigmented nodules on the iris surface with variable iris atrophy.

Such patients are generally asymptomatic, middle-aged adults. Usually findings are unilateral with increased intraocular pressure and corneal edema. No treatment is necessary unless corneal edema and glaucoma are present.

21. What types of secondary open-angle glaucoma occur in children?

1. Glaucoma associated with mesenchymal dysgenesis is a spectrum of disease, but two main categories are recognized:
   - Axenfeld's anomaly consists of a prominent Schwalbe's ring with attached iris strands. Axenfeld's syndrome is the anomaly with coincident glaucoma and occurs in 50% of cases. It is autosomal dominant or sporadic.
   - Rieger's anomaly is Axenfeld's anomaly plus iris thinning and distorted pupils. Sixty percent of patients develop glaucoma; it is also autosomal dominant or sporadic. Rieger's syndrome is the anomaly associated with dental, craniofacial, and skeletal abnormalities.
2. Aniridia is a bilateral, near-total absence of the iris. The strands may be seen only by gonioscopy. Glaucoma, foveal hypoplasia, and nystagmus may occur. The disorder may be autosomal dominant or sporadic. Patients with sporadic inheritance need to be evaluated for Wilms' tumor, which is associated in 25% of cases.
3. Oculocerebrorenal syndrome (Lowe) is an X-linked recessive disease. Patients have aminoaciduria, hypotonia, acidemia, cataracts, and glaucoma.
4. Congenital rubella may be associated with cataracts and pigmented retinal lesions. Cardiac, auditory, and central nervous abnormalities are often coexistent.
5. Sturge-Weber syndrome.
6. Neurofibromatosis.
7. Glaucoma after cataract removal is a long-term risk for such patients.

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CHAPTER 18

MEDICAL TREATMENT OF GLAUCOMA

Grace L. Kim, Alexander B. Theventhiran, Jeffrey D. Henderer, and Richard P. Wilson

1. What classes of medications are used to treat glaucoma?

See Table 18-1.

2. How do these medications work?

- **Prostaglandin analogs** increase outflow through the uveoscleral outflow channels. Aqueous is absorbed into the face of the ciliary body or into the trabecular meshwork and then flows posteriorly around the longitudinal muscle fibers of the ciliary body posteriorly. It is absorbed into the choroid or passes out through the sclera.
- **β-Blockers** and **carbonic anhydrase inhibitors** (CAIs) decrease aqueous production. β-Blockers decrease aqueous humor secretion by inhibiting cyclic adenosine monophosphate production in the ciliary epithelium. CAIs decrease aqueous humor production by directly antagonizing carbonic anhydrase in the ciliary epithelium.
- The **adrenergic agonist** epinephrine initially decreases aqueous production slightly, but its major action is to increase outflow through the trabecular meshwork. Because epinephrine is no longer manufactured for topical ophthalmic use, apraclonidine and brimonidine are the currently available adrenergic agonists that follow in the footsteps of the original epinephrine and its prodrug dipivefrin (Propine), which is also no longer produced. Apraclonidine and brimonidine decrease aqueous production. Brimonidine may have some increased uveoscleral outflow as well.
- **Miotics** constrict the longitudinal muscle of the ciliary body, which is attached to the scleral spur anteriorly and to the choroid posteriorly. When the longitudinal muscle constricts, it pulls the scleral spur posteriorly, pulling open the spaces between the trabecular beams and mechanically increasing the capacity for aqueous outflow.
- **Hyperosmotic agents** increase the osmolarity of the blood, which in turn draws fluid from the posterior chamber into the blood vessels of the ciliary body.

3. For patients in good health with primary open-angle glaucoma, what is the first drug to try?

The short answer is that any of the topical medications can be used. The choice is based on the desired amount of intraocular pressure (IOP) reduction, the possible side effects, and the relative costs of the medicines. The advantage of having four commonly used classes of medications (β-blockers, prostaglandin analogs, topical CAIs, and adrenergic agonists) is that therapy can be customized for each patient. Prostaglandin analogs are the most commonly used first-line therapeutic agents because of their ease of use, powerful hypotensive effect, and favorable side-effect profile. Prior to the development of prostaglandins, most ophthalmologists chose a β-blocker as first-line therapy.

If a patient would not be a good candidate for a prostaglandin, one of the other three classes of medicines can be used. Nonselective β-blockers are the most potent. The cardioselective β-blocker (betaxolol), topical CAIs, and adrenergic agonists are all about equal in hypotensive effect. When used alone, topical CAIs and α-adrenergic agonists should be used three times/day to prevent possible IOP fluctuation.[1]

4. What medicine should be used as second-line therapy? Third-line therapy?

As in the case of first-line therapy, any of the medicine classes can be used as second- or third-line therapy. With several options available, the physician can attempt to tailor the choice to the patient's particular situation. If a prostaglandin has been used as first-line therapy, a β-blocker is often chosen as second-line therapy, and vice versa. As these medicines are the most potent ones available and are both typically once-a-day medicines (most commonly a β-blocker once per day in the morning and prostaglandin once per day in the evening), this regimen typically results in a very good hypotensive effect for the number of drops used.

Table 18-1. Commonly Used Agents for Glaucoma Management

CHEMICAL NAME	COLOR TOP	STRENGTH	USUAL DOSAGE	SIZE (mL)
Miotics				
Pilocarpine hydrochloride	Green	1, 2, 4%	2-4 times/day	15
Adrenergic Agonists				
Apraclonidine hydrochloride	Purple	0.5, 1%	2-3 times/day	5
Brimonidine tartrate	Purple	0.1, 0.15, 0.2%	2-3 times/day	5, 10, 15
Prostaglandin Analogs				
Latanoprost	Teal	0.005%	Daily	2.5
Travoprost	Teal	0.004%	Daily	2.5, 5
Bimatoprost	Teal	0.03%	Daily	2.5, 5
Unoprostone isopropyl	Teal	0.15%	2 times/day	5
β-Blockers				
Betaxolol hydrochloride suspension	Light blue	0.25%	2 times/day	2.5, 5, 15
Betaxolol hydrochloride solution	Dark blue	0.50%	2 times/day	2.5, 5, 10
Levobunolol hydrochloride	Yellow	0.25, 0.5%	1-2 times/day	5, 10
Metipranolol	Yellow	0.3%	1-2 times/day	5, 10
Timolol maleate	Yellow	0.25, 0.5%	1-2 times/day	2.5, 5, 10, 15
Timolol XE gel-forming solution	Yellow	0.25, 0.5%	Daily	2.5, 5
Carbonic Anhydrase Inhibitors				
Acetazolamide sodium (oral)	NA	125, 250 mg	3-4 times/day po	NA
Acetazolamide sequels (oral)	NA	500 mg	2 times/day po	NA
Methazolamide (oral)	NA	25, 50, 100 mg	2-4 times/day po	NA
Dorzolamide	Orange	2%	2-3 times/day	5, 10
Brinzolamide	Orange	1%	2-3 times/day	5, 10
Hyperosmotic Agents				
Mannitol (intravenous)	NA	20%, 50% (IV)	0.5-2 g/kg	NA
Fixed Combinations				
Timolol/dorzolamide	Dark blue	0.5%/2%	2 times/day	5, 10
Brinzolamide/brimonidine tartrate	Pale green	1%/0.2%	3 times/day	10

The availability of the fixed combination of timolol/dorzolamide makes it easy to add dorzolamide as a second-line agent after timolol. This reduces the drop count from three or four to two per day, and fewer drops per day is likely to result in greater compliance.

Brimonidine or a topical CAI can be an excellent choice for additive therapy. The fixed combination of brimonidine/brinzolamide can, like timolol/dorzolamide, play a role in simplifying the drop regimen, especially if the patient cannot tolerate a β-blocker.

Miotics are more difficult to use because of the drop frequency and side effects, but can be quite effective, especially in aphakic (no crystalline lens in the eye) patients. In phakic patients with little remaining accommodation and little cataract, pilocarpine is often well tolerated. It provides a pinhole effect that gives an increased depth of field for most patients. Many patients can read without reading glasses when taking pilocarpine, and no one needs trifocals if the pupils are adequately miotic.

Oral CAIs were once quite commonly used and are among the most potent of all hypotensive medications. Their side-effect profile and the availability of a variety of topical medicines limit their use today.

5. What are some prescribing pearls and key side effects of prostaglandin analogs?

The prostaglandin analogs available today are all extremely effective at lowering intraocular pressure and are generally used as first-line therapy. They can be additive with any medicine, but tend not to work as well if added beyond second-line therapy.

Latanoprost, now available in generic form, was released first and remains the most commonly used of the four medicines. As a prostaglandin analog, latanoprost is a powerful ocular hypotensive agent. Latanoprost in a 0.005% concentration is 100 times more powerful than 0.5% timolol. Travoprost is equally effective compared to latanoprost, with greater conjunctival erythema but less effect on increased iris pigmentation. Bimatoprost appears to offer on average about 0.5 mm greater IOP reduction than the other prostaglandins, and in selected individuals, it may be significantly more powerful. The increased concentration of bimatoprost is accompanied by greater local ocular side effects. In 2013, unoprostone isopropyl (Rescula) was approved for use in the United States. The exact mechanism of IOP reduction is not clear, but it is hypothesized to increase aqueous outflow through the trabecular meshwork while having little to no effect on aqueous production and uveoscleral outflow like other prostaglandins. Unoprostone isopropyl has been reported potentially to have fewer known ocular side effects such as iris and lid pigmentation, although because it is so new, future studies will probably address this.

Although there have been rare reports of systemic side effects, such as flu-like symptoms, numerous ocular side effects can occur. The most common are conjunctival injection, increased pigmentation of the iris and eyelid skin, growth of eyelashes, and prostaglandin-associated periorbitopathy (PAP). PAP is a term used to describe the constellation of eyelid and periorbital changes that occur with chronic use of topical prostaglandins; such changes include upper lid ptosis, deepening of upper lid sulcus, periorbital fat atrophy, loss of lower eyelid fullness, and relative enophthalmos. These changes appear to be partially reversible with discontinuation of the medication. Increased iris pigmentation is the result of increased amount of melanin within iris melanocytes and seems to occur much more frequently in patients with hazel irides or who have iris nevi. Whereas the other side effects are reversible, increased iris pigmentation is not. Ocular inflammation, including anterior uveitis and keratitis, has been rarely reported, so in patients with a history of uveitis it may not be the drug of choice. Prostaglandin analogs have been associated with cystoid macular edema, especially in pseudophakic eyes. However, these eyes typically have other risk factors that may be responsible. Herpetic keratitis may be reactivated or exacerbated. It also has been reported to produce a herpes-like keratitis that clears when the drops are stopped.[2-4]

6. What are some prescribing pearls and key side effects of topical β-blockers?

Timolol was the first β-blocker and is still considered the gold standard against which all other ocular hypotensive medications are judged. It has been formulated as both a nonviscous and a viscous drop. The viscous formation (Timoptic XE from Merck, Timolol GFS from Falcon) remains in the tear film longer; consequently, intraocular absorption is greater, and systemic absorption is reduced. This drug provides the best diurnal curve for pressure control with once-daily dosing and can reduce the possibility of systemic side effects.

Nonselective β-blockers may be effective with the 0.25% dosage once daily for patients with light irides and the 0.5% dosage once daily for patients with dark irides. β-Blockers block intrinsic β1 and β2 receptor tone; thus, when patients are asleep, β-blockers are ineffective because there is little tone. However, because aqueous production also declines at night, this fact is usually considered inconsequential. Although β-blockers are labeled as twice a day and very frequently prescribed twice a day, many ophthalmologists will prescribe β-blockers once daily when patients awake in the morning to effectively minimize pressure rise as well as medication-induced hypoperfusion to the optic nerve. For patients with more advanced disease, a twice-daily regimen of 0.25% for lighter irides and 0.5% for darker irides is common. This regimen guards against going for a full day without medication in patients who miss one prescribed drop. Betaxolol as a selective β1 antagonist has far fewer systemic side effects than the nonselective β-blockers, but is not as potent. Betaxolol results in a roughly 25% drop in intraocular pressure, whereas nonselective β-blockers achieve about a 30% reduction. β-Blockers should be started as a one-eyed trial because 10% of patients show no effect from topical nonselective β-blockers, and 10% of patients who had a significant effect from nonselective β-blockers have no effect from selective β-blockers.

In general, the side effects of this class of medications are identical to those of the oral β-blockers. Patients, and even physicians, often forget that eyedrops have systemic effects. Physicians must remember to ask about eyedrops when taking a complete medical history.

β-Blockers can exacerbate asthma or chronic obstructive pulmonary disease and can cause arrhythmia, bradycardia, lowered blood pressure, increased heart block, lethargy, cardiac arrest, cardiac failure, alteration of serum lipids, exercise intolerance, impotence, altered mental status, and central nervous system (CNS) depression. The selective β-blocker betaxolol is much less likely

to trigger bronchospasm but still must be used with caution. In diabetics, they may cause reduced glucose tolerance and mask the symptoms of hypoglycemia. In hyperthyroidism, symptoms can be exacerbated with abrupt withdrawal of ocular β-blocker use. β-Blockers have been linked with impaired neuromuscular transmission; thus, myasthenia gravis symptoms can be exacerbated. Ocular side effects include blurred vision, irritation, corneal anesthesia, punctate keratitis, and allergy.

Concomitant use of topical and systemic β-blockers should be done judiciously. Although it is not clear what the additive effects of systemic and topical use are, there have been reports of patients taking both systemic and topical β-blockers with reduced ocular hypotensive efficacy and greater systemic side effects compared with patients who were taking a systemic β-blocker and a different class of topical IOP-lowering agent. One of the concerning systemic side effects is the exacerbation of blood pressure fluctuation. Such fluctuations (especially in diastolic blood pressure) leading to hypoperfusion potentially reduce ocular perfusion and increase susceptibility of the optic nerve to relative ischemic injury.[5-8]

7. What are some prescribing pearls and key side effects of adrenergic agonists?

Adrenergic agonists may be classified into two groups. The first group, which comprises epinephrine and dipivefrin, increases trabecular meshwork outflow. These drugs are no longer commonly used in the management of glaucoma as other classes of drugs have been found to be more effective in IOP control. Apraclonidine and brimonidine make up the second group. They are α2-selective agonists that reduce aqueous production. Brimonidine also may increase uveoscleral outflow.

The α-adrenergic compounds are characterized by a high allergic-reaction rate. Epinephrine is said to have an allergic rate of 50% by 5 years, and apraclonidine has an allergic rate of approximately 20% by 1 year. Because of its high allergy rate, apraclonidine is used almost exclusively for acute pressure control or to prevent acute pressure rise after laser procedures.

Brimonidine is less likely to cause an immediate allergic reaction, but many patients develop an intolerance or allergy months after starting the drug. Ocular adverse effects include contact blepharoconjunctivitis and follicular conjunctivitis. The generic form of brimonidine packaged with benzalkonium chloride preservative is available in two concentrations—0.15% and 0.2%. The brand form of brimonidine (Alphagan-P 0.1%) is available in only one concentration. Though Alphagan-P has a lower concentration of brimonidine, it is found to be comparable in lowering IOP. Alphagan-P is packaged with a less allergy-provoking preservative (Purite) than generic brimonidine and has a reduced incidence of allergic side effects.

Brimonidine has become an important drug for treating glaucoma. It works as well as a nonselective β-blocker at peak effect, although less well at trough 6 to 12 hours later, and almost all patients have some reduction in pressure. Aside from allergy, it is well tolerated by the eye. Systemically, it can cause dry mouth and fatigue, which can be debilitating. Brimonidine is contraindicated in infants because it causes CNS depression and apnea. Avoid coadministering brimonidine with a monoamine oxidase inhibitor or tricyclic antidepressant therapy, as potentiating or additive effects of CNS depression and/or adverse cardiovascular events can occur. There is some evidence from animal models of glaucoma that brimonidine may protect ganglion cells from death. There is no evidence of this property in humans, but this drug has sparked interest in treating glaucoma by mechanisms other than pressure reduction.[9]

8. What are some prescribing pearls and key side effects of carbonic anhydrase inhibitors?

Topical CAIs took more than 40 years to develop and were particularly welcome, as oral CAIs cause a myriad of side effects. The most common complaints with oral CAIs are lack of energy and lethargy, lack of appetite and weight loss, nausea and/or an upset stomach, paresthesias of extremities, and a metallic taste to foods. CAIs are chemically derived from sulfa drugs and should be avoided in patients with known sulfa allergies. The most dangerous side effect is hypokalemia, especially when a CAI is combined with a potassium-reducing diuretic. This combination is dangerous in patients taking digitalis. Severe mental depression and aplastic anemia are other serious side effects. The same sort of side effects can be seen with the topical medications, but they are extremely rare. Because complaints are frequent with oral CAIs, most ophthalmologists rarely use them unless there is a need for acute pressure control or if topical CAIs are not effective.

There is no additional benefit to using topical CAIs concurrently with oral CAIs in the same patient. Although topical dorzolamide has an IOP fluctuation when used twice daily, twice-daily usage gives an adequate response when combined with a topical β-blocker, which diminishes the washout effect of aqueous production. Brinzolamide can often be used twice daily when combined with another aqueous suppressant.

The two topical CAIs are equally effective, but brinzolamide is less irritating to the eye. Dorzolamide has been reported to augment blood flow to the optic nerve. This may help reduce the impact of free radicals that have been postulated to be a cause of glaucoma.

9. What are some prescribing pearls and key side effects of topical combination therapies?

Many patients medically managed for glaucoma are treated with more than one drug class for IOP control. Combining two different topical drug classes in a single formulation provides the benefit of improved convenience and compliance, less exposure to preservatives, and reduced cost. However, combination therapies are not generally used as a first-line therapy in initially treating a patient with glaucoma.

Combigan (brimonidine 0.2%/timolol 0.5%), Cosopt (dorzolamide 2%/timolol 0.5%), and Simbrinza (brinzolamide 1%/brimonidine 0.2%) are fixed-combination therapies available in the United States. All three fixed combinations have a greater IOP-lowering effect than their component medications dosed separately as a monotherapy. Combigan is clinically associated with 50% lower incidence in ocular allergy compared to monotherapy with brimonidine. Cosopt, which is available generically, has ocular side effects similar for both drugs individually. Simbrinza is a recent addition to the topical therapy landscape of glaucoma. Fixed-combination medications with prostaglandin analogs are available internationally, but not yet in the United States: Xalacom (latanoprost 0.005%/timolol 0.5%), Ganfort (bimataprost 0.03%/timolol 0.5%), and DuoTrav or Extravan (travoprost 0.004%/timolol 0.5%).[10-12]

KEY POINTS: GLAUCOMA TOPICAL MEDICATIONS

1. Allow 5 minutes between drops to prevent one drug from washing the other out of the eye.
2. Punctal occlusion can dramatically reduce systemic side effects of glaucoma drugs.
3. A patient on glaucoma drugs with dry or irritated eyes may be developing a medication allergy. Check the conjunctiva of the lower lid for a follicular reaction.
4. Noncompliance is the most common cause of ineffective treatment response.

10. Are there alternative therapies or nontraditional medication options for treating glaucoma?

At present, no non-pressure-lowering medication has been conclusively demonstrated to be helpful in treating glaucoma. Many drugs are under investigation for this purpose. Some data from neurologic studies indicate that antioxidants, such as ginkgo biloba and vitamin E, as well as free radical scavengers may be helpful. Oral calcium-channel blockers have been demonstrated to have a limited effect on preserving visual function in some studies. Aminoguanidine, an inhibitor of nitric oxide synthase, was found to be helpful in a rat model of glaucoma. Agents that increase blood flow to the optic nerve and retina may also be useful.

Other drugs that have been investigated for chronic neurologic disease are being evaluated for effectiveness in glaucoma. Retinal ganglion cell death in glaucoma occurs by apoptosis and in this way is similar to many chronic neurodegenerative diseases. Identifying the unique trigger in glaucoma and/or interfering with the mechanism of apoptotic cell death might yield multiple ways to treat glaucoma beyond IOP reduction. The trick will be to selectively target the tissue of concern and devise a drug delivery system that can bypass the blood–ocular barrier. Memantine, an antiparkinsonian drug that blocks *N*-methyl-D-aspartate-receptor-induced glutamate toxicity, was viewed as a promising agent, but an unmasked second phase 3 clinical trial revealed there was no clear benefit in patients receiving memantine versus placebo. It is likely that some type of neuroprotective agent will become an important adjunctive therapy for glaucoma in the future.

The medical use of cannabinoids has been a topic widely discussed in the United States. Inhalation of cannabinoid has an IOP-lowering effect for a duration of 3 to 4 hours. The mechanism of action is not fully understood, and the short duration of action would mean the drug would need to be consumed frequently to have around-the-clock effectivity. The deleterious effects of this level of consumption (altered mental capacity, lung damage, etc.) limit its recommendation by most glaucoma specialists. Although a topical, oral, or sublingual preparation may avoid the pulmonary impact, they are limited by other systemic side effects. Canasol is a cannabinoid-based eyedrop, but there are no FDA clinical trials ongoing or planned in the future.

Although antioxidants, vitamins, herbal supplements, exercise, etc., and their effects on IOP have been studied, currently there is no significant research-based evidence to support the implementation of alternative therapies in the prevention or progression of glaucoma.[13,14]

11. How many eyedrops can be used?

Most ophthalmologists believe that compliance becomes increasingly difficult the more medicines are used. Most consider the combination of a prostaglandin analog, timolol/dorzolamide, and brimonidine to represent maximum medical therapy (5 drops/day). Laser and/or surgical options are generally considered at this point, if not earlier. In selected cases additional medicines such as miotics or oral medication can be tried.

12. What are the general rules for using eyedrops?

1. Allow at least 5 to 10 minutes between applying any two topical eye medications.
2. Drops should be spaced at roughly stable intervals. Once-a-day medication should be used each evening or morning. Twice-a-day medicines should be used about 12 hours apart. It becomes harder to space three- and four-times-a-day medicines equally, but an effort should be made to try.
3. Topical medications all have systemic side effects. Punctal occlusion can reduce the systemic absorption to minimize these effects. The patient puts a finger adjacent to the nose where the two lids come together and pushes down on the bone. The drop is then instilled in the eye, and the lids are gently closed. This position is held for 3 minutes. This procedure dramatically reduces the amount of drug entering the system. Because a drug coming into contact with the nasal mucosa is absorbed rapidly and almost completely, it attains serum levels quite similar to those achieved by intravenous administration. Absorption through the nasal mucosa also prevents a first pass by hepatic enzymes, which gives the liver a chance to metabolize or detoxify the medication.
4. An important rule to remember is that topical medications should be initially prescribed as a one-eye therapeutic trial. This will help sort out a true drug effect from the patient's underlying diurnal intraocular pressure fluctuation. Although there can be some crossover effect (about 1 to 2 mm Hg) in the fellow eye, the one-eyed therapeutic trial is the best way to determine the drug's effect. Unfortunately, the response in the first eye does not always correlate with the response in the fellow eye once the drug is used bilaterally. Still, most glaucoma specialists believe that a therapeutic trial provides critical evidence to justify the use of a medication.[15,16]

13. Pilocarpine is often used in the treatment of angle-closure glaucoma. What is its effect on the anterior chamber?

Pilocarpine contracts the longitudinal muscle of the ciliary body, pulling on the scleral spur and mechanically opening the trabecular meshwork. However, it also pulls the lens–iris diaphragm forward, shallowing the anterior chamber. The contraction of the circular muscle of the ciliary body relaxes the stress on the zonules, allowing the lens to become rounder, to float forward on a longer tether, and to act more like a natural cork in the pupil. This effect increases pupillary block and bows the peripheral iris closer to the trabecular meshwork. All of these effects tend to shallow the anterior chamber and narrow the anterior-chamber angle. Luckily, these effects are balanced by the miosis caused by the contraction of the sphincter muscle of the iris. Miosis pulls the peripheral iris away from the trabecular meshwork. In most patients, although the anterior-chamber depth is decreased by pilocarpine, the peripheral angle is slightly widened. In some patients, however, shallowing of the peripheral angle may be more of a problem than angle crowding. In such patients, pilocarpine may cause angle closure. Therefore, one should perform gonioscopy on all patients with a narrow angle for whom a miotic is prescribed, both initially and periodically thereafter.

It is important to keep in mind that pilocarpine is virtually ineffective in treating acute angle closure. During such acute cases of angle closure with markedly elevated intraocular pressure, the iris becomes ischemic and does not respond to the acute miotic effects of pilocarpine.

14. If a patient does not show an expected response to a topical glaucoma medication, what should the ophthalmologist consider as the reason?

- **Noncompliance:** The most common cause for an ineffective medication is failure to take it. Kass et al. performed a study in which a microchip placed in the bottom of pilocarpine bottles recorded when the bottle was tipped upside down. The chip was camouflaged, and patients did not know that their drop use was being monitored. Overall, he found that 76% of the prescribed doses were

taken. Six percent of patients took less than 25% of the drops, whereas 15% took only 50%. However, 97% of his patients reported that they were taking all of their medication. Not surprisingly, compliance was best on the day before the office visit. This behavior can explain why many patients have completely controlled intraocular pressures in the ophthalmologist's office but evidence of progressive glaucoma damage.

- **Ineffective medication:** Make sure that any medication is properly evaluated by a one-eyed trial.
- **Inability to instill the drops properly:** Watch the patient instill the drops in the office. The patient may be compliant in taking the medications, but may not be getting the drops into the eye.
- **Inadequate interval between multiple drops:** Make sure that patients wait at least 5 minutes between drops and that the drops are spread evenly over the course of the day.
- **Concomitant use of IOP-elevating medications:** Review patient's list of active medications. Use of systemic or topical agents such as steroids can cause an elevated IOP.[17]

15. Many patients taking topical medications complain of dry or irritated eyes. What should the treating ophthalmologist include as a routine part of the examination of all patients taking topical medication?

The treating ophthalmologist should examine the lower lid and observe the conjunctiva. If only papillae are present, the patient does not have a chronic allergy. If there is a significant follicular reaction, especially if follicles are present on the bulbar conjunctiva, the patient is more than likely allergic to the topical drops. Ocular allergies can appear immediately upon using the drop or months later. Brimonidine is well known for this but such a late reaction is commonly underappreciated and unrecognized. Pilocarpine is famous for causing symblepharon with chronic use.

16. In a patient with an ocular allergy secondary to topical medication, which is the most likely offender?

Apraclonidine has the highest incidence of allergic reaction. As such, it went from being a regular in the topical glaucoma drop armory to limited use as a preoperative agent to prevent intraocular pressure spikes after laser procedures or for acute intraocular pressure control. Among the medications now in use brimonidine (less with the 0.15% and 0.1% formulation) has the highest incidence of allergic reaction, followed by (in order) topical CAIs, prostaglandin analogs, β-blockers, and pilocarpine.

Stopping the medicines in that order will usually help sort out which is the offender. Alternatively, have the patient instill one drop in one eye and a different one in the fellow eye.

The availability of generic formulations has also had an impact on the prevalence of allergic reaction secondary to topical glaucoma medications. For example, brimonidine is available in 0.1, 0.15, and 0.2% formulations. The last two are more likely to induce an allergic reaction and are the two formulations available in generic form. As such, prescribers may see increased rates of allergic reaction from brimonidine due to prescribing patterns aimed at patients' cost saving.

17. Are any of the glaucoma medications safe for use in pregnant women?

Few data exist regarding the safety of glaucoma medicines in pregnancy. Most specialists would strongly consider stopping all glaucoma medicines during pregnancy and either forgoing treatment for the duration or considering a laser or surgical option.

Brimonidine is a class B medication; all others are class C. In the postpartum period, topical CAIs and betaxolol may be useful, although both are secreted in breast milk and may affect the newborn. Brimonidine is also secreted in breast milk and as it causes severe CNS depression in neonates, it cannot be used in nursing women. Topical CAIs in high doses have demonstrated harm to animal fetuses. Prostaglandin analogs, which are associated with a high incidence of miscarriage in animal studies, are probably not a good choice in pregnancy.[18]

18. Are any of the glaucoma medications safe for use in children?

Glaucoma in children is principally a surgical disease. Medications are typically used to lower the IOP until an exam under anesthesia can be performed and surgery done if needed. Topical or oral CAIs are a good choice in this group. Because of systemic side effects, β-blockers are used with caution in children. Brimonidine is a dangerous medication in neonates and infants because of its association with profound CNS depression and apnea. It is contraindicated in children under the age of 3 years and probably should not be used in children under the age of 8. Pilocarpine is useful after goniotomy or trabeculotomy but is not frequently used on a chronic basis. Prostaglandin analogs in theory would not be a good option because the uveoscleral outflow pathways may be compromised by the angle dysgenesis that is typical of infantile glaucoma. In juvenile glaucoma, however, their effect is highly variable, and they can be used after a successful therapeutic trial.

KEY POINTS: COMMON SIDE EFFECTS OF TOPICAL GLAUCOMA MEDICATIONS

1. **Prostaglandin analogs:** Lash growth, iris and eyelid hyperpigmentation, allergic conjunctivitis, macular edema in pseudophakes, flu-like symptoms, and reactivation of herpetic keratitis.
2. **β-Blockers:** Bronchospasm, bradycardia, fatigue, poor exercise tolerance, depression, and decreased libido.
3. **Carbonic anhydrase inhibitors:** Stinging, metallic taste, rash, and nausea.
4. **Adrenergic agonists:** Dry mouth, allergic conjunctivitis, fatigue, and headache.

19. Is there any evidence that lowering intraocular pressure helps treat glaucoma?

Elevated IOP is not only the most important but also the sole modifiable risk factor in the development of glaucoma. Data from randomized, prospective controlled clinical trials such as the Collaborative Normal-Tension Glaucoma Study, the Advanced Glaucoma Intervention Study, the Ocular Hypertension Treatment Study, and the Early Manifest Glaucoma Study all indicate intraocular pressure reduction reduces the number of eyes that have continued glaucoma deterioration. Limited data suggest that the manner in which the pressure is reduced may be important. The Glaucoma Laser Trial found that patients initially treated with laser had less worsening of visual fields than patients who were initially treated with medication. This finding is probably due to the fact that the laser-first group had a 2-mm lower IOP on average, compared with the medicine-only group. On the other hand, the Collaborative Initial Glaucoma Treatment Study found no difference at 5 years of follow-up between medicine and trabeculectomy with regard to the rate of glaucoma worsening. These more recent data seem to support the current general approach that, in theory, it makes no difference how you lower pressure as long as you lower it adequately. There is no consensus as to how much pressure lowering is adequate. This depends on several factors such as the amount of disease, the rate of change of the glaucoma, the patient's wishes, and the life expectancy. Most glaucoma specialists would probably agree that, all things being equal, mild disease would require a 25 to 30% IOP reduction, moderate disease a 30 to 40% reduction, and advanced disease a 40 to 50% or more reduction.[19-22]

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TRABECULECTOMY SURGERY

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CHAPTER 19

1. **What are the indications for trabeculectomy surgery?**
Trabeculectomy is indicated when neither medical nor laser therapy sufficiently controls glaucoma progression and that progression is likely to diminish a patient's quality of life. Because visual needs and vision-related quality-of-life characteristics differ, patients should be assessed individually before a physician decides to perform surgery. Physicians should consider the likelihood of success and risk of complications from surgery prior to proceeding. Trabeculectomy surgery can also be considered as a primary treatment, especially in eyes with severe glaucoma at presentation. Outcomes from a large trial comparing primary trabeculectomy with medication were comparable. A smaller study comparing trabeculectomy with glaucoma drainage devices did not reach conclusive evidence about which technique is best.[1-3]

2. **What is the goal of glaucoma surgery?**
The goal of glaucoma surgery is to lower the intraocular pressure (IOP) sufficiently to prevent or minimize further damage to the optic nerve and visual function while avoiding severe complications. The target reduction of IOP will depend on individual factors. In the Advanced Glaucoma Intervention Study, patients with severe glaucoma with an average IOP of 12 mm Hg after surgery had stable visual function after long-term follow-up. Because many patients with glaucoma do not have elevated IOP, the goal of glaucoma surgery is *not* to reduce IOP to less than 21 mm Hg, but to tailor the pressure to the patient's needs and characteristics.[4]

3. **How do we inform patients about the risks of trabeculectomy surgery?**
The risks and benefits of glaucoma surgery and alternative options must be carefully outlined to all patients in language that is easily understood. It is imperative to explain clearly the remote possibility of blindness or loss of the eye owing to hemorrhage or infection. Discussion should include the possibility of sudden or permanent visual loss, failure to control IOP (which may be too high or too low), the need for repeated surgery, droopy lid, discomfort, and significant blurring (common for the first 2 weeks). Failure to control the IOP and need to restart medication is not uncommon. Other risks include late-onset infection and endophthalmitis (rare) or cataract (common).

4. **Describe the factors associated with failure of glaucoma filtering surgery.**
Risk factors for the failure of filtering surgery include pigmented skin (nonwhite), younger age, intraocular inflammation, neovascular changes, shallow anterior chamber, previous trauma, dislocated lens, complicated cataract surgery, vitreous in the anterior chamber, inability to use corticosteroids, previously failed glaucoma surgery, previous retinal surgery, scarred or abnormal conjunctiva, and an inexperienced surgeon (Fig. 19-1).

5. **Does a fornix versus a limbal–conjunctival approach affect outcome?**
Fornix-based and limbal-based approaches produce similar results after trabeculectomy surgery regarding IOP control. With a limbal-based approach the risk of a wound leak is much smaller. However, this incision appears to increase the likelihood of having a thin avascular and localized filtering bleb (Fig. 19-2) and possible bleb-related infections. If a limbal-based flap is chosen, it should be made sufficiently posterior so that the closure is at least 10 mm or more from the limbus. If a fornix-based flap is chosen, it is imperative to ensure that the closure is watertight. There are many ways to close a fornix-based conjunctival flap and it depends on surgeon preference. Most commonly individual 10-0 nylon mattress sutures or a running 8-0 vicryl suture are used. A wet fluorescein strip at the end of the case to check for leaks is useful.

6. **What medications should be stopped before filtration surgery?**
Patients should continue their systemic medications. Coumadin or other blood thinners do not necessarily need to be stopped. However, it is convenient to confirm that the anticoagulation levels are within therapeutic range for the patient's condition. If the surgeon desires to stop the Coumadin prior to surgery, it is imperative to discuss this with the patient's internist, as in some cases stopping may not be advisable because of increased systemic risks.

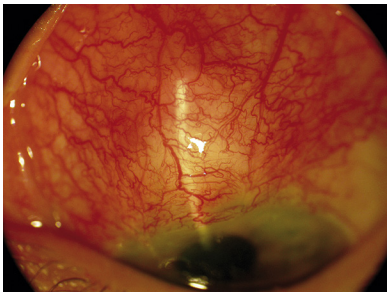

Figure 19-1. Failing filter with increased vascularization and inflammation surrounding the filtering bleb.

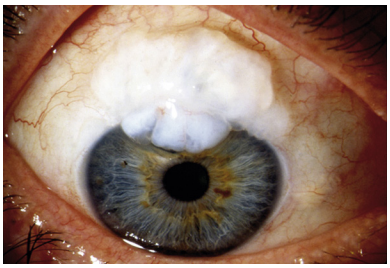

Figure 19-2. Corneal dissection of bleb after a limbal-based trabeculectomy causing discomfort and astigmatism.

7. What are the choices of anesthesia?

General anesthesia is used in children and other patients unable to cope with a local anesthetic procedure. Sub-Tenon's or subconjunctival anesthesia are our preferred choices. If a surgeon prefers regional anesthesia, peribulbar block is preferred to retrobulbar techniques. A detailed description of our current technique ("blitz" anesthesia) is as follows.

First, Xylocaine 1% jelly or lidocaine hydrochloride 2% jelly is placed in the fornix before surgery. In the operating room, a paracentesis is made temporally and a small amount of aqueous is released from the anterior chamber, followed by an irrigation of 0.1 mL of 1% nonpreserved lidocaine into the anterior chamber through a cannula. Next, inject a 1:1 mixture of 0.1 cc nonpreserved 1% lidocaine mixed with 0.1 cc mitomycin C (0.4 mg/cc). The total volume of 0.2 cc is injected under the conjunctiva with a 30-gauge needle. This precedes the formation of either a limbal- or a fornix-based flap. If using this method, additional lidocaine is usually not necessary, but can be used at the surgeon's discretion. For a fornix-based conjunctival flap, an initial cut is made at the limbus, and 0.5 mL of anesthetic is injected with a cannula under the Tenon's layer both temporally and nasally. With a limbal-based flap, a 30-gauge needle is used to inject 0.5 mL, 10 mm posterior and parallel to the limbus, ballooning the Tenon's capsule and conjunctival space in both the nasal and the temporal direction. When closing either a limbal- or a fornix-based flap, additional lidocaine 1% is irrigated through the Tenon's capsule so the patient has no discomfort.

8. Does a triangular versus a rectangular flap affect outcome?

No. The shape of the scleral flap is surgeon-dependent; there is probably no difference in clinical outcome with a triangular or rectangular flap. Although the shape of the flap is not important, its thickness may be. Thin flaps may offer better long-term filtration. However, very thin flaps should be avoided if mitomycin C is used. Regardless of the shape of the scleral flap, sufficient sutures are necessary to be able to control the outflow and prevent overfiltration.

9. Does the size of the internal block affect outcome?

No. A small (e.g., 1 mm) excision is sufficient, although some surgeons choose to create larger fistulas. Increased filtration results when one edge of the internal block coincides with one edge of the scleral flap. The internal block can be removed with Vannas scissors or a punch. Alternatively, a drainage implant under the scleral flap (Express) may be used.

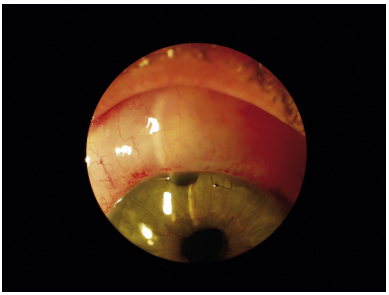

Figure 19-3. Low diffuse bleb with releasable suture in place 1 week following a trabeculectomy.

10. Are iridectomy and paracentesis always necessary during filtration surgery?

An iridectomy is always performed in angle-closure glaucoma to ensure that pupillary block does not occur. In addition, if the chamber shallows, the iris is less likely to occlude the ostium. However, iridectomy may not be necessary in patients with open-angle glaucoma and particularly in pseudophakic eyes. A paracentesis is always done, and it can be made with either a sharp blade temporally or a 27-gauge needle on a syringe. A paracentesis is considered essential with each procedure because it allows re-formation of the anterior chamber toward the end of surgery. By refilling the anterior chamber via the paracentesis, the surgeon has an appreciation of how much leakage is visible around the edges of the scleral flap.

11. How tight should I make the scleral flap?

The number of sutures and their tightness depend on the diagnosis, preoperative IOP, architecture of the scleral flap, location of the fistula, and how much leak is desired at the time of surgery. In general those patients at high risk for complications associated with hypotony should have tighter scleral flaps. For example, patients with inordinately high IOP, shallow anterior chamber, angle-closure glaucoma, aphakic glaucoma, or increased episcleral venous pressure are more likely to develop complications if there is overdrainage.

With low-tension glaucoma, looser sutures with more flow may be indicated to ensure a low initial postoperative intraocular pressure. The sutures can be lysed with an argon laser anywhere from day 1 through the first 2 weeks or longer if antimetabolites are used.

12. Are releasable sutures necessary?

Although releasable sutures have some advantages, they are not necessary to achieve a good result. We tend to use additional releasable sutures as they allow tighter closure of the scleral flap, avoiding hypotony, and because of the ease with which they can be removed at the slit lamp (Fig. 19-3). The flap can be closed moderately loosely with permanent sutures, and the releasable sutures decrease the flow further. Selective removal between the first postoperative day and 1 month can easily be done at the slit lamp.

13. Does it matter how far I dissect the scleral flap anteriorly?

We aim to open the fistula anterior to the trabecular meshwork. In large myopic eyes, a perpendicular incision just anterior to the corneoscleral sulcus carries the flap well anterior to the trabecular meshwork. In removing the internal block, a satisfactory fistula results. In contrast, in small hyperopic eyes and those with angle-closure glaucoma or peripheral anterior synechiae, an incision at the same point terminates just in front of the iris root. In these patients, an anterior dissection well into the cornea is necessary both to ensure that the fistula will not be blocked by uveal tissue and to prevent bleeding (Fig. 19-4).

14. Should atropine be used during the procedure?

Atropine is needed only in patients with small eyes, shallow anterior chamber, or angle-closure glaucoma. Sterile 1% atropine drops are placed on the cornea to dilate the pupil maximally and to move the lens–iris diaphragm posteriorly. This technique decreases the likelihood of a flat anterior chamber in the early postoperative period.

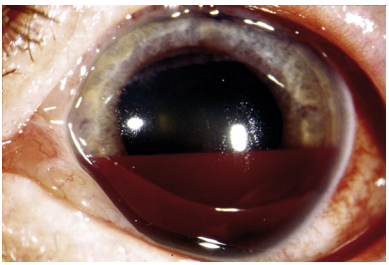

Figure 19-4. Spontaneous hyphema following a trabeculectomy in a 40-year-old woman with chronic angle closure and with no other risk factors.

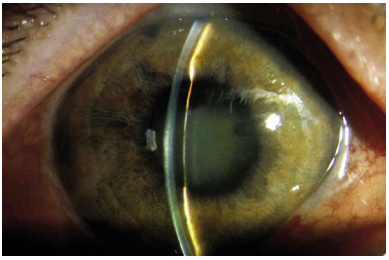

Figure 19-5. Flat anterior chamber, grade II (contact between peripheral and central iris and cornea), and resultant cataract following a trabeculectomy.

15. How often are steroids used in the postoperative period?

It varies according to the surgeon's preference and the apparent inflammation, but at a minimum they should be used four times/day for at least 1 month (e.g., prednisolone acetate 1% or betamethasone 0.1%). In phakic eyes, topical steroids are tapered quickly after 4 to 6 weeks to reduce the risk of cataract. In pseudophakic patients or eyes with signs of increased conjunctival or intraocular inflammation, the steroid treatment can be intensified and maintained for 2 to 3 months. Some surgeons prefer the addition of a nonsteroidal anti-inflammatory drug one time/day in conjunction with the steroids over a 1 to 2-month period. A commonly used regime is to taper steroids every 2 weeks for a period of 8 weeks. Typically, four times a day for 2 weeks, three times for 2 weeks, etc., down to "off."

16. How can you avoid a flat anterior chamber after trabeculectomy?

The most useful strategy is to prevent overdrainage and hypotony. The amount of leakage underneath the scleral flap ultimately determines the postoperative pressure. To minimize the chance of a flat anterior chamber (Fig. 19-5), additional 10–0 nylon sutures, with or without releasable sutures, should be used to minimize the flow at the end of the procedure. Laser suture lysis may then be used to increase selectively the flow under the scleral flap and improve control. If the sutures are cut too aggressively, a flat anterior chamber may result.

17. What do you do when a wound leak occurs in the immediate postoperative period?

Unless the leak is very brisk, it usually heals within the first few days. If the leak is near the limbus, either a collagen shield or a bandage contact lens may help. If a leak is very brisk or associated with a flat filtering bleb or with a shallow anterior chamber, surgical closure is necessary. If the leak is located at the wound, restitching is required. If there is a buttonhole, a purse-string knot with a rounded-body 11-0 nylon is very helpful. It is useful to use a fluorescein strip to confirm that the wound and buttonhole are Seidel negative before ending the procedure.

KEY POINTS: HOW TO AVOID COMPLICATIONS OF TRABECULECTOMY

1. Identify high-risk conditions (e.g., angle-closure, elevated episcleral venous pressure, previous conjunctival surgery).
2. Avoid hypotony with proper suture technique of the scleral flap (with or without releasable sutures).
3. Use paracentesis to evaluate the amount of filtration under the scleral flap and decide whether more or fewer sutures are required.
4. After closing the conjunctiva, inject balanced salt solution into the anterior chamber to raise the bleb and confirm the absence of leaks.

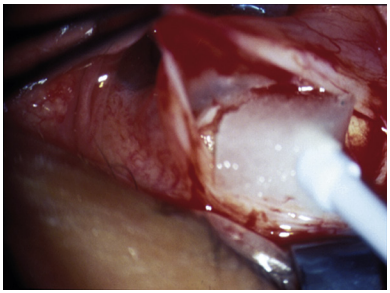

Figure 19-6. Sponge soaked with mitomycin C placed under the conjunctiva and Tenon's capsule prior to making the scleral flap.

18. What do you do if there is vitreous loss at the time of the trabeculectomy?

A "dry" vitrectomy (without balanced salt solution (BSS) infusion) with viscoelastic can be very helpful. It can be done through the scleral flap and peripheral iridectomy. If an inordinate amount of vitreous is present, it is probably best to proceed with a full anterior vitrectomy. Vitreous loss is rare in phakic eyes that have no history of trauma, surgery, or other predilection toward lens dislocation. Vitreous loss is more frequent in eyes that are aphakic or pseudophakic in the presence of zonular weakening (see next question).

19. What ocular conditions may predispose to vitreous loss during trabeculectomy surgery?

Preoperative conditions such as ocular trauma, Marfan's syndrome, pseudoexfoliation, homocystinuria, complicated cataract surgery, and high myopia may predispose to vitreous loss during trabeculectomy surgery.

20. Describe the indications for antimetabolites in trabeculectomy surgery.

Most surgeons routinely use mitomycin C in trabeculectomy surgeries. Both 5-fluorouracil and mitomycin C inhibit normal wound healing and facilitate the formation of highly functioning filtering blebs (Fig. 19-6). Although current antifibrotic agents have improved surgical outcomes, their associated complications should be considered. The use of antimetabolites is more important in eyes at high risk of failure, e.g., scarring of the superior conjunctiva, previously failed filters, younger age, pseudophakia, ocular inflammation, or advanced optic nerve and visual-field injury with desired postoperative pressure less than 14 mm Hg.[5]

21. How does 5-fluorouracil differ from mitomycin C?

Mitomycin C (0.1–0.5 mg/mL) is 100 times more potent than 5-fluorouracil (5-FU; 25–50 mg/mL). Whereas 5-FU affects primarily the S phase of the cell cycle, mitomycin C inhibits fibroblastic proliferation regardless of the phase of the cell cycle. Most surgeons prefer intraoperative mitomycin C. Intraoperative application is done with several Weck-cell sponges on the sclera under the conjunctiva and Tenon's capsule, treating a large area of the superior globe. The sponges are left in place for 1–5 minutes depending on the perceived risk of failure. Alternatively mitomycin C can be injected subconjunctivally (0.2–0.3 mL) at the beginning of the surgery.

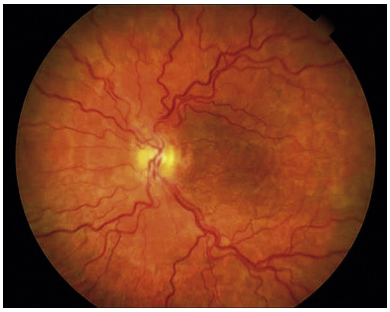

Figure 19-7. Hypotony with chorioretinal folds at the macula. IOP was 4 mm Hg.

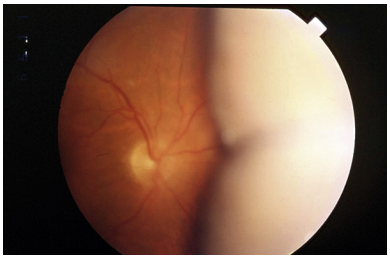

Figure 19-8. Suprachoroidal hemorrhage 1 week after filtering surgery in a patient with known heart disease, valve replacement, on blood thinners.

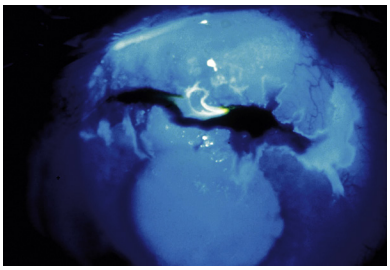

Figure 19-9. Leaking bleb following a mitomycin C trabeculectomy 6 months after surgery.

22. Are antimetabolites indicated in primary filtering procedures?

It depends on the surgeon's choice, but most surgeons use mitomycin C for primary trabeculectomy. With modern surgical techniques postoperative complications of hypotony (Fig. 19-7), suprachoroidal hemorrhage (Fig. 19-8), choroidal detachment, flat anterior chambers, and bleb leaks (Fig. 19-9) are uncommon, and late endophthalmitis (Fig. 19-10) is rare.

23. What do you do when the iris blocks the trabeculectomy site in the immediate postoperative period?

One option is to place Miochol via the paracentesis into the anterior chamber in an attempt to constrict the pupil and dislodge it from the trabeculectomy site. A viscoelastic agent is then injected, and either a cannula or a 30-gauge needle can be used to remove the iris carefully from the trabeculectomy site. On occasion, the iris does not occlude the ostium completely, and good filtration may occur around it.

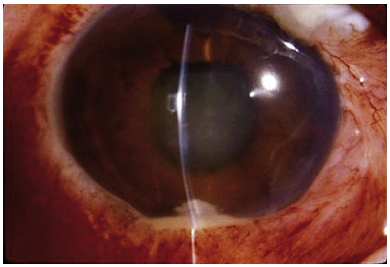

Figure 19-10. Endophthalmitis following a trabeculectomy resulting in poor vision.

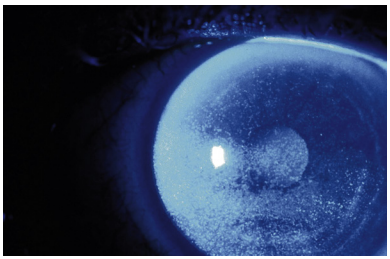

Figure 19-11. Superficial punctate keratopathy following repeated injections of 5-FU in a failing filter.

24. What if the ciliary processes roll anteriorly and block the trabeculectomy site during surgery?

Ciliary processes may block the trabeculectomy site in small hyperopic eyes, chronic angle closure, and nanophthalmos, especially if the fistula is not done anteriorly to the trabecular meshwork. After the fistula is done, the ciliary processes may roll into the filtering site. In most cases, closing the scleral flap, re-forming the anterior chamber, and reestablishing normal anatomy allow the ciliary processes to revert to their normal positions. If, after deepening the anterior chamber, the ciliary processes continue to block the trabeculectomy opening, they can be cauterized and cut away. Care must be taken not to disturb the vitreous face.

25. When is it necessary to give postoperative 5-fluorouracil injections?

Supplementary 5-FU injections, e.g., 0.1 mL (5 mg), may be given in the early postoperative period if the bleb is thickened, red, and vascularized. This option is left to the surgeon's discretion. This treatment is to decrease the chances of bleb scarring and failure. When repeated injections are used, corneal epithelial toxicity may appear and should be monitored. If there are signs of keratopathy, 5-FU injections should be delayed (Fig. 19-11).

26. What do you do if the bleb starts to fail?

If the bleb is thick, and injected, an increase in the topical steroid regimen and 5-fluorouracil injections is indicated. In addition, 2.5 mg of bevacizumab (Avastin) can also be injected into the bleb. Digital massage in the early postoperative period increases the outflow, but it is not effective in the long term to maintain the bleb function. Aggressive suture lysis should be considered. Sometimes, regardless of all efforts, the bleb fails and further glaucoma surgery may be required. Alternatively, bleb needling can be tried (see next question).[6]

KEY POINTS: HOW TO IMPROVE YOUR SUCCESS RATE

1. Use intraoperative mitomycin C.
2. Use postoperative 5-fluorouracil when the bleb shows early signs of scarring and failure.
3. Cut or release sutures when the function of the filtering bleb is suboptimal.
4. Consider needling with 5-fluorouracil or mitomycin C when the bleb has failed.

27. What is the technique of bleb needling?

Needling can be done in the operating room or at the slit lamp. A sterile technique is required, including the use of topical diluted Betadine. Sub-Tenon's or subconjunctival anesthetic, associated with either 5-fluorouracil or mitomycin C, is injected. A mixture of 1:1 lidocaine 0.1 cc and 0.1 mitomycin C (0.4 mg/cc) can also be injected first with a 30-gauge needle before the needling. The mixture is dispersed widely over the surgical area. After waiting a few minutes, needling can proceed. It is important to detect where the resistance to filtration is occurring. Most often, scarring at the scleral flap is responsible for bleb failure. In this case a 27-gauge needle is introduced into the subconjunctival space 8–10 mm away from the scleral flap, directed toward the flap edge, and, if possible, advanced under the scleral flap to ensure an outpouring of aqueous. The surgeon can try to maximize the efficacy of the bleb revision with some careful movements of the needle. Postoperative topical antibiotics and steroids are used. Although the needling procedure can be done at the slit lamp, we now prefer needling in the operating room, as the situation is more controlled, bleeding can be handled more easily, and everything is done under sterile conditions.[7]

28. What is the differential diagnosis for a flat anterior chamber?

The most common cause of a flat chamber after glaucoma surgery is excessive filtration. Other possibilities include serous choroidal detachment, hemorrhagic choroidal detachment, pupillary block, and malignant glaucoma (Table 19-1). With excessive filtration and serous choroidal detachment, the IOP is low. With a hemorrhagic choroidal detachment, the IOP may be low, normal, or high and usually is associated with pain. With both pupillary block and malignant glaucoma, the IOP is typically elevated and the cornea often edematous.

29. How urgent is the management of a flat anterior chamber?

Grade I (contact between the peripheral iris and the cornea) can be managed conservatively. If it is due to overfiltration, treatment includes the use of cycloplegics and mydriatics and careful observation. Improvement is usually spontaneous. Progression from grade I to grade II (contact between the peripheral and the central iris and cornea) despite treatment may be a poor prognostic sign, especially if the pressure is falling and the bleb is flattening. Grade II may recover spontaneously or progress to grade III (contact between the corneal endothelium and the lens). Grade III is an emergency and must be corrected promptly or the corneal endothelium will be damaged.

30. What are the indications to drain a choroidal detachment?

Drainage of the associated choroidal detachment is indicated whenever the pressure consistently falls, the bleb flattens, and the chamber shallows despite re-formation with viscoelastic material. Appositional "kissing" choroidal effusions that do not improve after a few days to weeks should also be drained (Fig. 19-12). A full-thickness scleral incision is made in one of the inferior quadrants to reach the suprachoroidal space. Re-formation of the anterior chamber is done simultaneously with BSS through the paracentesis tract. If the choroidal detachment is determined to be hemorrhagic, it is recommended to wait at least 10 days before drainage so that the blood can liquefy.

Table 19-1. Prevention of Malignant Glaucoma (Aqueous Misdirection)

1. Detect high-risk cases (angle-closure glaucoma, small, hyperopic eyes).
2. Minimize intraoperative shallowing of anterior chamber.
3. Perform a large peripheral iridectomy.
4. Avoid overfiltration.
5. Cautious suture lysis.
6. Use cycloplegics. Taper cycloplegics slowly.

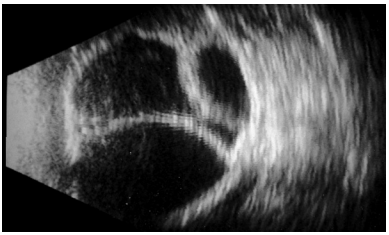

Figure 19-12. Ultrasound of kissing choroidals following a filtering procedure in an eye with chronic angle closure.

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CHAPTER 20

TRAUMATIC GLAUCOMA AND HYPHEMA

Douglas J. Rhee and Shipra Gupta

1. **What is a hyphema?**
   A hyphema is blood in the anterior chamber. The appearance of a hyphema may range from microscopic, seen only at the slit lamp as erythrocytes circulating in the aqueous, to a total hyphema that fills the entire anterior chamber.

2. **List the causes of a hyphema.**
   There are three major causes of hyphema: trauma to the globe, intraocular surgery, or spontaneous anterior segment hemorrhage in association with ocular or systemic conditions, such as neovascularization of the iris or anterior chamber angle, intraocular tumors, or clotting disorders (Table 20-1).

3. **What is the most common cause of a traumatic hyphema?**
   The most common cause of traumatic hyphema is blunt anterior segment trauma.

4. **Describe the pathophysiology of a traumatic hyphema.**
   Blunt ocular trauma results in ocular indentation, which causes a sudden expansion of ocular tissues and an immediate rise in the intraocular pressure. The sudden forceful displacement of the cornea and limbus posteriorly and peripherally may result in splitting or tearing of these tissues. As the tissues tear, blood vessels in the vicinity may rupture, resulting in a hyphema.

5. **List the anterior segment structures that may split or tear in response to blunt ocular injury.**
   - **Central iris:** Sphincter tear
   - **Peripheral iris:** Iridodialysis
   - **Anterior ciliary body:** Angle recession
   - **Separation of ciliary body from the scleral spur:** Cyclodialysis
   - **Trabecular meshwork:** Trabecular meshwork tear
   - **Zonules/lens:** Zonular tears with possible lens subluxation
   - **Separation of the retina from the ora serrata:** Retinal dialysis

6. **When a patient presents with a hyphema due to blunt ocular trauma, which anterior segment structure is the most likely source of the hemorrhage?**
   Hyphema as a result of blunt ocular trauma most commonly occurs as a result of angle recession, a tear in the anterior face of the ciliary body between the longitudinal and the circular ciliary body muscles. Rupture of the blood vessels in the vicinity of the tear results in a hyphema. The most frequently ruptured blood vessels include the major arterial circle of the iris, the arterial branches to the ciliary body, and the recurrent choroidal arteries and vein crossing between the ciliary body and the episcleral venous plexus.

7. **What ocular injuries may be associated with a traumatic hyphema?**
   - **Ocular wall:** Ruptured globe at the cornea, limbus, and/or sclera
   - **Cornea/conjunctiva:** Epithelial abrasion, laceration, subconjunctival hemorrhage
   - **Iris:** Sphincter tears, iridodialysis, mydriasis (long-term)
   - **Angle:** Angle recession, iris dialysis, cyclodialysis cleft
   - **Lens:** Traumatic cataract (acute, capsular rupture; chronic, direct injury), subluxation or total dislocation (damage of zonular attachments)
   - **Vitreous:** Vitreous detachment, vitreous prolapse
   - **Retina:** Retinal tear, detachment, and/or dialysis (vessel rupture, vascular occlusion)
   - **Retinal pigment epithelium and choroid:** Choroidal rupture
   - **Optic nerve:** Avulsion, optic nerve crush (chronic, glaucoma)

8. Describe an appropriate approach to the workup of a patient with a hyphema.

The primary responsibility is to rule out a ruptured globe and search for an ocular foreign body in all patients who present with a traumatic hyphema. The color, character, and extent of the hyphema and associated ocular injuries, including corneal blood-staining status, should be documented. Gonioscopy is usually best deferred, but, if necessary, it may be performed gently, taking care to avoid a rebleed. Before a possible rebleed obscures the view, a dilated lens and fundus examination should be performed without scleral depression.

Table 20-1. Hyphema Classification by Etiology

I. Trauma
- A. Blunt—rupture of iris or ciliary body blood vessels
- B. Penetrating—direct severing of blood vessels

II. Intraocular surgery
- A. Intraoperative bleeding
  1. Ciliary body or iris injury—most common when performing cyclodialysis, peripheral iridectomy, guarded filtration procedure, and cataract extraction
  2. Laser peripheral iridectomy—bleeding is more common with the YAG laser than with the argon laser
  3. Argon laser trabeculoplasty—rare
  4. Selective laser trabeculoplasty—extremely rare
  5. Cyclodestructive procedures—common, depending on the mechanism of elevated intraocular pressure (e.g., neovascular glaucoma)
- B. Early postoperative bleeding
  1. Dilation of a traumatized uveal vessel that was previously in spasm
  2. Conjunctival bleeding that enters the anterior chamber through a corneoscleral wound or a sclerostomy
- C. Late postoperative bleeding
  1. Disruption of new vessels growing across the corneoscleral wound
  2. Reopening of a uveal wound
  3. Chronic iris erosion from an intraocular lens causing fibrovascular tissue growth

III. Spontaneous
- A. Neovascularization of the iris secondary to (the conditions below cause the neovascularization):
  1. Retinal detachment
  2. Central retinal vein occlusion, central retinal artery occlusion, carotid occlusive disease
  3. Proliferative diabetic retinopathy
  4. Chronic uveitis
  5. Fuchs' heterochromic iridocyclitis
- B. Intraocular tumors
  1. Malignant melanoma
  2. Juvenile xanthogranuloma
  3. Retinoblastoma
  4. Metastatic tumors
- C. Iris microhemangiomas—may be associated with diabetes mellitus and myotonic dystrophy
- D. Clotting factor disfunction
  1. Leukemia
  2. Hemophilia
  3. Anemias
  4. Aspirin
  5. Coumadin
  6. Ethanol
  7. Nonsteroidal anti-inflammatory drugs
  8. Vitamin C/gingko

IV. Indirect: spillover from vitreous hemorrhage

Adapted from Gottsch JD: Hyphema: Diagnosis and management. Retina 10:S65–S71, 1990.

Past medical and ocular history may identify risk factors for the bleeding episode and the chance of future complications. Sickle cell test and Hgb electrophoresis are suggested for all black and Hispanic patients and anyone with a positive family history. Establishing the exact nature of the trauma helps to estimate the likelihood of a possible ocular or orbital foreign body and/or ruptured globe. The exact timing of the injury is crucial in enabling one to predict when a patient will be at greatest risk for a rebleed and to help determine the expected time of clearing and the length of necessary treatment.

Four to six weeks after the injury, careful gonioscopy of the recovered eye may reveal an angle recession. At this time, one may also perform a dilated fundus examination with scleral depression to rule out peripheral retinal injury, such as described in Table 20-1.

KEY POINTS: TRAUMATIC HYPHEMA

1. All patients should be evaluated for systemic injuries (e.g., computed tomographic scans, x-rays).
2. All patients should be evaluated for intraocular foreign bodies and ruptured globes as well as other ocular injuries.
3. Recurrent hemorrhages occur in 0.4 to 35% of patients, usually 2 to 5 days after trauma.
4. Corneal blood staining occurs in 5%.

9. What are pertinent questions to ask a patient who presents with a traumatic hyphema? Why?

1. **When did your injury occur?** Establishing the exact time of the injury is important because there is an increased rate of rebleed in patients who present more than 24 hours after trauma, and it will help to determine how soon a patient will be at greatest risk for a rebleed.
2. **What type of injury did you sustain?** The type and severity of an injury is important to help assess the likelihood of associated systemic injuries, an ocular or intraorbital foreign body, and the possibility of a ruptured globe.
3. **Do you or any of your family members have a medical history of bleeding disorders or sickle cell disease?** The answer to this question may help to establish a possible etiology for the hyphema and to determine what type and how aggressive the treatment should be.
4. **What types of medications do you take (including alcohol intake)?** Antiplatelet or anticoagulant effects of aspirin, nonsteroidal anti-inflammatory drugs, warfarin (Coumadin), and alcohol may predispose a patient to developing a hyphema or a rebleed after trauma and should be discontinued if possible.

10. How are hyphemas managed?

There is no consensus regarding the appropriate treatment for hyphema. Traditionally, most patients with a hyphema were admitted to the hospital for bed rest and sedation and were given a monocular or binocular patch for approximately 5 days. Today, compliant patients with a microhyphema and a low risk for rebleed are often followed as outpatients. It still appears prudent to hospitalize those patients who have a layered hyphema (Fig. 20-1), are at increased risk for rebleed, have a sickling hemoglobinopathy, or are noncompliant.

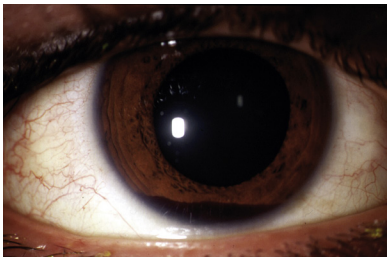

Figure 20-1. Layered hyphema.

Patients are given a protective shield over the affected eye to decrease any inadvertent trauma and are advised to limit activity. The head is elevated (to allow the blood to layer inferiorly and thus assist with visual rehabilitation and prevent clot formation in the papillary aperture), and systemic blood pressure is controlled in an attempt to decrease the hydrostatic pressure in the traumatized blood vessels to minimize the risk of recurrent hemorrhage. Patients should be examined gently once or twice a day.

The medical management of hyphema includes the following:

1. Discontinuation of antiplatelet, anticoagulant, and nonsteroidal anti-inflammatory medications
2. Treatment with cycloplegic drops, oral or topical steroids, antiemetics, and antifibrinolytics
3. Intraocular pressure control as necessary
   - β-Blockers
   - α-Agonists (avoid in young children because of the risk of bradycardia and hypotension)
   - Topical or systemic carbonic anhydrase inhibitors and hyperosmotics (except in sickle hemoglobinopathies because of the risk of increased sickling with these medications)
   - Avoid miotics, as they might increase pupillary block and disrupt the blood–aqueous barrier, and prostaglandin analogs, which may increase inflammation

11. Explain the rationale for the use of antifibrinolytic agents in the treatment of hyphema.

Systemic antifibrinolytic agents are used in an effort to reduce the chance of recurrent hemorrhage. Their use is rare now, especially in populations with a low risk of rebleeding. Fibrinolysis of a clot that seals a recently ruptured blood vessel may result in a repeat hemorrhage from that site. Tranexamic acid and aminocaproic acid decrease the rate of clot hemolysis by inhibiting the conversion of plasminogen to plasmin, which results in stabilization of the clot that seals the ruptured blood vessel. The injured vessel now has more time to heal permanently prior to fibrinolysis of the clot, thus reducing the risk of recurrent hemorrhage. Topical aminocaproic acid shows promise but remains investigational at present.

12. Name the most common adverse effects associated with aminocaproic acid treatment.

Nausea, vomiting, and postural hypotension are frequently encountered side effects of aminocaproic acid. It is therefore recommended that patients who receive aminocaproic acid be transported via wheelchair, particularly during the first 24 hours, to prevent possible complications from postural hypotension. Antiemetics may be used as necessary.

13. In what setting is aminocaproic acid contraindicated?

Aminocaproic acid use is contraindicated in the presence of the following:

- Active intravascular clotting disorders, including cancer
- Hepatic disease
- Renal disease
- Pregnancy

Cautious use is recommended in patients at risk for myocardial infarction, pulmonary embolus, and cerebrovascular disease.

14. Why are patients with sickle cell disease or sickle cell trait at a particularly high risk for developing complications from a hyphema?

Once pliable biconcave erythrocytes transform into elongated ridged sickle cells, they are unable to pass through the trabecular meshwork easily. The trabecular meshwork becomes obstructed with these cells, leading to a marked rise in intraocular pressure, even in the setting of a relatively small hyphema. Factors that encourage sickling include acidosis, hypoxia, and hemoconcentration. Patients with sickle cell are also predisposed to infarction of the optic nerve, retina, and anterior segment at minimally elevated intraocular pressures. Vascular sludging of sickled cells may cause ischemia and microvascular infarction. Therefore, vigorous and aggressive therapy for intraocular pressure control is suggested for patients with sickle cell disease.

Many glaucoma medications (except β-blockers and prostaglandin analogs) are generally avoided because they may increase sickling.

1. Carbonic anhydrase inhibitors, particularly acetazolamide, may increase the concentration of ascorbic acid in the aqueous, which decreases the pH and leads to increased sickling in the anterior chamber. Methazolamide may be a safer alternative in this setting because it causes less systemic acidosis than acetazolamide.

2. Epinephrine compounds and α-agonists may cause vasoconstriction with subsequent deoxygenation and increased intravascular and intracameral sickling.
3. Hyperosmotics may cause hemoconcentration, which may lead to vascular sludging and sickling, which increases the risk of infarction in the eye as well as other organs.
4. Surgical interventions are used earlier and at lower intraocular pressures than in people who do not have sickle cell trait or disease (see question 15).

KEY POINTS: TRAUMATIC HYPHEMA AND SICKLE CELL DISEASE

1. More aggressive management is required to prevent optic nerve damage and central retinal artery occlusion.
2. β-Blockers and prostaglandin analogs should be used for intraocular pressure control.
3. Carbonic anhydrase inhibitors, epinephrine compounds, α-agonists, and hyperosmotics may increase sickling and are therefore contraindicated.

15. What level of intraocular pressure is considered medically uncontrolled?

An intraocular pressure that is considered uncontrolled depends upon the patient in question. (Some guidelines are included in subsequent discussions.) Surgery is generally not indicated in a patient with a healthy optic nerve unless the intraocular pressure is around 50 mm Hg for 5 days or greater than 35 mm Hg for a more prolonged period of time despite medical therapy. However, in the patient with previous glaucomatous optic nerve damage, the threshold for surgical intervention is lower and depends upon the level at which the intraocular pressure is likely to cause further optic nerve damage. In such patients, surgery may be appropriate within hours or days of the initial trauma. As previously discussed, aggressive therapy is required for patients with sickle cell disease, as these patients are predisposed to optic nerve damage and central retinal artery occlusion at minimally elevated intraocular pressures. Surgery is generally indicated in a patient with sickle cell disease if the intraocular pressure exceeds 24 mm Hg for more than 24 hours despite medical therapy.

16. List the indications for surgical intervention in the management of a hyphema.

As a rule, patients with true eight-ball hyphemas require prompt surgical intervention (see question 26); in contrast, approximately 5% of all traumatic hyphemas demand surgical management. Indications for surgical intervention include the following:

- A large hyphema that persists for more than 10 days
- A total hyphema that persists for more than 5 days (after which time peripheral anterior synechiae are more likely to develop)
- Early corneal blood staining
- An intraocular pressure that cannot be controlled medically and threatens to damage the optic nerve or cornea or result in retinal vascular occlusion, particularly in patients with sickle cell trait or disease.

The Read Criteria for surgical intervention include the following:

- Microscopic corneal blood staining
- Total hyphema with intraocular pressures of 50 mm Hg or more for 5 days (to prevent optic nerve damage)
- Hyphema that is initially total and does not resolve below 50% at 6 days with intraocular pressures of 25 mm Hg or more (to prevent corneal blood staining)
- Hyphema that remains unresolved for 9 days (to prevent peripheral anterior synechiae)

17. Name the major complications associated with a hyphema.

- Corneal blood staining
- Recurrent hemorrhage
- Secondary glaucoma
- In addition to the preceding complications, patients with sickle cell anemia or sickle cell trait have a predisposition to central retinal artery occlusion and optic nerve damage at only minimally elevated intraocular pressure owing to vascular sludging of the sickled cells, which leads to ischemia and vasoocclusion.

18. What is corneal blood staining?

Endothelial cell decompensation results in passage of erythrocyte-breakdown products (particularly iron from hemoglobin and lipid from cell membranes) into the stroma, creating a yellowish-brown discoloration of the posterior stroma. Corneal blood staining may resolve over months or years, first peripherally and then posteriorly.

19. What percentage of patients with a hyphema develop corneal blood staining?

Corneal blood staining will develop in 5% of hyphema patients.

20. In what settings is corneal blood staining most likely to occur?

- Recurrent hemorrhage
- Compromised endothelial cell function
- Larger hyphemas that are prolonged in duration
- Usually, but not always, in association with an elevated intraocular pressure

21. What is the differential diagnosis of the appearance of bright red blood in the anterior chamber within the first 5 days after a patient has suffered a traumatic hyphema?

- Recurrent hemorrhage
- Fibrinolysis and hemolysis of a clotted hyphema

Recurrent hemorrhage must be differentiated from hemolysis that occurs as a clotted hyphema resorbs, particularly if the patient has been treated with aminocaproic acid. A rise in intraocular pressure associated with accelerated hemolysis can mimic a rebleed and may occur 24 to 96 hours after the use of aminocaproic acid has been discontinued.

A patient who has been treated with aminocaproic acid should continue to have his or her intraocular pressure monitored several days after discontinuation of therapy in the event that there is a spike in intraocular pressure associated with accelerated hemolysis.

22. In the setting of a traumatic hyphema, when is a patient at greatest risk for developing a recurrent hemorrhage?

The greatest risk is between 2 and 5 days following blunt ocular trauma, perhaps owing to clot fibrinolysis and retraction.

23. How common is a recurrent hemorrhage?

A recurrent hemorrhage generally occurs in 0.4 to 35% of patients who suffer a traumatic hyphema.

24. What is the significance of a recurrent hemorrhage? Why is it important to try to prevent it?

A recurrent hemorrhage carries a poorer prognosis than the initial hyphema. Most rebleeds are larger than the initial hyphema and carry an increased risk of developing a secondary glaucoma and corneal blood staining; visual outcome is worse, and there is a more frequent need for surgical intervention.

25. List the risk factors that may be associated with an increased risk of developing a recurrent hemorrhage.

- Antiplatelet or anticoagulant ingestion
- Black or Hispanic race
- Hypotony
- Younger age
- Larger initial hyphema
- Systemic hypertension

26. What is an eight-ball hyphema?

An eight-ball or black-ball hyphema is a hyphema that has clotted and taken on a black or purple color (Fig. 20-2). The black or purple appearance of an eight-ball hyphema is due to impaired aqueous circulation, which leads to a subsequent decrease in the oxygenation of the intracameral blood and results in the characteristic black- or purple-colored clot. It is believed that impaired aqueous circulation occurs as a result of either pupillary block from the clot or a direct tamponade effect of the clot at the level of the trabecular meshwork. The impairment in aqueous circulation prevents the clotted black-ball hyphema from being reabsorbed. These hyphemas carry a graver prognosis with respect to developing secondary glaucoma.

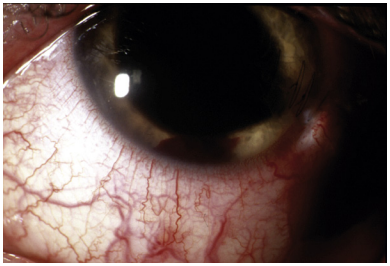

Figure 20-2. Clotted hyphema.

27. How is an eight-ball hyphema different from a total or 100% hyphema?

An eight-ball hyphema describes blood in the anterior chamber that has clotted and taken on a black or purple appearance. A total, or 100%, hyphema is one in which the blood filling the anterior chamber appears bright red. A hyphema that consists of bright red blood indicates that there is continuous aqueous circulation within the anterior chamber, which results in a significantly more favorable prognosis than an eight-ball hyphema.

28. What is the prognosis for an eight-ball hyphema?

Patients who develop an eight-ball hyphema carry a poor prognosis with respect to developing secondary glaucoma. Most, if not all, patients develop an elevated intraocular pressure that is usually severe and frequently difficult to control with medical therapy. Surgical intervention to evacuate the clot and/or decrease the intraocular pressure is generally required for most patients with an eight-ball hyphema.

29. When is the optimal time to remove a clotted or eight-ball hyphema? Why?

It is thought that the optimal time for evacuation of a clotted hyphema is 4 to 7 days after the hemorrhage, because it is at this time that there is maximal consolidation and retraction of a clot from adjacent structures and thus a decreased risk of causing new bleeding. However, extremely high intraocular pressures, with which vascular infarcts are a significant risk, are seen more commonly with eight-ball hyphema.

30. What types of surgical techniques can be used to evacuate a hyphema?

Surgical techniques in managing a hyphema include:

- Paracentesis and anterior-chamber washout alone or in association with a guarded filtration procedure (i.e., trabeculectomy)
- Clot expression with limbal delivery.
- Automated clot removal (hyphemectomy) with a vitrectomy instrument. (Take care to avoid lens and cornea; vasodilators can help maintain the chamber during removal of the clot. Keep the iris between the vitrectomy instrument and lens to minimize the risk of iatrogenic cataract).
- Peripheral iridectomy with or without a guarded filtration procedure to relieve pupillary block, which may be associated with an eight-ball hyphema.

  Figure 20-3 provides an algorithm for the workup and management of a patient who presents with a hyphema.
- Trabecular gonioaspiration has been reported as a successful way of managing intraocular pressure elevation resulting from blood obstructing the trabecular meshwork in sickle cell patients.

31. List the types of secondary glaucoma associated with a traumatic hyphema.

An acute rise in intraocular pressure (IOP) is generally due to obstruction of the trabecular meshwork by erythrocytes or their breakdown products. The intraocular pressure at which medical or surgical therapy is initiated should be individualized and depends upon the presence of previous glaucomatous optic nerve damage, corneal endothelial dysfunction, or sickle cell disease.

Late secondary glaucoma may develop weeks to years after a hyphema. Causes of late secondary glaucoma are listed in Table 20-2. In one retrospective case–control study reviewing patients with open-globe injuries, 17% of patients developed ocular hypertension defined as IOP > 22 mm Hg at more than one visit or requiring treatment. A predictive risk factor includes the presence of hyphema, which reiterates the importance of monitoring IOP closely after trauma.

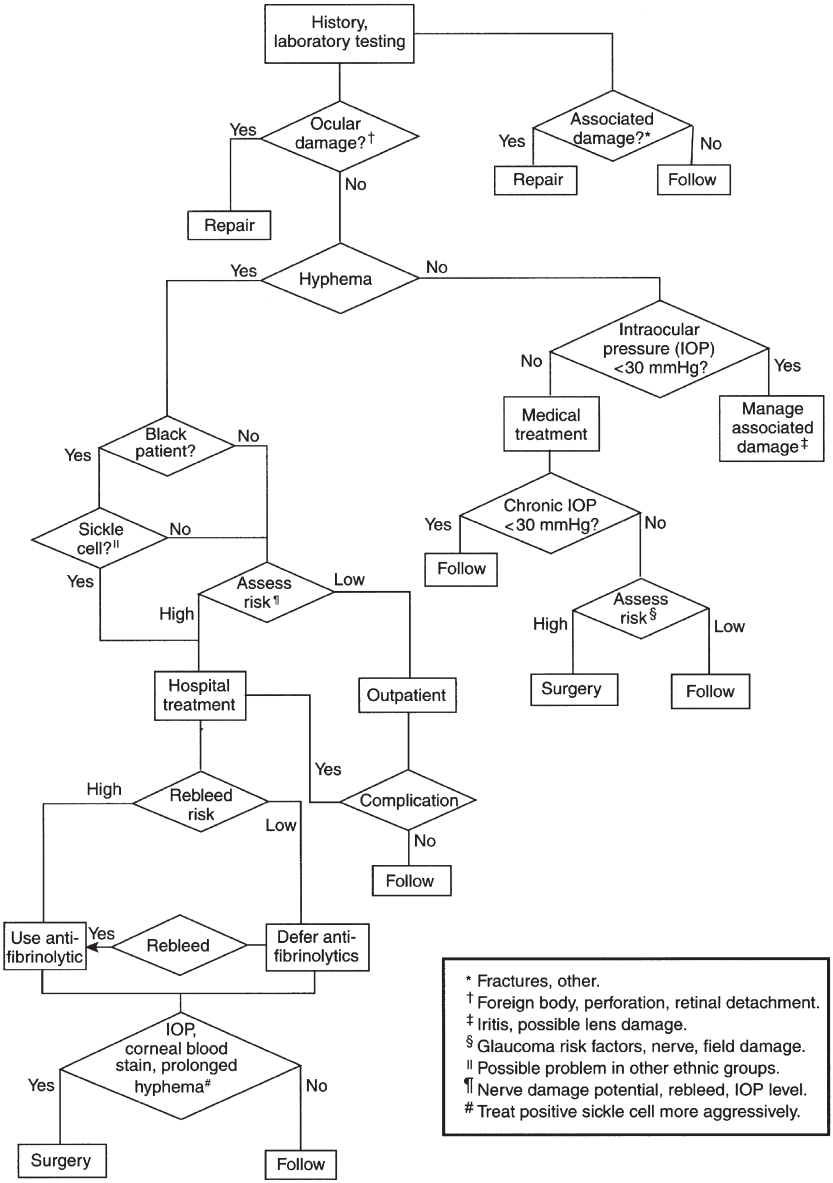

Figure 20-3. Treatment algorithm for ocular trauma and glaucoma. *(From Higginbottom EJ, Lee DA: Clinical guide to glaucoma management. Woburn, MA, Butterworth-Heinemann, 2004.)*

32. Is the chance of developing secondary glaucoma related to the size of the hyphema?

Although there are conflicting reports, the chance of developing a secondary glaucoma may be related to the size of the hyphema. Secondary glaucoma occurred in 13.5% of those eyes in which blood filled half of the anterior chamber, in 27% of those eyes in which blood filled greater than half of the

Table 20-2. Secondary Glaucomas Associated with Traumatic Hyphema

A. Early
1. Trabecular meshwork obstruction with fresh red blood cells and fibrin, resulting in secondary open-angle glaucoma
2. Pupillary block by the blood clot, resulting in secondary angle-closure glaucoma
3. Hemolytic glaucoma
4. Steroid-induced glaucoma from treatment

B. Late
1. Angle-recession glaucoma
2. Ghost-cell glaucoma
3. Peripheral anterior synechiae formation, resulting in secondary angle-closure glaucoma
4. Posterior synechiae formation with iris bombé, resulting in secondary angle-closure glaucoma
5. Hemosiderotic or hemolytic glaucoma

anterior chamber, and in 52% of those eyes in which there was a total hyphema. However, the amount of blood may simply be an indirect marker of the degree of trauma.

Recurrent hemorrhages are often larger than the initial hyphema and carry a greater risk for developing secondary glaucoma. Patients with eight-ball hyphemas develop glaucoma virtually 100% of the time.

33. Why and when is it important to perform gonioscopy on patients who have suffered a hyphema?

The gonioscopic appearance of angle recession may change with time. Immediately following blunt eye trauma, a hyphema may obscure adequate visualization of the angle. Thorough gonioscopic evaluation with indentation is recommended approximately 6 weeks after trauma, at which time the eye has recovered, the hyphema has resolved, and the risk of further injury has been minimized. Clues that may help the ophthalmologist diagnose an old angle recession include the presence of torn iris processes, depression or tears of the trabecular meshwork, and increased whitening of the scleral spur.

Up to 10% of patients with greater than 180 degrees of angle recession will eventually develop a chronic traumatic glaucoma. The term *angle-recession glaucoma* may also be used to describe the chronic traumatic glaucoma that occurs in association with an angle recession.

34. Given a history of ocular trauma, how can one make the diagnosis of angle recession on gonioscopic examination?

Angle recession can be diagnosed by careful gonioscopic examination of the injured eye and by comparing it with the fellow, nontraumatized eye. Gonioscopy may reveal an irregular widening of the ciliary body, indicating a tear between the longitudinal and the circular muscles of the ciliary body. A normal, nonrecessed ciliary body band is usually not as wide as the trabecular meshwork and should be roughly even in width throughout its entire circumference. Angle recession is found in 60 to 94% of patients with a traumatic hyphema (Fig. 20-4).

35. Explain the difference between a cyclodialysis and an angle recession

Although not as common as angle recession, cyclodialysis can occur secondary to blunt compressive trauma. An angle recession is a tear within the ciliary body itself, whereas a cyclodialysis is a tear between the ciliary body and the scleral spur. Disinsertion of the uvea from the sclera allows free passage of the anterior chamber aqueous fluid to the suprachoroidal space, thus permitting direct access to the uveoscleral outflow pathway. Temporary or permanent hypotony is usual. A cyclodialysis cleft should be suspected and carefully searched for when the intraocular pressure remains low after ocular trauma. Other causes for a low intraocular pressure following trauma are retinal detachment and an inflammatory-mediated decrease in ciliary body production.

36. Once a cyclodialysis cleft is suspected, how can it be diagnosed?

A traumatic cyclodialysis cleft can be diagnosed by careful gonioscopic examination. Although the wall of the cyclodialysis cleft is white (i.e., sclera), it appears shaded, owing to the fact that one is looking down into a hole. This is opposed to the gonioscopic appearance of angle recession, which appears simply as an enlarged ciliary body band secondary to a tear in the ciliary body itself. Treatment for a cyclodialysis cleft includes atropine, laser, and surgical repair. Ultrasound biomicroscopy provides high

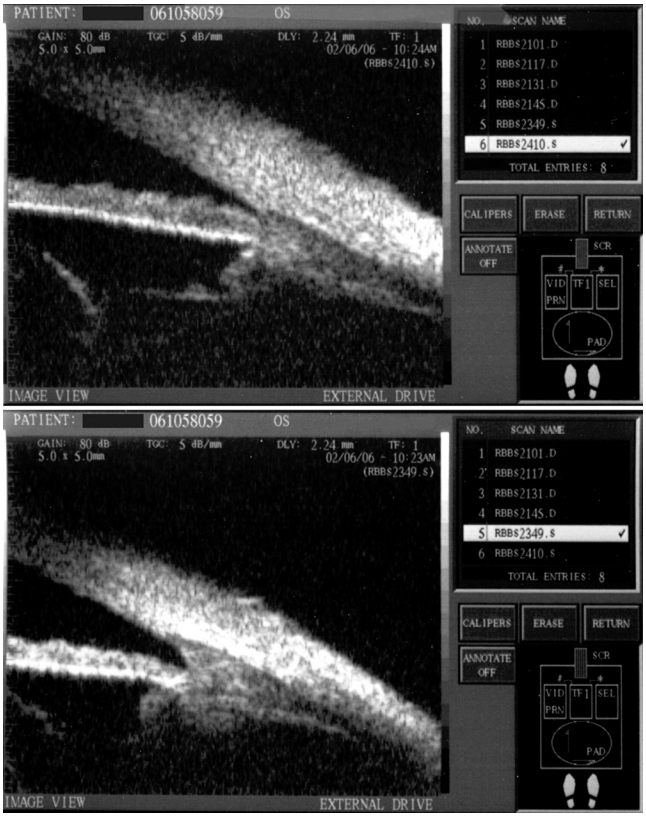

Figure 20-4. Angle recession ultrasound biomicroscopy. **Top,** Normal angle. **Bottom,** Angle recession.

resolution (up to 50 μm) images of the anterior chamber angle, which can be particularly helpful if the cleft is small or as part of the preoperative evaluation to map the extent of a large cleft (see Fig. 20-4).

37. How long after a traumatic hyphema is a patient at risk for developing angle-recession glaucoma?

Angle-recession glaucoma may develop weeks to many years after blunt ocular trauma. Patients who develop traumatic or subsequent angle-recession glaucoma may have an underlying predisposition to primary open-angle glaucoma (POAG). It is believed that the infliction of trauma to a meshwork that is already predisposed to reduced aqueous outflow (POAG) may be just enough to push an already compromised trabecular meshwork over the edge, resulting in an angle-recession glaucoma. Evidence to support this underlying predisposition to reduced aqueous outflow includes an unusually high incidence of POAG in the nontraumatized fellow eye and an increased tendency for the intraocular pressure to be increased by topical corticosteroids. Therefore, management of patients with angle recession includes long-term follow-up of both the injured and the uninjured eye.

38. Explain the pathophysiology of angle-recession glaucoma. Is it a direct result of injury to the ciliary body?

No. Angle recession is merely a marker for anterior segment contusion injury, specifically injury to the trabecular meshwork. Angle-recession glaucoma is thought not to be due to the angle recession itself (i.e., a tear in the ciliary body) but rather due to (1) direct trabecular meshwork damage and subsequent inflammation from the blunt trauma or (2) an extension of a Descemet's-like membrane covering the trabecular meshwork. Both mechanisms may ultimately lead to chronic obstruction in the aqueous outflow pathway.

39. Describe the treatment for angle-recession glaucoma.

Eyes with secondary traumatic glaucoma have reduced conventional outflow owing to trabecular meshwork injury and may therefore shift over to primarily uveoscleral outflow. Miotics may actually paradoxically increase the intraocular pressure, possibly by decreasing uveoscleral outflow. Laser trabeculoplasty does not have a high rate of success in this setting. Prostaglandin analogs, β-blockers, carbonic anhydrase inhibitors, cycloplegics, and filtration surgery are the most effective treatments for angle-recession glaucoma.

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CATARACTS

Richard Tipperman

CHAPTER 21

CATARACTS

1. **Explain the derivation of the word *cataract*.**
   Cataract comes from the Greek word *cataractos,* which describes rapidly running water. Rapidly running water turns white, as do mature cataracts.

2. **What is the leading cause of blindness worldwide?**
   Believe it or not, cataracts, which are treatable, remain one of the leading causes of blindness worldwide.

3. **What is a nuclear sclerotic cataract?**
   A nuclear sclerotic cataract describes the sclerosis or darkening that is seen in the central portion of the lens nucleus. This type of cataract is typically seen in older patients. As the equatorial epithelial cells of the lens continue to divide, they produce compaction of the more central fibers and sclerosis.

4. **What produces the brown color seen in cataracts?**
   The brown color comes from urochrome pigment.

5. **What is "second sight?" How is it associated with nuclear sclerotic cataracts?**
   As patients develop nuclear sclerotic cataracts, the increased density of the lens causes the patient to become increasingly nearsighted. As a result of their nearsightedness, many patients who required spectacles to help them read find that they are able to read small print up close without glasses. In the past, this phenomenon was termed "second sight." Of interest, patients erroneously believe that their eyes are getting stronger or better, whereas the opposite is the case. Second sight indicates progression of the cataract.

6. **What are the typical symptoms of nuclear sclerotic cataracts?**
   In general, all types of cataracts cause decreased vision. Nuclear sclerotic cataracts tend to cause problems with distance vision but preserve reading vision because of the above-mentioned nearsightedness.

7. **What are posterior subcapsular cataracts?**
   Posterior subcapsular cataracts are granular opacities seen mainly in the central posterior cortex just under the posterior capsule. They have a hyaline type of appearance.

8. **What are the symptoms of posterior subcapsular cataracts?**
   Unlike patients with nuclear sclerotic cataracts, patients with posterior subcapsular cataracts often have good distance vision but typically have blurred near vision. In addition, patients with posterior subcapsular cataracts often have extreme difficulty with glare so that in dim illumination they function well, whereas with bright illumination their vision decreases significantly.

9. **What are the associated systemic findings in patients with cataracts?**
   In general, **nuclear sclerotic cataracts** are seen in elderly patients, although they may occur in young patients as well. In younger patients, they are often associated with high myopia.
   Posterior subcapsular cataracts are common in patients with diabetes, patients who have taken steroids, and patients with a history of intraocular inflammation, such as uveitis.

10. **What are the major potential causes of cataracts in infants?**
    Common causes of congenital cataracts include familial inheritance, intrauterine infection (e.g., rubella), metabolic diseases (e.g., galactosemia), and chromosomal abnormalities. Complete evaluation by a pediatrician is mandatory for any infant with a congenital cataract.

11. **What is a morgagnian cataract?**
    A morgagnian cataract is a mature cataract in which the cortex liquefies and the mature central nucleus can be seen within the liquefied cortex.

12. What is phacolytic glaucoma?

Phacolytic glaucoma may occur with morgagnian and mature cataracts. Liquefied cortex traverses the capsular membrane and enters the posterior chamber, producing an inflammatory response that clogs the trabecular meshwork and results in elevated intraocular pressure.

13. What is phacomorphic glaucoma?

As the cataract matures, the lens becomes enlarged (intumescent). As the lens enlarges, it pushes the iris root and ciliary body forward, narrowing the angle between the iris and the peripheral cornea in the region of the trabecular meshwork. If the angle becomes narrow enough, the pressure may become elevated because of angle closure. Treatment involves removal of the cataract.

14. What is pseudoexfoliation? What is its relationship to cataracts?

Pseudoexfoliation is a condition in which basement membrane material from the zonules and lens capsule is liberated onto the anterior lens capsule and anterior chamber. Patients with pseudoexfoliation have a predisposition for the development of glaucoma, presumably because of clogging of the trabecular meshwork by the exfoliated material. Patients with pseudoexfoliation often present a challenge for the cataract surgeon because their pupils tend to dilate poorly, and they often have weak or loose zonules that cause intraoperative complications with disinsertion of the zonules. Because of their propensity for developing glaucoma, patients often have postoperative pressure elevations.

15. A patient underwent successful and uncomplicated cataract surgery, and years after the surgery, the intraocular lens (IOL) completely dislocated. What associated ophthalmic condition would the patient be likely to have?

The patient would be likely to have pseudoexfoliation.

16. What is true exfoliation syndrome as opposed to pseudoexfoliation syndrome?

True exfoliation is found in glassblowers who stand in front of hot furnaces throughout the day. Large sheets of material come off the anterior lens capsule. Such cataracts are termed **glassblower's cataracts**. With modern techniques of processing glass, they are no longer seen. Because the type of material produced in pseudoexfoliation seemed similar to the material produced in a glassblower's cataract, it was termed pseudoexfoliation to distinguish it from the exfoliative material produced by heat exposure.

17. What systemic syndromes should be considered in a patient with a spontaneously dislocated natural lens?

In these patients, the zonular support system has been disrupted. Spontaneous dislocation of the lens is most common in Marfan's syndrome and homocystinuria. Typical patients with Marfan's syndrome are tall, thin, and lanky and exhibit arachnodactyly. The lenses in Marfan's syndrome tend to dislocate superiorly. In homocystinuria, the lenses tend to dislocate inferiorly. Trauma also should be considered in all patients with a dislocated lens. Rarely, pseudoexfoliation can be a cause.

KEY POINTS: DISLOCATED AND SUBLUXATED LENSES

1. Patients with a natural lens that is dislocated should be evaluated for trauma.
2. Marfan syndrome most often causes lenses to dislocate superiorly. Patients need evaluation for possible cardiac and aortic abnormalities and retinal detachments.
3. Homocystinuria most often causes lenses to dislocate inferiorly. Patients have a high risk of thromboembolic events.

18. What other clinical findings are common in patients with a traumatic cataract?

Blunt trauma may produce a cataract. Patients often have associated sphincter tears and may even have iridodialysis or angle recession. If the trauma has been severe, some or all of the zonules may be broken, causing the lens to be mobile within the eye. This phenomenon is called **phacodonesis**. Retinal detachment and optic neuropathy also may be present and cause decreased vision.

19. What are the indications for cataract surgery?

The basic indication for cataract surgery is reduced visual function that interferes with activities of daily living. This indication obviously varies, depending on the patient's age and degree of activity. For instance, a 40-year-old accountant with an early posterior subcapsular cataract may be much

more symptomatic than an 85-year-old who no longer reads or drives. Cases in which cataract surgery is medically necessary (e.g., phacomorphic and phacolytic glaucoma) are extremely uncommon. Patients with cataracts should be informed that cataract surgery is almost always an elective procedure and that leaving the cataract alone will not hurt or damage the eye. However, it is important to be aware of state standards of Snellen visual acuity and visual field for driving vision and to inform patients accordingly. They can be found in the Physicians' Desk Reference for ophthalmic medicines. In addition to noting Snellen acuity, it is important to formally document the patient's subjective visual difficulties such as "trouble driving at night" or "difficulty reading."

20. Does a cataract need to be "ripe"?

Many years ago, when cataract surgery was performed by removing the entire lens and leaving the patient aphakic, the cataract needed to be dense enough to remove in a single entire piece and to be causing sufficiently poor vision that the patient would benefit from cataract surgery.

Currently "ripeness" of the cataract is no longer a consideration. The indications for cataract surgery in general are functional visual difficulties secondary to the cataract, interfering with the patient's day-to-day activities or overall quality of life. Typically if the patient has a Snellen visual acuity (or glare disability) that reduces his or her vision to 20/50 or worse, he or she may be considered a candidate for cataract surgery.

21. What is aphakia? What are aphakic spectacles? What is pseudophakia?

Aphakia is the condition in which the patient's natural lens *(phakos)* has been removed surgically, leaving the patient without a lens. This is the result of intracapsular surgery. **Aphakic spectacles** are the heavy "Coke-bottle" glasses patients had to wear to achieve the needed focusing power of the eye with the natural lens missing. **Pseudophakia** or "artificial lens" is the term used to describe an eye with an IOL.

22. How is the intraocular lens power determined? What is the most commonly used intraocular lens power?

The appropriate IOL power for a patient is determined by measuring the curvature of the patient's cornea (keratometry values) as well as the length of the eye (axial length measurement). These two measurements are then utilized by multivariable "IOL power equations" to help determine the most appropriate lens for the individual patient.

The most commonly used IOL power is 18 D.

23. What are multifocal intraocular lenses? How do multifocal intraocular lenses work?

With standard cataract surgery and conventional IOLs there is only one fixed focal distance. Therefore, if a patient achieves good uncorrected distance vision after cataract surgery, he or she will not be able to see at near without correction because the artificial lens cannot accommodate to adjust its focal length the way a natural phakic lens can.

New-technology multifocal IOLs now allow patients the ability to see both in the distance and up close. In the United States there are three Food and Drug Administration-approved IOLs that achieve these results with different technologies: The Crystalens (Bausch & Lomb) utilizes a thin small optic lens that is designed to flex and produce a degree of accommodation; the ReZoom (Abbott Medical Optics) lens uses differing radii of curvature to create a zonal refractive lens to achieve its multifocality; and the ReSTOR (Alcon) lens uses a combination of refractive and diffractive optics to create multifocal images.

24. What is IFIS? What is a Flomax pupil?

IFIS is an acronym for intraoperative floppy iris syndrome. This condition occurs in patients who are taking tamsulosin (Flomax) for benign prostatic hypertrophy. Tamsulosin is a systemic sympathetic α1-A receptor blocker, which improves lower urinary tract flow by relaxing the neck of the bladder and prostatic smooth muscle.

Patients taking tamsulosin who undergo cataract surgery manifest pupillary abnormalities that include a flaccid iris, which undulates and billows in response to intraocular fluid currents. There is also a tendency for the iris to prolapse through both the phaco incision and the paracentesis. Last, there is typically a progressive intraoperative pupillary constriction despite apparent adequate pharmacologic dilation at the initiation of surgery. These iris abnormalities are believed to occur because the smooth muscle in the iris also has α1-adrenoreceptors that are affected by tamsulosin.

Because cataract surgery is more difficult in patients with poorly dilating pupils and the abnormalities noted above, cataract surgery in patients taking tamsulosin can be more difficult as well.

Interestingly, even if patient discontinues his tamsulosin for up to 4 weeks prior to cataract surgery, the pupil abnormalities persist. Surgical strategies for dealing with this situation include utilizing a highly cohesive viscoelastic agent and iris retractors.

www.ascrs.org.

25. What is the difference between an anterior chamber lens and a posterior chamber lens? What is "the capsular bag"?

A posterior chamber lens is typically utilized in routine cataract surgery. During surgery a circular opening termed a capsulorrhexis is made in the capsule that surrounds the cataractous lens. The cataract is removed and then the new lens is placed into the capsular bag, which is the membrane that is left behind once the cataract is removed. This region of the eye is termed the posterior chamber, hence the IOL that resides there is termed a posterior chamber lens.

At times it is not possible to place a posterior chamber lens because of either inherent weakness in the capsular bag or an intraoperative complication that disrupts its integrity. In these cases one of the options is to place a lens in the front (or anterior) portion of the eye, hence the term anterior chamber lens. Anterior chamber lenses fixate in the eye by resting on the scleral spur. If not positioned correctly, these IOLs have the potential to chafe the sensitive uveal tissue in the iris and create complications.

26. What is posterior capsular opacification? What is a secondary membrane? Can a cataract grow back?

The new IOL replaces the cataractous lens by resting inside the capsular bag. Slowly, over time, residual epithelial cells in the capsular bag can grow across the posterior portion of the capsule and cause it to become hazy or cloudy. Over time, the capsule can become so cloudy it may seem as if the cataract has "come back." The cataract can never come back, but the secondary membrane can become cloudy, causing the vision to deteriorate as if the cataract were recurring.

27. What is a YAG capsulotomy?

When the reduced vision becomes clinically significant, the patient may undergo an Nd:YAG capsulotomy. The initials are an acronym for neodymium, yttrium, aluminum, and garnet, which are the materials utilized to allow the laser to function properly and open the membrane.

28. What is the origin of the term laser?

Laser is actually an acronym for light amplification by stimulated emission of radiation.

29. What is the difference between an "intracap" and an "extracap"?

An **intracap** describes intracapsular cataract extraction. This is the "old" type of cataract surgery back in the days when patients had a very large incision made at the corneoscleral limbus and the entire lens surrounded by the lens capsule was removed (usually with the aid of a freezing probe termed a *cryoprobe* as well as α-chymotrypsin to dissolve the zonules). In these cases no lens was replaced and the patient was left aphakic.

In an **extracap** or extracapsular surgery, the capsule surrounding the lens is opened and the cataractous lens removed. The capsule, however, remains in the eye to support and hold the new posterior chamber IOL.

30. What is couching?

Couching describes an ancient technique for cataract surgery in which a needle was inserted into the eye and used to push the opaque cataract back into the vitreous cavity. Although the complication rate of this was extremely high and the visual result limited, in antiquity it would allow patients with mature light perception cataracts to be able to regain a limited degree of vision.

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TECHNIQUES OF CATARACT SURGERY

Sydney Tyson

CHAPTER 22

1. What are the indications for cataract surgery?

In general, the decision to have cataract surgery is elective. It is based on a patient's personal needs and the physician's judgment as to the probability of vision improvement. For some people, even a slight loss of vision is unacceptable. Others may choose to delay surgery because their cataracts do not seriously interfere with their lives. The key question is whether the patient perceives the cataract as interfering with his or her quality of life. Of course, the physician must be aware of state visual acuity requirements for driving.

2. What are two nonsurgical methods of managing a cataract?

- **Refraction:** Patients with a cataract may experience a myopic (nearsighted) shift or so-called second sight. Occasionally, glasses can compensate for such shifts. However, if the shift is large and unilateral, binocular vision may be compromised by image size differences between the two eyes. This anisometropia may push patients to have surgery.
- **Pupillary dilation:** An expanded pupil allows light rays to enter around a central cataract (such as a posterior subcapsular cataract) rather than be blocked by light rays that attempt to pass through a hazy cataract.

3. What preoperative tests are used to gauge visual impairment?

No single test adequately describes the effect of cataracts on a patient's visual functioning, but the most widely used tests are:

- Snellen visual acuity (i.e., 20/20).
- Potential acuity testing. This test estimates postoperative visual acuity by projecting a Snellen acuity chart through the patient's cataract. Most often, it is used to determine whether a patient's visual symptoms are due more to cataract or to retinal disease.
- Glare/contrast sensitivity testing. This test simulates lighting conditions outdoors and determines a patient's vision when functioning under more normal conditions. The high-contrast situation in a Snellen test can overestimate a patient's abilities. A patient may have 20/40 acuity in a dark room but may have 20/100 with glare testing, which could significantly impair driving.

KEY POINTS: TESTS OF VISUAL IMPAIRMENT

1. Snellen visual acuity
2. Potential acuity testing
3. Glare testing
4. Contrast sensitivity testing

4. What are the basic steps in removing a cataract?

1. The pupil is dilated with medications.
2. The eye and eyelids are disinfected with an antiseptic, usually iodine based.
3. The eye and eyelids are anesthetized, and a speculum is placed to keep the eyelids open.
4. An incision is made into the anterior chamber (AC).
5. A viscoelastic (viscous, protective gel) is injected into the AC.
6. The anterior capsule is opened with a capsulotomy or capsulorrhexis to gain access to the lens mass.
7. The nucleus is removed manually or by phacoemulsification.

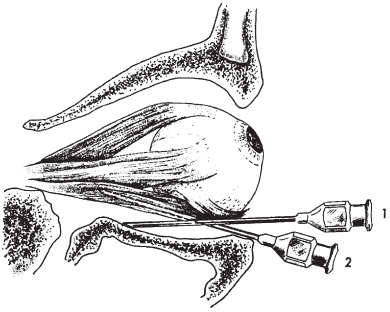

Figure 22-1. Retrobulbar injection. If the tip of the needle strikes the floor of the orbit as it is inserted (see *1* above), it is withdrawn slightly and directed more superiorly (see *2* above). *(From Jaffe NS, Jaffe MS, Jaffe GF: Cataract surgery and its complications. St. Louis, Mosby, 1990.)*

8. The residual cortex is removed.
9. An intraocular lens (IOL) is inserted.
10. The wound is closed.

5. How is the eye anesthetized for surgery?

Most surgeons prefer local rather than general anesthesia for adult cataract surgery. Less commonly, facial akinesia with a short-acting agent such as lidocaine or hyaluronidase (a diffusion enhancer) may be given to prevent squeezing of the eyelids during surgery. There are three types of local anesthesia:

- **Retrobulbar:** Anesthetic (usually a combination of a short- and a long-acting agent with hyaluronidase) is injected inside the muscle cone to achieve akinesia and anesthesia of the globe (Fig. 22-1).
- **Peribulbar:** Anesthetic is injected outside the muscle cone. Although this block takes longer to take effect (12–25 minutes), there are fewer potential complications because a shorter needle is used.
- **Topical:** Advances in technology have allowed skilled surgeons to perform the cataract procedure in 10–15 minutes. With such short operative times, prolonged anesthesia and akinesia become less critical. Topical drops or gels of short-acting agents such as lidocaine or tetracaine may be used to anesthetize the eye sufficiently to complete the procedure. The advantage to the patient is instantaneous binocular vision postoperatively without the risk of injection-related, potentially sight-threatening complications.
- **Intracameral:** As an adjunct to or substitute for topical anesthetics, intraocular administration of preservative-free lidocaine with or without dilating agents is being adopted by many surgeons.

6. What are the disadvantages of topical anesthesia for cataract surgery?

- Because there is no akinesia, the eye can move during surgery.
- Patient selection is crucial. Patients need to be able to follow the commands of the surgeon.

7. What is couching?

Couching is one of the most ancient surgical procedures and it was the first known technique of cataract removal. Although, the technique was first described by the Indian physician Susruta ca. 800 BC, copper surgical instruments that could have been used for couching have been found in the tomb of the Egyptian king Khasekhemwy ca. 2700 BC[11]. Popular in the United States until the 1850s, couching involves piercing the eye with a needle, then dislocating the entire lens backward and downward into the posterior chamber. Although it may seem crude by modern surgical standards and prone to myriad complications, it is still performed in the Third World where advanced technology is not available.

8. What are the two most common ways to remove a cataract?

- **Intracapsular surgery** was the procedure of choice from its discovery by Jacques Daviel in 1752 until the early 1970s. It is accomplished with a cryoprobe, an instrument that freezes the tissue. Intracapsular surgery is rarely performed in the United States today except in cases of dislocated lenses.
- **Extracapsular cataract extraction (ECCE)** is the most popular technique. There are two types—manual extraction and phacoemulsification. Both methods require the use of an operating microscope that permits magnification. In extracapsular surgery the anterior capsule of the lens

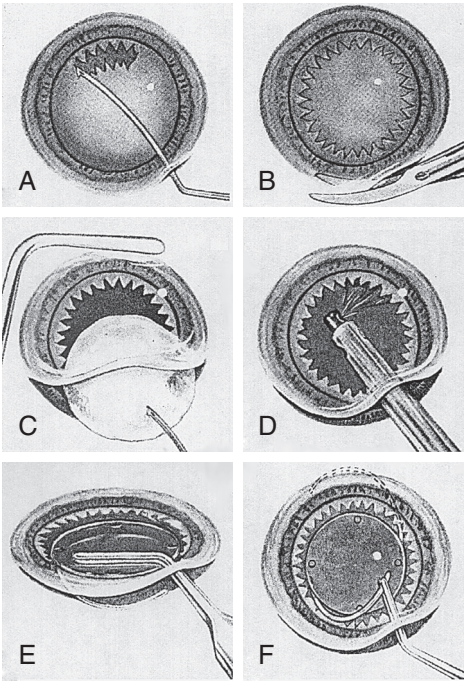

Figure 22-2. Extracapsular extraction. **A,** Multiple small cuts are made in the anterior capsule. **B,** A full-thickness incision is completed with scissors. **C,** The nucleus is removed. **D,** The cortex is aspirated. **E,** The inferior haptic is inserted through the incision and passed under the iris. **F,** The tip of the superior haptic is grasped with a forceps and advanced into the anterior chamber; as the superior pole is clearing the edge of the pupil, the arm is pronated to ensure that when the haptic is released, it will spring open under the iris and not out of the incision. *(From Kanski JJ: Clinical ophthalmology: a systematic approach, ed 2, Boston, Butterworth-Heinemann, 1989.)*

is removed, the hard nucleus is expressed, and the remaining soft cortical fragments are removed with either an automated or a manual device (Fig. 22-2). The advantage of extracapsular surgery is preservation of the posterior capsule, which permits a pocket for an intraocular lens. This method also minimizes the complications associated with vitreous loss.

9. What is phacoemulsification?

Invented by the late Dr. Charles Kellman in 1967, phacoemulsification is a sophisticated form of extracapsular surgery that permits mechanical removal of a cataract through a 3.0-mm incision (Fig. 22-3). This reduction in incision size results in faster visual recovery and fewer complications, making phacoemulsification still one of the most significant advances in cataract surgery. Conventional extracapsular surgery requires a wound size of 150 degrees (approximately 10 mm).

10. How does the phacoemulsification machine work?

Although the machine is complex, its functions are simple: irrigation, aspiration, and ultrasonic vibration via a handpiece. The phacoemulsification handpiece consists of a hollow 1-mm titanium needle that fragments a cataract by vibrating at 40,000 times per second. The fragmented pieces are then aspirated through the tip of the needle and into a drainage bag. An irrigation solution flows from a bottle suspended above the machine and into the eye through the needle. This fluid serves to cool the needle and to maintain proper anterior chamber depth.

11. What are the advantages and disadvantages of phacoemulsification?

- **Advantages** are a small incision, fewer wound problems, less astigmatism, more rapid physical rehabilitation, and less risk of expulsive hemorrhage.

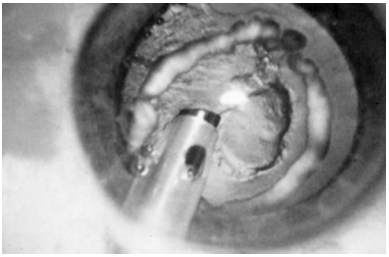

Figure 22-3. The removal of nuclear material by phacoemulsification. *(From Koch PS, Davidson JA: Textbook of advanced phacoemulsification techniques. Thorofare, NJ, Slack, 1991.)*

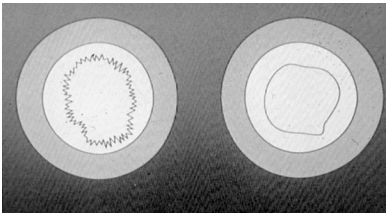

Figure 22-4. Left, Can-opener capsulotomy. **Right,** Continuous-curve capsulorrhexis. *(From Koch PS, Davidson JA: Textbook of advanced phacoemulsification techniques. Thorofare, NJ, Slack, 1991.)*

- **Disadvantages** are machine dependency, a longer learning curve with complications while transitioning, and expensive equipment. Phacoemulsification is more difficult in patients with dense nuclei and/or poor pupillary dilation.

12. How is a capsulotomy performed?

There are two types of capsulotomies: a can-opener capsulotomy and a continuous-curve capsulorrhexis (CCC). The can-opener capsulotomy is a series of jagged punctures performed with a bent needle. Although it is simple to perform, it is prone to peripheral extension of its jagged edges. The CCC is made by tearing the capsule so that the edges remain sharp, well demarcated, and strong. Forces are distributed more evenly and prevent an anterior capsule extension from becoming a posterior capsular tear. This approach permits safe utilization of phaco techniques that use shearing or rotational forces. Implants are held more securely and center better (Fig. 22-4)

13. Where is the nucleus phacoemulsified in the eye?

The nucleus can be disassembled in the anterior chamber or in the capsular bag. Anterior chamber removal is less popular because of the higher risk of corneal endothelial damage. However, in cases with capsular rupture, this method of removal can prevent nuclear pieces from moving posteriorly into the vitreous.

14. Are there different ways to phacoemulsify the nucleus?

The nucleus can be disassembled as a whole (sculpting) or by first being split (nucleofractis) into pieces. Harder nuclei are more readily and safely removed with a splitting technique within the capsular bag. However, a capsulorrhexis is mandatory because the forces exerted during splitting may cause peripheral extension of a can-opener capsulotomy with possible posterior capsular rupture.

The type of capsulotomy and anticipated method of cataract extraction are closely interrelated. The planned location and technique of nucleus emulsification are affected by such variables as nucleus consistency (hard or soft lens), pupil size, zonular (lens ligament) integrity, and the presence of intraoperative complications.

15. Are lasers used to remove cataracts?

Patients love lasers, and this is a question they frequently ask. Femtosecond lasers can now assist or replace several aspects of manual cataract surgery. These include the creation of the initial incisions

in the cornea, the creation of the capsulotomy, the reduction of preexisting astigmatism, and the initial disassembly of the lens. Phacoemulsification is still required to remove the partially disassembled, presoftened lens. The technology is purported to be safer and to deliver improved outcomes by many; however, further data will be required to prove these assertions.

16. Once a cataract is removed (aphakia), what are the options to restore vision?

- **Thick aphakic glasses** are rarely used today because they create visually annoying magnification (approximately 25%) and distortion.
- **Contact lenses** are a better alternative to visual restoration (magnify only 7%), but many elderly patients do not possess the manual dexterity necessary to handle them. Long-term extended-wear lenses can help in this regard.
- **Intraocular lenses** are the best and most common alternative to restoration of normal vision after cataract surgery, because they almost duplicate the aphakic eye. Magnification is minimal, and peripheral vision is normal.

17. Who invented intraocular lenses?

In 1949, Sir Harold Ridley was the first person to insert an implant into the posterior chamber. Most authorities agree that this was one of the most significant advances in cataract surgery.

18. Of what are implants made?

During World War I it was noted that British Spitfire fighter pilots who had Plexiglas (polymethylmethacrylate (PMMA)) embedded in their eyes from shattered canopies tolerated the material well. PMMA lenses became the gold standard. Advances in technology led to the creation of soft or foldable materials made from silicone and acrylic materials. These materials have come into favor mainly because they can be inserted through much smaller incisions.

19. Describe the most common design and shape of IOLs

Implants are composed of an optical portion called the "optic" and a nonoptical portion called the "haptic," which is used for fixating the IOL.

Most optic designs are unifocal (distance only). Multifocal and accommodating designs, which reduce or eliminate the need for computer and/or reading glasses, are now available. Toric IOLs, which can correct preexisting astigmatism, are also available. Optics can be round or oval, with or without positioning holes, and range in size from 5 to 7 mm. Lens haptics can be looped or plate style (mostly seen in foldable implants) and made of the same material as their optics or a different one. Anterior chamber lenses are designed with special haptics that allow proper fixation in the delicate anterior chamber angle.

20. What are the most common positions of IOLs?

The most common positions are capsular bag, ciliary sulcus, and anterior chamber. Capsular bag fixation is preferred because it affords excellent lens stability far away from the corneal endothelium. In more complex cases with no means of capsular support, iris or scleral fixation of the IOL are reasonable options.

21. Is an implant indicated in every aphakic patient?

No. Implants are generally not used in children or in eyes with severe anterior segment disease or inflammation. However, implants to treat children who are aphakic are becoming more common.

22. How is the power of an IOL determined?

The most common method of determining IOL power (*P*) uses a regression formula called SRK. The formula is $P = A - 2.5L - 0.9K$. The components of this formula include the axial length (length of the eye) measurement (*L*), which is determined by A-scan ultrasonography or more accurately by partial coherence interferometry; the average corneal curvature (*K*), which is determined by keratometry; and an *A* constant (*A*), which is specific for each lens type. The closer the implant is to the retina, the greater the *A* constant. Therefore the *A* constant is larger for posterior chamber implants than for anterior chamber implants. Newer IOL calculation formulas have been gaining in popularity. These third- and fourth-generation formulas, such as the SRK/T, Haigis, Olsen, and Holladay II formulas, have offered surgeons the ability to predict IOL powers with uncanny accuracy. These next-generation formulas are especially important in determining IOL power in extremely short or long eyes and in eyes that have had previous refractive surgery.

Intraoperative wavefront aberrometry with the ORA (Wavetec) and Holos (Clarity Medical Systems) devices has added yet another dimension of precision and accuracy to these power determinations.

23. How is the surgical wound closed?

The need for wound closure is directly related to wound size and construction. Larger ECCE incisions can be reapproximated with 10-0 nylon sutures, in a radial, running, or combination technique. The major consideration with these closure techniques is postoperative astigmatism. The tighter sutures are tied, the greater the astigmatism and the more distorted the early postoperative vision. Phaco incisions are smaller and valvelike in construction. This makes them essentially self-sealing and astigmatism free, although some surgeons sleep better at night if at least one suture is placed. The FDA recently approved the first synthetic gel sealant, ReSure, for surgical wound closure, obviating the need for sutures.

24. How should patients be managed postoperatively?

The postoperative patient is seen within the first 48 hours of surgery—preferably within 24 hours. Intraocular pressure, wound integrity, anterior chamber inflammation, and IOL positioning are assessed.

Typical postoperative medications include (1) antibiotic solutions for infection control and (2) steroids and/or nonsteroidal anti-inflammatory drugs for controlling the inflammation. A growing trend among some surgeons has been the elimination of postoperative drops altogether by infusing various combinations of steroids and/or antibiotics inside the eye at the end of the surgery. In this way, compliance, drop cost, and confusion issues for patients are eliminated. Patients are then seen at 1 week, 1 month, and 3 to 6 months. In advanced small-incision surgeries, refractions are usual stable by 1 month. Eyeglasses may be given at this visit, if necessary.

25. What are the most significant trends in cataract surgery?

- Topical and intracameral versus needle anesthesia for cataract surgery.
- Diminished surgical incision size: microincisional cataract surgery allows incision size reduction of 50% or more.
- Conversion to femtosecond from manual cataract surgery.
- Presbyopia- and astigmatism-correcting versus monofocal implants.
- Improved drug delivery methods with intracameral cocktails, pellets. or implants. Phase 3 studies being conducted currently are evaluating sustained release, drug-eluting intracanalicular plugs.
- Sutureless wound closure with gel sealants.

26. What does the future hold for cataract surgery?

Improvements and advances in the way that cataracts are removed will continue. Important hardware and software advances in ultrasound technology will include new phaco needles, improved fluidics, and improved instrumentation, which will allow safer, more efficient removal of cataracts.

The role of the femtosecond laser in cataract surgery will continue to grow along with breakthroughs in IOL design and function. Different IOL materials, such as collamer and hydrogel, promise improved biocompatibility and reduced postoperative inflammatory response. These lenses are ideal for patients with iritis, glaucoma, or diabetes. IOL design will more closely mimic the natural lens. The Crystalens is the only FDA-approved accommodating IOL. This IOL restores accommodation by closely approximating the function of original lenses, thereby reducing or eliminating the need for reading glasses postoperatively. IOL designs are available to correct for the eye's optical aberrations. The Tecnis Z9000 is the first FDA-approved IOL designed to reduce these aberrations and improve the quality of vision by enhancing contrast sensitivity. Finally, a light-adjustable IOL by Calhoun Vision, Inc., is an experimental IOL design now entering its third and final phase of FDA approval. It is made of a light-absorbing polymer that allows precise and noninvasive postoperative modification of the lens power by applying light to the IOL. The era of high-quality, spectacle-free postoperative vision is on the horizon.

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CHAPTER 23

COMPLICATIONS OF CATARACT SURGERY

John D. Dugan, Jr. and Robert S. Bailey, Jr.

1. What complications may result from local anesthesia for cataract surgery?

- **Retrobulbar hemorrhage** is the most common complication from retrobulbar injection. Blood collects in the retrobulbar space, often causing proptosis of the involved eye and a tense orbit. If not treated, it may lead to severe, irreversible optic nerve ischemia.
- **Ocular perforation** may occur if the needle perforates the globe. The risk of this complication is greatest in highly myopic eyes with long axial lengths.
- **Optic nerve sheath hemorrhage** may occur if the needle penetrates the optic nerve. It may result in a secondary central retinal vein and/or central retinal artery occlusion.

Peribulbar injections given with a shorter needle have become more popular recently, as has topical anesthesia for cataract surgery.

2. How do you treat a retrobulbar hemorrhage?

Blood collecting in the retrobulbar space may cause a secondary increase in intraocular pressure from the pressure of the blood on the globe. When a retrobulbar hemorrhage occurs, intermittent pressure is applied initially to the globe to tamponade the bleeding. The intraocular pressure should be measured. If it is significantly elevated, a lateral canthotomy should be performed. This technique is often successful in relieving the pressure on the globe. Surgery is usually canceled when a retrobulbar hemorrhage occurs.

KEY POINTS: MOST COMMON INTRAOPERATIVE COMPLICATIONS OF CATARACT SURGERY

1. Posterior capsule rupture
2. Dislocated lens fragment
3. Iris trauma
4. Thermal corneal injury
5. Descemet tear/detachment
6. Poor intraocular lens placement
7. Choroidal/expulsive hemorrhage

3. What are the common complications related to the cataract wound?

- **Wound leak or dehiscence:** Occurs when apposition of the cataract wound is inadequate. Aqueous humor can be seen leaking from the involved area of the wound.
- **Wound burn:** Transfer of heat from the vibrating needle of the phacoemulsification instrument can induce an incision burn adversely affecting wound apposition.
- **Hypotony:** If a wound leak is present, the intraocular pressure is usually low.
- **Flat anterior chamber:** If the wound leak is large enough, the anterior chamber becomes shallow and may become flat with the iris contacting the cornea.

Most wound leaks require repair in the operating room with additional sutures to achieve a watertight closure.

4. What is iris prolapse? How is it treated?

If a wound leak is present, the iris often becomes incarcerated in the wound and may prolapse, leading to increased inflammation and increased risk of infection. Prolapse requires repair in an operating

room. If the iris is viable, it can be reposited in the eye; if not, it can be excised. Additional sutures are necessary in the area of the wound dehiscence.

5. What types of intraocular hemorrhage may occur during or after cataract surgery?

- **Hyphema or blood in the anterior chamber** can be seen as a layering or meniscus of blood in the anterior chamber. Blood vessels in the base of the cataract wound or possibly from the iris are usually the source of the blood. Most often the blood clears spontaneously, and no treatment is required. The intraocular pressure needs to be monitored closely because secondary elevation may occur.
- **Expulsive choroidal hemorrhage** is the most feared complication of cataract surgery and is caused by rupture of choroidal vessels, most often during surgery. The rupture causes a rapid rise in intraocular pressure with loss of the anterior chamber, iris prolapse, and possible prolapse of the entire intraocular contents if not recognized and treated promptly. Fortunately, it has an occurrence rate of 0.2%.

6. What is the incidence of posterior capsule rupture for an experienced surgeon during cataract surgery?

Most studies report between 1% and 3%.

7. What are the possible consequences of posterior capsule rupture?

Posterior capsule rupture is often associated with vitreous loss. It may result in loss of lens material into the vitreous cavity (Fig. 23-1). It also increases the risk of endophthalmitis and retinal detachment.

8. What are some of the risk factors for expulsive choroidal hemorrhage? How are they treated?

Patients with advanced age, systemic hypertension, arteriosclerosis, glaucoma, and long axial-length eyes are at greater risk. Time is of the essence in responding to this operating room emergency. The wound must be closed as quickly as possible; in fact, the surgeon may tamponade the wound with his or her thumb until a suture is ready. Sutures should be rapidly placed and the patient's eye closed. Some surgeons advocate performing posterior sclerotomies to release accumulated blood. The prognosis for visual outcome is usually quite poor.

KEY POINTS: POSTOPERATIVE CATARACT SURGERY COMPLICATIONS

1. Corneal edema
2. Cystoid macular edema
3. Inflammation/uveitis
4. Wrong intraocular lens power
5. Secondary membrane
6. Glaucoma/elevated intraocular pressure
7. Wound leak
8. Retinal detachment
9. Diplopia
10. Ischemic optic neuropathy

9. What are the causes of postoperative inflammation?

- **Operative trauma.** All eyes show some postoperative uveitis, characterized by cell and flare reaction in the anterior chamber. Despite individual variation, the degree of inflammation is usually proportionate to the degree of trauma induced by the surgical procedure. Procedures with longer surgical times and/or additional procedures (i.e., vitrectomy or iris manipulation) show greater amounts of inflammation.
- **Retained lens material.** Fragments of lens material—either nucleus or cortical remnants—may cause inflammation. In almost all cases cortical remnants resorb and require no additional treatment. Nuclear fragments may become a source of chronic inflammation that leads to macular edema. Most nuclear remnants require surgical removal.

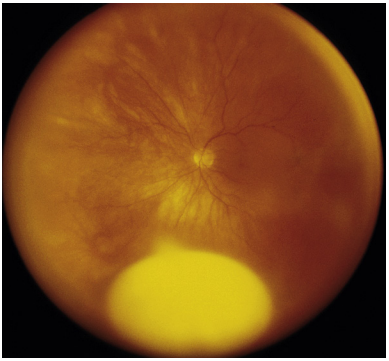

Figure 23-1. Posterior capsule rupture may lead to loss of nuclear fragments into the vitreous. In this case nearly the entire lens "dropped" following a circumferential extension of a radial tear during capsulorrhexis.

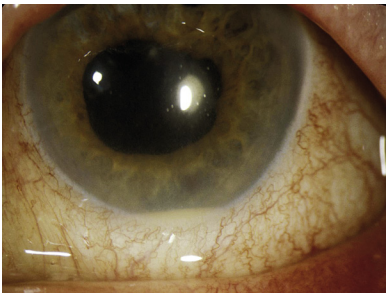

Figure 23-2. A layered hypopyon is seen in this case of postoperative endophthalmitis.

- **Foreign body reaction to intraocular implants** may occur. This is more common when implants are poorly positioned, especially when they are in contact with uveal tissue. Some patients, particularly those with a history of uveitis, may react to the intraocular lens (IOL) material.

10. How does infectious endophthalmitis present? When does it usually occur?

The classic presentation includes severe ocular pain, decreased vision, eyelid swelling, conjunctival chemosis, and hypopyon. Corneal edema and diminution or loss of the red reflex often occurs. This condition must be suspected in any patient who presents with more inflammation than expected postoperatively. On average, patients developed signs and symptoms 6 days after surgery. More than three-fourths of patients developed signs and symptoms within 2 weeks (Fig. 23-2).

11. What are the common organisms cultured from the vitreous of endophthalmitis patients?

In the Endophthalmitis Vitrectomy Study the most common causative pathogens were gram-positive, coagulase-negative organisms (e.g., *Staphylococcus epidermidis*), followed by other gram-positive organisms, such as streptococci and *Staphylococcus aureus*.
https://www.nei.nih.gov/news/clinicalalerts/alert-evs.

KEY POINTS: FINDING OF ENDOPHTHALMITIS VITRECTOMY STUDY

1. Systemic antibiotics provide *no* benefit in treating endophthalmitis
2. Intravitreal antibiotics should be given to *all* endophthalmitis patients
3. If vision is *better* than hand movements: intravitreal tap and biopsy
4. If vision is *worse* than hand movements: full three-port pars plana vitrectomy

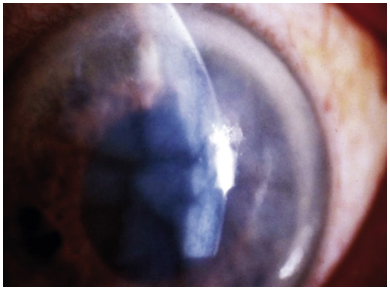

Figure 23-3. Corneal edema such as this is characterized by thickening of the cornea with Descemet's folds and, frequently, microcystic epithelial changes. It is more commonly seen in patients with preexisting endothelial cell loss (Fuchs' dystrophy) or dysfunction.

12. What are the causes of corneal edema after cataract surgery?

Corneal edema frequently occurs adjacent to the cataract wound and usually resolves spontaneously. Surgical trauma, preexisting endothelial corneal dystrophy, and elevated intraocular pressure may cause central corneal edema. Treatment of elevated intraocular pressure and topical steroids, as necessary for inflammation, are important. Often, central edema resolves. Corneal or epithelial transplantation may be necessary for patients when corneal edema persists (Fig. 23-3). Evaluate for a Descemet's detachment if the edema does not clear or worsens.

13. What are the causes of vitreous loss during cataract surgery? Why is vitreous loss important?

Vitreous loss may result from rupture of the posterior lens capsule or weakness or dehiscence of lens zonular apparatus. Vitreous loss increases risk of retinal detachment, cystoid macular edema, and endophthalmitis. The additional surgical trauma also may lead to an increase in corneal trauma and secondary central corneal edema.

14. What is the incidence of retinal detachment after cataract surgery? Which patients are at greater risk?

Retinal detachment occurs in 1% to 2% of patients in most reported series. Patients predisposed to retinal detachment because of high myopia, lattice degeneration, and a history of retinal detachment in the fellow eye are at greatest risk. Vitreous loss at the time of surgery also raises the risk of retinal detachment. The risk of retinal detachment after cataract surgery has decreased with the advent of extracapsular cataract extraction, which has replaced intracapsular extraction.

15. What is cystoid macular edema?

Cystoid macular edema (CME) occurs when fluid accumulates in the cells in and around the center of the macula, known as the fovea. Fluid may leak from the capillaries surrounding the fovea. CME typically presents 4 to 8 weeks after cataract surgery with a decrease in central visual acuity (Fig. 23-4).

16. Which patients are likely to suffer from cystoid macular edema? How is it treated?

Cystoid macular edema is more common after intracapsular than after extracapsular cataract extraction. It is also more common when vitreous loss occurs, especially if the vitreous or iris becomes incarcerated in the wound. However, it may occur even in uncomplicated cases.

Treatment of CME is controversial because a significant percentage of cases resolve spontaneously. Initial treatment often includes topical steroids or nonsteroidal anti-inflammatory medications such as Acular or Prolensa. Acetazolamide (Diamox) has been shown to reduce edema in some cases and is often used as an oral medication. More recently, intravitreal triamcinolone has been shown to help cystoid macular edema, although the improvement may be transient. When the vitreous or iris is adherent to the wound, lysis of vitreous strands with surgery, neodymium:yttrium–aluminum–garnet (Nd:YAG) laser, or wound revision may be beneficial. Pars plana vitrectomy has been used with success in some patients who suffer from chronic CME.

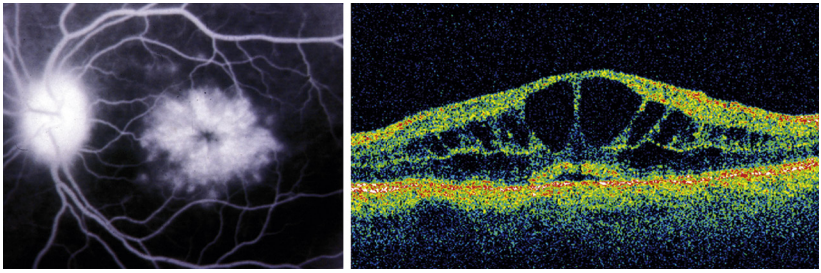

Figure 23-4. Cystoid macular edema after cataract surgery (Irvine-Gass syndrome) has historically been documented with fluorescein angiography *(left),* in which it has a classic petaloid appearance in late frames of the angiogram. Optical coherence tomography is increasingly being used to diagnose and follow macular edema *(right).*

17. What is a secondary membrane?

A secondary or "after-cataract" membrane develops after extracapsular cataract surgery. The posterior capsule opacifies when persistent lens fibers adhere to the capsule or the remaining lens fibers undergo metaplasia. Patients typically present with progressive decrease in vision or problems with glare after surgery.

18. When does a secondary membrane develop? How frequently does it occur?

Usually, secondary membrane begins to develop several months after surgery, although in many cases the membrane may take 1 year or more to become visually significant. The opacification rate varies from 8% to 50% in various series. Recently, squared posterior optic edge designs have lowered this rate, particularly with acrylic material optics.

19. How is a secondary membrane treated? What complications may occur?

A physician can perform a capsulotomy as a primary or secondary surgical procedure by cutting open the posterior capsule with a needle knife. This technique has been largely replaced by use of the Nd:YAG laser. Complications of laser capsulotomy include transient intraocular pressure rise, retinal detachment, and CME.

20. What are the most common complications related to IOLs?

- Implantation of the wrong power IOL may result in unacceptable refraction.
- Decentration or dislocation of the IOL may produce unwanted optical images, including monocular double vision.
- Mechanical chafing of the IOL against the iris or ciliary body may cause chronic inflammation. Chronic uveitis and secondary glaucoma, CME, or corneal decompensation may develop. Patients with these complications may require IOL repositioning or exchange.

21. Why are patients with diabetes at greater risk when undergoing cataract surgery?

Diabetic retinopathy may accelerate dramatically after cataract surgery. This risk is greatest if the posterior capsule ruptures.[1]

22. What are the major problems in managing patients with preexisting glaucoma and cataracts?

- Many patients have been on glaucoma therapy, including miotics that constrict the pupil. Such therapy may make cataract surgery more difficult and often requires surgical maneuvers to enlarge the pupil.
- Postoperative pressure may rise because of retained viscoelastic material and inflammation. This elevation in pressure is often more severe and prolonged in patients with glaucoma. Elevation of pressure may cause additional optic nerve damage and visual field loss and result in loss of central vision in patients with advanced glaucoma. A glaucoma procedure may be combined with cataract surgery in patients with advanced or poorly controlled glaucoma.
- Patients with glaucoma who have had previous filtration surgery and develop cataracts may require a different approach to cataract surgery. A shift in the location of the incision to avoid damage to the filtration site is often necessary. Inflammation from the surgical procedure may cause failure of a previously functioning filter postoperatively.

23. What medication is associated with intraoperative floppy iris syndrome?

Tamsulosin (Flomax) is a systemic $\alpha 1$ antagonist medication used to treat prostatic hypertrophy. This drug relaxes the smooth muscle in the bladder neck and prostate. It has been postulated that the same receptor is present in the iris dilator smooth muscle, resulting in loss of normal iris muscle tone.

24. What are the indications for capsular tension rings?

Capsular tension rings may be used in a variety of patients. Most frequently they are used in patients with zonular laxity or instability. Most often this is in patients with pseudoexfoliation syndrome. It may also be a useful management tool in trauma cases or in patients who develop zonular dialysis as a result of the surgical procedure.

25. What complications have been reported with femtosecond laser-assisted cataract surgery?

- Increased incidence of anterior capsule tears compared with traditional phacoemulsification cataract surgery. Laser anterior capsulotomy integrity seems to be compromised by postage-stamp perforations. This leads to an increased incidence of anterior capsule tears compared with manual continuous capsulorrhexis.
- Incomplete anterior capsulotomy resulting in capsule tags or bridges
- Posterior capsule rupture possibly resulting in posterior dislocation of lens material[2]

26. What are the common reasons that patients may be unhappy with multifocal IOLs?

- Uncorrected refractive error (either myopia, hyperopia, or astigmatism).
- Ocular conditions that reduce contrast sensitivity or image quality that were undiagnosed prior to surgery, including but not limited to dry eye syndrome, anterior basement membrane dystrophy, macular degeneration, and/or epiretinal membrane.
- Loss of contrast sensitivity related to IOL design with resulting image quality degradation.
- Disabling glare or halos.
- Intermediate vision complaints.
- Decentered or tilted IOL.

27. What is the difference between positive and negative dysphotopsia?

- Negative dysphotopsia represents an undesired optical phenomenon after cataract surgery. It is classically described as a dark temporal shadow. It is seen only with in-the-bag posterior chamber with overlap of the anterior capsulorrhexis onto the anterior surface of the IOL. If disabling to the patient, it has been successfully treated with two surgical strategies: reverse optic capture (the lens optic is moved anterior to the capsulotomy) and placement of a secondary piggyback IOL.
- Positive dysphotopsia is characterized by light streaks, starbursts, or glare.

28. What are the reasons for residual astigmatism following toric IOL implantation?

- Implantation of a toric IOL on the wrong axis or rotation of the IOL off axis during the postoperative period.
- An effect of posterior corneal astigmatism. A recent study showed that posterior corneal astigmatism on average will increase against-the-rule astigmatism and decrease with-the-rule astigmatism.
- Irregular astigmatism. Patients with irregular astigmatism from keratoconus, corneal scars, and other causes are not good toric IOL candidates. Attempted correction may result in undesirable postoperative results.[3]

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CHAPTER 24

AMBLYOPIA

Lauren B. Yeager and Steven E. Brooks

1. What is amblyopia?

Amblyopia may be defined as a potentially reversible loss in visual function (e.g., acuity, contrast sensitivity, motion perception, binocularity), in one or both eyes, that results from inadequate or abnormal stimulation of the visual system during a critical period of early visual development.[1]

2. Explain the concept of the "critical" or "sensitive" period.

This period is central to the concept of amblyopia. It refers to a developmental time frame early in life during which there is robust plasticity within the visual system, particularly the visual cortex. Although not precisely defined, this period extends from birth to approximately 8 to 10 years of age. During this period the visual system is profoundly affected by the quality of visual stimulation it receives. Abnormal visual experience can lead to developmental abnormalities at both the structural and the functional level. If amblyopia occurs, it must be detected and treated during the critical period for vision to develop normally.[2]

3. How is amblyopia classified?

Amblyopia is classified according to the underlying mechanism: strabismic, optical defocus, pattern or form deprivation, and organic.

Strabismus can lead to amblyopia if one eye becomes dominant, which causes the afferent input from the deviating, nondominant eye to be chronically suppressed. Optical defocus encompasses anisometropia as well as bilateral severe ametropia. Pattern or form deprivation amblyopia is caused by lesions that physically obstruct the visual axis, such as a congenital cataract, corneal opacity, vitreous hemorrhage, or ptosis. Organic amblyopia occurs secondary to a defined lesion of the visual pathways, such as a macular scar or coloboma. It is fundamentally different from the other types, because some or all of the vision loss is irreversible, and not simply a secondary effect on receptive fields in the lateral geniculate nuclei and visual cortex.

4. How does strabismus cause amblyopia?

Manifest strabismus disrupts sensory fusion. As a result, the vision from one eye must be suppressed to avoid diplopia and visual confusion. If a child with strabismus develops a strong preference for the use of one eye over the other, the nondominant eye may become amblyopic because of chronic suppression.

5. How prevalent is amblyopia?

The incidence of amblyopia is 1% to 3.5% in developed countries, and it is the most common cause of unilateral vision loss in children and young adults.

6. What factors place children at increased risk for amblyopia?

- Developmental delay
- Positive family history of amblyopia
- Prematurity

These factors lead to a two- to sixfold increase in a child's chance of developing amblyopia.

7. What anatomic changes have been shown to occur in amblyopia?

Extensive animal studies have shown several neuroanatomic alterations in amblyopia. The primary abnormality appears to be the atrophy of cells in the layers of the lateral geniculate nucleus and visual cortex serving the amblyopic eye. These changes can be partially or wholly reversed if the amblyopia is successfully treated.[3-5]

8. How early should children be screened for amblyopia?

The American Academy of Ophthalmology, American Academy of Pediatrics, and American Association of Pediatric Ophthalmology and Strabismus recommend routine vision screening in children by a pediatrician or properly trained health care provider as follows:

- In newborns in the newborn nursery
- At each routine well visit from 1 month to 4 years of age
- A formal visual acuity should be documented by 5 years of age, or earlier if possible

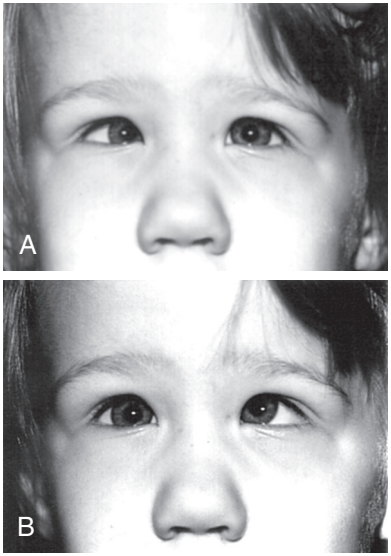

Figure 24-1. Child with esotropia showing spontaneous alternation in fixation. **A,** The left eye is used for fixation. **B,** The right eye is used for fixation. Alternating fixation is good evidence against the presence of amblyopia in children with strabismus.

The optimal time to diagnose and treat amblyopia is as soon as it occurs, but it is critical to do so before the close of the critical period (ideally before the child is 5 years of age).[6]

9. What are some clinical techniques to check for amblyopia in nonverbal children?

Fixation preference testing is especially useful. In strabismic patients, a lack of spontaneous alternation in visual fixation between the two eyes suggests amblyopia in the nonpreferred eye (Fig. 24-1). In patients with straight eyes or small-angle strabismus the vertical prism test is used to determine fixation preference. A child who consistently objects to occlusion of one eye but not the other can be assumed to have decreased vision in the eye that he or she will allow to be covered. Visual evoked potentials and preferential looking (e.g., Teller acuity cards) tests can be used to measure visual acuity. The Bruckner test, comparing the quality and symmetry of the red reflex between the two eyes using a direct ophthalmoscope, can help detect small-angle strabismus or anisometropia.[7-9]

10. Describe photoscreening and its role in detecting amblyopia.

A photoscreener is a device used by pediatricians or other individuals to screen for amblyogenic risk factors in children. The photoscreener is a camera that takes multiple images of a child's undilated eyes to detect amblyogenic risk factors including high refractive errors, anisometropia, anisocoria, and the presence of strabismus (Fig. 24-2). Children who are identified as having risk factors for amblyopia by the photoscreener should be referred to a pediatric ophthalmologist for a complete examination. Photoscreeners may have significant advantages over traditional eye chart acuity screening, especially in younger children who are preverbal or may not be able or willing to participate in the eye chart acuity test.

11. What is the usual presenting complaint of a child with anisometropic amblyopia and at what age does it occur?

Similar to other forms of amblyopia, anisometropic amblyopia is generally asymptomatic. Detection in children depends on effective screening programs. Because of the lack of an overt external sign, such as strabismus or ptosis, the average age at presentation for anisometropic amblyopia is approximately 5 to 6 years, when school-initiated screening programs begin.

Figure 24-2. Image taken from a commercially available photoscreening device. Similar to the Bruckner test, the red reflex is evaluated. Based on the shape, size, and location of the bright crescents in the pupillary light reflexes of the undilated pupils, a determination can be made as to whether the child has significant refractive error, anisometropia, or strabismus. Digital analysis software available in many of the commercially available devices can analyze the images and provide referral recommendations to the tester.

12. How does anisometropia cause amblyopia?

In anisometropia the retinal image in one eye is always defocused. If fixation is not alternated, the chronically defocused eye becomes incapable of processing high-resolution images. In addition, the binocular rivalry between the blurred image in one eye and the clear image in the other eye leads to foveal suppression of the blurred image as a way to avoid visual confusion. In the absence of strabismus, the suppression affects the foveal region, where high-grade visual acuity is processed and binocular rivalry is poorly tolerated. As a result, such patients often display peripheral sensory fusion and gross stereopsis (monofixation syndrome) and maintain good ocular alignment.[10,11]

13. In addition to visual acuity, what other aspects of visual function may be affected in amblyopia?

- Binocular vision and stereoacuity
- Contrast sensitivity
- Motion perception and processing
- Spatial localization

14. Which is more likely to produce amblyopia—unilateral or bilateral ptosis? Why?

Unilateral ocular abnormalities are much more likely to lead to amblyopia than binocular ones. If one eye has a competitive advantage over the other, its afferent connections become stabilized and more numerous while those of the other eye atrophy and retract. This competition also forms the basis for treating amblyopia. The amblyopic eye, by one means or another, must be given a temporary competitive advantage over the dominant eye.

KEY POINTS: AMBLYOPIA FUNDAMENTALS

1. Amblyopia is a potentially reversible loss of vision caused by abnormal visual stimulation during early visual development.
2. The critical period for amblyopia extends from birth to ages 8 to 10 years.
3. Testing vision with isolated optotypes may overestimate acuity in amblyopia because the effects of crowding are eliminated.
4. Amblyopia is characterized by functional and structural changes in the visual cortex and lateral geniculate nuclei.

15. What steps should be taken before patching or penalization?

The first step is to identify and treat any organic causes for vision loss. The second step is to ensure a clear visual axis. For example, this may require removal of a congenital cataract or vitreous hemorrhage. Significant refractive errors should also be corrected. It may be helpful, during the course of treatment, to correct even relatively low degrees of hyperopia or astigmatism in the amblyopic eye, because the accommodative effort of an amblyopic eye is often reduced. Some cases of refractive amblyopia may be treated by wearing glasses alone, obviating or delaying the need for patching or penalization therapy.[12]

16. How effective is part-time patching compared with full-time patching?

Part-time patching is equally effective as full-time patching in the treatment of amblyopia. Greater compliance is seen with part-time patching regimens. With full-time occlusion there is a greater risk of amblyopia being induced in the sound eye. Children can safely receive full-time occlusion of the

sound eye for up to 1 week per year of life before the next follow-up visit without significant risk of inducing occlusion amblyopia in the sound eye.

17. What is penalization and how is it used to treat amblyopia?

Penalization refers to the intentional degradation of visual acuity in the sound eye by either optical or pharmacologic means. For example, the sound eye might be effectively blurred by intentional undercorrection of its refractive error, using atropine drops to prevent accommodation, or both. Translucent filters can be placed over the spectacle lens of the sound eye to degrade the vision. Penalization techniques are best suited for patients with a high degree of hyperopic refractive error in the sound eye and in whom the amblyopia is mild to moderate (20/100 or better).[13-16]

18. At what point can amblyopia treatment be discontinued?

When the acuity in the treated eye is equal to that of the sound eye. The decision is less clear when there is some persistent deficit in visual acuity. If poor compliance can be ruled out, many practitioners continue to patch until no further improvement is noted after three consecutive treatment intervals (3 to 4 weeks per interval). The eye examination and refraction should also be repeated to detect uncorrected refractive error or structural lesions. These guidelines may be modified, especially if there is a component of organic amblyopia. Once treatment is discontinued, the child should be periodically rechecked to detect recurrences.

19. What are some of the factors affecting the success of amblyopia treatment?

- Age of onset
- Age at which treatment is initiated
- Compliance with treatment regimen
- Depth of amblyopia
- Presence of associated ocular anomalies or injuries

20. Can the vision of an amblyopic eye ever improve in adulthood?

Although the critical period has passed, significant improvements in adulthood have been reported in cases in which the sound eye was lost to enucleation. The presence of central fixation in the amblyopic eye before the loss of the sound eye seemed to be the single most important predictor of the extent of visual improvement.

Studies looking at the potential use of pharmacologic agents such as levodopa to recover vision from amblyopic eyes in visually mature patients have demonstrated only small and temporary improvements. Such agents are not used in routine clinical practice.[17-21]

21. Is color vision affected in amblyopia?

Generally speaking, color vision is not affected by amblyopia, although some investigators have found mild abnormalities in color perception. Eyes with severe amblyopia, particularly those with loss of foveal fixation, tend to demonstrate such abnormalities more consistently than eyes with milder degrees of amblyopia.

22. Does amblyopia cause a relative afferent pupillary defect?

Generally speaking, amblyopia does not cause an afferent pupillary defect (APD), because the pathologic changes in amblyopia are located in the posterior visual pathways, not in the retina or optic nerve. If an eye suspected of having amblyopia is found to have a relative APD, it is imperative that a retinal or optic nerve lesion is ruled out.[22]

23. In which of the following conditions is amblyopia most likely to occur: congenital esotropia, accommodative esotropia, intermittent exotropia, or constant exotropia?

Amblyopia is most likely to occur in accommodative esotropia. Patients with this condition, particularly if there is significant anisometropia, are less likely to alternate fixation than patients with congenital esotropia or exotropia. Patients with intermittent exotropia are unlikely to develop amblyopia, because they spend a fair amount of time being bifoveal.

24. What is the effect of neutral density filters on the vision of an amblyopic eye compared with a normal eye?

The visual acuity of a normal eye is progressively reduced by neutral density filters, whereas that of an amblyopic eye may remain unchanged or even improve slightly. This finding has led investigators to postulate that the vision in an amblyopic eye more closely resembles that normally occurring under scotopic conditions (i.e., rod mediated).

25. What is the crowding phenomenon? What is its significance in amblyopia?

The crowding phenomenon refers to a loss of spatial acuity when optotypes are presented in close proximity, or surrounded by other visual details, rather than in isolation. The crowding phenomenon is seen in both normal and amblyopic eyes but tends to be much more pronounced in amblyopia. Because of this, measurement of acuity by isolated optotypes may overestimate acuity in amblyopia.

26. What is eccentric fixation?

Eccentric fixation is seen in severe amblyopia as well as other conditions in which foveal fixation is severely compromised. It refers to the use of nonfoveal areas of the retina for visual fixation. The fixation in such eyes is generally unsteady and poorly maintained. It appears as though the eye is looking elsewhere when, in fact, it is simply attempting to fixate using a nonfoveal area of the retina.

27. Can refractive surgery be used to treat anisometropic amblyopia in children?

Currently, refractive surgery is not considered a good treatment option. Although investigators have reported successfully performing laser-assisted in situ keratomileusis and photorefractive keratectomy in pediatric patients, the surgical risks, lack of data on long-term safety and predictability, and continued need for occlusion or penalization treatment render this form of treatment highly investigative at the present time.[23,24]

KEY POINTS: AMBLYOPIA TREATMENT GUIDELINES

1. Part-time occlusion therapy can be as effective as full-time occlusion if compliance is good.
2. Atropine penalization is most effective if the sound eye is at least moderately hyperopic.
3. Amblyopia treatment can be successful, with good compliance, up to 10 years of age.
4. Refractive errors in the amblyopic eye should be fully corrected during treatment.

28. What is the upper age limit for treatment of amblyopia?

Generally speaking, for optimal outcome, amblyopia should be detected and treated before age 6 years. However, there are several reports of successful treatment in older children (e.g., 7 to 14 years), if excellent compliance with treatment is maintained. This is particularly true for anisometropic amblyopia and less so for strabismic and pattern-deprivation amblyopia.[25-27]

29. Should anisometropia be corrected if amblyopia is not present?

Several studies have found a positive relationship between the degree of anisometropia and the incidence of amblyopia, whereas others have failed to find such a relationship. The American Academy of Ophthalmology's current preferred practice guidelines regarding amblyopia suggest that anisometropia in excess of 3 diopters (D) of myopia, 1.5 D of hyperopia, and 2.0 D of astigmatism be considered for empirical correction in young children in an attempt to minimize the risk of amblyopia. Experimental data in adults suggest that even lower levels of anisometropia can significantly affect high-grade binocular interactions.[10,28]

30. When should strabismus surgery be performed in a patient with amblyopia?

Traditional teaching dictates that amblyopia should be fully treated before strabismus surgery. More recent studies suggest that surgery may be performed during the course of amblyopia treatment if the physician believes that recovery of binocular vision may be improved or treatment of the amblyopia facilitated. It is likely that the management of any given case will need to be determined individually and that both practice patterns can be effectively used.[29]

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CHAPTER 25

ESODEVIATIONS

Scott E. Olitsky and Leonard B. Nelson

1. What is an esodeviation?

A convergent deviation, noted by crossing or in-turning of the eyes, is designated by the prefix *eso*.

2. What are the different types of esodeviations?

- **Esophoria** is a latent tendency for the eyes to cross. This latent deviation is normally controlled by fusional mechanisms that provide binocular vision or avoid diplopia. The eye deviates only under certain conditions, such as fatigue, illness, stress, or tests that interfere with the maintenance of normal fusional abilities (e.g., covering one eye).
- **Esotropia** is a manifest misalignment of the eyes. The condition may be alternating or unilateral, depending on the vision. In alternating strabismus, either eye may be used for fixation while the fellow eye deviates. In cases of unilateral esotropia, the deviating eye is noted in the description of the misalignment (left esotropia).

3. How common is strabismus in infants?

Infants are rarely born with straight eyes. Alignment may vary intermittently from esotropia to orthotropia to exotropia during the first few months of life. Forty percent of newborn infants seem to have straight eyes, 33% may display exotropia, and approximately 3% may be esotropic. Many infants have variable alignment and cannot easily be classified in any single category. Few patients with an esotropia of 40 or more prism diopters that is constant at 10 weeks of age will demonstrate spontaneous resolution of their deviation.[1,2]

4. What is pseudoesotropia?

Pseudoesotropia is the false appearance of esotropia when the visual axes are actually aligned. A flat, broad nasal bridge, prominent epicanthal folds, or a narrow interpupillary distance causes the observer to see less sclera nasally than expected. This creates the impression that the eye is turned in toward the nose.

5. What is congenital or infantile esotropia?

Congenital or infantile esotropia is a convergent strabismus, with no identifiable cause, that develops in a child before the age of 6 months. Although the two terms are often used interchangeably, there is an important difference between them. A child with true congenital esotropia is born with strabismus, whereas a child with infantile esotropia will develop it during the first few months of life. The period of time during early infancy in which the eyes are straight may play an important role in the development of binocular vision after the eyes are aligned.

6. What are the characteristics of congenital esotropia?

- **Large deviation:** The characteristic angle of congenital esotropia is considerably larger than angles of esotropia acquired later in life (Fig. 25-1). In most series reported in the literature, average deviations are between 40 and 60 prism diopters. The diagnosis of congenital esotropia should be reconsidered in a child with a relatively small deviation.
- **Normal refractive error:** Children with congenital esotropia tend to have cycloplegic refractions similar to those of normal children of the same age.[3]

7. What is cross-fixation?

Children with equal vision and a large esotropia have no need to abduct either eye. They use the adducted, or crossed, eye to look to the opposite field of gaze. This is called cross-fixation.

8. Why do some children with congenital esotropia appear to have an abduction deficit?

In children with good vision in both eyes and who demonstrate cross-fixation, neither eye will appear to abduct. If amblyopia is present, only the eye that sees better will cross-fixate, making the amblyopic eye appear to have an abduction weakness.

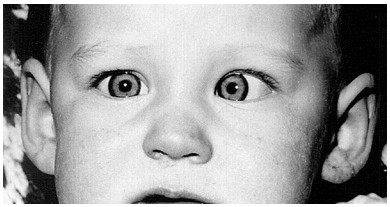

Figure 25-1. A child with congenital esotropia. Note the characteristic large angle of crossing.

9. How can a pseudoabduction deficit be distinguished from a true abduction deficit?

- By rotating the infant's head, either with the infant sitting upright in a moveable chair or by using a doll's head maneuver
- By patching one eye for a short period. The child will eventually move the unpatched eye

10. What is the differential diagnosis of an infant with esotropia?

- Pseudoesotropia
- Congenital sixth nerve palsy
- Duane's retraction syndrome
- Early-onset accommodative esotropia
- Möbius syndrome
- Sensory esotropia
- Nystagmus blockage syndrome
- Esotropia in the neurologically impaired

11. How is vision evaluated in a child with congenital esotropia?

The following observations can be made to look for equal vision in a child with a large-angle esotropia:

- Spontaneously alternates fixation
- Holds fixation with either eye when one eye is covered and then uncovered
- Cross-fixation present in both eyes

12. How common is amblyopia in congenital esotropia?

Amblyopia may occur in as many as 19% to 72% of infants with congenital esotropia.

13. What are the goals in the treatment of congenital esotropia?

- Development of normal sight in each eye
- Reduction of distant and near deviation as close to orthotropia (straight eyes) as possible
- Development of at least a rudimentary form of binocular vision

14. What level of binocular vision can develop in children with congenital esotropia?

- Classically, it has been taught that patients with congenital esotropia do not develop bifoveal fixation (perfect binocular vision) regardless of their age at treatment.
- Alignment within 10 prism diopters of orthotropia early in life is often associated with the attainment of some degree of binocular vision and stereopsis.
- Some surgeons have suggested that surgery performed on a patient at a very early age can lead to the development of bifoveal fixation.

15. When is congenital esotropia treated?

- Most surgeons attempt to operate on children with congenital esotropia between 6 and 12 months of age, usually with bilateral medial rectus recessions.
- Some surgeons operate on patients who are younger than 6 months of age in hopes of providing higher levels of binocular vision.[4,5]

16. Why is it important to treat amblyopia before surgical correction of congenital esotropia?

- Detecting reduced vision in an infant is easier in the presence of a large esotropia.
- Judgment about fixation preference is difficult in a preverbal child with straight eyes.

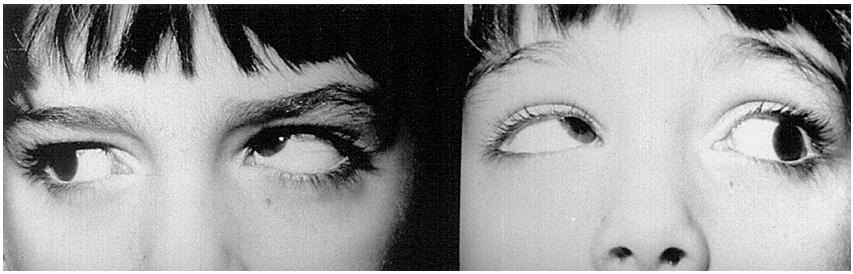

Figure 25-2. Inferior oblique overaction. As the eye adducts (moves toward the nose), it elevates.

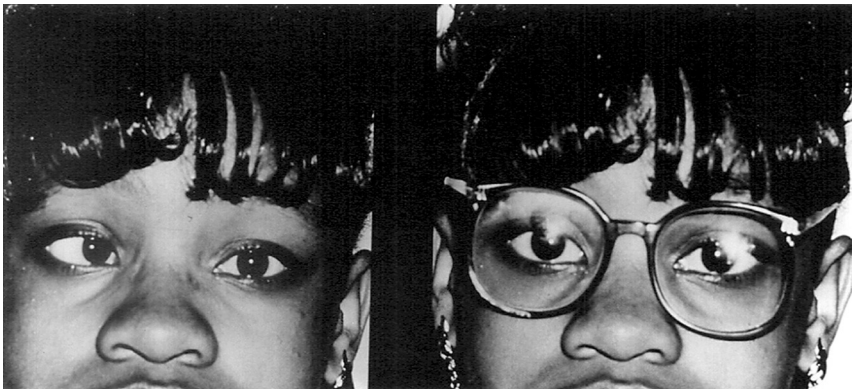

Figure 25-3. Accommodative esotropia. As the child attempts to accommodate (focus), the eyes cross *(left)*. With glasses that eliminate the need to accommodate, the eyes are straight *(right)*.

- Occlusion therapy in children at a young age generally requires only a small amount of time to equalize vision.
- If the vision is not equal after surgery, the chance of developing binocular vision and maintaining ocular alignment is lowered.
- Parental incentive to comply with the often arduous task of occlusion therapy is greatly diminished once the child's eyes are straight.

17. What other motility disorders are often associated with congenital esotropia?

- **Inferior oblique overaction:** Elevation of the eye during adduction (Fig. 25-2); occurs in 78% of cases; most common in second or third year of life; may require surgery
- **Dissociated vertical deviation:** Slow upward deviation; occurs in 46% to 90% of cases; onset greatest in second year of life; may require surgery
- **Nystagmus:** Latent or rotary possible; occurs in 50% of cases; usually diminishes with time[6]

18. What is accommodative esotropia?

Accommodative esotropia is a convergent deviation of the eyes associated with activation of the accommodative reflex (Fig. 25-3).

19. At what age does accommodative esotropia develop?

Accommodative esotropia usually occurs in a child between 2 and 3 years of age. Occasionally, children who are 1 year of age or younger present with all of the clinical features of accommodative esotropia.[7]

20. What are the three types of accommodative esotropia?

- Refractive
- Nonrefractive
- Partial or decompensated

21. What three factors influence the development of refractive accommodative esotropia?

- Uncorrected hyperopia
- Accommodative convergence
- Insufficient fusional divergence[8]

22. How do the aforementioned three factors lead to accommodative esotropia?

A hyperopic person must exert excessive accommodation to clear a blurred retinal image. This, in turn, stimulates excessive convergence. If the amplitude of fusional divergence is sufficient to correct the excessive convergence, no esotropia results. However, if the fusional divergence amplitudes are inadequate, or if motor fusion is altered by some sensory obstacle, esotropia results.

23. What is the AC:A ratio?

The accommodative convergence:accommodation (AC:A) ratio describes how many prism diopters a person's eyes converge for each diopter that he or she accommodates. The normal AC:A ratio is approximately 3 to 5 prism diopters of convergence per diopter of accommodation.

24. How can the AC:A ratio be measured?

- The heterophoria method: A strabismic deviation is recorded in prism diopters for a distance at 6 meters (*D*) and a near at ⅓ meter (*N*). After the patient's interpupillary distance is measured in centimeters (PD), the AC:A ratio can then be calculated as follows:

$$\text{AC:A} = \frac{(\text{PD}) + N - D}{\text{Near measurement distance (in diopters)}}$$

- The gradient method: A strabismic deviation is measured at distance with any refractive error fully corrected. The deviation is then remeasured at distance through a convex or concave lens. The AC:A ratio is then calculated as:

$$\text{AC: A} = \frac{(\text{deviation at near} - \text{deviation at distance})}{\text{fixation at distance at near in diopters}}$$

- Distance–near comparison: Most physicians prefer to assess the ratio using the distance–near comparison. This method is easier and quicker because it uses conventional examination techniques and requires no calculations. The AC:A relationship is derived simply by assessing the distance and near deviation. If the near measurement in an esotropic patient is >10 prism diopters, the AC:A ratio is considered to be abnormally high.

25. How is refractive accommodative esotropia treated?

Spectacles correct the hyperopic refractive error. Generally the full hyperopic correction as determined by cycloplegic refraction is given to the child.

26. What is the relationship between accommodative esotropia and congenital esotropia?

Recurrent esotropia may occur in approximately 25% of patients who have been successfully treated for congenital esotropia. Most of these patients (80%) respond to correction of hyperopia, even if the level of hyperopia is small.

KEY POINTS: ESOTROPIA

1. Amblyopia is best treated before surgery for congenital esotropia.
2. The diagnosis of congenital esotropia should be reconsidered in the presence of a small-angle deviation.
3. A complete exam is required to rule out other disorders in all patients who present with early-onset esodeviation.
4. Refractive accommodative esotropia is treated with spectacles.
5. A neurologic workup should be considered for patients who present with an acute esotropia and normal levels of hyperopia.

27. What is nonrefractive accommodative esotropia?

Nonrefractive accommodative esotropia is associated with a high AC:A ratio. The effort to accommodate elicits an abnormally high accommodative convergence response. The amount of esotropia

is greater at near deviation than at distance because of the additional accommodation required to maintain a clear image at near.

28. How can nonrefractive accommodative esotropia be treated?

- Bifocals eliminate the additional accommodative effort required at near and therefore reduce the near esotropia.
- Surgery may be performed to eliminate the esotropia at near and to correct the AC:A ratio permanently.
- Observation. Some ophthalmologists choose simply to observe patients as long as the patients' eyes remain straight at distance. The esotropia at near may resolve on its own as the AC:A ratio normalizes during childhood.

29. What is partial or decompensated accommodative esotropia?

Refractive or nonrefractive accommodative esotropias do not always occur in their "pure" forms. Glasses may reduce the esodeviation significantly. Sometimes the esotropia may initially be eliminated with glasses, but a nonaccommodative portion slowly becomes evident despite the maximal amount of hyperopic correction consistent with good vision. The residual esodeviation that persists is called the deteriorated or nonaccommodative portion. This condition commonly occurs with a delay of months between onset of accommodative esotropia and antiaccommodative treatment.

30. How is partial or decompensated accommodative esotropia treated?

- Surgery may be indicated if the deviation is larger than an amount that allows development of binocular vision.
- Surgery is generally performed for the nonaccommodative portion of the esotropia only, not for the full deviation that is present without glasses in place.

31. What is cyclic esotropia?

- A rare disorder that classically describes a large-angle esotropia alternating with orthophoria or a small-angle esodeviation on a 48-hour cycle
- It may result from an aberration in the biologic clock or a combination of defects in the clock, oculomotor nuclei, superior colliculi, or other nuclei
- Unpredictable response to various forms of therapy with the exception of surgery, which is usually curative

32. What are the characteristics of acute acquired comitant esotropia?

- Rare condition that occurs in older children and adults
- Dramatic onset of a large angle of esotropia with diplopia
- Normal levels of hyperopia
- Has been reported after periods of interruption of fusion, such as occlusion therapy for amblyopia

33. How should patients with acute acquired comitant esotropia be managed?

- A careful motility analysis to rule out a paretic deviation
- Consider further workup, including computed tomography or magnetic resonance imaging

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MISCELLANEOUS OCULAR DEVIATIONS

Janice A. Gault

CHAPTER 26

1. What is the differential diagnosis of exotropia?

- Congenital exotropia
- Sensory exotropia
- Third-nerve palsy
- Duane's syndrome
- Craniofacial abnormalities with divergent orbit (e.g., Apert's syndrome or Crouzon syndrome)
- Myasthenia gravis
- Thyroid disorder
- Medial wall fracture
- Slipped medial rectus muscle or excessively resected lateral rectus
- Orbital inflammatory pseudotumor
- Convergence insufficiency
- Internuclear ophthalmoplegia

2. A mother notices that her 4-month-old infant seems to be "wall-eyed." What is your concern as a physician?

First, check whether deviation or pseudostrabismus is present. A wide interpupillary distance or temporal dragging of the macula from retinopathy of prematurity or toxocariasis may cause pseudoexotropia. The light reflex test or cover testing elucidates this point. Also, make sure that the eyes move normally. Have the patient follow a light or a brightly colored toy to exclude paralysis or muscle restriction. If this test is normal and you notice true strabismus, quantify it with prisms at near and far. Check the cycloplegic refraction, and do a complete dilated exam. Anisometropic amblyopia may cause an eye to deviate, but it usually presents as esotropia in the younger age group. Also, a corneal lesion, cataract, glaucoma, or retinal lesion such as a toxoplasmosis scar or retinoblastoma may cause the deviation. These conditions must be ruled out.

Once you have determined that the remainder of the exam is normal, you realize that the infant has an alternating exotropia of 40 prism diopters. Congenital exotropia is much rarer than congenital esotropia, but they have much in common. Both have a large angle of deviation and rarely develop amblyopia because of alternating fixation. The refractive error is normal. Early surgery is recommended to allow development of stereoacuity.

3. A mother notices that her 2-year-old boy has a left eye that deviates outward when he is tired or has a fever. What is your concern as a physician?

Intermittent exotropia, which is the most common type of exotropia. The onset varies from infancy to 4 years of age. It may progress through the following three phases:

- **Phase 1:** Exophoria at distance and orthophoria at near occur when the patient is fatigued or daydreaming. He has diplopia and often closes one eye. When aware of the deviation, he is easily able to straighten his eyes, often after a blink.
- **Phase 2:** Exotropia at distance and exophoria at near. When the exotropia becomes more constant, suppression develops and the diplopia becomes less frequent. The exotropia remains after a blink.
- **Phase 3:** The exotropia is constant at distance and near. There is no diplopia because of suppression.

Vision must be equalized by correcting any significant refractive error and patching the nondeviating eye. Surgery should be done when the patient progresses beyond phase 1, but preferably before phase 3.

4. An 18-year-old patient complains of blurred near vision and headaches while reading. Do you believe her, or is she just trying to get out of doing her homework?

Check her ocular deviations at near and far. She may be experiencing convergence insufficiency, which is common in teenagers and young adults. It is rare in children under 10 years of age. It is often idiopathic but may be exacerbated by fatigue, drugs, uveitis, or an Adie's tonic pupil. Exodeviation is greater at near than at distance and causes asthenopia. Exophoria at near may be all that is seen. The near point of convergence is more distant than normal (>3 to 6 cm for patients younger than age 20; >12 cm for patients older than age 40), and the amplitude of accommodation is reduced.

Her fusional ability will be decreased. If you have her focus on a target at the reading distance that forces her to accommodate, you will see that she will have a low break point or a low recovery point when slowly increasing the amount of base-out prism in front of one eye. The break point is when she begins to see double vision with increasing prism; the recovery point is when she can fuse to single images working down from the higher amount of prism. Ten to 15 prism diopters is considered low.

Because she is symptomatic, treat her with base-in prisms for reading to help convergence. Near-point exercises or "pencil push-ups" can improve fusional amplitudes. These exercises are performed by having the patient slowly move a pencil from arm's length toward the face while focusing on the eraser. Have the patient concentrate on maintaining one image of the eraser. Repeat 10 times several times a day. Once this is mastered, pencil push-ups can be done while holding a 6-D base-out prism over one eye. Rarely, medial rectus resection may be necessary.

5. What if the fusional capacities are normal and there is no exodeviation?

The problem may be accommodative insufficiency, which has similar symptoms in the same age group. However, accommodation is reduced. First check the manifest and cycloplegic refraction. The patient may be underplussed and need a stronger hyperopic refraction. If refraction is normal, plus-lens reading glasses will help.

6. How do you differentiate a patient with convergence insufficiency versus accommodative insufficiency clinically?

In accommodative insufficiency, a 4-D base-in prism will cause blurring during reading, whereas patients with convergence insufficiency will note that print becomes clearer.

7. Some patients have the opposite problem: esotropia that is worse at distance than at near. What is this condition called?

This is divergence insufficiency. Fusional divergence is reduced. Treatment is with base-out prisms and, rarely, lateral rectus resections. However, divergence insufficiency is a diagnosis of exclusion, and divergence paralysis must be ruled out because it may be associated with pontine tumors, head trauma, and other neurologic abnormalities. Neuro-ophthalmic evaluation is necessary.

8. What is Duane's syndrome? What are the different types of this disorder?

Duane's syndrome is a congenital motility disorder characterized by limited abduction, limited adduction, or both. The globe retracts, and the palpebral fissure narrows on attempted adduction. A "leash effect" may cause upward deviation at the same time. There are three types of the syndrome:

- Type 1—limited abduction (most common) (Fig. 26-1)
- Type 2—limited adduction
- Type 3—both limited abduction and limited adduction (rarest type)

There are three females to every two males afflicted with Duane's syndrome. The left eye is involved in 60% of cases; in 18% of cases, both eyes are involved. Sixty percent of patients also have an associated esotropia, 15% have exotropia, and 25% are orthophoric. A and V patterns are common. Amblyopia, attributable to anisometropia, occurs in approximately one-third of cases. Surgery is done to correct a head turn, but resection should not be performed because it exacerbates the narrowing of the fissure and globe retraction.

9. What is the cause of Duane's syndrome?

The cause is unclear, but it appears that the lateral rectus muscle is innervated by the third nerve, causing cocontraction of the medial and lateral rectus muscles. This theory explains the globe retraction and fissure narrowing.

10. What other features may be associated with Duane's syndrome?

Goldenhar's syndrome, deafness, crocodile tears, and uveal colobomas.

Figure 26-1. Duane's syndrome affecting the right eye. In primary position *(middle),* the eyes are aligned. There is reduction in the right palpebral fissure height on left gaze *(top)* and right upper eyelid retraction as well as an abduction deficit on right gaze *(bottom). (From Burde RM, Savino PJ, Trobe JD: Clinical decisions in neuro-ophthalmology, ed 3, St. Louis, Mosby.)*

11. What is the differential diagnosis of hypertropia?

- Myasthenia gravis
- Thyroid eye disease
- Orbital inflammatory pseudotumor
- Orbital trauma (may cause inferior rectus entrapment)
- Fourth cranial nerve palsy
- Pseudohypertropia
- Skew deviation—see Chapter 30

KEY POINTS: BROWN'S SYNDROME

1. Inability to elevate affected eye when adducted.
2. Hypertropia may be present in primary gaze.
3. Patient may turn head away from affected eye with chin-up position.
4. Ten percent of cases are bilateral.
5. Forced adduction reveals superior oblique muscle restriction.

12. What is the cause of Brown's syndrome?

Brown's syndrome (Fig. 26-2) may be congenital or acquired. The cause may be related to mechanical restriction of the superior oblique tendon. Examples include trauma, surgery, or inflammation in the region near the trochlea.

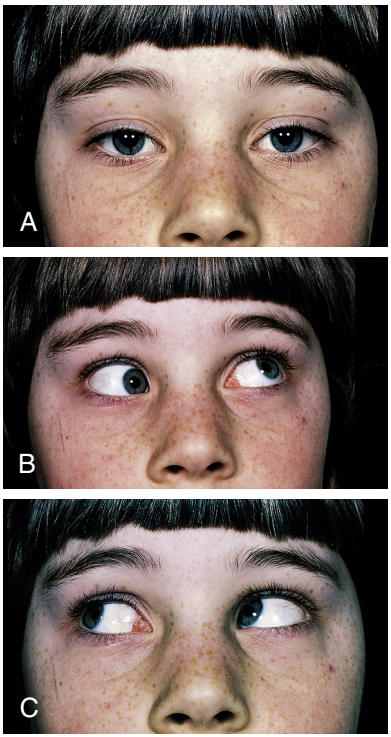

Figure 26-2. Brown's syndrome affecting the right eye. **A,** Usually straight in the primary position. **B,** Limited right elevation in adduction and occasionally also in the midline. **C,** Usually normal right elevation in abduction. *(From Kanski JJ: Clinical ophthalmology: a systematic approach, ed 5, New York, Butterworth-Heinemann, 2003.)*

13. How is Brown's syndrome treated?

Acquired cases may be observed because they may improve spontaneously. Some improve with steroid injections near the trochlea. If no improvement is seen by 6 months, the superior oblique muscle may be weakened with a tenotomy. Some surgeons recess the ipsilateral inferior oblique at the same time to prevent an inferior oblique overaction postoperatively. Patients need to be aware that they will never be able to elevate the affected eye normally in adduction.

14. What is the differential diagnosis of Brown's syndrome?

- **Inferior oblique palsy:** The three-step test reveals a superior oblique overaction that is not present in Brown's syndrome. In patients with diplopia, vertical deviations in primary gaze, or an abnormal head position, a superior oblique tenotomy or recession of the contralateral superior rectus is done. Forced ductions reveal no restriction.
- **Double elevator palsy:** Patients cannot elevate the affected eye in any field of gaze (Fig. 26-3). Ptosis or pseudoptosis may be seen. A chin-up position helps to maintain fusion if a hypotropia is present in primary gaze. If no chin-up position is seen with hypotropia, amblyopia is present. Treatment for a large vertical deviation or an abnormal head position is inferior rectus recession, if the inferior rectus is restricted, or transposition of the medial and lateral rectus toward the superior rectus (Knapp procedure), if no restriction is present.
- **Blow-out fracture with entrapment of the inferior rectus muscle:** History elucidates this injury, and forced ductions show restriction. Confirm with an orbital computed tomographic (CT) scan.
- **Thyroid disease:** Restriction is found on forced ductions, the strabismus is acquired and incomitant, lid retraction also may be noted. A CT scan reveals enlarged extraocular muscles.

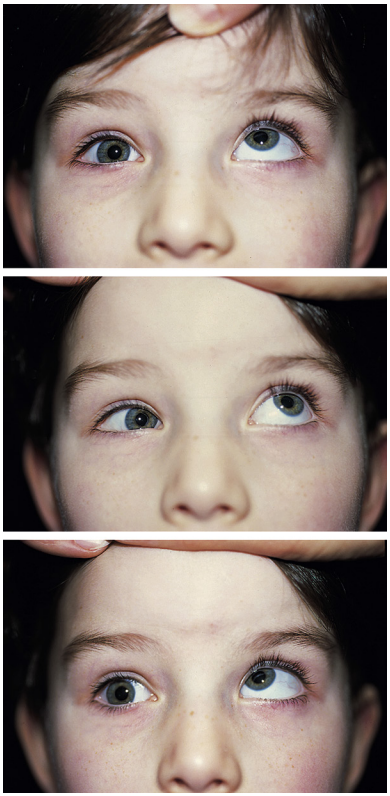

Figure 26-3. Right monoelevation deficit showing defective elevation in all positions. *(From Kanski JJ: Clinical ophthalmology: a systematic approach, ed 5, New York, Butterworth-Heinemann, 2003.)*

15. What is Möbius syndrome?

This is a congenital syndrome with varying abnormalities of the fifth through twelfth cranial nerves. Patients may have a unilateral or bilateral esotropia with inability to abduct the eyes even on doll's head maneuvers. Patients also may exhibit limb, chest, and tongue defects and may have significant feeding difficulties.

16. A 48-year-old man undergoes medial rectus resection and lateral rectus recession for a sensory exotropia of 35 prism diopters in the left eye. He presents the next day with an exotropia of 60 prism diopters in primary position and an inability to abduct the eye. What is your diagnosis?

The diagnosis is a slipped or lost medial rectus muscle. It is important to double-lock the suture through the tendon and muscle when reattaching the rectus muscle to the globe to prevent this complication. Reoperation is necessary to find the muscle and reattach it in the appropriate position. If you cannot locate the muscle, a transposition of the superior and inferior rectus muscles helps to correct the exotropia.

17. A patient complains that her right eye is hypertropic. The light-reflex test and covering test show her to be orthophoric. What may be going on?

Pseudohypertropia. She may have a vertically displaced macula from retinopathy of prematurity or toxocariasis. Eyelid retraction of the right eye may cause the right eye to appear hypertropic. Vertical displacement of the globe superiorly by a mass, such as a mucocele, may cause a similar appearance.

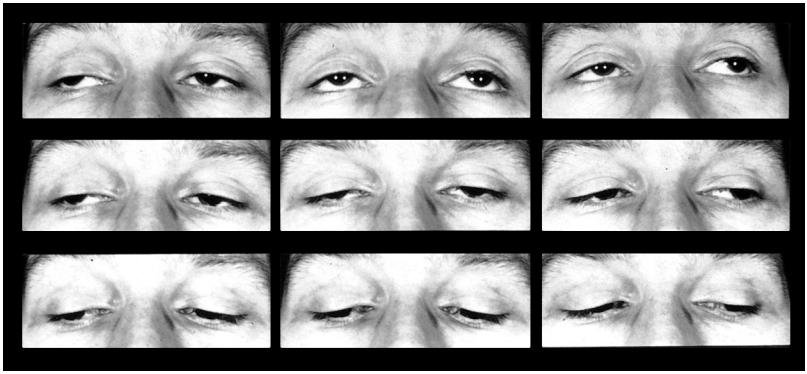

Figure 26-4. Chronic progressive external ophthalmoplegia. *(From Kanski JJ: Clinical ophthalmology: a test yourself Atlas, ed 2, New York, Butterworth-Heinemann, 2002.)*

18. A young boy has developed chin-up position and seems to move his head rather than his eyes to locate objects. On examination, he has poor ductions and versions in all fields of gaze as well as bilateral ptosis. Forced ductions reveal restrictions in all extraocular muscles. What is your diagnosis?

The diagnosis is congenital fibrosis syndrome. The normal muscle tissue is replaced by fibrous tissue to varying degrees. It may be unilateral or bilateral. The eyes may exhibit little to no vertical or horizontal movements, depending on the number of muscles involved, as well as esotropia or exotropia. Amblyopia is common. Ptosis with chin elevation is a frequent manifestation. The cause is unknown. The goal of surgery is to restore orthophoria in primary gaze.

19. A 20-year-old man with no history of strabismus complains that he cannot open his eyes well. You notice that ductions and versions are severely reduced and that he has bilateral ptosis. There is no restriction on forced ductions. What is your diagnosis?

The diagnosis is chronic progressive external ophthalmoplegia (CPEO). This condition begins in childhood with ptosis and progresses slowly to total paresis of the eyelids and extraocular muscles (Fig. 26-4). It may be sporadic or familial. Patients usually do not have diplopia. A frontalis sling procedure may be necessary to elevate the eyelids.

20. What other evaluations are important?

Check for retinal pigmentations, and order an electrocardiogram to check for heart block. The triad of CPEO, retinal pigmentary changes, and cardiomyopathy is known as Kearns-Sayre syndrome (Fig. 26-5). Patients may require pacemakers to prevent sudden death. Inheritance is by maternal mitochondrial DNA.

21. What other diseases may be associated with chronic progressive external ophthalmoplegia?

- **Abetalipoproteinemia (Bassen-Kornzweig syndrome):** Patients have retinal pigmentary changes similar to retinitis pigmentosa (RP), diarrhea, ataxia, and other neurologic signs.
- **Refsum's disease:** Patients have an RP-like syndrome with an increased phytanic acid level. They also may have neurologic signs.
- **Ocular pharyngeal dystrophy:** Patients have difficulty with swallowing. The condition may be autosomal dominant.

22. What is congenital ocular motor apraxia?

In this rare disorder patients are unable to generate normal voluntary horizontal saccades. To change horizontal fixation, a head thrust that overshoots the target is made. The head is then rotated back in the opposite direction once fixation is established. Vertical saccades are normal, but vestibular and optokinetic nystagmus are impaired. Strabismus may be associated.

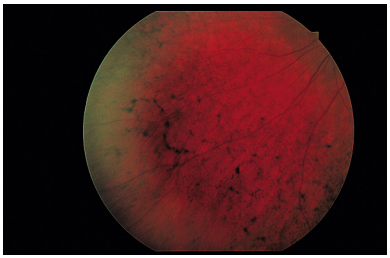

Figure 26-5. Kearns-Sayre syndrome. *(From Kanski JJ: Clinical ophthalmology: a test yourself Atlas, ed 2, New York, Butterworth-Heinemann, 2002.)*

23. A patient complains of diplopia. On examination, he has paresis of the third, fourth, and fifth cranial nerves on the right side. What can cause multiple ocular motor nerve palsies?

Anything that damages the cavernous sinus and/or superior orbital fissure, including the following:

- Arteriovenous fistula—carotid–cavernous sinus dural shunts
- Cavernous sinus thrombosis
- Tumors metastatic to cavernous sinus
- Skin malignancy with perineural spread to cavernous sinus
- Pituitary apoplexy—patients often have extreme headache with bilateral signs and decreased vision; need emergent intravenous steroids and neurosurgical consultation
- Intracavernous aneurysm
- Mucormycosis—more likely in diabetics, especially in ketoacidosis, and any debilitated or immunocompromised patient; look for an eschar in the nose and palate; emergent consultation with otolaryngology for débridement imperative
- Herpes zoster
- Tolosa-Hunt syndrome—acute idiopathic inflammation of the superior orbital fissure or anterior cavernous sinus (diagnosis of exclusion)
- Mucocele
- Meningioma
- Nasopharyngeal carcinoma

Multiple cranial nerve palsies also may occur with brain-stem lesions and carcinomatous meningitis.

Other entities that can mimic multiple cranial nerve palsies include:

- Myasthenia gravis
- CPEO
- Orbital lesions such as thyroid disease, pseudotumor, or tumor
- Progressive supranuclear palsy
- Guillain-Barré syndrome

24. What is Parinaud's syndrome?

Also known as dorsal midbrain syndrome, Parinaud's syndrome is characterized by a supranuclear gaze paresis with nuclear oculomotor paresis and pupillary abnormalities. Active upward gaze is diminished, but elevation is seen with doll's head maneuver. Attempts at upward gaze cause retraction-convergence nystagmus and palpebral fissure widening (Collier's sign). Pupils are middilated and do not react to light but react normally to accommodation.

25. What is the cause of Parinaud's syndrome?

In children, pinealoma and aqueductal stenosis are the most common causes. In adults, demyelination, infarct, and tumor are most common.

26. Describe the presentation of a patient with internuclear ophthalmoplegia

A young woman with a history of optic neuritis complains of double vision when looking to one side. She is unable to adduct on attempted contralateral gaze and exhibits horizontal nystagmus in the abducting eye. Adduction on convergence is normal. The condition may be unilateral or bilateral. Exotropia may be present if the condition is bilateral.

27. Where is the causative lesion?

The lesion is in the medial longitudinal fasciculus. Causes include multiple sclerosis, ischemic vascular disease, brain-stem tumor, and trauma.

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STRABISMUS SURGERY

Bruce M. Schnall

CHAPTER 27

1. **How are forced ductions performed?**
   Before beginning surgery, place an eyelid speculum in both eyes. Using one- or two-toothed forceps, grasp the conjunctiva at the limbus. Move the eye horizontally and vertically. The resistance encountered in moving the eye is compared with what normally would be expected, as well as with the resistance encountered in performing the same forced duction on the other eye.

2. **Why perform forced ductions?**
   Forced ductions are performed to detect "tight muscles" or restrictions in eye movement. If the forced ductions indicate that a muscle is restricted, the affected muscle should be recessed. For example, if a patient has a vertical deviation, the superior rectus on the hypertropic side or the inferior rectus on the fellow eye may be recessed. If forced ductions show resistance to elevating the fellow eye, the preferred surgery is recession of the inferior rectus.

3. **When correcting a horizontal or vertical strabismus, how do you decide how many muscles to recess or resect?**
   The angle of the deviation determines the number of muscles to recess or resect. Whereas a small-angle strabismus (<20 D) may be corrected by operating on one muscle only, a large deviation may require surgery on three or four rectus muscles. Most major texts contain tables that provide a guide as to how much surgery should be performed for the angle (measured in prism diopters) of strabismus. The tables indicate how many muscles should be operated on and the amount of recession or resection.

4. **When doing a recess–resect procedure, should you first perform the recession or the resection?**
   The recession is performed first. In a resection the muscle is shortened and then brought forward to the insertion. This procedure creates tension on the resected muscle, making it difficult to bring the resected muscle to the insertion site. Initial recession of the antagonist muscle decreases the tension pulling the globe away from the resected muscle and makes it easier to bring the resected muscle to the insertion site and to tie the sutures tightly.

5. **When performing surgery on an oblique muscle and rectus muscle of the same eye, on which muscle do you operate first?**
   The oblique muscles are more difficult to identify and isolate on the muscle hook than the recti. Strabismus surgery creates swelling of the Tenon's capsule and bleeding, which can obscure the view and make identification of the oblique muscles difficult. Therefore, it is preferable to operate on the oblique muscles first when the Tenon's capsule and the tissues surrounding the oblique muscles are the least swollen and distorted. The recti are more easily hooked and identified. There should be no difficulty in isolating the correct rectus muscle, even in the presence of significant bleeding and swelling of the Tenon's capsule following oblique muscle surgery.

6. **What type of needle is used to suture the muscle to the sclera?**
   A spatulated needle has cutting surfaces only on the side and is flat on the bottom. This decreases the risk of perforating the globe. The sclera is thinnest just posterior to the insertion of the rectus muscles (0.3 mm).
   Chapter 3: Parasurgical procedures and preparation"; © 2003-2014 Project Orbis International Inc. Link: http://telemedicine.orbis.org/bins/volume_page.asp?cid=1-2161-2253-2258

7. **What is an adjustable suture?**
   Various techniques of placing and tying scleral sutures allow the muscle to be moved forward or backward during the immediate postoperative period. If a patient has an immediate overcorrection or undercorrection, the muscle can be moved to improve the alignment. This suture adjustment is performed within 24 hours of the initial surgery, often in the office.

8. When should an adjustable suture be used?

The use of an adjustable suture is at the discretion of the surgeon. Some surgeons do not perform adjustable suture surgery, citing the fact that the correction seen immediately after strabismus surgery is variable and may not be indicative of the long-term result. Others use adjustable sutures in cases in which the results of strabismus surgery are difficult to predict, such as reoperations and restrictive or paralytic strabismus. Adjustable sutures are often used in patients with thyroid disease.

9. What is a transposition procedure?

A transposition procedure places the partial or entire tendon of the adjacent rectus muscles to the insertion of the palsied or underacting muscle. For instance, in double-elevator palsy the tendon of the lateral and medial recti may be sutured to the nasal and temporal borders of the superior rectus insertion.

10. When is a transposition procedure performed?

A transposition procedure is the procedure of choice when the function of one or more rectus muscles is severely limited, as with third-nerve, sixth-nerve, or double-elevator palsy.

11. How are A and V patterns of strabismus treated?

In cases of oblique muscle overaction, the appropriate oblique muscle should be weakened. Weakening of the inferior oblique muscles corrects a V pattern, whereas weakening of the superior oblique muscles corrects an A pattern (Fig. 27-1). In patients with no oblique muscle dysfunction, the horizontal recti are supraplaced or infraplaced. The medial recti are displaced toward the point of the A or V pattern, whereas the lateral recti are moved in the opposite direction. A useful acronym is MALE, which stands for *m*edial recti to the *a*pex, *l*ateral recti to the *e*mpty space. For example, to treat a V-pattern esotropia without oblique muscle overaction, the medial recti are recessed and infraplaced (moved inferiorly) by half of the tendon width.

12. What surgery can be done for Brown's syndrome?

In Brown's syndrome, a congenitally short or tight superior oblique tendon creates a mechanical restriction of elevation when the eye is in adduction, as confirmed at surgery with forced duction testing. Brown's syndrome is treated surgically by superior oblique tenotomy, recession, or a tendon expander.

13. What are the indications for surgery in Brown's syndrome?

Hypotropia in primary gaze or abnormal head position (face-turn or chin-up position) are indications for surgery. A significant deviation in primary gaze or abnormal head posture is the indication for strabismus surgery in most incomitant strabismus (Brown's, Duane, superior oblique palsy, inferior oblique palsy, and monocular elevation deficit.)

14. In strabismus surgery in patients with Duane's syndrome, is it better to recess or resect?

Resection would increase the globe retraction; therefore, resections are avoided. Recessions or, less commonly, transposition procedures are performed.

15. When performing vertical rectus transposition to treat a sixth-nerve palsy do you transpose both vertical recti or just one of the vertical recti?

One or both vertical recti can be transposed. Historically the superior and inferior recti are transposed temporally to treat a sixth-nerve palsy. More recently superior rectus transposition with recession of

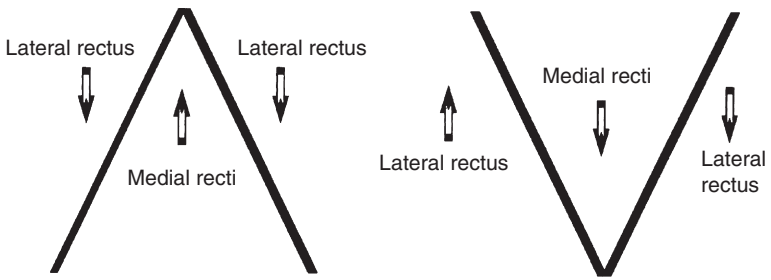

Figure 27-1. Displacement of horizontal arch in the treatment of A- and V-pattern strabismus.

the medial rectus has been shown to be effective in treatment of sixth-nerve palsy. Transposing only the superior rectus reduces the risk of anterior segment ischemia.[1]

KEY POINTS: MOST COMMON COMPLICATIONS OF STRABISMUS SURGERY

1. Overcorrection or undercorrection
2. Anterior segment ischemia
3. Infection
4. Adherence syndrome
5. Diplopia
6. Scleral perforation
7. Slipped or lost muscle
8. Operating on the wrong muscle

16. What are the signs of infection after strabismus surgery?

Signs of infection are cellulitis, subconjunctival abscess, or endophthalmitis. Cellulitis is most common, with an estimated incidence between 1 case in 1000 and 1 case in 1900 surgeries. It typically begins 1 to 4 days after surgery. The most common symptoms are marked swelling and pain. Suspected cellulitis requires prompt treatment with systemic antibiotics as well as careful examination to make certain that the patient does not develop endophthalmitis.[2]

17. What are the signs and symptoms of endophthalmitis after pediatric strabismus surgery?

The signs of endophthalmitis appear 1 to 4 days after surgery and include lethargy, asymmetric eye redness, eyelid swelling, and fever. Patients who develop endophthalmitis experience an increase in eyelid swelling and redness during the postoperative period rather than a decrease, as expected during a normal postoperative course. On examination, the patient has a decreased red reflex and signs of vitreal inflammation. If endophthalmitis is suspected, prompt evaluation and treatment are required.[3]

18. What should you do if you suspect that you perforated the globe when passing the scleral suture?

If a scleral perforation is suspected, indirect ophthalmoscopy should be performed in the operating room at completion of the strabismus surgery. If a retinal perforation is seen on ophthalmoscopy, retinal consultation or repeat examinations with the indirect ophthalmoscope are indicated. Treatment is controversial. Whereas some surgeons advocate treatment with cryotherapy or indirect laser, others simply observe the patient. The incidence of retinal detachment after scleral perforation is believed to be low. At the same time, cryotherapy may increase the incidence of retinal detachment by stimulating vitreous changes. In patients predisposed to retinal detachment (for example, high myopes), however, serious consideration should be given to treatment of a retinal perforation at the time of strabismus surgery. Some strabismus surgeons believe that scleral perforation increases the risk of endophthalmitis and therefore recommend a sub-Tenon's injection of prophylactic antibiotics if the globe is perforated.[4,5]

19. What is a slipped muscle?

The muscle is contained within a capsule. While operating on a rectus muscle it is possible to mistakenly engage only the capsule on the suture. After the muscle is reattached to the eye, it may slip back within its capsule, which results in further weakening of the muscle and consecutive deviation. For instance, if a slipped muscle occurred in recessing a medial rectus muscle for esotropia, exotropia and limited adduction will develop in the involved eye over time.

20. How is a slipped muscle prevented?

When placing the suture through the muscle, make locking bites on either end of the muscle. Locking bites are made by placing the suture through the muscle perpendicular to its insertion, engaging the tendon, rather than tangentially. Tangential placement may engage only the capsule.[6]

21. What is the adherence syndrome?

The orbital fat is separated from the globe by the Tenon's capsule. If an accidental opening is made in the portion of the Tenon's capsule that separates the orbital fat from the sclera, orbital fat may be pressed through the opening and adhere to the globe. This adherence often results in limited eye moments. It is best treated by prevention. Because the orbital fat comes forward around the equator of the globe to within 10 mm of the limbus, care should be taken not to cut the Tenon's capsule more than 10 mm from the limbus.

22. How can strabismus surgery cause anterior segment ischemia?

The anterior ciliary arteries accompany the rectus muscles. They penetrate the sclera at the muscle's insertion site, contributing significantly to the blood supply of the anterior segment. In standard strabismus surgery the anterior ciliary vessels are cut when the rectus muscle is disinserted.[7]

23. How is anterior segment ischemia avoided?

Anterior segment ischemia is avoided by not operating on more than two rectus muscles in one eye at the same time. It is also possible to dissect the anterior ciliary vessels from the rectus muscle and preserve them. Surgery to preserve the anterior ciliary vessels is performed only when the risk of anterior segment ischemia is high, such as in older patients with cardiovascular disease or patients with a history of previous rectus muscle surgery.[8]

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NYSTAGMUS

Jonathan H. Salvin

CHAPTER 28

1. **What is nystagmus?**
   Nystagmus is an involuntary ocular oscillation of the eyes. Typically it has a pathologic slow eye movement followed by a fast eye movement. The movements can be exclusively horizontal, exclusively vertically, exclusively torsional, or a combination of all three. Congenital nystagmus may present in early childhood. Acquired cases may develop in adulthood or childhood.

2. **Do affected patients see the world moving constantly?**
   Oscillopsia is the symptomatic perception of the visual world moving from variable eye movements. In early-onset nystagmus, most patients do not experience oscillopsia. In some forms of adult acquired nystagmus and in other irregular-eye-movement disorders (such as opsoclonus) there may be symptomatic oscillopsia.

3. **Why do nystagmus patients not experience oscillopsia?**
   It is not entirely clear what mechanisms are in place that eliminate symptomatic oscillopsia in early onset nystagmus. It had been speculated that retinal information was sampled during foveation only and then suppressive mechanisms were in place during eye motion—like a strobe light effect. Studies have shown that there is indeed processing of retinal information continuously. Based on this information, there is speculation of "extraretinal signals" that somehow cancel out the visual information during eye movement. Changes in nystagmus waveforms (by new pathology, surgical or medical intervention) can result in oscillopsia in some nystagmus patients.

4. **Are patients with well-adapted nystagmus (i.e., no oscillopsia or diplopia) able to see their own eyes move when they look in a mirror?**
   No, they cannot see their own eyes move in a mirror. The presumption is that the eye movements match the mirrored image so they do not see it. To show a patient what he or she looks like to others, you must make a video of the eye movements.

5. **Why don't many nystagmus patients see well?**
   Many of these patients have underlying eye pathology that causes decreased acuity and then leads to the development of nystagmus. In those that do not have other eye disease, the nystagmus itself limits fixation time (foveation) and thus decreases acuity.

6. **What are the classifications of nystagmus?**
   The National Eye Institute has reclassified eye-movement disorders in the Classification of Eye Movement Abnormalities (CEMAS). See Table 28-1.

7. **What is the infantile nystagmus syndrome?**
   Typically this is binocular conjugate horizontal nystagmus, but can have vertical or rotary components. It tends to also be uniplanar, staying horizontal in all gazes. Infantile nystagmus syndrome (INS) can be primary motor nystagmus, unrelated to any other eye pathology. It can also be primary sensory nystagmus-related poor vision associated with optic nerve hypoplasia, albinism, congenital cataracts, or other intraocular pathology.

8. **What is the typical waveform of the nystagmus seen in infantile nystagmus syndrome?**
   Onset of the nystagmus is typically within the first 6 weeks of life, with wide pendular movements and apparent poor visual behavior. By 6 to 8 months of age, it converts to smaller pendular waveforms. Between 18 and 24 months of age, the waveform progresses to more jerk-type movements and with possible formation of a null point.

9. **What is the null point in nystagmus?**
   The null point is the direction of gaze in respect to orbital coordinates that minimize the amplitude and frequency of nystagmus. Because a position of gaze that minimizes the nystagmus allows better vision, it is common for patients to seek out the null point with an anomalous head position.

Table 28-1. Nystagmus Classification Nomenclature

CEMAS DESIGNATION	"CLASSIC" NOMENCLATURE
Physiologic Nystagmus	
• Vestibular nystagmus	—
• Optokinetic nystagmus	—
• Eccentric gaze nystagmus	—
Pathologic Nystagmus	
• Infantile nystagmus syndrome	• Congenital motor nystagmus • Congenital sensory nystagmus
• Fusion maldevelopment nystagmus syndrome	• Latent/manifest latent nystagmus
• Spasmus nutans syndrome	—
• Vestibular nystagmus	• Includes periodic alternating nystagmus
• Gaze-holding deficiency nystagmus	—
• Vision loss nystagmus	—

10. Is the null point the same for each eye?
Yes, but there is an exception—nystagmus blockage syndrome. See question 11.

11. What is nystagmus blockage syndrome?
Patients find that convergence dampens their nystagmus and manifest a large-angle esotropia as their null point. They may manifest a face turn toward the fixating adducted eye and may alternate face turn with alternating fixation.

12. Do patients with infantile nystagmus syndrome associated with poor vision (congenital sensory nystagmus) also have the same natural history of the nystagmus waveform evolution?
Yes. Care must be taken to look for albinism, achromatopsia, Leber's congenital amaurosis, hypoplasia of the optic disc, and delayed visual development.

13. Is a distinctive nystagmus associated with specific ocular pathology?
To date, only the unique nystagmus of achromatopsia seems somewhat distinctive as it evolves to an oblique direction from a horizontal pendular direction.

14. Does infantile nystagmus syndrome ever disappear spontaneously?
Rarely, yes. More commonly the patient has spasmus nutans, which is not recognized, and, of course, by its very definition the spasmus nutans disappears after a year or so.

15. What is spasmus nutans?
Spasmus nutans is acquired in the first 2 years of life and consists of the triad of nystagmus, head nodding, and torticollis. It is a benign condition that generally resolves by 3 to 4 years of age. Magnetic resonance imaging (MRI) is indicated, as midbrain pathology can mimic these findings.

16. What is the hallmark of the nystagmus seen in spasmus nutans?
Most often, there is binocular small-amplitude high-frequency "shimmering" nystagmus. It can be monocular or asymmetric and multiplanar.

17. Does nystagmus mean that the patient is blind?
No, to the contrary. You must have or have had some vision to develop nystagmus. Many patients with sensory nystagmus have significant visual impairment, though, depending on their pathology.

18. Are some types of nystagmus present at birth?
Yes, physiologic bidirectional jerk nystagmus can be seen soon after birth. This includes vestibular and optokinetic nystagmus and eccentric "end gaze" nystagmus. These are normal and typically are associated with normal vision.

19. Does a patient need vision to have nystagmus?
Yes, but the vision may be poor. The retinal or systemic conditions may worsen or cause blindness, and the typical INS persists.

20. If one sees what seems to be the natural history of infantile nystagmus syndrome, should an MRI be obtained?
A full ophthalmologic examination should be performed, looking for underlying pathology that would cause the nystagmus. If an intraocular cause for sensory nystagmus can be found, then no imaging is indicated (except for optic nerve hypoplasia, for which imaging should be ordered to evaluate for other midline central nervous system defects). If there is optic atrophy or pallor found, then MRI is indicated to look for midbrain lesion. If spasmus nutans is considered, then an MRI should be obtained (see question 15.)

21. If the nystagmus is vertical, will the patient develop a preferred chin-up or chin-down head position?
Yes. Patients may develop a head position in relationship to the null point in the same fashion as patients with horizontal nystagmus. The null point is in the direction of the slow phase of the nystagmus. Therefore, if the patient has obvious downbeat nystagmus, it will be worse on upgaze and the null zone will be downward, with a preferred chin-up head position.

22. Do patients with torsional infantile nystagmus syndrome exhibit a head tilt in respect to torsion?
Occasionally. The physician needs to examine the infant with torticollis carefully with the slit lamp to look for torsional nystagmus if no other etiology for the torticollis is found.

23. How can torsional nystagmus be observed and diagnosed?
Slit lamp observation of the iris is the most sensitive test. Eye-movement recordings can be used, but these are more involved and may be difficult to obtain.

24. Is the pivot of the torsional nystagmus always on the visual axis?
No, and exceptions may cause some difficulty in diagnosis. If the pivot is on the visual axis, the eye rotates clockwise and counterclockwise about the visual axis—the object of fixation (visual axis)—and vision is only modestly degraded. In fact, the nystagmus often is not noted unless an examiner studies the iris or disc. If, however, the pivot is to the left (e.g., on the left brow), the patient will have a component of horizontal and vertical nystagmus. This combination results in a "windshield wiper" nystagmus in which the radii of each eye varies much like an automobile windshield wiper when the pivot of rotation is located asymmetrically.

25. Do patients develop torsional nystagmus late in childhood or later in life?
Both. If the nystagmus is asymmetric, it is most likely caused by midbrain pathology. More commonly, the torsional nystagmus was present all along, but not observed.

26. What is alternating in periodic alternating nystagmus (central vestibular instability nystagmus by CEMAS terminology)?
The mostly horizontal (may have a torsional component) nystagmus will alternate in the direction of the fast phase. Patients may develop alternating head turns toward the fast phase to compensate for the changing direction of the null position.

27. What is the time cycle of periodic alternating nystagmus?
The time cycle is 60 to 90 seconds with intervals of 10 to 20 seconds without nystagmus in between alternations.

28. Is congenital periodic alternating nystagmus commonly associated with any other ocular problem?
Yes. Oculocutaneous albinism is the most common association—and most commonly overlooked. Look for it carefully.

29. Does acquired periodic alternating nystagmus imply central nervous system pathology?
Yes, but be careful. Often the nystagmus is overlooked if the patient compensates well by changing head position. If it is truly acquired, midbrain pathology is most common.

30. Does acquired periodic alternating nystagmus respond to pharmacologic treatment?
Yes. Baclofen may work.

31. Does *congenital* infantile nystagmus respond to any pharmacologic treatment?
Gabapentin (600 to 2400 mg/day) and memantine (10 to 40 mg/day) have been studied, with some results showing improved visual acuity with decreased nystagmus intensity.

KEY POINTS: REFRACTION WITH NYSTAGMUS

To get the best visual acuity in a patient with nystagmus:
1. Use careful dry and cycloplegic refraction.
2. Correct all astigmatism.
3. Use the top line of a full projector screen.
4. Watch for latent nystagmus—add +4.00 to 6.00 over the nonfixating eye to blur rather than occluding.

32. What nonsurgical treatment options should be consider for nystagmus patients?
Glasses first should be given to try to maximize the visual acuity. Many of these patients will have high astigmatic errors that should be corrected. Prisms can be used in the glasses to attempt to shift the eyes into the null position. Prisms can also be used to stimulate convergence, which can sometimes dampen nystagmus. Pharmacologic treatments (see questions 30 and 31) can be considered for some forms of nystagmus, particularly some adult-onset acquired cases of vestibular nystagmus.

33. What surgical treatment options should be considered for nystagmus patients?
Kestenbaum-Anderson recession–resection procedures can be performed for anomalous head positions to rotate the eyes toward the direction of the head turn (away from the null position). Recession of all four horizontal rectus muscles to positions behind the equator has been shown to be effective in improving visual function without significant face turns. Disinsertion and reattachment to the original insertion has been reported to have a similar effect.

34. Most patients with infantile nystagmus syndrome have vision that is better at near than at distance. Why?
Most patients have an accommodative convergence:accommodation ratio that results in exophoria at near. The patient uses fusional convergence to overcome the exophoria. Fusional convergence dampens the nystagmus amplitude and frequency and in so doing improves the vision.

35. Because convergence improves vision, should minus lenses be used to stimulate accommodative convergence?
No. Only fusional convergence (i.e., overcoming exophoria) dampens nystagmus. Accommodative convergence does not dampen nystagmus and even works against the patient by increasing accommodative demands and may cause the near point to recede, with reduced visual acuity at near.

36. Is photophobia common with nystagmus?
No. If photophobia is present with nystagmus, look for achromatopsia or other intraocular pathology.

37. Do patients with albinism have photophobia?
For the most part, no. However, some albinos do not like excessive light, and dark-tinted glasses are occasionally helpful.

38. Do contact lenses help with nystagmus?
There have been reports of decreased nystagmus with contact lens use. Many patients with nystagmus have significant astigmatism. Those that do may be helped with toric contact lenses, particularly if the null point is eccentric at points where spectacles distort the images. The nystagmus, though, may make toric contact lens fitting difficult because of the constant eye movements causing shifting of the lens off axis.

39. Many patients with nystagmus have vision of approximately 20/50 and want to pass the magic barrier of 20/40 to obtain a driver's license. What can you do to help?
For the most part, such patients are safe drivers as far as vision is concerned. If you project the full screen of letters and ask them to read the top line as you reduce the print size, you will find that many read two lines or so better. Hence, you can endorse their improved vision as adequate for driving.

40. Aside from using a full screen of letters, what should one do when checking the visual acuity of a nystagmus patient with unexpected poor vision?

Be sure to measure binocular visual acuity first. If binocular vision is better, try blurring the nonfixating eye with a +6.00 lens and ask the patient to read with the opposite eye. Many patients will have worsening nystagmus with monocular occlusion (latent nystagmus), which makes measuring monocular acuity difficult.

41. What is latent nystagmus (fusion maldevelopment nystagmus syndrome by CEMAS terminology)?

This is a jerk nystagmus that is evident only with monocular occlusion. It is typically associated with other pathology that results in poor fusion development early in life, such as strabismus or significant amblyopia.

42. What is manifest latent nystagmus?

This is the decompensation of latent nystagmus to manifest nystagmus with binocular vision.

43. Clinically, how do you distinguish manifest latent nystagmus from infantile nystagmus syndrome?

As you occlude each eye, with manifest latent nystagmus the direction of the jerk changes toward the fixing eye. With INS the direction of the nystagmus remains constant on covering either eye, but the direction of the nystagmus fast phase changes when you cross to the other side of the null zone.

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CHAPTER 29

THE PUPIL

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1. **What muscles control the size of the pupil? Describe their innervation.**
The iris sphincter muscle causes pupillary constriction and is innervated by the parasympathetic nervous system. The iris dilator muscle causes pupillary dilation and is innervated by the sympathetic nervous system. Thus, when sympathetic tone is increased, the pupil is larger, and when parasympathetic tone is increased, the pupil is smaller.

2. **Trace the pathway of the parasympathetic innervation of the pupil.**
Parasympathetic fibers begin in the Edinger-Westphal nucleus in the oculomotor nuclear complex. With cranial nerve (CN) III they exit the midbrain and travel in the subarachnoid space and cavernous sinus. They follow the inferior division of CN III into the orbit, where they synapse at the ciliary ganglion. Postganglionic fibers are then distributed to the iris sphincter and ciliary body via short ciliary nerves.

3. **Trace the pathway of the sympathetic innervation of the pupil.**
The first-order neuron begins in the posterior hypothalamus. The fibers travel caudally to terminate in the intermediolateral cell column of the spinal cord at levels C8–T1, otherwise known as the ciliospinal center of Budge. Pupillomotor fibers exit from the spinal cord and ascend with the sympathetic chain to synapse in the superior cervical ganglion, constituting the second-order neuron. The third-order neuron begins with postganglionic fibers of the superior cervical ganglion. These fibers travel with the internal carotid artery to enter the cranial vault. In the cavernous sinus the fibers leave the carotid artery to join the ophthalmic division of CN V and enter the orbit through the superior orbital fissure. The sympathetic fibers reach the ciliary body and dilator of the iris by passing through the nasociliary nerve and long posterior ciliary nerves.

4. **Trace the pathway of the pupillary light reflex.**
The pupillary light response begins with the rods and cones of the retina. Afferent pupillomotor fibers travel through the optic nerves and slightly greater than 50% decussate at the optic chiasm. They follow the optic tracts and exit before the lateral geniculate body to enter the brain stem via the brachium of the superior colliculus. Pupillomotor fibers synapse in the pretectal nuclei and then project equally to the ipsilateral and contralateral Edinger-Westphal nuclei. The pupillary fibers travel with CN III to innervate the iris sphincter and cause pupillary constriction, as described in question 2.

5. **What is an afferent pupillary defect? How should you examine for it?**
The swinging flashlight test is used to elicit a relative afferent pupillary defect (RAPD). If you shine a light into one eye of a normal subject, both pupils constrict to the same degree. If you swing the light over to the other eye, the pupil stays the same size or constricts minimally. In patients with RAPD the affected eye behaves as if it perceives a dimmer light than the normal eye; therefore, both pupils constrict to a lesser degree when the light is shone in the affected eye. Thus, if you shine the light in the right eye of a patient with left RAPD, both pupils constrict. If you swing the light to the left eye, it is perceived as dimmer and the pupils dilate. Note that this is a *relative* APD and signifies a difference in the pupillary response between the two eyes. However, if both eyes are equally abnormal, there may be no RAPD (Fig. 29-1).

6. **A lesion in which anatomic areas may cause an afferent pupillary defect?**
A lesion anywhere in the afferent pupillary pathway may cause an RAPD—that is, retina, optic nerve, optic chiasm, optic tract, or along the course of pupillary fibers from the optic tract to the pretectal nuclei. Pupillary fibers leave the optic tract prior to the lateral geniculate body. Therefore, any lesion from the lateral geniculate body posteriorly does not cause an RAPD. A retinal lesion causes an RAPD only if it is rather large. An optic nerve lesion causes an RAPD in the ipsilateral eye. A lesion in the optic chiasm may cause an RAPD if fibers from one optic nerve are affected more than those from the other. An optic tract lesion causes an RAPD in the eye with the most visual field loss. Typically, in patients with a mass lesion of the optic tract, an RAPD is produced in the ipsilateral eye because of

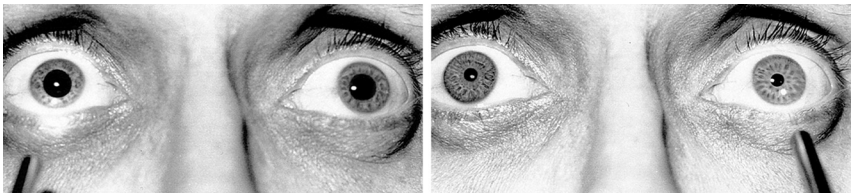

Figure 29-1. Demonstration of a large afferent defect in the right eye. This is best demonstrated when the light is alternated from eye to eye at a steady rate. The light is kept just below the visual axis and 1 to 2 inches (3 to 5 cm) from each eye. Each eye is illuminated for approximately 1 second, then the light is switched quickly to the other eye. This technique allows comparison of the initial direct pupil contraction with light in each eye. *(From Kardon RH: The pupil. In Yanoff M, Duker JS [eds]: Ophthalmology, ed 2, St. Louis, Mosby, pp 1360–1369, 2004.)*

ipsilateral optic nerve compression, but an ischemic lesion causes an RAPD in the contralateral eye because slightly more fibers cross than remain uncrossed. A lesion in the brain stem in the area of the pretectal nuclei may cause an RAPD without visual defects if the pupillomotor fibers are affected between the optic tract and the pretectal nuclei.

7. What is anisocoria? How should one examine a patient with anisocoria?

Anisocoria is a difference in the size between the two pupils. In anyone who has anisocoria, the pupil size should be measured in both bright and dim light. If the anisocoria is greater in bright light, the larger pupil is abnormal and constricts poorly, which is usually caused by a defect in parasympathetic innervation. If the anisocoria is greater in dim light, the smaller pupil is abnormal because it dilates poorly, usually because of a defect in pupillary sympathetic innervation. If the difference in the size of the two pupils remains the same in bright and dim light, the anisocoria is probably physiologic and not pathologic.

8. What is the differential diagnosis of a unilateral dilated, poorly reactive pupil?

- Third-nerve palsy
- Pharmacologic paralysis (an anticholinergic medication such as atropine)
- Adie's tonic pupil
- Iris damage (e.g., sphincter tears secondary to trauma or posterior synechiae)

9. What are the clinical findings in a third-nerve palsy?

CN III innervates the superior, medial, and inferior recti and inferior oblique and levator palpebrae muscles. Therefore, in a complete CN III palsy, ptosis is complete and the eye is in the down-and-out position; it does not move up, down, or medially. The parasympathetic nerves that innervate the pupillary sphincter travel with CN III; therefore, if those fibers are affected, the pupil will be dilated and nonreactive.

10. What are some possible causes of third-nerve palsy?

In adults the most common causes are microvascular ischemia in the nerve, aneurysm (usually of the posterior communicating artery), trauma, and neoplasm. In children, aneurysm is rare, and consideration must be given to ophthalmoplegic migraine although injury, infection, and tumor are more common.

11. What is the significance of pupil involvement or pupil sparing in third-nerve palsy?

Pupil involvement in third-nerve palsy suggests a compressive lesion such as aneurysm or tumor. Pupil sparing is suggestive of microvascular ischemia. The parasympathetic fibers are on the outer portion of CN III and are more susceptible to external compression and less susceptible to ischemia, which is usually axial in the nerve.

12. What is the appropriate workup for an isolated third-nerve palsy with pupillary sparing?

In patients in the vasculopathic age group, the most likely cause is microvascular ischemia. The classic teaching is that patients may simply be followed with the expectation that the ocular misalignment will improve. However, the recommendation is evolving that all third-nerve palsy patients should have imaging with either magnetic resonance imaging (MRI)/magnetic resonance

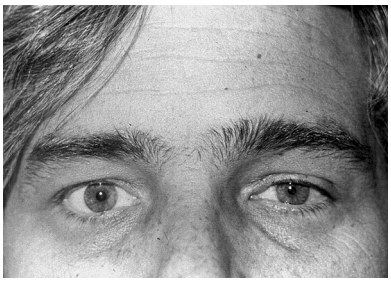

Figure 29-2. Horner's syndrome with ptosis and miosis on the left. Note that the left lower eyelid is higher than the right lower eyelid. This inverse ptosis is a result of interruption of sympathetic innervation to the analog of the Mueller's muscle in the lower eyelid.

angiography (MRA) or computed tomography (CT)/computed tomography angiography (CTA). Certainly a medical workup for hypertension or diabetes is appropriate. If there is no improvement in 3 to 6 months, neuroimaging should be performed. Patients too young for the vasculopathic age group should all have an MRI and MRA scan. If the scan is negative, other hematologic investigations and lumbar puncture should be considered.

13. What is the appropriate workup for an isolated third-nerve palsy with pupillary involvement?

The first step is to perform an emergent MRI and MRA or CT and CTA scan. This important MRA or CTA must be done before catheter arteriography. If the scan is negative, a catheter arteriogram must be performed to rule out an aneurysm in institutions in which MRA or CTA may not confidently exclude small ones. If the scan is negative in children younger than age 10, an arteriogram is not necessary because the likelihood of an aneurysm is very low in young children.

KEY POINTS: MANAGEMENT OF THIRD-NERVE PALSY

1. Pupil involvement in third-nerve palsy suggests a compressive lesion.
2. Pupil-involving third-nerve palsy requires immediate MRI and MRA or CT and CTA. If negative, conventional catheter angiography should be performed in cases in which the MRA or CTA does not fully rule out aneurysm.
3. Pupil-sparing third-nerve palsy in a patient in the vasculopathic age group may be observed with the presumption that the palsy is caused by microvascular ischemia. However, noninvasive imaging may be considered.
4. Pupil-sparing third-nerve palsy in a patient not in the vasculopathic age group warrants an MRI and an MRA.

14. What is an Adie's tonic pupil? What is its natural history?

Adie's tonic pupil is a postganglionic defect in the parasympathetic innervation to the pupil. The clinical finding is a dilated pupil that is usually slightly irregular and shows segmental iris constriction at the slit lamp. There also may be light/near dissociation, with characteristically slow and tonic constriction and redilation phases. This condition is benign and most commonly affects women in their second to fourth decades.

15. How do you test for an Adie's pupil?

An Adie's tonic pupil constricts to dilute pilocarpine 0.1% to 0.12%, whereas a normal pupil does not. This is a result of denervation hypersensitivity.

16. What is Horner's syndrome?

Horner's syndrome is a clinical syndrome characterized by ptosis, miosis, and occasionally anhidrosis (Fig. 29-2). Any lesion in the sympathetic innervation to the eye can cause this syndrome.

17. What is the cause of ptosis in Horner's syndrome?

Ptosis in Horner's syndrome is caused by decreased sympathetic tone in the Mueller's muscle. The Mueller's muscle is responsible for approximately 2 mm of elevation of the upper eyelid. Thus, the ptosis in Horner's syndrome is mild (only approximately 2 mm).

18. What are the possible causes of Horner's syndrome?

The course of the sympathetic innervation to the eye was discussed in question 3. A lesion anywhere along this course may cause Horner's syndrome. Isolated third-order neuron lesions are concerning for a dissection of the internal carotid artery. Second-order neuron lesions may be caused by apical lung tumors. First-order neuron lesions are uncommon in isolation. They are found in demyelinating disease, cerebrovascular accidents, and neoplasms.

19. How do you test for Horner's syndrome pharmacologically?

A cocaine test has been the standard test for Horner syndrome. Cocaine blocks the reuptake of norepinephrine. A normal pupil dilates in response to a drop of cocaine, whereas in Horner's syndrome the pupil fails to dilate. Cocaine is often unavailable and has largely been replaced by the apraclonidine (iopidine) test. Apraclonidine, widely available as a glaucoma medication, has mild $\alpha 1$ agonist activity, usually too mild to cause pupillary dilation. However, with Horner syndrome there is sympathetic denervation of the pupil and it will dilate to topical stimulation with apraclonidine. Therefore there will be a reversal of the anisocoria, with the miotic pupil now becoming larger. An additional finding is that the ptosis may resolve as well.

20. What pharmacologic testing helps to localize the lesion in Horner's syndrome?

Localization is important because the etiology and possibly the focus of the workup are quite different, depending on whether the lesion is a first-, second-, or third-order neuron. Hydroxyamphetamine 1% causes release of epinephrine from the third-order neuron junction with the iris. Thus, in third-order neuron lesions there is no pupillary response to hydroxyamphetamine drops. In a first- or second-order neuron lesion, the pupil dilates in response to hydroxyamphetamine drops.

21. What is the appropriate evaluation for a patient with Horner's syndrome?

Patients suspected of having Horner's syndrome should have apraclonidine or cocaine testing to confirm the diagnosis, unless the diagnosis is obvious. If testing confirms the syndrome, imaging studies should be performed to evaluate the entire course of the sympathetic innervation of the eye, which would include head, neck, and chest. Hydroxyamphetamine testing is helpful, but because there are some false positives and false negatives, it should not be totally relied upon, but should be used when it supports the rest of the clinical picture.

22. What is light/near dissociation? What are its possible causes?

In light/near dissociation a pupil does not constrict to light but will constrict as part of the near response. Causes include Adie's syndrome, dorsal midbrain syndrome (Parinaud's syndrome), Argyll-Robertson pupils, diabetic neuropathy, prior CN III palsy with aberrant regeneration, and blindness from any anterior afferent cause.

23. What is an Argyll-Robertson pupil?

Argyll-Robertson pupils are small, often irregular pupils that do not react to light but have a brisk near response. The cause of Argyll-Robertson pupils is almost always tertiary syphilis.

24. What is Parinaud's syndrome?

Found in dorsal midbrain disease, this syndrome is composed of light/near dissociation of the pupils, supranuclear paralysis of upward gaze, convergence–retraction nystagmus with attempted upward saccades, and eyelid retraction.

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CHAPTER 30

DIPLOPIA

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1. What is diplopia?

Diplopia is a condition in which the patient perceives two images of a single object. Diplopia may be monocular or binocular, constant or intermittent. Check if the double vision resolves with each eye closed. If it does not, the patient has monocular diplopia. If it does, the patient has binocular diplopia.

2. List the causes of monocular diplopia.

- Refractive error: astigmatism is the most common cause of monocular diplopia
- Chalazion or other eyelid tumor producing irregular astigmatism
- Keratopathy: dry eyes, keratoconus, irregular astigmatism (use a retinoscope to see scissoring reflex)
- Iris atrophy, polycoria, large nonreactive pupil
- Cataract, subluxated lens, intraocular lens decentration, capsular opacity
- Retinal disease may produce metamorphopsia or aniseikonia; also consider a psychogenic etiology

3. What are the causes of binocular diplopia?

Causes of binocular diplopia may be grouped into three general categories:

1. Neuropathic: The pathology may be supranuclear, nuclear, or infranuclear. Specific neuropathic causes include traumatic, vaso-occlusive infarction, compression, inflammation, infection, demyelination, degeneration, decompensated phorias, spasm of the near reflex, and neuromyotonia.
2. Myopathic: The pathology is within the extraocular muscles. Causes include inflammatory pseudotumor or myositis and thyroid-related eye disease (TED).
3. Neuromuscular junction disorders. The major etiology in this category is myasthenia gravis (MG).

4. What is the most important sign to check for in a third-nerve (oculomotor) palsy?

Check for the presence of a dilated, poorly reactive, or nonreactive pupil. A pupil-involving oculomotor palsy is an emergency. An aneurysm must be ruled out. One should be suspicious in a patient with mild anisocoria if the larger pupil is ipsilateral to the side of oculomotor nerve dysfunction. Note that diabetic patients without an aneurysm may nonetheless have pupil-involving third nerve palsy.

KEY POINTS: CRANIAL NERVE PALSIES

1. A pupil-sparing palsy is probably vasculopathic in adults. In children, obtain a magnetic resonance image or angiograph to rule out tumor and aneurysm.
2. To test for trochlear nerve palsy in a patient with an oculomotor palsy, have the patient look down and in to check for intorsion.
3. Primary oculomotor aberrant regeneration suggests a compressive lesion.
4. Sixth-nerve palsy may be a false-localizing sign of elevated intracranial pressure.
5. Always rule out trapdoor, “white-eyed” muscle entrapment in a pediatric facial trauma patient with otherwise seemingly normal-looking eyes.

5. What is the workup of a pupil-involving third-nerve palsy?

In adults, perform magnetic resonance imaging/angiography (MRI/A) or spiral computed tomography (CT) angiography. If the results are consistent with an aneurysm or even if the results are negative, consider performing angiography after discussion with neuroradiology and neurosurgery. In children, perform MRI/A regardless of the state of the pupil. If the results are negative, children usually do not need an angiogram.

6. Why do aneurysms involve the pupil in oculomotor nerve palsies, whereas infarctions generally do not?

Pupillary parasympathetic fibers travel superficially and dorsomedially in the third nerve as it traverses the subarachnoid space. These fibers are often affected first in a compressive lesion. Ischemic infarction often occurs in the center of the nerve, so the superficial fibers remain unaffected.

7. What is the workup of an isolated pupil-sparing but otherwise complete oculomotor nerve palsy in the vasculopathic age group?

A lesion that compresses the central third-nerve fibers sufficiently to produce a complete paresis should affect the peripheral pupillary fibers sufficiently to produce at least some degree of pupil involvement. If not, the likelihood of an aneurysm or other compressive etiology is extremely low. The patient may be treated for an assumed vaso-occlusive etiology. At a minimum, diagnostic workup includes measuring systemic blood pressure, a lipid panel, and fasting blood glucose and/or hemoglobin A1c. If the patient has symptoms of giant cell arteritis, check for an elevated erythrocyte sedimentation rate, C-reactive protein, and platelet count; administer corticosteroids; and perform a temporal artery biopsy; otherwise, the patient may be seen again in 6 weeks. Some physicians reexamine the patient within 5 days to ensure the pupil remains uninvolved. If no resolution of symptoms occurs over 3 months, neuroimaging with an MRI is generally performed.

8. What are the causes of isolated cranial neuropathies?

Many cranial neuropathies are idiopathic, but the causes of isolated cranial neuropathies are summarized in Table 30-1.

9. How do you test for a trochlear nerve palsy in the presence of an oculomotor nerve palsy?

It is important to specifically test trochlear, abducens, and trigeminal nerve function in a patient with an oculomotor nerve palsy to localize the lesion. Because the third-nerve palsy may prevent adduction, it may be difficult to test fourth-nerve function. When the patient attempts to look down and in with the paretic eye, you will observe intorsion if the trochlear nerve is intact. This can be done by telling the patient to look at his or her nose.

10. Describe the three-step test.

This is a test to determine if a hypertropia is due to superior oblique palsy or other causes (Fig. 30-1).

Step 1: Which eye is hyperdeviated? A right hyperdeviation could be caused by palsy of any of the muscles circled in Fig. 30-1, *A*. Determine which muscles might cause this.

Step 2: Is the hyperdeviation worse in the right gaze or the left gaze? Isolate these muscles. A right superior oblique palsy reveals worsening of the right hyperdeviation in the left gaze (Fig. 30-1, *B*).

Step 3: Is the hyperdeviation worse on right head tilt or left head tilt (Fig. 30-1, *C*)? The muscle isolated in all three steps is the palsied muscle. A right superior oblique palsy reveals increased hyperdeviation upon head tilt to the right. A double Maddox rod can then be used to determine if the trochlear nerve palsy is bilateral. If excyclotorsion is more than 10°, bilateral superior oblique palsies exist.

Table 30-1. Causes of Isolated Cranial Neuropathies

CRANIAL NEUROPATHY	CAUSE
III (pupil-sparing)	Adults: infarction, trauma, giant cell arteritis (GCA), tumor; rarely, an aneurysm. Children: congenital, trauma, tumor, aneurysm, migraine
III (pupil-involving)	Usually posterior communicating artery aneurysm (rarely, basilar artery)
IV	Adults: trauma, infarction, congenital, GCA Children: congenital, trauma
VI	Adults: infarction, tumor, trauma, multiple sclerosis, Wernicke's encephalopathy, sarcoidosis, GCA, herpes zoster, Lyme disease, increased intracranial pressure as in pseudotumor cerebri Children: trauma, tumor, post-viral infection

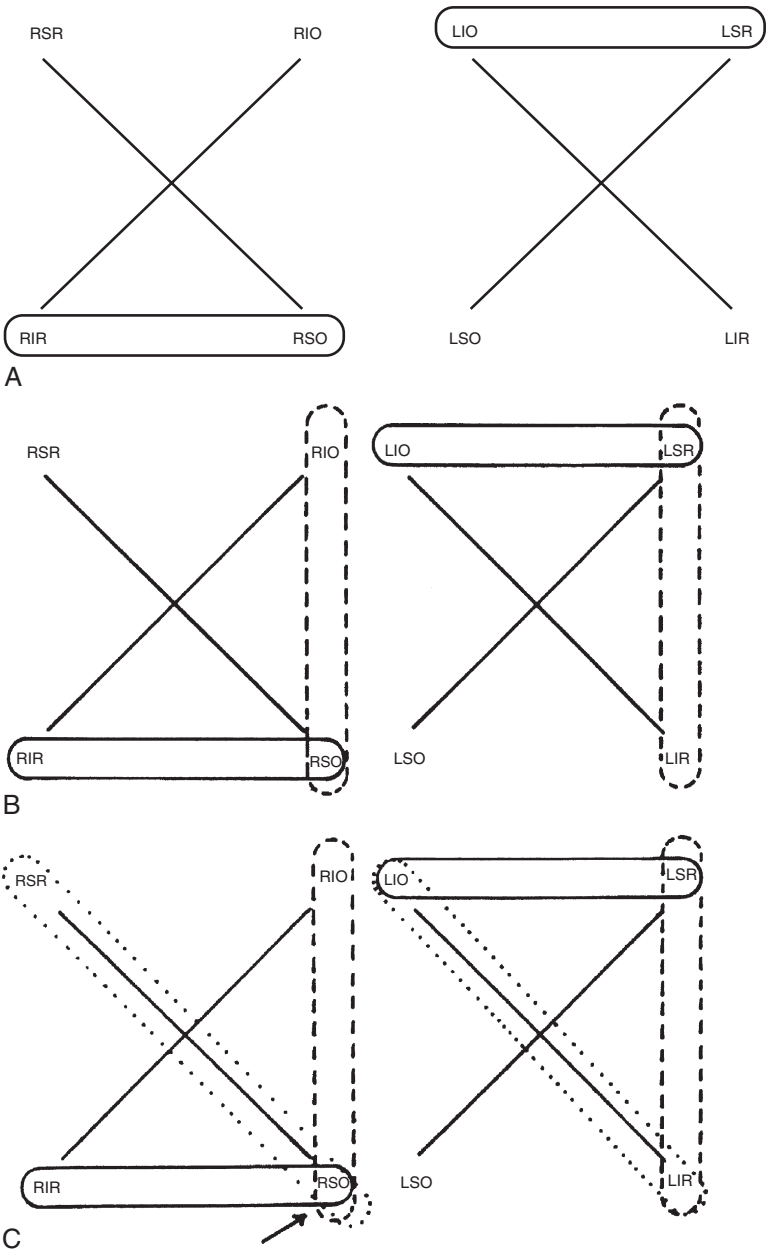

Figure 30-1. The three-step test to determine if hypertropia is a result of superior oblique palsy or other causes. **A.** Step 1. **B.** Step 2. **C.** Step 3. (See question 10 for explanations.) *(From American Academy of Ophthalmology: Pediatric ophthalmology and strabismus, Section 8. San Francisco, American Academy of Ophthalmology, 1992-1993.)*

11. What is the best procedure to treat unresolved superior oblique palsy? Does one have to memorize Knapp's Rules?

Knapp published his treatment scheme some years ago, and many surgeons use similar schemes. It is not necessary to memorize his particular scheme, but the principles should be understood. Generally, there are three possible surgical approaches:

1. Strengthen (tuck) the palsied superior oblique muscle.
2. Weaken (recess or myectomize) the antagonist ipsilateral inferior oblique muscle.
3. Weaken the yoke contralateral inferior rectus muscle.

Typically, the surgeon operates on the muscle or muscles that act in the field of gaze where the diplopia is worst. For example, if the left hyperdeviation in a left superior oblique (LSO) palsy is worse in downgaze, one would consider an LSO tuck or a right inferior rectus recession. The latter procedure may be favored because an adjustable suture technique can be used and there is no chance of producing an iatrogenic Brown's syndrome.

12. Explain the Harada-Ito procedure.

The Harada-Ito procedure involves anterior and lateral displacement of the anterior portion of the palsied superior oblique muscle. This procedure is used primarily for correction of excyclotorsion but will correct a small degree of hyperdeviation. The amount of incyclotorsion created is variable, but the procedure is generally successful, especially in patients with <10 degrees of preoperative torsion.

13. What else should you know about trochlear nerve palsy?

1. It is the longest and most commonly injured cranial nerve in trauma.
2. It crosses to the contralateral side as it exits the dorsal midbrain.
3. Patients of all ages with trochlear nerve palsy and increased vertical fusional amplitudes do not need further evaluation; they have decompensated "congenital" trochlear nerve palsies.
4. Always consider MG and TED in the evaluation of diplopia, even if the palsy "maps out" to a specific cranial nerve.

14. List the major causes of abduction deficit other than cranial neuropathy.

- Restricted medial rectus muscle
- Trauma (entrapment, damage)
- Inflammatory pseudotumor or myositis
- Thyroid-related eye disease
- Spasm of the near reflex
- Myasthenia gravis
- Prior strabismus surgery (slipped lateral rectus, highly recessed lateral rectus)

15. How do you treat an unresolved abducens nerve palsy?

1. Weaken the ipsilateral medial rectus with strengthening of the ipsilateral lateral rectus muscle.
2. Vertical transposition procedure.
3. Botulinum toxin (Botox) injections may be used with the above procedures or alone.

16. What else should you know about abducens nerve palsy?

1. It may occur as a nonspecific sign of increased intracranial pressure. It may also occur after lumbar puncture.
2. In the case of bilateral abducens paresis, you must consider tumor, multiple sclerosis, subarachnoid hemorrhage, or infection.
3. In children with bilateral abducens paresis, reconsider strabismus and check for "doll's eyes." Doll's eyes should be incomplete in a paretic disorder.
4. Third-order sympathetic fibers briefly join the abducens nerve in the cavernous sinus. Horner's syndrome with an abducens nerve palsy localizes to this region.
5. Always consider MG and TED in the evaluation of diplopia, even if the palsy "maps out" to a specific cranial nerve. (Sound familiar?)

17. What are the localizing symptom complexes of nerve palsy?

See Table 30-2.

18. What is internuclear ophthalmoplegia?

The medial longitudinal fasciculus carries nerve fibers from the abducens nucleus on each side to the contralateral medial rectus subnucleus to coordinate horizontal gaze. This area of the brain stem may be damaged by demyelination, ischemia, or tumor. Ipsilateral decreased adduction and contralateral

Table 30-2. Localizing Symptom Complexes of Nerve Palsy

SYMPTOMS/SIGNS	SYNDROME	ANATOMIC LOCATION
Ipsilateral III-nerve palsy with a contralateral hemiplegia	Weber's syndrome	Midbrain—third nerve and cerebral peduncle
Ipsilateral III-nerve palsy with contralateral choreiform movement	Benedikt's syndrome	Midbrain—third nerve fascicle and red nucleus
Ipsilateral VI-nerve palsy with hearing loss and facial pain	Gradenigo's syndrome	Petrous apex
Ipsilateral gaze palsy with facial palsy, Horner's syndrome, and deafness	Foville's syndrome	Dorsolateral pons
Ipsilateral VI- and VII-nerve palsies with contralateral hemiparesis	Millard-Gubler syndrome	Ventral pons
III-, IV-, VI-nerve (and V_1, V_2) palsies with Horner's syndrome	Cavernous sinus syndrome	Cavernous sinus
II-, III-, IV-, and VI-nerve (and V_1) palsies, often with proptosis	Orbital apex syndrome	Orbital apex
V-, VI-, VII-, and VIII-nerve palsies	Cerebellopontine angle syndrome	Cerebellopontine angle (often tumor)

abduction nystagmus are observed on attempted contralateral gaze. Saccadic velocity may be decreased in the adducting eye and may be the only sign of a subtle internuclear ophthalmoplegia (INO). Skew deviation (see below) may be observed. Bilateral INO often presents with esotropia and upward-beating nystagmus on attempted convergence in addition to the above findings.

19. What is ocular myasthenia gravis?

Intermittent diplopia and ptosis are common symptoms of this condition, and diurnal variability increases suspicion. On exam, ptosis will frequently worsen with prolonged upgaze, and obicularis strength is frequently affected. Myasthenia may mimic any isolated ocular motor nerve palsy or an INO. Both eyes may be affected differently at different times.

20. What is the workup for myasthenia gravis?

Three types of acetylcholine receptor antibody tests are available for diagnosis: binding, blocking, and modulating. Binding antibodies are found in more than 80% of generalized myasthenia gravis, but in about 50% of the ocular type. Anti-MuSK antibodies may be found in generalized myasthenia gravis negative for acetylcholine receptor antibodies. Electrophysiologic tests such as repetitive nerve stimulation and single-fiber electromyography (EMG) assist in diagnosis. Workup additionally includes MRI of the chest and thyroid studies to rule out associated thymomas and hyperthyroidism. Myasthenia that is purely ocular after 2 years is likely to remain so.

21. What is the Tensilon test?

Tensilon (edrophonium chloride) is a short-acting anticholinesterase that can cause improvement of symptoms and signs of MG by competing with acetylcholine for enzyme degradation. Intravenous Tensilon is administered. A positive test shows improved facial expression, lid position, or double vision within 3 minutes of injection. A positive test is quite specific for the diagnosis of MG; however, false-negative tests occur. An EMG may also show improvement after Tensilon administration. Atropine must be readily available in case adverse reactions occur (abdominal cramps and bradycardia are common).

22. What is convergence insufficiency?

Typical convergence insufficiency presents with asthenopia and double vision at near. It is diagnosed by observing an exotropia near an abnormally remote near point of convergence and inadequate

amplitudes of fusion. Patients can fully adduct during conjugate gaze movements, and the deviation is comitant for a given distance. The isolated condition is rarely associated with tumor or other serious pathology. Patients are treated with near-point exercises such as focusing on the end of a pencil while moving from arm's length toward the face.

23. What is skew deviation?

Skew deviation is a vertical deviation that is caused by a prenuclear disturbance and cannot be isolated to a single extraocular muscle or muscles. It is distinguished from a superior oblique palsy in that it is associated with incyclotorsion, rather than excyclotorsion, as seen in a superior oblique palsy. It is associated with other manifestations of posterior fossa disease.

24. What other supranuclear conditions commonly produce diplopia?

Progressive supranuclear palsy produces a variety of systemic and ocular motility disturbances, including bradykinesia, axial rigidity, and difficulty with vertical eye movements. If diplopia is present, it is typically caused by convergence difficulty. Similarly, patients with parkinsonism, Huntington's disease, and Parinaud's dorsal midbrain syndrome may also have diplopia at near owing to convergence difficulty.

25. Explain divergence paresis.

Patients with divergence paresis present with an esodeviation at distance causing diplopia. Patients are able to fuse at near. The esodeviation is comitant, and horizontal versions are normal. This condition tends to be benign and self-limited; however, it may be associated with infection, demyelinating disease, and tumor. A thorough neurologic evaluation should be performed, and consideration should be given to MR imaging, especially if any neurologic signs or symptoms are present.

26. Do vaso-occlusive nerve palsies present with aberrant regeneration?

No. Aberrant regeneration of the third nerve does not occur after a vaso-occlusive (e.g., diabetic) third-nerve palsy. Primary oculomotor aberrant regeneration is highly suggestive of a lesion that is slowly compressing the third nerve, such as an intracavernous meningioma or aneurysm.

27. To what anatomic region does Horner's syndrome with an abducens nerve palsy localize?

It localizes to the cavernous sinus. Third-order sympathetic fibers briefly join the abducens nerve in the cavernous sinus. Often, however, diseases of the cavernous sinus such as a carotid cavernous fistula or cavernous sinus thrombosis cause cranial nerve III, IV, and VI deficits in addition to proptosis, elevated intraocular pressure, conjunctival hyperemia, and reduced vision.

28. What is the ice test?

The ice test is a noninvasive test for myasthenia gravis. The palpebral fissure is measured before and immediately after a 2-minute application of ice to the ptotic eyelid. Many patients with myasthenia gravis will show an improvement in the ptosis after ice application. The sensitivity of the ice test in patients with complete ptosis decreases considerably.

KEY POINTS: MYASTHENIA GRAVIS

1. Always suspect MG in any patient with diplopia, especially if it is variable and associated with ptosis.
2. Have atropine available for adverse reactions if Tensilon tests are performed.
3. If a patient has classic MG symptoms and signs but negative acetylcholine receptor antibodies, consider checking for anti-MuSK or obtaining electrophysiological studies.
4. Thymomas and hyperthyroidism are common in patients with MG. Patients need a chest MRI and thyroid function tests.

29. Why is a trapdoor orbital fracture important to recognize?

A trapdoor fracture occurs when an orbital wall, most often the floor, breaks and then springs back together, entrapping a herniated extraocular muscle within it. This is more often seen in pediatric

patients who may otherwise appear to have minimal ocular or adnexal trauma ("white-eyed" fracture). Examination of the extraocular muscles reveals restrictive deficits and diplopia at gaze opposite the fracture. CT scan of the orbits may reveal a fracture with entrapped muscle, but this may be easily missed. This type of fracture with muscle entrapment requires urgent surgical repair as ischemic damage and fibrosis of the muscle may occur if not treated promptly.

30. In facial trauma involving orbital fractures, what are indications for repair?

Emergent repair is indicated for globe luxation into the maxillary sinus or if an oculocardiac reflex is observed. Urgent repair is recommended for muscle entrapment due to trapdoor fractures. Repair within 1 to 2 weeks is often suggested in patients with sustained diplopia due to non-trapdoor entrapment, early enophthalmos of more than 3 mm, significant hypoglobus, large orbital wall fractures that will probably cause enophthalmos, or associated rim or other facial fractures. Indications for observation without treatment include lack of or improving diplopia or entrapment, lack of enophthalmos, and small fractures with low risk of future enophthalmos.

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OPTIC NEURITIS

Mark L. Moster, Barry Schanzer, and Peter J. Savino

CHAPTER 31

1. **What is optic neuritis?**
   Optic neuritis is any inflammation of the optic nerve. It may be idiopathic or associated with systemic disease.

2. **Which systemic diseases are associated with optic neuritis?**
   The most common disease associated with optic neuritis is multiple sclerosis (MS). However, neuromyelitis optica, syphilis, sarcoidosis, Lyme disease, and other collagen vascular diseases such as Wegener's granulomatosis and systemic lupus erythematosus are less commonly associated.

3. **Who most commonly gets optic neuritis?**
   Women between the ages of 15 and 45 years are most commonly affected.

4. **What are the typical clinical findings in optic neuritis?**
   Optic neuritis causes acute or subacute visual loss that is preceded or accompanied by pain on eye movement and that may progress over 10 to 14 days. Visual acuity may range from 20/20 to no light perception. However, even if visual acuity is 20/20, the patient usually has a defect in color vision, contrast sensitivity, and visual field. If the neuritis is unilateral, an afferent pupillary defect is present. The optic disc may be normal or swollen.

5. **Which clinical test is most sensitive for patients with optic neuritis?**
   The most sensitive test—that is, the test most likely to be abnormal in a patient with optic neuritis—is contrast sensitivity.

6. **How common is pain on eye movement in patients with optic neuritis?**
   Pain around the eye or pain exacerbated with eye movement was present in 92% of patients in the Optic Neuritis Treatment Trial (ONTT).

7. **What visual field defects are found in patients with optic neuritis?**
   The classic visual field defect in optic neuritis is central scotoma. However, results of the ONTT showed that any optic nerve visual field defect is compatible with optic neuritis, including altitudinal defects and arcuate defects as well as diffuse visual field defects.

8. **What is the natural history of optic neuritis?**
   The visual loss of optic neuritis may progress over 10 to 14 days. At that point it should stabilize and shortly thereafter begin to improve.

9. **What is the expected visual outcome for patients with optic neuritis?**
   The ONTT found that at 12 months, 93% of patients were 20/40 or better, 69% were 20/20 or better, and 3% were 20/200 or worse. At 10 years, 91% of patients had acuity of 20/40 or better and 74% were 20/20. At 15 years, 66% had visual acuity of 20/20 or better in both eyes. On average, visual acuity was worse in those who developed MS.

10. **Are there any predictors of poor visual outcome?**
    The ONTT found that the only predictor for poor visual outcome was poor visual acuity at presentation. Nevertheless, all patients with an initial visual acuity of 20/200 or less showed some improvement. However, 5% of the patients were still 20/200 or less at 6 months.

11. **What were the objectives of the ONTT?**
    The ONTT was a multicenter, randomized, prospective clinical trial to determine whether corticosteroid treatment of optic neuritis was beneficial for visual outcome. A secondary objective was to determine the risk of developing MS in patients with optic neuritis. The patients who participated in the ONTT were randomized to three treatment arms. One group of patients received oral placebo; one group received oral prednisone, 1 mg/kg for 14 days; and one group received intravenous (IV) methylprednisolone (Solu-Medrol), 250 mg every 6 hours for 3 days, followed by oral prednisone, 1 mg/kg for 11 days.

12. What were the conclusions of the ONTT regarding treatment of optic neuritis?
No treatment group had statistically significantly better visual acuity at 6 months. However, patients treated with IV methylprednisolone began to recover vision more quickly. The surprising result was that patients treated with oral prednisone, 1 mg/kg for 14 days, had an increased incidence (2×) of recurrence of optic neuritis in the affected or contralateral eye. The researchers concluded that oral prednisone at a dose of 1 mg/kg is contraindicated in the treatment of optic neuritis.

13. What was the strongest predictor for the development of MS?
An abnormal magnetic resonance imaging (MRI) scan (Fig. 31-1) was the strongest predictor for development of clinically definite MS at 2 years. Placebo-treated patients whose MRI scan at study entry showed two or more periventricular white matter lesions >3 mm had a 36% chance of developing MS within 2 years. Patients with one lesion had a 17% chance, and patients with no signal abnormalities had only a 3% chance.

14. What were the other predictors for developing MS?
Previous optic neuritis in the fellow eye, previous nonspecific neurologic symptoms, race (white), and family history of MS were associated with an increased risk of developing MS. Although young age and female gender have been reported to be risk factors for MS, they were not shown to increase the risk within 2 years in the ONTT.

15. What were the conclusions of the ONTT about the effect of treatment on the risk of developing MS?
The results of the ONTT showed that IV methylprednisolone significantly decreased the risk of developing MS at 2 years. Most of the beneficial effect was seen in patients with abnormal MRI scans, because patients with normal MRI scans had a low incidence of MS, regardless of treatment. Among patients with two or more signal abnormalities on MRI, MS developed in 36% treated with placebo, 32% treated with prednisone, and 16% treated with IV methylprednisolone. Thus, the risk of developing MS at 2 years was cut in half by treatment with IV methylprednisolone. After 2 years, the beneficial effect seemed to wear off, and at 3 years and beyond the three groups had a similar incidence of MS.

16. What is the 15-year risk of developing MS after optic neuritis?
A total of 50% of patients enrolled in the ONTT developed MS in a 15-year period. White matter lesions on MRI were the most potent predictor of MS. Patients with one or more lesions had an incidence of MS of 72%. Those with no lesions on MRI had a 25% incidence of MS.

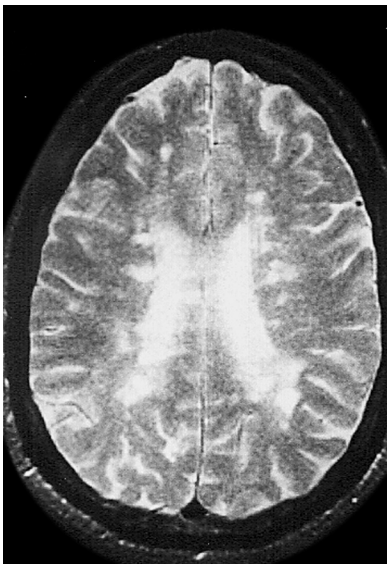

Figure 31-1. Abnormal MRI in a patient with multiple sclerosis. Classic periventricular white matter lesions appear bright on T2-weighted image.

KEY POINTS: OPTIC NEURITIS

1. Optic neuritis causes vision loss that may progress over 10 to 14 days.
2. Pain is present in more than 90% of patients with optic neuritis.
3. A total of 93% of patients with optic neuritis will recover vision of 20/40 or better.
4. Patients with at least one white matter lesion on MRI scan have a 72% chance of developing MS at 15 years.

17. What is the 10-year risk of recurrence of optic neuritis?

A total of 35% of patients in the ONTT who completed the examination at 10 years had a documented recurrence of optic neuritis in the previously affected eye or an attack in the fellow eye. Patients who had a diagnosis of MS had a higher recurrence rate (43%) than those who did not have MS (24%).

18. Are there any other medications that may influence the risk of developing MS?

Numerous medications approved for the treatment of MS have been shown to decrease the progression to MS in patients with optic neuritis. The first study was the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study, which was a randomized double-blind trial to determine whether treatment with interferon β-1a (Avonex) would affect the risk of developing MS in patients who have a first demyelinating event involving the optic nerve, spinal cord, brain stem, or cerebellum. The patients studied had an acute demyelinating event and an MRI that demonstrated two or more lesions 3 mm or larger in diameter, at least one of which was periventricular or ovoid. All patients were treated with 1 g intravenous methylprednisolone for 3 days, followed by an oral prednisone taper. They were then randomized to receive weekly intramuscular injections of Avonex or placebo. The results demonstrated that at 3 years the probability of developing clinically definite MS was significantly lower in the patients treated with Avonex (35%) than in patients receiving placebo (50%). Similar findings occurred with Betaseron (BENEFIT study), Rebif (ETOMS study), Copaxone (PreCISe study), and now an oral agent—Aubagio (TOPIC study).

19. Describe the appropriate workup and treatment for patients with optic neuritis.

Patients presenting with optic neuritis should have an MRI scan of the brain and orbits. Almost all patients will have enhancement of the optic nerve on the orbital MRI. If the brain MRI scan is normal, no further workup is warranted and sequential follow-up is indicated. If the brain MRI shows white matter lesions consistent with demyelination, the patient should be offered treatment with IV methylprednisolone and should be referred to a neurologist to discuss treatment with one of the immune-modulating agents noted above. The ONTT found no significant benefit in obtaining blood tests for antinuclear antibody or fluorescent titer antibody in patients with typical optic neuritis and no other signs of collagen vascular disease.

20. When do I consider neuromyelitis optica?

Neuromyelitis optica (NMO; Devic's disease) is a distinct condition that used to be considered a variant of MS. It presents with recurrent and bilateral optic neuritis and transverse myelitis. It should be considered in patients with bilateral optic neuritis, sequential or early recurrence of optic neuritis, or poor recovery of optic neuritis. Other features include transverse myelitis with a lengthy spinal cord lesion (three segments, e.g., C3 to C6) and a brain MRI with little demyelinating activity. It is associated with a positive NMO (anti-aquaporin 4) antibody test, which is now commercially available.

21. Why diagnose neuromyelitis optica? Is it different from multiple sclerosis?

NMO is treated differently, with various immunosuppressants. The interferons, a mainstay of MS treatment, do not help and may even worsen NMO.

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CHAPTER 32

MISCELLANEOUS OPTIC NEUROPATHIES AND NEUROLOGIC DISTURBANCES

Janice A. Gault

1. **A young woman complains of headaches. Her vision is 20/20 in each eye with no evidence of afferent pupillary defect. She has a bitemporal visual-field cut. What do you suspect?**
   Suspect a chiasmal lesion. Schedule a magnetic resonance imaging (MRI) scan to make an evaluation.

2. **What may simulate a bitemporal field defect?**
   A bitemporal field defect may be simulated by sector retinitis pigmentosa, coloboma, or a tilted disc.

3. **A patient has 20/20 vision in her right eye and 20/400 in her left eye. Her left eye has an afferent pupillary defect and decreased color plates. What should you evaluate in her right eye?**
   Check visual fields in *both* eyes. A central scotoma in one eye may be accompanied by a superior temporal field loss in the other. This condition, called a *junctional scotoma,* is also found in chiasmal lesions. See the chapter on visual fields (Chapter 6).

KEY POINTS: DIFFERENTIAL DIAGNOSIS OF CHIASMAL VISUAL DEFECTS

1. Pituitary lesion—tumor or apoplexy
2. Craniopharyngioma
3. Meningioma
4. Glioma
5. Aneurysm
6. Trauma
7. Infection

4. **Is there a difference in the treatment of secreting and nonsecreting symptomatic pituitary tumors?**
   Yes. A prolactinoma secretes prolactin and may be treated successfully with bromocriptine. A nonsecreting tumor probably requires surgery. Of course, an endocrinologist should fully evaluate the patient for other hormonal imbalances.

5. **What visual field is often seen in a toxic or metabolic optic neuropathy?**
   Bilateral central or centrocecal scotomas. Optic nerves show temporal pallor (Fig. 32-1). Alcohol, tobacco, and vitamin B_{12} deficiency, as well as drugs such as chloramphenicol, ethambutol, digitalis, chloroquine, and isoniazid, have been implicated. Check for heavy metals and order a complete blood count as well as serum levels of vitamins B_{11}, B_{12}, and folate. Consider Leber's hereditary optic neuropathy as a diagnosis.

6. **A 60-year-old man presents with gradual vision loss to 20/400 in his right eye. On examination, the right optic nerve is pale and dot-and-blot retinal hemorrhages are seen. The left eye is normal. What history may be helpful?**
   A history of radiation treatment. The patient reports radiation to his right frontal sinus 3 years earlier. There is no treatment for radiation optic neuropathy. Panretinal photocoagulation for neovascular disease and anti-vascular endothelial growth factor treatment is used for radiation retinopathy.

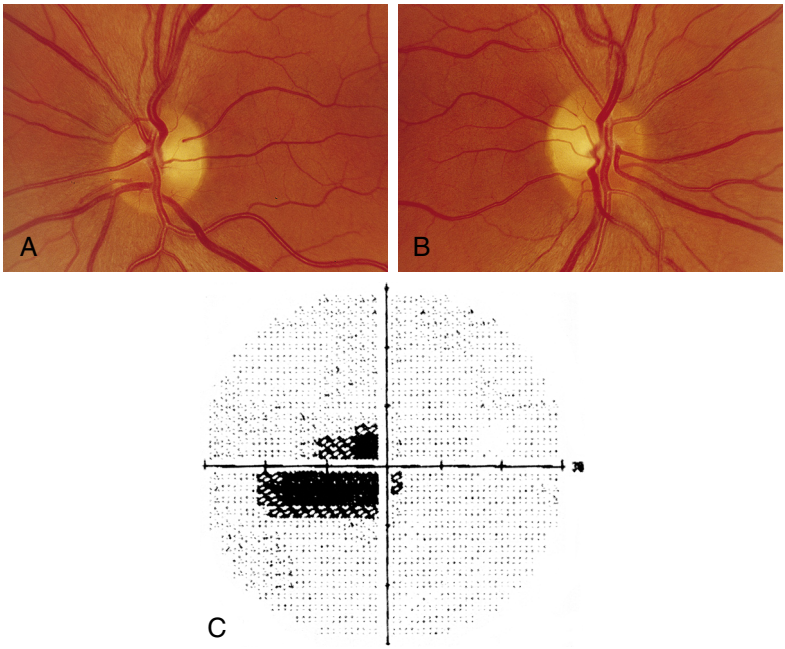

Figure 32-1. Fundus views reveal mild temporal optic disc pallor in right optic disc **A,** and left optic disc **B**. More interesting in **B,** however, is the loss of the nerve fiber layer in the papillomacular bundle. This patient, who had tobacco–alcohol amblyopia (mixed toxic and nutritional deficiency optic neuropathy), also had a visual acuity of 20/400 in each eye, which recovered to only 20/100 after changes in habit and diet and vitamin therapy. In this class of optic neuropathies, relatively severely compromised visual acuity and dyschromatopsia often are found with minimal optic disc atrophy. *(From Sadun AA, Gurkan S: Hereditary, nutritional, and toxic optic atrophies. In Yanoff M, Duker JS [eds]: Ophthalmology, ed 2, St. Louis, Mosby, 2004, 1275–1278.)* **C,** Visual field exam reveals centrocecal scotoma. A lesion of the papillomacular bundle (nerve fiber layer or optic nerve) is the usual cause of this defect. *(From Burde RM, Savino PJ, Trobe JD: Unexplained visual loss. In Burde RM, Savino PJ, Trobe JD [eds]: Clinical Decisions in Neuro-Ophthalmology, ed 3, St. Louis, Mosby, 2002, pp 1–26.)*

7. **What may cause a constricted visual field?**
   - Retinitis pigmentosa
   - End-stage glaucoma
   - Thyroid ophthalmopathy
   - Optic nerve drusen
   - Vitamin A deficiency
   - Occipital strokes
   - Panretinal photocoagulation
   - Hysteria
   - Malingering

8. **How do you differentiate hysteria and malingering from real disease?**
   Have the patient do a tangent screen at two different distances. The closer the patient stands, the smaller the field should be. In a patient with nonphysiologic visual loss, the fields are often of equal size. Patients also may demonstrate spiraling with kinetic visual-field testing (see Chapter 6).

9. **A 55-year-old man notices that the vision in his left eye has worsened suddenly. He has 20/30 vision in his right eye and 20/100 in his left eye. The left eye also shows an afferent pupillary defect and decreased color plates. Visual-field examination reveals an inferior altitudinal defect on the left with a normal full field on**

Table 32-1. Nonarteritic and Arteritic Ischemic Optic Neuropathy

	NAION	AION
Age of onset	40-60 years	Usually older than 50 years
Gender	Either equally	More often female
Presenting visual acuity	May be better than 20/100	Often count fingers or worse
Visual-field defect	Altitudinal or involving central visual field	Altitudinal or involving central visual field
Ophthalmic exam	Hyperemic disc swelling, may be segmental with flame-shaped hemorrhages; later atrophy without cupping	Pale, swollen disc with few flame hemorrhages; later, optic atrophy and cupping
Symptoms	None	Jaw pain, scalp tenderness, night sweats, fever, weight loss
Systemic associations	Diabetes, hypertension, hyperlipidemia, sleep apnea; potential increase in use of erectile dysfunction drugs if a crowded disc initially	Polymyalgia rheumatica
Lab evaluation	Lab tests normal	Elevated ESR, C-reactive protein, and platelet counts Disruption of internal elastic lamina on temporal artery biopsy

the right. On fundus examination, the left optic nerve appears pale and swollen superiorly. What is your concern?

An altitudinal defect is a classic finding with ischemic optic neuropathy (ION). The two types are arteritic and nonarteritic (see Table 32-1). Because they are treated differently, you must differentiate the two. First, it is important to ask about symptoms of giant cell arteritis, such as weight loss, anorexia, fever, jaw claudication, headache, scalp tenderness, and proximal joint and muscle pain. Check for a palpable, tender, nonpulsatile temporal artery. Immediately order an erythrocyte sedimentation rate (ESR), a C-reactive protein (CRP), and a platelet count if you believe that giant cell arteritis is a consideration. The upper limits of normal for an ESR is age divided by 2 for men and age +10 divided by 2 for women. The CRP is not affected by age and may be more sensitive than ESR. However, both are nonspecific tests; any inflammatory process can elevate them. Temporal arteritis patients have elevated platelet counts.

The patient denied any of the symptoms, and his ESR was 20. He was diagnosed with nonarteritic ION. Because 50% of these patients have cardiovascular disease, diabetes, and/or hypertension, he was sent to his internist. He was told that his prognosis for significantly improved vision was low. Forty percent of patients may have a mild improvement in vision over 6 months. However, some patients note an initial decrease in visual acuity and field, which is followed by a second decrease in visual acuity or field days to weeks later. Unfortunately, there is no proven treatment. A study showed no improvement with optic nerve sheath decompressions. With time, the patient's optic nerve should atrophy in the area of damage. He has a 35% risk of involvement of the other eye.

10. An 80-year-old man presents with the same history of sudden vision loss and the same visual field as the man in question 9. However, his vision consists of counting fingers at 10 feet, and his optic nerve is pale and swollen with flame-shaped hemorrhages. He admits to jaw pain when he chews, weight loss of 10 pounds, and difficulty in getting up from a chair. He has a tender temporal artery without pulses. His ESR is 120. What do you do?

First, you make a diagnosis of giant cell arteritis and place him on 250 mg of methylprednisolone intravenously every 6 hours for 12 doses, followed by 80 to 100 mg/day of prednisone orally for

2 to 4 weeks after reversal of symptoms and normalization of ESR. Treatment may last for 1 year or more. (Evidence suggests that such high doses can prevent the same process in the other eye, of which there is a 30% risk.) The patient is then scheduled for temporal artery biopsy.

11. Should the biopsy be done before the steroids are started, to ensure that the diagnosis can be made?

Absolutely not. The steroids will not affect the biopsy results for at least 7 days, and it may be positive for up to a month after steroids. The therapeutic effect of the steroids is necessary immediately, because the second eye can become involved in as little as 24 hours.

12. What biopsy finding makes the diagnosis?

Disruption of the internal elastic lamina. Giant cells are often present but are not necessary for the diagnosis.

13. What if the temporal artery biopsy is normal?

Giant cell arteritis is a diagnosis based mainly on symptoms. The ESR may be normal, and your suspicion should be extremely high because of the patient's history. Because skip areas also occur, make sure to get a significant length of artery for biopsy. Sometimes it is necessary to also biopsy the other side. In a patient with less classic symptoms, a negative biopsy warrants discontinuing steroids. Ocular pneumoplethysmography may help if it shows reduced ocular blood flow.

14. What else may herald giant cell arteritis?

Amaurosis fugax, cranial nerve palsies, or central retinal artery occlusion. Polymyalgia rheumatica and giant cell arteritis often occur together.

KEY POINTS: DIFFERENTIAL DIAGNOSIS OF OPTOCILIARY SHUNT VESSELS

1. Meningioma
2. Glaucoma
3. Old central retinal vein occlusion
4. Optic nerve glioma
5. Chronic papilledema
6. Idiopathic disease

15. A 35-year-old woman says that she has binocular diplopia. On examination, you find weakness of nasal eye movement in her right eye and horizontal jerk nystagmus of the left eye with attempted temporal movement. What does she have?

She has internuclear ophthalmoplegia. She also may have a skew deviation in which either eye can have a hypertropia that does not map to a specific muscle on the three-step test.

16. Internuclear ophthalmoplegia can be bilateral or unilateral. What might you find in bilateral disease?

You might find upbeat nystagmus in upgaze and exotropia.

17. What causes internuclear ophthalmoplegia?

Multiple sclerosis, ischemic vascular disease, or masses of the brain stem. The differential diagnoses that mimic weakness of inward eye movement include the following:

- **Myasthenia gravis:** Ptosis and orbicularis muscle weakness are common; symptoms worsen with fatigue. Results of a Tensilon test are often positive.
- **Orbital disease:** Nystagmus is usually not seen. Pain, ptosis, and/or globe displacement may coexist. Orbital computed tomography (CT) reveals the cause.

18. An obese 30-year-old woman presents with severe headaches and occasional double vision. Her vision is 20/20 in both eyes. How do you evaluate her?

Check pupillary responses, color plates, visual fields, and extraocular motility; do a full slit lamp and dilated examination. You notice that she has bilateral swollen optic nerves.

19. How do you differentiate between papilledema and pseudopapilledema?

Pseudopapilledema is not true disc swelling. The vessels surrounding the disc are not obscured, the disc is not hyperemic, and the peripapillary nerve fiber layer is normal. Spontaneous venous pulsations, if present, strongly suggest pseudopapilledema. Nerve fiber layer hemorrhages are not present in pseudopapilledema. Causes of pseudopapilledema include optic nerve drusen and congenitally anomalous discs.

20. What do you do after the evaluation?

You must emergently evaluate the patient for increased intracranial pressure. First, she needs a CT or MRI of the head and orbit to rule out a mass. Provided the scan is normal, a lumbar puncture should follow. If the only abnormality is an increased opening pressure, the diagnosis is pseudotumor cerebri (Fig. 32-2), also known as idiopathic intracranial hypertension.

21. How should the patient be treated?

If she has no optic nerve damage on visual fields, encourage her to lose weight. If the headaches continue or she has evidence of decreased visual acuity or visual-field loss, treatment is indicated. Medications include a diuretic, such as acetazolamide, or systemic steroids. Optic nerve sheath decompression is used for worsening visual fields, and lumboperitoneal shunts have been used for headaches. The intraocular pressure should be treated if elevated.

KEY POINTS: CAUSES OF PSEUDOTUMOR CEREBRI

1. Obesity
2. Pregnancy
3. Drug use: Steroids (use or withdrawal), oral contraceptives, nalidixic acid, tetracycline, vitamin A
4. Idiopathic disease

22. Why did the patient have double vision?

Increased intracranial pressure may cause sixth-nerve palsies.

23. A mother brings in her firstborn for his first exam. He is 6 months of age and appears not to see well. Dilated exam reveals optic nerve hypoplasia. What is the differential diagnosis?

Optic nerve hypoplasia (Fig. 32-3) seems to occur in the firstborn of young mothers who may have diabetes or who may have used lysergic acid diethylamide (LSD), phenytoin, or alcohol during pregnancy. Patients also may have optic nerve hypoplasia in association with Goldenhar's syndrome or septo-optic dysplasia of de Morsier. The latter patients have seesaw nystagmus and chiasmal anomalies. Because of the risk of growth retardation, diabetes insipidus, and other pituitary abnormalities, patients with optic nerve hypoplasia should have a scan of the optic chiasm and an endocrine evaluation.

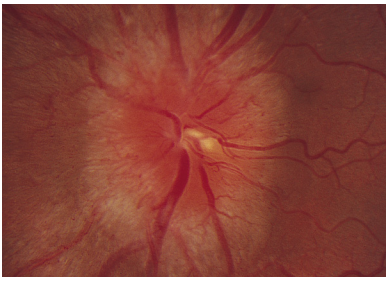

Figure 32-2. Developed papilledema. This is the optic disc of a 30-year-old woman who suffered headaches and blurred vision for 2 months. Disc edema is fully developed. Note the engorged veins and peripapillary hemorrhages. *(From Brodsky MC: Congenital optic disc anomalies. In Yanoff M, Duker JS [eds]: Ophthalmology, ed 2, St. Louis, Mosby, 2004, pp 1255–1258.)*

24. A patient has a bilateral, right-sided superior field defect. Where do you suspect the lesion is located?

A "pie-in-the-sky" defect is located in the temporal lobe. The inferior fibers loop around the temporal lobe (Meyer's loop).

25. What other symptoms may the patient have?

Formed hallucinations, déjà vu experiences, or uncinate fits.

26. What if the patient has a bilateral, inferior right-sided visual-field loss?

This "pie-on-the-floor" defect is typical for the parietal lobe. Patients have spasticity of conjugate gaze and optokinetic nystagmus abnormalities.

27. A patient presents with the visual field illustrated in Figure 32-4. Where is the lesion located?

It is in the right occipital lobe. The more congruous the defect, the more posterior its location. In addition, the nasal retina is larger and allows a temporal crescent in the visual field in the contralateral eye. Macular sparing or splitting also may occur.

28. What else may the patient experience?

Patients with occipital lobe lesions often do not experience other neurologic abnormalities. If they do, they may have unformed hallucinations, dyschromatopsia, prosopagnosia, and alexia without agraphia.

29. What causes pseudo–Foster Kennedy syndrome?

Pseudo–Foster Kennedy syndrome is optic atrophy with contralateral optic disc edema. A frontal lobe tumor causes true Foster Kennedy syndrome. The pseudosyndrome is usually the result of an acute ischemic optic neuropathy in one eye with contralateral atrophy caused by a past episode of the same process. An olfactory groove meningioma also may cause the pseudosyndrome.

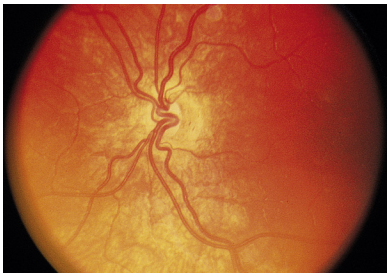

Figure 32-3. Hypoplasia of the left optic nerve. Note the double ring sign. *(From Sadun AA: Differentiation of optic nerve from retinal macular disease. In Yanoff M, Duker JS [eds]: Ophthalmology, ed 2, St. Louis, Mosby, 2004, pp 1253–1254.)*

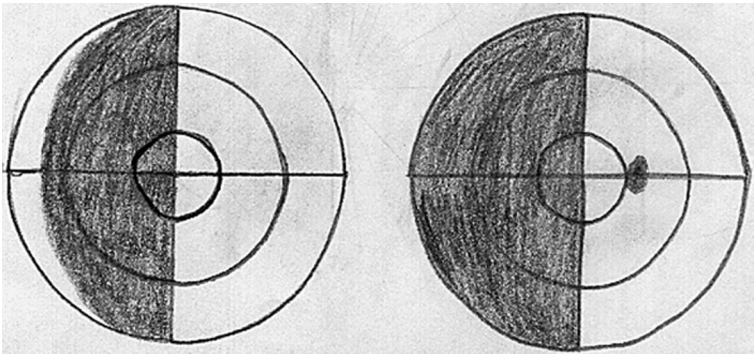

Figure 32-4. Left homonymous hemianopia with temporal crescent in left eye.

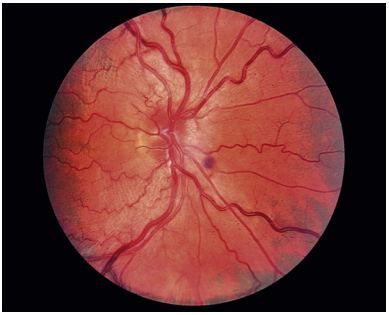

Figure 32-5. Leber's optic neuropathy, acute. Note hyperemic appearance of disc and opacification of the peripapillary nerve fiber layer. *(From Burde RM, Savino PJ, Trobe JD: Clinical Decisions in Neuro-Ophthalmology, ed 3, St. Louis, Mosby, 2004.)*

30. An 18-year-old man presents with sudden vision loss in one eye, followed by the other eye within days. He denies pain. He has 20/20 vision in both eyes with decreased color plates and bilateral mild disc swelling with peripapillary telangiectatic microangiopathy (Fig. 32-5). Affected vessels do not leak on fluorescein angiography. What does he have?

Leber's hereditary optic neuropathy. The patient's history is typical. The disorder is transmitted by mitochondrial DNA; all female carriers transmit it to their offspring. Ten percent of daughters and 50 to 70% of sons manifest the disease. All daughters are carriers. None of the sons are carriers. Young men present with symptoms at 15 to 30 years of age. No effective treatment is known, but some mutations are more likely to have spontaneous improvement in the future; thus genetic evaluation of the mitochondria is worthwhile. Because patients have a higher incidence of cardiac conduction defects, referral to a cardiologist is indicated.

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TEARING AND THE LACRIMAL SYSTEM

Nancy G. Swartz and Marc S. Cohen

CHAPTER 33

OCULOPLASTICS

1. What are the causes of tearing?

Tearing, also known as *epiphora,* occurs when there is an increase in the amount of tears produced or when there is a problem with the tear drainage system. We produce too many tears when the cornea is irritated. This tearing is adaptive, because if there is a foreign body present, it will wash it away. Acute corneal irritation typically results from mechanical irritants, such as an eyelash, or chemical irritants, such as the fumes from a freshly cut onion. Chronic tearing from irritation may also result from mechanical irritation as in entropion and trichiasis. However, it often occurs as a result of tear-film deficiencies (seen in dry eye syndrome and blepharitis), exposure keratopathy, or allergic conjunctivitis. When the production of tears is normal, tearing indicates an inadequate drainage of tears. A blockage at any point in the tear drainage system can cause tearing. Eyelid malpositions, such as ectropions and punctal ectropions, will also reduce the drainage of tears, as will lower eyelid laxity, which interferes with the eyelid's ability to pump the tears naturally through the lacrimal drainage system. For many patients, tearing is multifactorial.

KEY POINTS: COMMON CAUSES OF CHRONIC TEARING

1. Ocular irritation
   a. Dry eyes
   b. Allergies
   c. Computer vision syndrome
2. Tear-drainage dysfunction, such as from lower eyelid laxity
3. Blockage of the lacrimal drainage system, such as from a nasolacrimal duct obstruction

2. Describe the normal path of tear drainage in the eyelids

The most important function of our tears is to lubricate the surface of the eye. Our tears travel across the cornea and conjunctiva, keeping them moist. Gravity then guides most tears to rest on the margin of the lower eyelid. Here, they are carried medially to the puncta, small openings in the eyelid located approximately 6 to 7 mm lateral to the medial canthal angle. Once inside the puncta, the tears enter the canaliculi, mucosa-lined ducts approximately 10 mm in length that carry the tears to the lacrimal sac. The first portion of each canaliculus is a 2-mm dilated, vertical segment called the ampulla. Distal to the ampulla, the canaliculus bends acutely and runs parallel to the eyelid margin toward the medial canthus. In 90% of the population, the upper and lower canaliculi join together, forming the common canaliculus before merging with the lacrimal sac. However, in 10% of the population, each canaliculus merges with the lacrimal sac independently.

3. Where do tears go after leaving the eyelids?

The tears exit the canaliculi and enter the lacrimal sac, a mucosa-lined structure lying in a bony fossa in the medial orbit formed by the maxillary and lacrimal bones. The superior portion of the sac extends a few millimeters superior to the medial canthal tendon. It extends inferiorly approximately 10 mm and then continues as the nasolacrimal duct.

Tears travel from the sac to the nasolacrimal duct. The first 12 mm of the duct lies in a bony canal in the maxillary bone. The duct then continues inferiorly for an additional 3 to 5 mm before opening into the inferior meatus of the nose. The tears exit the duct through its ostium into the nasal cavity.

The ostium of the nasolacrimal duct can be found 30 mm posterior to the external nares in an adult. In young children, this distance is approximately 20 mm.

4. What is the tear pump?

The tear pump is a muscular "pump" that drives the tears through the drainage system by peristalsis. Tears first enter the puncta by capillary action. During a blink, the orbicularis oculi muscle contracts, closing the puncta, shortening the canaliculi, and moving them medially, while dilating the lacrimal sac. As the sac dilates, it creates a vacuum, drawing in the tears from the canaliculi. When the orbicularis muscle relaxes, the lacrimal sac collapses, the canaliculi lengthen, and the puncta reopen. The valve of Rosenmüller sits between the canaliculi and the sac, preventing the tears from reentering the canaliculi. Thus, tears are forced to continue their course down the nasolacrimal duct into the nose.

5. How does lower eyelid laxity affect tear drainage?

Normal drainage of tears requires normal structure and function of the eyelids. The pretarsal orbicularis muscle surrounds the canaliculi and attaches to the wall of the lacrimal sac. Contraction and relaxation of this muscle help draw the tears into the canaliculus and the sac and eventually force the tears down the nasolacrimal duct. When lower eyelid laxity is present, contraction of the orbicularis muscle does not compresses the canaliculi or force open the lacrimal sac, and the lacrimal pump mechanism cannot function adequately.

6. How can you tell if a patient has lower eyelid laxity?

Stretching of the medial and/or lateral canthal tendon causes lower eyelid laxity. In the distraction test, if the lower eyelid can be pulled more than 6 mm from the globe, it is lax.

Poor orbicularis oculi tone, most obvious in patients with seventh cranial nerve palsy, also causes laxity of the lower eyelid. This is best demonstrated with the "snap-back" test, in which the lower eyelid is pulled down inferiorly and allowed to snap back into place. If the eyelid returns to its correct position immediately, the muscle tone is good. If the patient must blink to place the eyelid back in its normal position, eyelid tone is poor.

7. How do you correct lower eyelid laxity?

If there is laxity of the lateral canthal tendon, a horizontal lid shortening procedure is performed to tighten the eyelid. This is typically accomplished with a lateral tarsal strip procedure. In this operation the inferior limb of the lateral canthal tendon is disinserted from the periosteum of the lateral orbital rim, a portion or the entire tendon is removed, and a new lateral canthal tendon is created from the lateral portion of the tarsus. The newly formed lateral canthal tendon is sutured back to the periosteum of the lateral orbital rim. This effectively shortens the lower eyelid, making the eyelid margin more stable and improving tear pump function.

8. Why do patients with dry eyes complain of tearing?

Patients tear when they have dry eyes for the same reason that they tear when cutting an onion. Onion fumes cause corneal irritation, which, in turn, causes reflex tearing.

Likewise, abnormalities in the tear film coating the cornea and conjunctiva cause irritation. Tear-film abnormalities can be caused by a decrease in the overall production of tears or by an imbalance in the composition of the tears. Inadequacies in any of the components of the tears cause a tear-film deficiency that can result in tearing.

9. What is computer vision syndrome?

Computer vision syndrome refers to a group of symptoms including tearing, eyestrain, and pain experienced by computer users. According to the National Institute of Occupational Safety and Health, computer vision syndrome affects some 90% of the people who spend three hours or more a day at a computer. Many of the symptoms relate to corneal exposure and the resultant dryness that occurs when extended time is spent staring at a computer screen.

10. Of what are tears composed?

Tears are composed of three layers. *Mucin,* made by the conjunctival goblet cells found mainly in the conjunctival fornices, covers the epithelium, ensuring a smooth, uniform tear film. The middle *aqueous* layer, made by the main lacrimal gland and accessory glands of Krause and Wolfring, provides hydration, oxygen, and nutrients. On the surface is the *lipid* layer, made in the meibomian, Zeis, and Moll glands of the eyelids. It prevents rapid evaporation of the tears and provides a smooth surface for the eyelids to glide across the cornea with each blink.

11. How can you determine if a patient produces enough tears?

The volume of tears can be indirectly assessed by visualization of the tear meniscus, the tear layer resting on the lower eyelid adjacent to the globe, which should be approximately 1 mm in height. However, the tear meniscus is also affected by tear drainage. The Schirmer test directly tests production. Gently dry the palpebral conjunctiva with a cotton swab and then place the small, folded end of a 5-mm-wide strip of Whatman No. 41 filter paper into the inferior conjunctival fornix at the junction of the middle and lateral third of the lower eyelid. In 5 minutes, measure the amount of wetting of the filter paper. When performed on an anesthetized cornea, it measures basal tear secretion. A normal result is 10 mm or greater. When performed on a nonanesthetized cornea, it measures both basal and reflex tearing. In this instance, normal wetting is 15 mm or greater.

12. How do you know if the tear composition is inadequate?

A decrease in the tear break-up time or the presence of protein, mucus, or debris in the tears indicates a tear inadequacy. The tear break-up time is the time it takes after a blink to develop a dry spot on the cornea. It is measured by touching the palpebral conjunctiva with a moistened fluorescein strip and observing the tear film through the slit lamp with a cobalt-blue filter. It is important to avoid using other eyedrops mixed with fluorescein, because this will change the composition of the tear film you observe. Once the patient blinks, the time is measured until the tear film begins to break up on the cornea, forming a dry spot. Less than 10 seconds is considered abnormal.

13. What are ectropion and entropion? How do they cause tearing?

Ectropion is an outward rotation of the eyelid margin. Entropion is an inward rotation of the eyelid margin. When either is present, patients tear. This occurs because both can cause corneal irritation with its associated reflex tearing, and both displace the punctum, so tears do not enter the tear-drainage system.

KEY POINTS: TESTING PATIENTS WITH CHRONIC TEARING

1. Tear quantity and quality evaluation
2. Evaluation of eyelid position
3. Evaluation of eyelid laxity
4. Probing and irrigation of lacrimal drainage system

14. What causes obstructions of the punctum, canaliculus, or lacrimal sac?

Complete and partial obstructions can occur anywhere in the lacrimal drainage system and may be caused by congenital agenesis, inflammation, infection, autoimmune disease, trauma, malignancy, radiation, and the toxic effects of medication. Here are the more common causes by location:

- **Punctal obstructions** are most commonly seen in congenital agenesis, herpetic infections, iatrogenic closure in the treatment of dry eyes, and mechanical obstruction in the setting of conjunctivochalasis.
- **Canalicular obstructions** can occur in one or both canaliculi or in the common canaliculus. These are often acquired from trauma, cicatrizing mucosal diseases such as Stevens-Johnson syndrome and ocular cicatricial pemphigoid, herpetic infections, canaliculitis associated with *Actinomyces israelii*, chemotherapeutic agents such as 5-fluorouracil and docetaxel, or long-term use of topical medications such as pilocarpine, epinephrine, phospholine iodide, and idoxuridine. Foreign bodies, such as silicone punctal and canalicular plugs, can occlude the canaliculi.
- **Lacrimal sac obstructions** occur most frequently from scarring as a result of a prior infection. Dacryoliths may develop from infections or chronic use of topical medications. Lacrimal sac tumors are rare.

15. What causes nasolacrimal duct obstructions?

Congenital nasolacrimal duct obstructions are found in 6% of normal newborns, and approximately 90% resolve spontaneously in the first year of life. In adults, primary acquired nasolacrimal duct obstruction is the most common cause of these obstructions. The cause of these is not well understood. However, it is commonly believed that obstruction of the ostium of the duct most likely is caused by inflammation of the lining of the duct and nasal mucosa. Dacryocystitis commonly causes scarring, which leads to nasolacrimal duct obstructions. Abnormalities in adjacent structures are often associated with these obstructions, such as nasal polyps, sinus disease, trauma, and deviated septa.

16. How do you evaluate the lacrimal system for obstructions?

Obstructions can occur anywhere in the lacrimal system. Punctal obstructions can be visualized on examination. To determine the presence of an obstruction in the canaliculus, lacrimal sac, and nasolacrimal duct, a dye-disappearance test or a Jones dye test can be performed.

Obstruction in the canaliculus can also be determined directly by probing the canaliculus and feeling for partial and complete obstructions. Irrigation of the system will uncover obstructions in the lacrimal sac and nasolacrimal duct.

Imaging techniques of the lacrimal system, including ultrasound, computed tomographic scans, contrast dacryocystography, and radionuclide dacryoscintigraphy, are rarely necessary.

17. What is a dye-disappearance test?

In the dye-disappearance test, a drop of fluorescein is placed in the inferior conjunctival fornix. After 5 minutes, the amount present in the tear lake is assessed using a cobalt-blue light. The presence of little or no fluorescein indicates a normal functioning system. If most of the fluorescein remains, the system is not functioning properly.

18. What is a primary Jones dye test?

A primary Jones dye test involves placing fluorescein in the inferior conjunctival fornix. A cotton swab is placed under the inferior turbinate at 2 and 5 minutes. If dye is recovered on the swab, the system is patent and functioning well. If no dye is recovered, this indicates a poorly functioning system.

19. What is a secondary Jones dye test?

A secondary Jones dye test is performed when no dye is recovered during the primary test. In a secondary Jones dye test, the inferior fornix is first irrigated to remove all residual fluorescein from the primary test. Clear saline is then irrigated through the canaliculus with a cannula. If fluorescein-stained fluid is recovered from the nose, the fluorescein must have passed freely through the punctum and canaliculus and to the lacrimal sac during the primary Jones test, indicating a partial blockage of the nasolacrimal duct. If clear fluid is recovered, a partial obstruction or functional disorder of the punctum or canaliculus is indicated. If no fluid is recovered from the nose but instead regurgitates from the adjacent punctum, an obstruction at or distal to the common canaliculus is present.

20. How do you treat obstructions of the eyelid portion of the lacrimal system?

When the punctum is not patent, this can frequently be opened with a sharp probe or cut-down procedure to find the proximal canaliculus. In most patients, placement of a temporary silicone stent is helpful to prevent the punctum from reclosing. This office-based procedure is performed with local infiltrative anesthesia. If the canaliculus is stenotic but not completely occluded, dilation with silicone intubation is typically performed. If the canaliculus is completely occluded, a canaliculodacryocystorhinostomy (CDCR) is performed. In this surgery, a fistula is created between the caruncle and the nasal mucosa and a permanent glass tube (Jones tube) is placed in this tract to maintain its patency. A CDCR can be performed on an outpatient basis under general anesthesia or with monitored sedation.

21. How do you treat obstructions of the nasolacrimal duct?

The majority of lacrimal system obstructions occur in the nasolacrimal duct, which connects the lacrimal sac to the nose. When a nasolacrimal duct obstruction is present, a dacryocystorhinostomy (DCR) is performed. In this procedure, the lacrimal sac is marsupialized to the nasal passages, so the tears can bypass the blocked nasolacrimal duct and drain directly from the lacrimal sac into the nose.

22. Describe acute dacryocystitis.

An acute infection of the lacrimal sac is called *dacryocystitis*. Patients typically present with a painful, erythematous swelling in the medial canthus just inferior to the medial canthal tendon. A purulent discharge from the punctum can often be seen with gentle pressure on the lacrimal sac. Acute dacryocystitis is nearly always the result of a blocked nasolacrimal duct.

23. What is the appropriate treatment for acute dacryocystitis?

Dacryocystitis is a serious infection that must be treated as an emergency. If not adequately treated, an orbital cellulitis may develop. There is also the potential for the infection to spread intracranially. Appropriate systemic antibiotics should be given, and warm compresses should be applied to the medial canthus. Patients should be watched carefully to assure improvement. After resolution of the acute infection, unless the nasolacrimal duct is patent, a DCR should be performed to avoid recurrent infections.

24. What are the signs of congenital nasolacrimal duct obstructions?

Approximately 6% of newborns have a congenital obstruction of the nasolacrimal system. Infants may present with epiphora, conjunctivitis, amniocele formation, or dacryocystitis. The lacrimal drainage system begins embryologically as a cord in the medial canthus that expands laterally to the punctum and inferiorly to the nasal mucosa of the inferior meatus. The lumen first develops in the medial canthal portion of the system, and canalization progresses laterally and inferiorly. The distal end of the duct is the last portion to canalize. This may not yet be patent at birth and is the most common site of congenital obstructions.

KEY POINTS: TREATMENT OF CONGENITAL EPIPHORA

1. Treat initially with massage.
2. If it persists in patients younger than 13 months, probe the nasal lacrimal duct under anesthesia, often with balloon dacryoplasty.
3. Then use silicone intubation.
4. Finally, perform a DCR.

25. How are congenital obstructions first managed?

Most clinicians recommend massaging the infant's lacrimal sac (in the medial canthus) in an inferior direction to increase the hydrostatic pressure in the nasolacrimal duct and, it is hoped, force open any obstruction. If there is an associated conjunctivitis or discharge, topical antibiotics are also used. When dacryocystitis is present, systemic antibiotics are used, followed by a DCR.

26. What if this does not work?

If a child has a persistent tearing because of blockage of the nasolacrimal duct, a probing of the system should be performed in the first 13 months of life. Katowitz and Welsh have shown that the success rate of probing drops significantly if performed after 13 months of age. In this procedure, the child is placed under general anesthesia and a Bowman probe is passed into the punctum, through the lacrimal system, and out through the nasolacrimal duct. Some surgeons elect to perform a balloon dacryoplasty at the time of the initial probing. Here, a deflated balloon is passed into the duct and then inflated to dilate the duct and the ostium.

27. What if the tearing is still present after a probing?

Approximately 90 to 95% of infants who undergo a probing enjoy a resolution of their symptoms. When the problem persists after probing or balloon dacryoplasty, intubation with silicone tubes is indicated. Tubes are generally left in place for approximately 6 months and serve to keep the passageway patent. Durso et al. reported an 84% success rate for patients intubated for nasolacrimal duct obstruction. When probing and intubation are unsuccessful, a DCR is performed.

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CHAPTER 34

PROPTOSIS

David G. Buerger

1. What is proptosis?

Proptosis is a forward protrusion of one or both eyeballs. Unilateral proptosis is frequently defined as asymmetric protrusion of one eye by at least 2 mm. Normal upper limits for proptosis are approximately 22 mm in Caucasians and 24 mm in African Americans.

2. How is proptosis diagnosed?

Clinically, proptosis can be recognized best by observing the globes from above, over the patient's forehead, or from below with the head tilted back. It is measured with an exophthalmometer based at the lateral orbital rim. The amount of proptosis can also be quantified by measuring globe protrusion on a computed tomographic (CT) scan (Fig. 34-1).

3. List common problems associated with proptosis.

- **Exposure keratopathy** frequently develops secondary to a poor blink mechanism over the protruding globe. Patients can have mild symptoms of irritation and foreign body sensation, or they may experience more severe symptoms associated with corneal abrasions and ulcers (Fig. 34-2).
- **Diplopia** (double vision) can result from unilateral or bilateral proptosis with displacement of the globes or poor extraocular muscle function.
- **Optic nerve compression** can occur with space-occupying lesions of the orbit, which cause proptosis. Indications of nerve compression include decreased visual acuity, relative afferent pupillary defect, color vision deficit, and visual field defect of the affected eye. This is a medical emergency and requires prompt therapeutic intervention, surgically or medically.

4. What is the most common cause of unilateral proptosis?

Thyroid eye disease (Graves' ophthalmopathy).

5. What is the most common cause of bilateral proptosis?

Thyroid eye disease.

6. What are other causes of proptosis?

- Idiopathic orbital inflammatory disease (orbital pseudotumor)
- Orbital infectious cellulitis
- Orbital tumors (benign or malignant)
- Lacrimal gland tumors
- Trauma (retrobulbar hemorrhage)
- Orbital vasculitis (i.e., polyarteritis nodosa, Wegener's granulomatosis)
- Mucormycosis
- Carotid–cavernous fistula
- Orbital varix

7. List the causes of pseudoproptosis.

- Unilateral high axial myopia can mimic proptosis, owing to the increased length of the myopic eye.
- Actual enophthalmos of one eye may cause apparent proptosis of the contralateral eye (Fig. 34-3).
- Upper eyelid retraction produces a more prominent-appearing eye. This often coexists in cases of thyroid ophthalmopathy.

8. Which neuroimaging test is best to evaluate the etiology of proptosis?

CT scans are superior in most cases of proptosis, because the relationship of the orbital process to the orbital bones is better visualized. Magnetic resonance imaging (MRI) may be desirable in certain cases when optic nerve dysfunction is present. Plain films are not used for diagnostic accuracy in cases of proptosis.

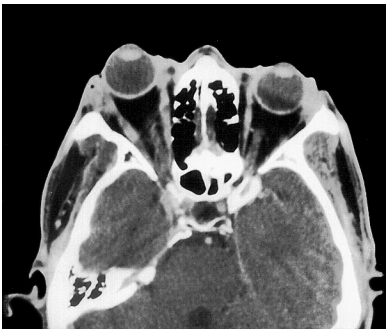

Figure 34-1. Computed tomographic scan demonstrating proptosis of the right globe secondary to thyroid-related enlargement of the rectus muscles.

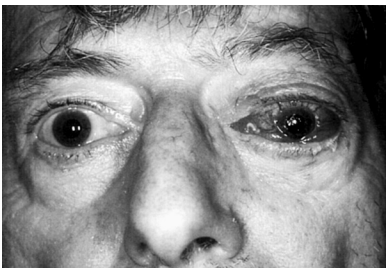

Figure 34-2. Severe conjunctival chemosis with corneal erosion secondary to proptosis caused by an orbital lymphoma.

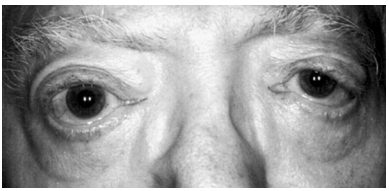

Figure 34-3. Patient with enophthalmos of the left eye secondary to old trauma, which is causing apparent proptosis of the right eye.

9. What clinical entity is frequently associated with unilateral or bilateral painless proptosis, eyelid retraction, eyelid lag on downward gaze, and motility disturbances?

Thyroid ophthalmopathy associated with Graves' disease (Fig. 34-4) is a complex, multisystem, autoimmune disorder. Patients can be hyperthyroid, hypothyroid, or euthyroid when manifesting ophthalmic symptoms. Eye problems develop as a result of inflammation and enlargement of various extraocular muscles (most frequently the inferior rectus and medial rectus) and peribulbar tissues. CT scan or MRI results often show fusiform enlargement of the involved extraocular muscles with sparing of the tendon that attaches the muscle to the globe. Proptosis and eyelid retraction cause corneal problems, and muscle enlargement in the orbit causes diplopia and possibly optic nerve compression. Treatment is in stages, depending on the severity of the eye disease. Systemic and laboratory evaluation is mandatory.

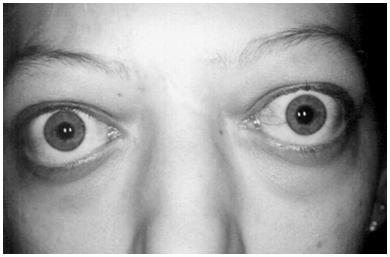

Figure 34-4. Proptosis and eyelid retraction caused by thyroid ophthalmopathy.

KEY POINTS: CLINICAL SIGNS OF GRAVES' DISEASE

1. Unilateral or bilateral proptosis
2. Eyelid retraction with lateral flare
3. Lagophthalmos
4. Diplopia
5. Pretibial myxedema

10. What clinical entity is frequently associated with unilateral proptosis, pain, conjunctival injection, and motility disturbances in an adult?

Orbital inflammatory pseudotumor is a nonspecific idiopathic inflammatory disease of the orbit. Inflammation may be localized to a muscle, the lacrimal gland, or sclera or may be diffuse. Other possible signs include eyelid erythema or edema, palpable mass, decreased vision, uveitis, hyperopic shift, and optic nerve edema. Bilateral disease is more common in children. CT scan results may show thickening of one or more extraocular muscles (including the tendons), lacrimal gland enlargement, or thickening of the posterior sclera. Treatment is primarily with corticosteroids and possibly radiation therapy.

11. What clinical entity is characterized by unilateral proptosis, pain, fever, decreased ocular motility, erythema, and edema of the eyelids?

Infectious orbital cellulitis involves an infection (usually bacterial) that has extended posterior to the orbital septum. Once past the orbital septum barrier, infection can spread rapidly and cause serious complications such as meningitis or cavernous sinus thrombosis. The most common organisms include staphylococci, streptococci, anaerobes, and *Haemophilus influenzae* (in children younger than 5 years of age). The most common source of infectious spread to the orbit is an ethmoid sinusitis. Treatment is with intravenous antibiotics.

12. What should be done for persistent proptosis or progression of infection despite adequate antibiotic treatment in a case of orbital cellulitis?

The situation is highly suggestive of an orbital subperiosteal abscess. CT scanning should be performed to confirm this diagnosis and locate the abscess. Definitive treatment consists of surgical drainage and continued intravenous antibiotics.

13. What clinical entity is characterized by a child younger than 6 years of age with gradual, painless, progressive, unilateral axial proptosis with visual loss?

Optic nerve glioma (juvenile pilocytic astrocytoma) is a slow-growing tumor of the optic nerve that causes axial proptosis. Decreased visual acuity is usually associated with a relative afferent pupillary defect. CT scan or MRI results show fusiform enlargement of the optic nerve. Many cases are associated with neurofibromatosis and may be bilateral. Systemic evaluation and genetic counseling for neurofibromatosis are essential.

14. What clinical entity is characterized by a child with rapidly progressive unilateral proptosis, displacement of the globe inferiorly, and edema of the upper eyelid?

Rhabdomyosarcoma is the most common primary orbital malignancy of childhood. This malignant growth of striated muscle tissue typically produces a rapidly progressive mass in the superior

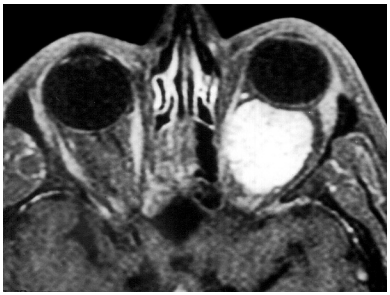

Figure 34-5. Cavernous hemangioma of the left orbit, which is causing proptosis.

orbit with proptosis, globe displacement, and eyelid swelling. The average age of presentation is 7 years. Prompt diagnosis with orbitotomy and biopsy is crucial, because *overall mortality is 60%* once the disease has extended to the orbital bones. Current treatment strategies with radiation and chemotherapy have lowered mortality rates to 5 to 10% for orbital rhabdomyosarcoma.

15. What is the most common benign orbital tumor in adults that causes unilateral proptosis?

The cavernous hemangioma (Fig. 34-5) is a slow-growing vascular tumor that is usually diagnosed in young adulthood to middle age. CT scanning usually shows a well-defined orbital mass within the ocular muscle cone. Visual acuity is often not affected. Treatment is observation or surgical excision.

16. What is the most common malignant orbital tumor in adults that causes unilateral proptosis?

Orbital lymphomas typically develop in the superior orbit with a slow onset and progression. These lesions may be associated with a subconjunctival "salmon-colored" mass in the fornix. CT scanning shows a poorly defined mass conforming to the shape of the orbital bones and globe without bony erosion. Diagnosis is made following orbital biopsy, and definitive treatment is radiation therapy. Orbital lymphoma can be associated with systemic lymphoma; therefore a medical consult and systemic evaluation are necessary for all patients.

17. Of the various orbital tumors causing proptosis, list those tumors that are encapsulated or appear well circumscribed on neuroimaging.

- Cavernous hemangioma
- Fibrohistiocytoma
- Hemangiopericytoma
- Schwannoma
- Neurofibroma

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CHAPTER 35

THYROID EYE DISEASE

Robert B. Penne

1. **What is thyroid eye disease?**
   Thyroid eye disease (TED) is a chronic inflammatory disease of the orbits that occurs most often in patients with a systemic thyroid imbalance. Chronic inflammation results in scarring and dysfunction of the orbit. The course and severity are variable.

2. **Who is at risk for thyroid eye disease?**
   TED occurs in a wide range of ages. It has been reported from 8 to 88 years of age, with the average age of onset in the forties. Females are affected three to six times more often than males. Children are rarely affected.

3. **Is everyone with thyroid eye disease hyperthyroid?**
   Ninety percent of patients who develop TED have Graves' hyperthyroidism, 3% have Hashimoto thyroiditis, 1% have primary hypothyroidism, and 6% are euthyroid. As many as one-third of patients do not develop clinical hyperthyroidism for more than 6 months after the onset of symptoms of TED. Thus, a significant number of patients who present with TED have not yet developed hyperthyroidism.

4. **What causes thyroid eye disease?**
   We do not know. TED is an immune-mediated process with the primary target the orbital fibroblast. Many theories link the orbit and thyroid gland by a shared antigen, the thyroid-stimulating hormone receptor. Research continues to try to better understand TED.

5. **Do environmental factors affect thyroid eye disease?**
   Smoking is the one environmental factor that has been shown to affect TED. Multiple studies have shown a higher incidence of smoking in patients with TED than in patients with Graves' disease who do not have TED. Research suggests that smokers with TED have more severe disease and the disease lasts longer than in nonsmokers. The effects of secondhand smoke can only be speculated on.

6. **Does thyroid eye disease improve when the systemic thyroid imbalance is treated?**
   Treatment of the systemic thyroid dysfunction has little predictable effect on the course of TED. Post-treatment hypothyroidism may worsen TED, especially if the hypothyroidism is profound. Also debated is whether radioactive iodine (RAI), surgery, and medical treatment have different effects on the course of TED. A large study suggested that treatment with radioactive iodine has a greater chance of causing progression of TED. The study also showed that giving systemic steroids during the treatment decreases and may eliminate this risk.

7. **Should all patients who receive radioactive iodine be treated with systemic steroids?**
   Unless the patient has specific contraindications or until further studies show otherwise, we recommend that patients undergoing radioactive iodine treatment receive a course of systemic steroids. The dosage and length of treatment are controversial. The patients at the highest risk of worsening TED with RAI are smokers and patients with active disease.

8. **What are the early signs of thyroid eye disease?**
   Many patients initially present with intermittent eyelid swelling along with nonspecific ocular irritation, redness, and swelling (Fig. 35-1). Because all of these symptoms are nonspecific, early-onset TED is infrequently diagnosed. The disease is not recognized until the appearance of more obvious clinical signs, such as eyelid retraction, eyelid lag, or early proptosis (Fig. 35-2). Suspecting TED in patients with the aforementioned nonspecific symptoms is important, especially if they have symptoms or history of a thyroid imbalance.

9. **What studies need to be done in the workup for thyroid eye disease?**
   The most effective screening tool for systemic thyroid imbalance in patients with TED is the level of thyroid-stimulating hormone. An internist or endocrinologist can do further evaluation and workup.

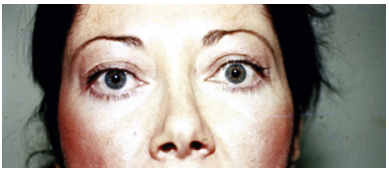

Figure 35-1. Early thyroid eye disease with mild eyelid retraction of the left upper eyelid and the right lower eyelid.

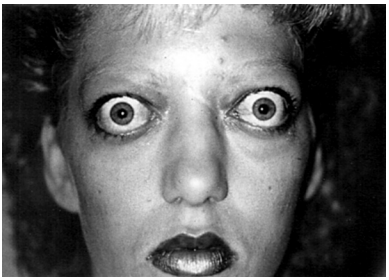

Figure 35-2. Thyroid eye disease with proptosis and eyelid retraction.

Patients require a complete ophthalmic exam. Special attention should be paid to visual function, including acuity, pupils, color vision, and, if indicated, visual fields. In particular, the ophthalmic exam should include noting eyelid position, evaluation of ocular motility with note of any diplopia, and checking for corneal exposure and proptosis.

10. Which patients require orbital imaging?

Not all patients with TED require orbital imaging. Indications for imaging include suspicion of optic nerve compression, evaluation for orbital decompression surgery and/or orbital irradiation, unclear diagnosis, and a need to rule out other orbital processes. We prefer a computed tomographic scan without contrast in patients with thyroid-related ophthalmopathy who require imaging.

11. What findings are present on orbital imaging?

The classic finding is enlargement of the rectus muscle belly with sparing of the tendon (Fig. 35-3). The inferior rectus is the most commonly involved muscle, followed by the medial rectus and the superior rectus. The lateral rectus is least likely to be involved.

12. Does everyone with proptosis have thyroid eye disease?

No. TED is the most common cause of both unilateral and bilateral proptosis in adults, but it is not the only cause. Patients with systemic thyroid disease may develop orbital tumors and nonthyroid orbital inflammation. TED is a bilateral disease, whereas most orbital tumors are unilateral. TED may present asymmetrically and appear unilateral, especially early in the disease. In rare cases, the disease may remain unilateral. If the entire clinical picture is not consistent with TED, orbital imaging is indicated.

13. How do the tissues of the orbit change in thyroid eye disease?

The extraocular muscles, eyelid muscles, and orbital fat are the main tissues affected in TED. When stimulated, orbital fibroblasts secrete glycosaminoglycans, cytokines, and chemoattractants. Orbital and eyelid swelling are common early in the disease. Late in the disease the inflammation resolves and the enlarged muscles are left fibrotic and scarred.

14. How long does the disease last?

Most patients go through a period of active inflammation causing their eyes and orbital tissues to change. This period lasts from 6 months to more than 2 years. In some patients the process may involve slow, mild changes over many months, whereas in others the process is more acute with rapid changes over weeks. Once the disease activity has quieted and the eyes are stable, reactivation is rare (5 to 10%). Careful examinations that note changes in motility, eyelid position, proptosis, and general inflammation help to determine disease activity.

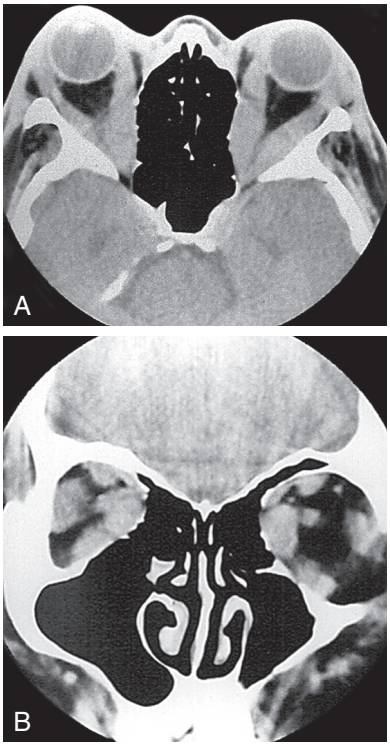

Figure 35-3. Axial **A,** and coronal **B,** computed tomographic scans showing enlargement of all four rectus muscles.

15. Is everyone who develops thyroid eye disease affected in the same way?

No. There is a wide variation from mild irritation and eyelid retraction that totally resolve to severe orbital infiltration with visual loss. Visual loss may result from optic nerve compression or corneal scarring due to corneal exposure. More severe disease involves older patients (average age of 52 years versus 36 years for milder disease) and has less of a gender difference (female-to-male ratio of 1.5:1 in severe disease versus 8.6:1 in mild disease).

16. What can be done to treat thyroid eye disease?

Many patients do not require any treatment, but monitoring during the active phase of the disease is important. Ocular lubrication often relieves symptoms. Systemic steroids decrease inflammation. Because of their side effects, systemic steroids are best used as a temporizing measure until more definitive treatment is given. Cessation of steroids generally results in return of orbital inflammation. Orbital irradiation may decrease inflammation in the orbit. Surgical treatment is also an option.

17. When are systemic steroids used?

Systemic steroids are used to decrease orbital inflammation acutely, usually on a temporary basis until other treatment can be started. The most common indication is visual loss from optic nerve compression. Severe proptosis with resultant corneal exposure is a second indication. Both short-term and long-term side effects of steroids limit their usefulness as long-term treatment. High-dose pulsed steroids have been studied, looking for any long-term improvement in TED. The results have been inconclusive.

18. Is orbital irradiation standard treatment for thyroid eye disease?

The use of orbital radiation is controversial. A study published in 2001 from the Mayo Clinic concluded that orbital irradiation does not improve TED. Subsequent smaller studies have shown stabilization of disease progression compared to controls. Many oculoplastic specialists believe that orbital irradiation

has a role in the treatment of TED and that it stops progression of the disease but does not improve preexisting changes such as proptosis. Radiation may help stabilize ocular motility. How orbital radiation is used varies with the individual physician.

19. How does orbital irradiation affect thyroid eye disease?

The exact mechanism of action of irradiation in the orbit is unclear. Multiple theories of localized immunosuppression in the orbit have been postulated, but all remain unproven. Many patients have a definite decrease in orbital inflammation and edema after orbital irradiation. Irradiation seems to be most effective at stopping disease progression and less effective at reversing changes that have already occurred.

20. Does orbital irradiation work immediately?

No. It takes 2 to 4 weeks to see the initial effects of irradiation, and improvement may continue for 6 months. If steroids are stopped immediately after completion of irradiation, inflammation may recur rapidly.

21. Which patients are candidates for orbital irradiation?

Any patient with *active* TED is a candidate. The exception is patients with diabetes and vasculitic disease, as radiation may worsen their retinopathy. Early treatment, if effective, prevents the chronic orbital changes associated with TED. Later in the disease, irradiation can quiet the active disease and allows earlier and more effective surgical rehabilitation. Orbital irradiation has resulted in fewer patients with severe TED when used in select patients.

22. Which patients require surgery?

Surgery may be indicated on an emergent basis because of optic nerve compression or corneal exposure. More often, patients require nonemergent surgery because of severe disfiguring proptosis, double vision from restrictive myopathy, or eyelid retraction.

23. What kinds of surgery are done in patients with thyroid eye disease?

Surgery falls into three basic categories: orbital decompression, eye muscle surgery, and eyelid surgery. Surgery needs to be done in this order because earlier surgeries affect the results of later surgeries. Decompression should be done before eye muscle surgery. Decompression affects ocular motility and may alter muscle surgery. Likewise, muscle surgery should be completed before eyelid surgery is done.

24. What is orbital decompression?

Orbital decompressive surgery involves removal of bone and/or fat to allow the eye to settle back in the orbit. Bone is removed from the inferior and medial walls of the orbit to let the expanded orbital tissue move partially into the sinus space. Lateral wall decompression can also be done. Removal of orbital fat has a decompressive effect to a much lesser degree. The amount of decompression is related to the amount of fat removed.

25. Which patients require orbital decompression?

Patients with optic nerve compression require decompressive surgery to relieve pressure on the optic nerve. Patients with severe proptosis resulting in corneal exposure or disfigurement are also candidates for orbital decompressive surgery.

26. What is optic nerve compression?

Optic nerve compression involves squeezing of the optic nerve at the apex of the orbit. When the extraocular muscles swell in TED, there is relatively little space at the apex of the orbit; therefore enlargement of muscles exerts pressure on the nerve lying in the center of the muscles. Pressure decreases vision because the function of the optic nerve is affected. This loss of function can manifest as decreased vision, decreased color vision, or visual-field loss.

27. What are the complications of orbital decompression?

The most common complication is worsening of existing diplopia or new double vision. Patients with preexisting motility problems have a much higher risk of postoperative diplopia. Many patients have infraorbital hypesthesia postoperatively, but it usually improves with time. Risk of visual loss is small. Bleeding and infection, as with any surgery, must be considered.

28. When do patients require muscle surgery?

Patients with double vision in their functional field of vision require muscle surgery. Every effort must be made to ensure that the inflammation is quiet and the patient's motility pattern is stable. Repeated stable measurements over months help to ensure that motility is stable.

KEY POINTS: THYROID EYE DISEASE

1. Suspect the diagnosis of TED in nonspecific ocular irritation even without a systemic thyroid imbalance.
2. Eyelid retraction is often the earliest clinical sign of TED.
3. Monitor visual function closely in progressive TED.
4. Get patients who are smokers to stop smoking.
5. TED patients will take extra time during an office visit.

29. What are the alternatives to muscle surgery?

The use of prisms in glasses works for patients with double vision and relatively small deviations. Larger deviations or patterns of diplopia in which the deviation changes with small changes in the direction of gaze are poor candidates for prisms. It is also important that the motility is stable before prisms are prescribed. Temporary Fresnel prisms may be helpful during periods of instability.

30. What type of muscle surgery is required?

Recession of muscles, usually on an adjustable suture, is needed. Because the muscles are tight and scarred, resection is not done. The inferior and medial rectus muscles are the most common targets of surgery. Surgery can be done under local or general anesthesia with adjustment of the sutures later in the day or on the following day.

31. Does eye muscle surgery affect the eyelids?

Recession of the tight inferior rectus muscle often improves upper eyelid retraction. The superior rectus muscle has to work against the tight inferior rectus; thus the associated levator muscle is overactive, causing eyelid retraction. When the inferior muscle is recessed, the overactivity ends and often the upper eyelid retraction is less. Large recessions of the inferior rectus muscle may worsen inferior eyelid retraction.

32. What kind of eyelid surgery is done?

Eyelid retraction is the main eyelid problem in patients with TED. In patients undergoing orbital decompression, the eye is lowered, often improving the lower eyelid retraction. For mild eyelid retraction, recession of the eyelid retractors (upper or lower) is adequate. For more severe retraction, spacers are needed, such as hard palate or acellular dermis in the lower eyelids. Patients also may require a blepharoplasty and/or brow lift to deal with the excessive skin that results from stretching caused by chronic swelling. This goal may be met at the time of eyelid repositioning or at a later date.

33. How many surgeries do patients with thyroid eye disease require?

Most patients with TED do not require surgery. Patients who do need surgery may need from 1 to as many as 8 to 10 operations. Patients with severe disease may require many operations over 2 to 3 years of reconstruction.

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ORBITAL INFLAMMATORY DISEASES

Nicole A. Langelier, Usiwoma Abugo, and Roberta E. Gausas

CHAPTER 36

1. **What is inflammation?**
   The concept of inflammation is ancient and was used to describe a combination of rubor (redness), dolor (pain), tumor (swelling), calor (heat), and *functio laesa* (loss of function). We now recognize inflammation as a tissue response governed by multiple cellular processes.

2. **How does inflammation affect the orbit?**
   Inflammation is the most common problem that affects the adult orbit, leading to a spectrum of clinical presentations with variable onset and variable orbital tissues affected, causing mass effect, inflammation, and/or infiltration resulting in variable deficits in function or vision.[1]

3. **What are the best terms to describe orbital inflammation?**
   For purposes of better understanding and better management, orbital inflammation should be classified based on pathology, anatomic location, and/or associated systemic disease as either specific or nonspecific in nature.

4. **What is specific orbital inflammation?**
   The diagnosis of specific orbital inflammation is based on the identification of a specific etiology causing the disorder, such as a specific pathogen (infection, as in orbital cellulitis), specific histopathology (granulomatous disease, as in sarcoidosis), or specific local and/or systemic constellation of findings that define a distinct entity (vasculitis, as in granulomatosis with polyangiitis) (Box 36-1).[2]

5. **How is nonspecific orbital inflammation different?**
   Orbital inflammation that has no identifiable cause is considered nonspecific. It is a diagnosis of exclusion.

6. **What is orbital pseudotumor?**
   "Nonspecific orbital inflammation" and "idiopathic orbital inflammatory syndrome" are more accurate terms that replace orbital pseudotumor.

7. **What, then, is the etiology of nonspecific orbital inflammation?**
   The exact etiology is unknown but it is generally believed to be an immune-mediated process, possibly related to previous bacterial or viral infection, previous trauma, or other autoimmune conditions, such as Crohn's disease, rheumatoid arthritis, and systemic lupus erythematosis.[3]

8. **Describe a typical clinical presentation of nonspecific orbital inflammation.**
   Anterior orbital nonspecific orbital inflammation (NSOI) commonly presents as painful periorbital swelling and erythema, S-shaped eyelid deformity, and chemosis that may be unilateral or bilateral. Onset is typically acute (hours to days) or subacute (days to weeks) but can also be insidious or chronic (weeks to months). The symptoms and physical findings will vary based on the degree and anatomic location of the inflammation. Disease affecting the posterior orbit may present with proptosis and motility disturbances, and disease affecting the orbital apex may present with functional deficits and/or vision loss.

9. **Is the symptom of pain necessary to make the diagnosis?**
   Although pain or discomfort is a typical symptom, absence of pain may occur less commonly.[4]

10. **How is nonspecific orbital inflammation in children different?**
    In the pediatric population, bilateral manifestation is much more common, as well as concurrent uveitis, elevated erythrocyte sedimentation rate, and eosinophilia. When present, uveitis in particular appears to portend a poor outcome in children. Overall, NSOI in children is rare and cases should be monitored closely for future development of autoimmune disease.[5-7]

BOX 36-1. Differential Diagnosis of Orbital Inflammation

Nonspecific Orbital Inflammation (NSOI)
Diagnosis after exclusion of specific inflammations

Specific Orbital Inflammation
Thyroid-associated orbitopathy
Infection/infestation
Bacterial
- Contiguous spread from sinusitis
- Retained orbital foreign body

Fungal
- Rhino-orbital mucormycosis
- Aspergillosis
- Endogenous spread from septic emboli

Parasitic
- Echinococcosis
- Cysticercosis

Tuberculosis and syphilis
Vasculitis
Granulomatosis with polyangiitis
Polyarteritis nodosa
Hypersensitivity angiitis
- Orbital vasculitis secondary to systemic lupus erythematosus

Giant cell arteritis
Granulomatous inflammation
Sarcoidosis/sarcoidal reactions
Xanthogranulomatous disorders of orbit
Foreign-body granuloma
Erdheim-Chester disease
Sjögren's syndrome
IgG4-related disease of the orbit
Sclerosing inflammation of the orbit
Idiopathic granulomatous inflammation

Nonspecific Orbital Inflammation (NSOI)
Noninflammatory Diseases of the Orbit that Mimic Inflammation
Vascular disorders
Dural–cavernous sinus arteriovenous fistula
Neoplasia
Lymphoproliferative disorders

11. Name the five most common anatomic patterns of nonspecific orbital inflammation.

1. Extraocular muscle (myositis)
2. Lacrimal gland (dacryoadenitis)
3. Anterior orbit including scleritis
4. Orbital apex
5. Diffuse

12. How is the diagnosis of nonspecific orbital inflammation made?

Because NSOI is a diagnosis of exclusion, all known specific triggers of inflammation should be ruled out first. Ultimate diagnosis and treatment rely on complete history and detailed clinical examination followed by judicious use of ancillary diagnostic testing. Diagnostic testing includes neuroimaging, laboratory testing, and biopsy when appropriate.

13. What is the best imaging technique for nonspecific orbital inflammation?

Orbital computed tomography (CT), gadolinium-enhanced magnetic resonance imaging (MRI), or ultrasound can all provide useful information, but orbital MRI with fat saturation is the imaging study with the highest yield. Subtle edema of the retrobulbar fat is often one of the earliest changes seen in NSOI. The use of diffusion weighted imaging is helpful in differentiating NSOI from lymphoid lesions and orbital cellulitis.[8,9]

14. What blood tests can be ordered to evaluate nonspecific orbital inflammation?

Complete blood count, electrolytes, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, anti-double-stranded DNA, anti-neutrophil cytoplasmic antibody (ANCA), angiotensin-converting enzyme level, rapid plasma reagin, and thyroid function tests.[10]

15. When should an orbital biopsy be performed?

Although the role of orbital biopsy has previously been an area of controversy, the only way to obtain an accurate and definitive diagnosis of an infiltrative lesion is through pathologic examination. Most orbital surgeons advocate biopsy, except for two clinical scenarios—that of orbital myositis, in which the clinical and radiographic findings are classic, and that of an orbital apex syndrome—in which the risk of biopsy must be weighed against the risk of a missed diagnosis. Empiric steroid treatment may be employed in such cases. However, recurrent or nonresponsive orbital myositis and orbital apex syndrome warrant orbital biopsy.[11]

16. What is the histopathology of nonspecific orbital inflammation?

In the acute phase, pathology reveals a diffuse polymorphous infiltrate composed of mature lymphocytes, plasma cells, macrophages, eosinophils, and polymorphonuclear leukocytes. In the subacute and chronic phases, an increasing amount of fibrovascular stroma is seen.

17. Name two histological subtypes of orbital inflammation.

A distinct sclerosing form of orbital inflammation exists, which is characterized by dense fibrous replacement. Clinically, the sclerosing subtype typically produces limited inflammatory signs and atypical pain.

Another distinct form displays granulomatous inflammation similar to sarcoidosis but is not associated with systemic sarcoidosis.

18. What is IgG4-related disease?

IgG4-related disease is a systemic fibroinflammatory condition that should be considered in patients with NSOI, particularly in cases with bilateral lacrimal gland involvement. Histology reveals IgG4-positive plasma cells and fibrosis, with or without obliterative phlebitis. Serum IgG4 is often elevated. Systemic manifestations of IgG4-related disease include sclerosing pancreatitis, retroperitoneal fibrosis, sclerosing cholangitis, Reidel's thyroiditis, and interstitial lung disease. IgG4-related orbital inflammation is typically exquisitely and rapidly responsive to steroid treatment.[12,13]

19. How is nonspecific orbital inflammation treated?

High-dose oral corticosteroids are the mainstay of treatment. The recommended starting dose for prednisone is 1.0 to 1.5 mg/kg/day with a maximum adult dose of 60 to 80 mg/day for 1 to 2 weeks, then tapering off over the course of 6 to 12 weeks. For patients with vision loss or apical involvement, intravenous methylprednisone 1.0 g/day can be administered for 1 to 3 days. The response is usually quick with resolution of pain and proptosis within 24 to 48 hours of onset of the treatment.[14]

20. What if a patient fails to respond to or is intolerant of steroids?

Alternative therapies include antimetabolites (azathioprine, methotrexate), T-cell inhibitors (cyclosporine), and alkylating agents (cyclophosphamide). Low-dose external beam radiation has also been shown to be effective.

Local injection of betamethasone can also be effective in treating acute idiopathic dacryoadenitis, myositis, and anterior diffuse orbital inflammation.[1,15]

KEY POINTS: NONSPECIFIC ORBITAL INFLAMMATION

1. Nonspecific orbital inflammation is a diagnosis of exclusion.
2. Onset is usually acute and painful.
3. Inflammation may be unilateral or bilateral.
4. Children often have uveitis and eosinophilia concurrently.
5. Subtle edema of retrobulbar fat is an early finding on imaging.

21. What is the most common specific orbital inflammation?
Thyroid-associated orbitopathy.

22. Which extraocular muscle is most likely to be involved in thyroid eye disease?
The inferior rectus is the most likely. An easy-to-remember mnemonic is IMSLO for the order of extraocular muscle involvement: inferior rectus, medial rectus, superior rectus, lateral rectus, and then the obliques.[16]

23. What infections can occur in the orbit?
The orbit may undergo bacterial (e.g., *Staphylococcus,* tuberculosis, syphilis), fungal (e.g., rhino-orbital mucormycosis, aspergillosis), parasitic (e.g., echinococcosis, cysticercosis, trichinosis), and viral (e.g., herpetic) infections.

24. Where do orbital infections originate?
- The most common source is contiguous spread of bacteria from the sinuses, often the ethmoid sinus.
- Direct inoculation following trauma or skin infection is another source.
- Infection may spread endogenously from septic emboli.

25. In adults, what pathogens usually cause orbital cellulitis?
Staphylococcus aureus or streptococci are most common. It is important to note that adults need broad-spectrum antibiotics, because multiple organisms tend to be involved, versus children, in whom a single gram-positive organism is usually the culprit.[17]

26. In a 2-year-old patient, what pathogen might be a likely cause of orbital cellulitis?
Historically, it has been *Haemophilus influenza B* (Hib), but with the advent of the Hib vaccine most pediatric cases are now the result of gram-positive cocci infection. Vaccination status is an important consideration.

27. How is orbital cellulitis treated?
Medical care consists of the proper use of the appropriate antibiotics. Preseptal cellulitis may be treated with oral antibiotics. Orbital cellulitis requires intravenous administration of antibiotics. Care must be taken to distinguish community-associated methicillin-resistant *S. aureus* (MRSA) from hospital-acquired MRSA, as the treatment differs and the potential for morbidity and long-term disability is significant.

28. When should surgery be undertaken?
If the response to appropriate antibiotic therapy is poor within 48 to 72 hours or if the CT scan shows the sinuses to be completely opacified, surgical drainage should be considered. Subperiosteal or intraorbital abscess formations are other indications for surgical drainage if there is a decrease in vision, development of an afferent pupillary defect, or failure of proptosis to resolve despite appropriate antibiotic therapy.

KEY POINTS: ORBITAL INFECTIONS

1. The most common source of an orbital infection is an adjacent sinus.
2. Bacterial infection is the most common cause of cellulitis.
3. The orbital septum defines preseptal vs orbital cellulitis.
4. Orbital cellulitis in adults is usually caused by multiple organisms vs a single organism in children.
5. Intravenous antibiotics are required to treat orbital cellulitis.

29. What are the major categories of orbital vasculitis?
Granulomatosis with polyangiitis (GPA; formerly known as Wegener's granulomatosis), hypersensitivity vasculitis, polyarteritis nodosa, and Churg-Strauss syndrome.

30. What is Wegener's granulomatosis?
Wegener's granulomatosis is an outdated term. The condition is now referred to as granulomatosis with polyangiitis, which provides a better description of the pathophysiology of the disease.

31. Are orbital and ocular involvement common in granulomatosis with polyangiitis?

Yes, involvement is seen in approximately 50% of cases in both systemic and limited GPA.

32. Describe the features of orbital granulomatosis with polyangiitis.

- **Clinical:** Bilaterality, respiratory tract/sinus/mastoid involvement, scleritis, limbal corneal infiltrates
- **Imaging:** Three patterns; diffuse orbital involvement (may or may not be bilateral), lacrimal involvement, or midline involvement associated with bone erosion
- **Laboratory:** Positive for ANCA (although initially not positive in limited form)
- **Pathology:** Mixed inflammation, "cuffing" vessels, fat necrosis, lipid-laden macrophages, granulomatous microabscesses. Remember the commonly accepted triad of vasculitis, granulomatous inflammation (with or without giant cells), and tissue necrosis.[18,19]

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CHAPTER 37

PTOSIS

Carolyn S. Repke

1. How is ptosis classified?

Ptosis is classified by either time of onset or etiology. By onset, ptosis is either congenital or acquired. By etiology, ptosis may be neurogenic, aponeurotic, mechanical, myogenic, or traumatic.

2. What is the most common cause of acquired ptosis?

Acquired ptosis is most often the result of disinsertion or attenuation of the levator aponeurosis, which is most commonly related to aging but can be related to chronic ocular inflammation or eyelid edema (Fig. 37-1).

3. What clinical findings help to differentiate congenital ptosis from acquired aponeurotic ptosis?

Patients with aponeurotic ptosis have a ptotic eyelid in all positions of gaze. In downgaze the ptotic eyelid remains ptotic. Patients with congenital ptosis, however, demonstrate eyelid lag in downgaze. The ptotic eyelid frequently appears higher than the normal eyelid as the patient moves toward downgaze. This is caused by the maldevelopment of the levator muscle, with poor ability to contract in elevation as well as inability to relax as the eyelid moves to downgaze.

KEY POINTS: FEATURES OF APONEUROTIC PTOSIS

1. High eyelid crease (>10 mm)
2. Moderate ptosis (3-4 mm)
3. Good levator function (>10 mm)
4. No eyelid lag on downgaze

4. What are the features of congenital ptosis?

Congenital ptosis is caused by a dystrophy or maldevelopment in the levator muscle/superior rectus complex (Fig. 37-2). Most patients demonstrate poor levator function on examination and, at surgery, have fatty infiltration of the levator muscle. This myogenic abnormality causes an inability of the levator to relax on downgaze, resulting in eyelid lag and in some cases, lagophthalmos. Patients may or may not demonstrate motility defects because of superior rectus dysfunction (double elevator palsy with ptosis, vertical strabismus, and poor Bell's phenomenon). Approximately 75% of cases are unilateral.

With congenital ptosis, it is critical to evaluate visual function and refractive error as amblyopia will occur in up to 20% of cases.[1]

5. What causes pseudoptosis?

Causes of pseudoptosis (Fig. 37-3) include the following:

- Hypotropia on the ptotic side
- Eyelid retraction on the opposite side
- Enophthalmos/phthisis bulbi
- Anophthalmos/microphthalmos
- Severe dermatochalasis—with skin obscuring the position of the eyelid margin

6. What is the primary cause of ptosis after intraocular surgery?

It is thought that levator dehiscence causes ptosis related to previous intraocular surgery. The exact etiology is uncertain; however, it has been linked to superior rectus bridal sutures, eyelid speculums, retrobulbar and peribulbar injections, and other draping maneuvers associated with manipulation of the eyelids. Affected patients probably had a tendency toward levator dehiscence preoperatively.

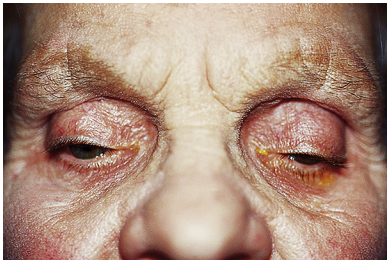

Figure 37-1. Involutional (aponeurotic) ptosis is characteristically mild to moderate with high upper eyelid crease. Deep sulci are seen in severe cases. Levator function is essentially normal. *(From Kanski JJ: Clinical Ophthalmology: A Synopsis. New York, Butterworth-Heinemann, 2004.)*

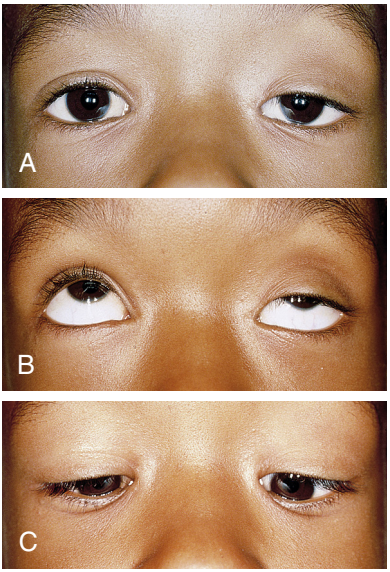

Figure 37-2. Simple congenital ptosis. **A,** Decreased levator muscle function occurs along with an indistinct upper eyelid crease. **B,** The ptosis is exaggerated in upgaze because of the poor function of the levator muscle. **C,** In downgaze the ptosis is reduced or absent because the fibrotic levator muscle cannot stretch. *(From Custer PL: Blepharoptosis. In Yanoff M, Duker JS [eds]: Ophthalmology, ed 2, St. Louis, Mosby, 2004.)*

Figure 37-3. Left pseudoptosis caused by ipsilateral hypotropia. *(Kanski JJ: Clinical Ophthalmology: A Systematic Approach, ed 5, New York, Butterworth-Heinemann, 2003.)*

7. What is the anatomic cause for the eyelid crease?

The eyelid crease is formed by the levator aponeurotic attachments that travel through the orbicularis muscle to the skin. With aponeurotic ptosis, these attachments are disinserted, causing the eyelid crease to elevate.

8. What neurologic conditions are associated with ptosis?

Neurologic conditions that must be considered in a ptosis evaluation include third-nerve palsy, Horner's syndrome, myasthenia gravis, Marcus Gunn's jaw-winking syndrome, ophthalmoplegic migraine, multiple sclerosis, and the Miller-Fisher syndrome, a variant of Guillain-Barre syndrome.

KEY POINTS: FEATURES OF THIRD-NERVE PALSY

1. Ptosis—mild to complete
2. Decreased elevation, adduction, and depression—may not all be present, depending on superior or inferior division involvement
3. Possible ipsilateral pupillary dilation—may be subtle to complete

9. What are the myogenic causes of ptosis?

Muscular abnormalities associated with ptosis include myasthenia gravis, muscular dystrophies, chronic progressive external ophthalmoplegia (CPEO), oculopharyngeal dystrophy, and congenital maldevelopment of the levator.

KEY POINTS: FEATURES OF CPEO

1. Slowly progressive ophthalmoplegia
2. Bilateral ptosis
3. Rarely have diplopia—owing to symmetry of disease
4. No variability (as in myasthenia gravis)

10. What are the features of blepharophimosis syndrome?

Blepharophimosis syndrome (Fig. 37-4) is a congenital autosomal dominant disorder characterized by ptosis, epicanthus, blepharophimosis (narrowing of the palpebral fissure in all dimensions), and telecanthus (widening of the distance between the medial canthi). Some patients also may demonstrate a flat nasal bridge, lower eyelid ectropions, and hypoplastic orbital rims.

11. What are the signs and symptoms of myasthenia gravis?

The history of any patient with acquired ptosis should include questions searching for symptoms of myasthenia gravis. Patients may comment on variability in the degree of ptosis from day to day. They also may notice increased ptosis during periods of fatigue or toward the end of the day. They may give a history of diplopia or difficulty with swallowing as well as dysphonia, dyspnea, and proximal muscle weakness.

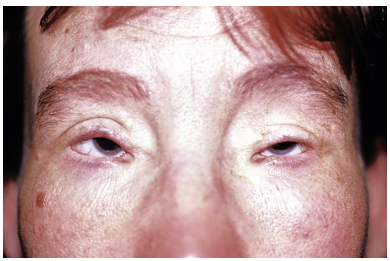

Figure 37-4. Blepharophimosis with bilateral ptosis, eyelid phimosis, telecanthus, and epicanthus inversus. *(From Kanski JJ: Clinical Ophthalmology: A Test Yourself Atlas, ed 2, New York, Butterworth-Heinemann, 2002.)*

On examination, patients may demonstrate eyelid fatigue on sustained upgaze, with curtaining of the eyelid on returning to the primary position. They also may demonstrate a Cogan's eyelid twitch after attempted upgaze. On return to primary position, the eyelid may show an upward twitch before it settles to its final resting place. Orbicularis strength may be weak, allowing the examiner to open the patient's eyelids even during attempted forceful closure.

KEY POINTS: FEATURES OF OCULAR MYASTHENIA GRAVIS

1. Ptosis—variable over time
2. Ocular misalignment
3. Fatigability of eyelids
4. Cogan's lid twitch
5. Orbicularis weakness

12. What measurements should be taken during the preoperative examination of patients with ptosis?

- **Marginal reflex distance:** The distance from the corneal light reflex in primary gaze to the upper eyelid margin; it demonstrates the distance of the upper eyelid from the visual axis; evaluated in primary position with the action of the frontalis muscle negated. The normal MRD is 4.0 to 4.5 mm.
- **Levator function:** Measures the entire excursion of the eyelid in millimeters from extreme downgaze to upgaze, with the action of the frontalis muscle manually negated; determines the surgical procedure to be performed; function is considered to be normal (>15 mm), good (>8 mm), fair (5 to 7 mm), or poor (>4 mm).
- **Eyelid crease height:** The crease height is the distance from the eyelid margin to the skin crease. Normally the crease height is 8 to 10 mm and is higher in women.
- **Palpebral fissure width:** The distance between the upper and the lower lid margins. This is not an accurate measurement of ptosis because the lower eyelid position can affect this value (e.g., Horner's syndrome with reverse ptosis of the lower eyelid).

Other critical parts of the preoperative evaluation include a careful pupillary examination for anisocoria, a cover test for strabismus, and evaluation of corneal sensation and tear film. Often a Schirmer test is performed to measure basal tear production. The lid position is carefully evaluated in primary position with the action of the frontalis muscle negated. The eyelid position is also evaluated in downgaze, looking for eyelid lag that suggests congenital ptosis or previous thyroid ophthalmopathy. The eyelid is evaluated in upgaze for signs of muscle fatigue and curtaining, suggesting myasthenia gravis. History should include a history of contact lens wear, with an evaluation for giant papillary conjunctivitis or a lost contact lens under the upper lid. Finally, it is important to document the presence of a good Bell's phenomenon (upshoot of the cornea with eyelid closure).[2]

13. How does Hering's Law affect ptosis?

Hering's Law of equivalent innervation of yoke muscles applies to the two levator muscles. It needs to be considered during the preoperative evaluation to determine accurately the degree of ptosis on each side. The normal eyelid in a patient with unilateral ptosis may become ptotic when bilateral stimulation is broken. The eye with which the patient prefers to fixate affects the degree to which Hering's Law contributes to ptosis. If the ptotic eye is preferred for fixation, the opposite eyelid may develop a retracted position because of increased stimulation during attempts to open the ptotic eyelid. On occluding the ptotic fixating eye, the previously retracted eyelid may resume a more normal position.[3]

14. What is the Neo-Synephrine test?

The Neo-Synephrine test is an evaluation of the effect of Müller's muscle contraction on the degree of ptosis. One drop of 2.5% phenylephrine is placed in the eye. After 5 minutes, the degree of ptosis is reevaluated. The phenylephrine causes contraction of the sympathetic Horner's muscle, sometimes causing dramatic improvement in the degree of ptosis. If phenylephrine corrects the ptosis completely, many surgeons elect to perform a Müller's muscle resection as opposed to a levator resection.[4]

15. What are the surgical and nonsurgical approaches to the correction of ptosis?

The most common surgical approaches to ptosis correction include levator resection, from either an internal or an external approach; Müller's muscle resection; and frontalis suspension. A nonsurgical option is ptosis eyelid crutches, which may be secured to spectacle lenses. Although rarely used,

spectacle adaptations are a reasonable option for patients with neurologic ptosis who have a poor Bell's phenomenon and are considered to be at high risk for exposure keratopathy.[5]

16. What are the complications of ptosis surgery?

The most common complication is overcorrection or undercorrection of the ptosis and/or abnormalities in eyelid contour. Other complications include scarring, wound dehiscence, eyelid crease asymmetry, loss of eyelashes, conjunctival prolapse, upper lid ectropion and/or tarsal eversion, eyelid lag on downgaze, and lagophthalmos on eyelid closure, leading to dry eyes or exposure keratopathy, corneal thinning, ulceration, and/or scarring. In addition, the rare but vision-threatening complication of retrobulbar hemorrhage is a risk with all eyelid surgery, and precautions must be taken to discontinue all medications or supplements that may cause prolonged bleeding or clotting times. Last, although rare, infection is a potential complication.[6]

17. What is Marcus Gunn's jaw-winking syndrome?

Marcus Gunn's syndrome is a unilateral congenital ptosis with synkinetic innervation of the levator and ipsilateral pterygoid muscle. It is caused by aberrant connections between the motor division of cranial nerve V and the levator muscle. Patients demonstrate retraction of the ptotic eyelid on stimulation of the ipsilateral pterygoid muscles by either opening the mouth or moving the jaw to the opposite side.

18. Describe the anatomy of the Whitnall's ligament and its significance in ptosis.

The Whitnall's ligament, also known as the superior transverse ligament, is a condensation of collagen and elastic fibers on the anterior levator sheath as it changes from muscle to aponeurosis. It attaches medially near the trochlea and laterally traverses through the lacrimal gland, attaching to the lateral orbital wall approximately 10 mm above the lateral orbital tubercle. It serves as a suspensory ligament for the upper eyelid and is the point at which the vector forces of the levator muscle transfer from an anterior–posterior direction to a superior–inferior direction. It is an important landmark for performing large levator resections.[2]

19. What is the concern when Horner's syndrome presents with pain?

Patients with neck pain, facial pain, or headache and acute Horner's syndrome should be suspected of having a carotid artery dissection. Workup should be urgent and include magnetic resonance imaging or angiography of the head and neck. Carotid Doppler sonography is not accurate in detecting carotid artery dissection. A carotid dissection usually requires urgent anticoagulation and neurovascular consultation.[7]

KEY POINTS: FEATURES OF HORNER'S SYNDROME

1. Mild ptosis (1-2 mm)
2. Miosis
3. Anhidrosis
4. Reverse ptosis of the lower eyelid
5. Hypopigmentation of iris (congenital cases)

20. Name some useful tests for diagnosing myasthenia gravis.

- Ice test (in office)
- Blood tests:

Acetylcholine receptor antibody test: Binding antibodies are detectable in up to 90% of patients with systemic myasthenia gravis (MG) and up to 70% of patients with ocular MG, with false-negative results in 50% of cases.

MuSK antibodies: These are antibodies to muscle-specific kinase. In those patients with seronegative MG (no antibodies to acetylcholine receptors), testing for MuSK antibodies may be positive in 40 to 70%.

- Edrophonium chloride (Tensilon) test
- Single-fiber electromyography (orbicularis muscle)[8]

21. Name some causes of acquired ptosis in young adults.

Levator aponeurosis dehiscence can certainly occur in a younger age group, but ptosis in younger adults should prompt thought of other causes as well. History and clinical exam should look for

obvious neurologic, myogenic, and mechanical causes. Old photographs should be viewed to rule out a longstanding problem. In addition, consideration should be given to the following:

- Contact lens wear (ptosis from manipulation of eyelids or a lost lens under the eyelid, giant papillary conjunctivitis)
- Allergies, blepharochalasis, or other source of recurrent eyelid edema
- Eyelid rubbing
- Botox—ptosis is a possible side effect of treatment and is being seen more frequently owing to the rise in popularity of cosmetic treatments in younger patients. (Patients should be assured that the ptosis will not be permanent.)
  - Trauma—exposure of prominent preaponeurotic fat pads may suggest levator injury; may resolve spontaneously, so most wait 6 months before operating.[4]

22. Describe the ice test and its use in the diagnosis of ptosis

An ice pack is held over the ptotic eyelid for 2 to 5 minutes, and the patient is then reexamined. The cold temperature inhibits acetylcholinesterase at the neuromuscular junction, therefore enhancing neuromuscular transmission and raising the ptotic eyelid in myasthenics (poor man's Tensilon test). The test is 80 to 90% sensitive and 100% specific for MG. A positive result should prompt a further workup.[9]

23. How does prostaglandin-associated periorbitopathy affect eyelid position?

Prostaglandin eyedrop use (for glaucoma and possibly cosmetics) can cause atrophy of fat cells in the periorbital area after as few as 3 weeks of use, causing the upper lids to become ptotic or giving the appearance of pseudoptosis owing to deepening of the superior sulcus. In addition, there may be lengthening of the lashes and darkening of the periorbital skin.[10]

24. What are the features of floppy eyelid syndrome?

Floppy eyelid syndrome is caused by decreased elastin in the tarsal plate with easy and sometimes spontaneous eversion of the upper lid. The upper eyelid can become ptotic, and the lashes themselves become ptotic with the direction of lash growth vertically downward, sometimes obstructing vision. In addition to lid and lash malposition, the patient may suffer chronic conjunctivitis with discharge and keratopathy. The syndrome is strongly associated with sleep apnea. All patients with floppy eyelid syndrome should be evaluated with sleep studies.

25. Compare and contrast the two most common types of ptosis surgical correction.

The two most common types of surgical correction are the external levator resection and the Müller's muscle resection (with or without skin resection).

The levator resection allows for the removal of skin and fat through the external incision. The contour and height of the eyelid is less predictable and is dependent on the placement of tarsal levator sutures. The reoperation rate is approximately 10 to 20%.

The Müller's muscle resection can be done from an internal or an external approach. This allows for removal of skin and fat if necessary, or the procedure can be done without the external eyelid being touched. This can be desirable in younger patients in whom dermatochalasis does not coexist. The contour of the postoperative eyelid is generally excellent and the reoperation rate is low, approximately 3%.[11]

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CHAPTER 38

EYELID TUMORS

Janice A. Gault

1. **What clues are helpful in determining whether an eyelid lesion is benign or malignant?**
   The size, location, age of onset, rate of growth, and presence of bleeding or ulceration; any color change; and a history of malignancy or prior radiation therapy are important. A thorough examination is necessary. Malignant or inflammatory lesions may cause loss of eyelashes and distortion of meibomian gland orifices, but only malignant lesions destroy the orifices. If a lesion is near the lacrimal punctum, evaluate for invasion into the lacrimal system. Probing and irrigation may be necessary. Palpate lesions for fixation to deep tissues or bone. Regional lymph nodes also should be examined for enlargement. Restriction of extraocular motility and proptosis are clues to localized invasion. If a sebaceous adenocarcinoma or melanoma is diagnosed, systemic evaluation should target lung, liver, bones, and neurologic systems. Photographic documentation is important for any lesion to be treated or observed.

2. **What is the difference between seborrheic keratosis and actinic keratosis?**
   Both are papillomas, an irregular frondlike projection of skin with a central vascular pedicle. These lesions are more common in elderly patients.
   - **Seborrheic keratosis** is pigmented, oily, and hyperkeratotic. It appears stuck onto the skin (Fig. 38-1). A shaved biopsy is all that is needed to diagnose and treat. It has no increased risk for malignant change.
   - **Actinic keratosis** is found in sun-exposed areas and appears as a flat, scaly, or papillary lesion (Fig. 38-2). This premalignant lesion may evolve into either a basal cell or a squamous cell carcinoma.

3. **What eyelid lesion is associated with a chronic follicular conjunctivitis?**
   Molluscum contagiosum. A virus causes the multiple waxy nodules with umbilicated centers. They may resolve spontaneously but frequently require surgical excision or cautery to prevent reinfection.

4. **What blood tests should you order in young patients with the lesions shown in Figure 38-3?**
   The appropriate tests are cholesterol level, triglyceride level, and fasting blood sugar. Xanthelasma are yellowish plaques found at the medial canthal area of the upper and lower eyelids. They are collections of lipid. In older patients, xanthelasma are common and no cause for concern. In younger patients they may be a sign of hypercholesterolemia, a congenital disorder of cholesterol metabolism, or diabetes mellitus. They may be removed for cosmetic purposes, but they can recur.

5. **What is a keratoacanthoma? What malignancy does it simulate?**
   A keratoacanthoma is a rapidly growing lesion that appears over several weeks. It is hyperkeratotic with a central crater that often resolves spontaneously (Fig. 38-4). Clinically, the lesion simulates a "rodent ulcer" basal cell carcinoma. Microscopically, the lesion appears similar to squamous cell carcinoma. It may occur near the edge of areas of chronic inflammation, such as a burn, or on the periphery of a true malignant neoplasm. If you are sure of the diagnosis, it is reasonable to observe. However, because it may cause destruction of the eyelid margin, lesions in this area are often removed surgically. In addition, steroids may be injected into the lesion to hasten resolution.

6. **What is the most common malignant eyelid tumor?**
   Basal cell carcinoma. It is most common in middle-aged or elderly patients.

7. **What are its two clinical presentations?**
   It presents as a nodular (Fig. 38-5) or morpheaform (Fig. 38-6) tumor. A nodular tumor is a firm, raised, pearly, discrete mass, often with telangiectasias over the tumor margins. If the center of the lesion is ulcerated, it is called a *rodent ulcer*. Morpheaform tumors are firm, flat lesions with indistinct borders. They tend to be more aggressive and have a worse prognosis than the nodular variety.

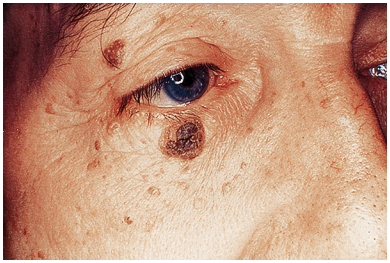

Figure 38-1. Seborrheic keratosis is a greasy, brown, flat lesion with a verrucous surface and a "stuck-on" appearance. *(From Kanski JJ: Clinical Ophthalmology: A Synopsis. New York, Butterworth-Heinemann, 2004.)*

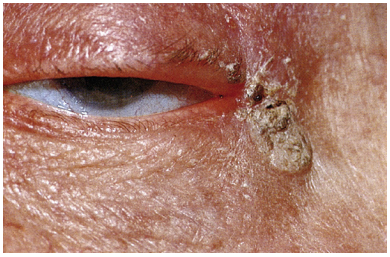

Figure 38-2. Actinic keratosis is a dry, scaly lesion caused by sun exposure and occurring in fair-skinned people. *(From Spalton DJ, Hitchings RA, Hunter PA: Atlas of Clinical Ophthalmology, ed 2, St. Louis, Mosby, 1994.)*

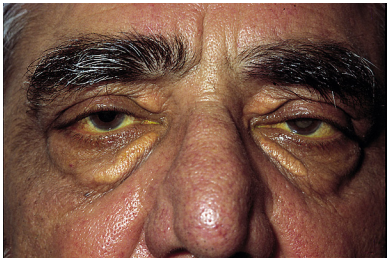

Figure 38-3. Patient with xanthelasma. *(From Kanski JJ: Clinical Ophthalmology: A Systematic Approach, ed 5, New York, Butterworth-Heinemann, 2003.)*

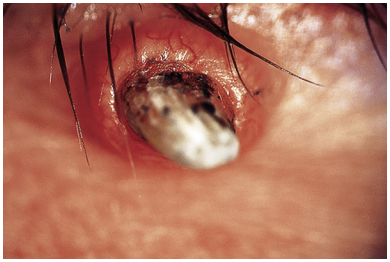

Figure 38-4. Keratoacanthoma is a fast-growing nodule with a keratin-filled crater that spontaneously involutes after several months. *(From Kanski JJ: Clinical Ophthalmology: A Synopsis. New York, Butterworth-Heinemann, 2004.)*

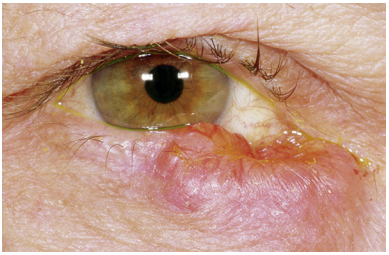

Figure 38-5. Nodular basal cell carcinoma of the eyelid. A firm, pink-colored basal cell carcinoma of the left upper eyelid with raised border, superficial telangiectatic vessels, and characteristic central ulceration. These lesions are more commonly seen on the lower eyelid. *(From Wojno TH: Eyelid Abnormalities. In Palay DA and Krachmer JH (eds): Primary Care Ophthalmology, ed 2, Philadelphia: Mosby, 2005. Fig. 4-13*, B.*)*

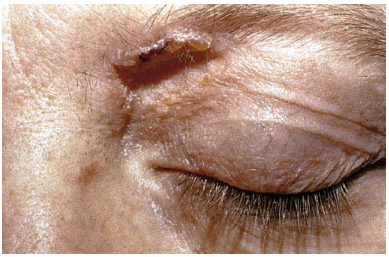

Figure 38-6. Unlike nodular basal cell tumors, morpheaform basal call carcinomas have less clearly defined surgical margins. *(From Spalton DJ, Hitchings RA, Hunter PA: Atlas of Clinical Ophthalmology, ed 2, St. Louis, Mosby, 1994.)*

8. **In order of frequency, where do basal cell carcinomas present?**
   The most common location is the lower eyelid, followed by the medial canthus, lateral canthus, and upper eyelid.

9. **Do basal cell carcinomas metastasize?**
   Lesions grow only by local extension.

10. **If basal cell carcinomas do not metastasize, why be concerned with them?**
    Ocular adnexal basal cell carcinomas have a 3% mortality rate. The vast majority of these patients have canthal area disease, prior radiation therapy, or clinically neglected tumors. Tumors near the medial canthus may invade the orbit via the lacrimal drainage system. Rarely, extension can occur to the brain. Removal of the tumor can be quite disfiguring.

11. **How do you treat tumors with a suspicious lesion?**
    First, do an incisional biopsy of the lesion to confirm the diagnosis. Permanent sections must be done, not merely frozen sections. If a basal cell lesion is found, there are several possibilities for treatment.
    - **Large surgical resection:** A large surgical resection with frozen sections is performed to confirm the entire tumor has been removed. If the lacrimal system must be removed, do not perform a dacryocystorhinostomy at the same time as the primary surgery. Wait at least 1 year to prevent iatrogenic seeding of the nose.
    - **Mohs' lamellar resection:** The complete tumor is removed, sparing as much healthy tissue as possible. The excised bits of tissue are sent to pathology during the procedure to confirm the presence or absence of tumor and therefore direct the subsequent course of the surgery. This procedure preserves a larger amount of normal tissue, allowing improved function and cosmesis. Sometimes it even saves the globe, whereas conventional surgery may require exenteration. This time-consuming procedure is not available everywhere. After the tumor is completely removed and confirmed by pathology, the patient is sent to a plastic surgeon for reconstruction the same or the next day.

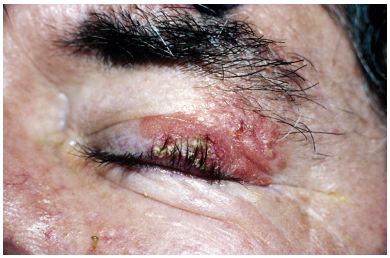

Figure 38-7. Squamous cell carcinoma of the upper eyelid. *(From Kanski JJ: Clinical Ophthalmology: A Synopsis. New York, Butterworth-Heinemann, 2004.)*

- **Radiation:** Basal cell carcinoma is radiosensitive, but treatment is not curative, only palliative (see question 10). Radiation should be reserved for elderly patients who are unable to undergo surgery.
- **Cryotherapy:** This treatment is not curative and should be used only palliatively.
- **Topical treatments:** Newer FDA-approved treatments for superficial basal cell include imiquimod and 5-fluorouracil. Trials are under way for their use in more invasive basal cell carcinomas.

12. How do you treat a recurrent tumor that has limited the extraocular motility from invasion of the orbit?
It is treated with exenteration.

13. Describe basal cell nevus syndrome.
This autosomal dominant disease is characterized by development of multiple basal cell carcinomas at an early age. Patients also have skeletal, endocrine, and neurologic abnormalities.

14. What are the complications of radiation to the area around the eye?
Keratitis sicca, cataracts, radiation retinopathy (if more than 3000 rads are used), optic neuropathy, entropion, lacrimal stenosis, and dermatitis. In young children the bones of the orbit may not grow normally, causing a significant cosmetic deformity.

KEY POINTS: COMPLICATIONS OF RADIATION TREATMENT AROUND THE OCULAR AREA

1. Keratitis sicca
2. Cataracts
3. Radiation retinopathy
4. Optic neuropathy
5. Entropion
6. Lacrimal stenosis
7. Dermatitis
8. Cosmetic deformity in children (orbital bones may not develop normally)

15. Where do squamous cell carcinomas usually present around the eye?
They usually present on the upper eyelid (Fig. 38-7). However, basal cell carcinomas are 40 times more common.

16. How are patients with squamous cell carcinomas treated?
They are treated similar to patients with basal cell carcinomas. However, squamous cell carcinomas are more aggressive locally and metastasize via the blood or lymph system. Neuronal spread is described and can be fatal. Exenteration is suggested for recurrences.

17. A 60-year-old man has had a chalazion removed from his left upper eyelid three times. It has recurred yet again. How do you treat it?
A sebaceous gland carcinoma must be suspected. Such lesions arise from the meibomian glands in the tarsal plate, Zeis' glands near the lashes, and sebaceous glands in the caruncle and brow. Any

recurrent chalazia must be biopsied for pathologic evaluation. The lesion can mimic benign ocular diseases such as chronic blepharoconjunctivitis, corneal pannus, and superior limbic keratitis. Patients who do not respond to treatment should be biopsied, especially those with loss of lashes and destruction of meibomian gland orifices.

18. How is the biopsy performed? How is the specimen sent to the lab? What stains should be requested?

Sebaceous cell carcinoma is multicentric and undergoes pagetoid spread. Multiple sites must be biopsied, including bulbar and palpebral conjunctiva, even if they appear uninvolved. A full-thickness eyelid biopsy may be necessary to make the diagnosis because the lesion originates deep in the tissues. The tissue should not be placed in alcohol, which will dissolve the fat from the specimen and make the diagnosis more difficult. Oil red O stain will stain the fat red.

19. How are patients with sebaceous cell carcinoma treated?

Because sebaceous cell carcinoma is an aggressive and potentially fatal disease, wide surgical excision is mandatory. Some physicians prefer exenteration as a primary treatment. Mohs' microsurgery should be used with caution because the disease is multicentric with skip areas and some lesions may be missed. The tumor may spread hematogenously, lymphatically, or by direct extension.

20. What is the most common type of malignant melanoma of the eyelid?

Superficial spreading melanoma accounts for 80% of cases; lentigo maligna and nodular melanoma each occur in 10% of cases. However, all are rare and represent less than 1% of eyelid tumors. Superficial spreading melanoma occurs both in sun-exposed and in nonexposed areas. Lentigo maligna, also known as melanotic freckle of Hutchinson, is sun induced. Both have a long horizontal growth phase before invading the deeper tissues. Nodular melanoma is more aggressive with earlier vertical invasion. Treatment is wide surgical excision and lymph node dissection if microscopic evidence of lymphatic or vascular involvement is noted.

21. How do you follow a patient who has had an eyelid malignancy?

Once the patient has healed from the initial treatment, reevaluate every 6 to 12 months. Patients are at risk for additional malignancies. A thorough examination by a dermatologist may reveal cutaneous malignancies elsewhere. Patients with a history of cutaneous malignant melanoma and squamous cell carcinoma need periodic systemic evaluations for possible metastasis.

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UVEITIS

Tamara R. Vrabec, Caroline R. Baumal, and Vincent F. Baldassano, Jr.

CHAPTER 39

UVEITIS IN THE IMMUNOCOMPETENT PATIENT

1. What is uveitis?

Inflammation of the uvea, the pigmented layer of the eye, is classified as follows:

- Anterior uveitis, anterior segment inflammation predominantly affecting the iris
- Intermediate uveitis, or inflammation of the ciliary body and vitreous with associated vitreous cells but no retinal or choroidal involvement
- Posterior uveitis, or inflammation of the retina and/or choroid or sclera
- Panuveitis, or inflammation of both the anterior and the posterior segment

The incidence of various types of uveitis may differ among populations. This chapter focuses on uveitis in the Western world.

2. Describe the presenting symptoms of anterior uveitis.

Acute or sudden-onset anterior uveitis typically presents with pain, redness, and photophobia (sensitivity to light). Nonacute forms of anterior uveitis present with fewer symptoms and may be asymptomatic.

3. Name and describe the typical clinical signs of anterior uveitis.

The typical clinical signs of anterior uveitis (iritis) are cell and flare in the aqueous fluid in the anterior chamber and keratic precipitates (KPs). Flare is leakage of protein into the aqueous secondary to increased permeability of iris vessels. Keratic precipitates are accumulations of white blood cells on the endothelial surface of the cornea that may vary in size and location. Depending on the duration and severity of uveitis, adhesions can develop between the iris and the lens surface (posterior synechiae [PS]) and between the iris and the peripheral cornea (peripheral anterior synechiae [PAS]).

4. How is granulomatous uveitis distinguished from nongranulomatous uveitis?

Uveitis may be classified as granulomatous or nongranulomatous based on pathologic features. Histopathologically, granulomatous uveitis is characterized by nodular collections of epithelioid cells and giant cells surrounded by lymphocytes. Nongranulomatous uveitis is characterized by diffuse infiltration of lymphocytes and plasma cells. Both of these entities have relatively distinct clinical appearances.

5. What are the *distinctive* clinical features of granulomatous anterior uveitis?

Granulomatous uveitis is often chronic (greater than 4 months duration). Anterior segment examination may reveal "mutton-fat" (large, "greasy") KPs, nodules on the iris surface (Busacca nodules), and PAS. Anterior chamber cell and flare are also present (Table 39-1).

6. What are the clinical features of nongranulomatous anterior uveitis?

Nongranulomatous anterior uveitis (NGAU) is typically acute with an abrupt onset of symptoms and self-limited course less than 4 months duration. Clinical signs include fine KPs usually located on the inferior cornea, anterior chamber cells, and flare. PS may or may not be present, depending on the duration and severity of the inflammation. Certain forms of NGAU may present with hypopyon (Table 39-1).

7. Can iris nodules occur in nongranulomatous anterior uveitis?

Koeppe nodules are grayish-white nodules that appear at the pupillary margin. They may be present in either granulomatous or nongranulomatous anterior uveitis.

8. Can the distribution of keratic precipitates be helpful in narrowing a differential diagnosis?

Yes. The typical location for KPs is on the inferior cornea, an area referred to as the Arlt triangle (Fig. 39-1). In Fuchs' heterochromic iridocyclitis, the fine "stellate" KPs are found scattered diffusely on the entire posterior surface of the cornea. In herpes simplex keratouveitis, KPs are localized to the area of corneal involvement.

Table 39-1. Features of Granulomatous and Nongranulomatous Anterior Uveitis

FEATURES	GRANULOMATOUS	NONGRANULOMATOUS
Onset	Often insidious	Acute (usually)
Course	Chronic	Acute or chronic
Injection	+	+++ (usually)
Pain	+/–	+++ (usually)
Iris nodules	+++ (Busacca and Koeppe)	– (Koeppe on occasion)
Keratic precipitates	Large, mutton-fat	Small, fine
Other	Dense posterior synechiae	+/– posterior synechiae, hypopyon

+, Present; –, absent.

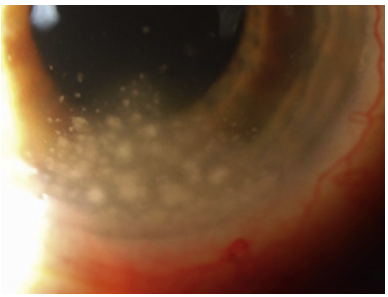

Figure 39-1. Granulomatous KPs in the Arlt's triangle.

9. Is a dilated fundus examination indicated in all patients with anterior uveitis?
Yes. All patients who appear to have anterior uveitis require a dilated examination to identify potentially blinding posterior segment disease.

10. What is the most common cause of nongranulomatous anterior uveitis?
Human leukocyte antigen (HLA)-B27-associated conditions account for approximately 45% of acute NGAU. Although this HLA marker can be seen associated with NGAU without systemic inflammatory disease, inflammatory spondylarthropathies including ankylosing spondylitis (AS), Reiter disease, psoriatic arthritis, and inflammatory bowel disease are present in 50 to 80% of patients with HLA-B27-positive NGAU. A review of systems aids differentiation (Table 39-2).[1,2]

11. Describe the typical nongranulomatous anterior uveitis seen in HLA-B27 disease.
The anterior uveitis is unilateral and self-limited. It is usually recurrent and may be present in alternate eyes over time. A fibrinous response in the anterior chamber and, in some cases, hypopyon may occur.

12. What is the incidence of HLA-B27 in the general population?
The incidence of HLA-B27 in the general population is 8%. In contrast, it is present in 90% of patients with AS and 80% of those with Reiter's disease.

13. What other conditions are in the differential diagnosis of acute nongranulomatous anterior uveitis?
More than 50% of cases are idiopathic. Other uveitides that may present with clinical findings consistent with NGAU are listed in Tables 39-3 and 39-4. Note that some forms of granulomatous uveitis (e.g., sarcoidosis, syphilis, Lyme disease, and toxoplasmosis) may present with nongranulomatous features. However, nongranulomatous conditions do not present in a granulomatous fashion.

14. Discuss the most common cause of uveitis in children
Juvenile idiopathic arthritis (JIA) is the most common identifiable cause of uveitis in children. The uveitis is anterior and chronic and can lead to serious vision loss. The eye is white and quiet so that children often do not complain of symptoms. For these reasons, diagnosis may be delayed.

Table 39-2. Differentiation of HLA-B27-Associated Conditions

HLA-B27-ASSOCIATED DISEASE	SYMPTOMS	SYSTEMIC CLINICAL FINDINGS
Ankylosing spondylitis	Stiffness and low back pain worsen with inactivity	Spinal fusion, sacroiliac joint disease; no skin findings; 25% develop NGAU
Reiter's disease	Same plus painless mouth ulcers, heel pain, painful urination	Keratoderma blennorrhagica, circinate balanitis, urethritis, polyarthritis; conjunctivitis is typically bilateral and papillary
Psoriatic arthritis	Skin rash, arthritis	Psoriasis
Inflammatory bowel disease	Gastrointestinal symptoms	Erythema nodosum

HLA, Human leukocyte antigen; *NGAU*, nongranulomatous anterior uveitis.

Table 39-3. More Common Infectious Causes of Uveitis

DISEASE	GRANULOMATOUS VERSUS NONGRANULOMATOUS	CLINICAL PRESENTATION	INFECTIOUS AGENT
Syphilis	Granulomatous*	Anterior, pan, or posterior	*Treponema pallidum*
Acute retinal necrosis	Granulomatous	Panuveitis	Herpes simplex or zoster virus
Chronic postoperative endophthalmitis	Granulomatous	Anterior or intermediate	*Propionibacterium acnes*
Lyme disease	Granulomatous*	Predominantly intermediate	*Borrelia burgdorferi* via *Ixodes* tick bite
Tuberculosis	Granulomatous	Panuveitis	*Mycobacterium tuberculosis*
Toxoplasmosis	Granulomatous*	Pan or posterior	*Toxoplasma gondii*
Cat-scratch disease	Granulomatous	Panuveitis	*Bartonella henselae*
Toxocariasis	Granulomatous	Panuveitis	*Toxocara canis*
Onchocerciasis	Nongranulomatous	Panuveitis	*Onchocerca volvulus*
Ocular histoplasmosis	No anterior chamber or vitreous cells	Posterior	*Histoplasma capsulatum*
Fungal choroiditis	Granulomatous	Predominantly posterior	*Cryptococcus, Aspergillus, Candida* species
Diffuse unilateral subacute neuroretinitis	Nongranulomatous	Posterior	*Baylisascaris procyonis*

*May also have nongranulomatous anterior uveitis.

Young girls (age 4 years) with pauciarticular JIA who are rheumatoid factor-negative and antinuclear antibody-positive are at highest risk. These children should be screened every few months for uveitis. Boys may develop more acute recurrent inflammation at a later age (9 years). A majority of these children with later onset JIA are HLA-B27-positive and may develop AS later in life.

15. What condition may produce spontaneous hyphema in a child?

Juvenile xanthogranuloma is a systemic condition that consists of one or more nonmalignant inflammatory tumors. Ocular lesions include iris xanthogranuloma masses, recurrent anterior chamber cellular reaction, and spontaneous hyphema (Fig. 39-2). Diagnosis is made with iris biopsy or by finding similar lesions on the skin.[3,4]

Table 39-4. More Common Noninfectious Causes of Uveitis

DISEASE	GRANULOMATOUS VERSUS NONGRANULOMATOUS	CLINICAL PRESENTATION	SECRETS
JIA	Nongranulomatous	Anterior	See text
HLA-B27-associated uveitis	Nongranulomatous	Anterior	See text
Fuchs' iridocyclitis	Nongranulomatous	Anterior	Iris heterochromia; no PAS/PS
Kawasaki syndrome	Nongranulomatous	Anterior	Rash, lymphadenopathy, fever, cardiac disease in children
TINU syndrome	Nongranulomatous	Anterior	Cellular casts in urine
Sarcoidosis	Chronic granulomatous; acute nongranulomatous	Anterior, posterior, or panuveitis	Clinical findings depend on age
Pars planitis	Nongranulomatous; if granulomatous, suspect MS	Intermediate	16% may develop MS
Juvenile xanthogranuloma	Nongranulomatous	Anterior or intermediate	See text
Phacoanaphylactic uveitis	Granulomatous	Intermediate uveitis	Autoimmunity to lens proteins after trauma or cataract surgery
Multifocal choroiditis	Nongranulomatous	Panuveitis	Myopia; 30% develop CNVM
Birdshot chorioretinitis	Nongranulomatous	Posterior or panuveitis	HLA-A29 in more than 90%
APMPPE	Nongranulomatous	Posterior or panuveitis	Young patients, viral prodrome, bilateral; recurrence and CNVM rare
MEWDS	Nongranulomatous	Posterior	IVFA wreath; hyperfluorescence
Serpiginous choroiditis	Nongranulomatous	Posterior	Older patients, lesions contiguous to disc, unilateral; recurrence common, CNVM 30%
Behçet's disease	Nongranulomatous	Anterior, posterior, or panuveitis	Hypopyon iritis
Vogt-Koyanagi-Harada syndrome	Granulomatous	Panuveitis	Starry sky
Sympathetic ophthalmia	Granulomatous	Panuveitis	See text

APMPPE, Acute posterior multifocal placoid pigment epitheliopathy; *CNVM*, choroidal neovascular membrane; *IVFA*, fluorescein angiography; *JIA*, juvenile idiopathic arthritis; *MEWDS*, multiple evanescent white dot syndrome; *MS*, multiple sclerosis; *PAS*, peripheral anterior synechiae; *PS*, posterior synechiae; *TINU*, tubulointerstitial nephritis–uveitis.

16. What is the most common cause of granulomatous anterior uveitis?

Sarcoidosis is the most common cause of granulomatous anterior uveitis in adults. Differential diagnosis includes syphilis, Lyme disease, *Propionibacterium acnes* (pseudophakic patients), tuberculosis, and herpesvirus infection. Other more common causes are also listed in Tables 39-3 and 39-4.[5]

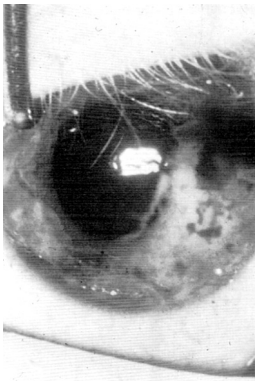

Figure 39-2. Large, solitary juvenile xanthogranuloma that had given rise to a spontaneous hyphema in a 7-month-old patient. *(From Shields JA, Shields CL: Intraocular Tumors: A Text and Atlas, Philadelphia, W.B. Saunders, 1992.)*

17. What is the leading cause of blindness in the world?

Onchocerciasis (river blindness) is the most common cause of blindness in the world. It is caused by *Onchocerca volvulus* and transmitted by the bite of a *Simulium* black fly. Sclerosing keratitis and extensive chorioretinal and optic atrophy cause severe visual impairment. The disease predominantly affects people in western and central Africa and Central America. Treatment of at-risk populations with antifilarial agents such as ivermectin can dramatically reduce disease.[6]

18. When is a systemic workup indicated in uveitis?

A systemic evaluation should be performed in patients with granulomatous uveitis, a second episode of nongranulomatous uveitis, posterior uveitis, a positive review of systems, or severe disease that may require systemic immunosuppression.

19. What studies should be ordered?

A chest x-ray for sarcoidosis, fluorescent treponemal antibody absorption (FTA–ABS) or rapid plasmin reagin (RPR) test, urinalysis, and complete blood count should be ordered in all patients. HLA-B27 titers should be ordered in patients with NGAU. Additional diagnostic tests may be appropriate based on clinical history and ocular and physical examination and positive review of systems.

20. When ocular tests are helpful?

Ocular tests including intravenous fluorescein angiography, indocyanine green angiography, B-scan ultrasound, and ocular coherence tomography may help to characterize uveitis with posterior segment findings, as well as to detect cystoid macular edema.

21. What may confound interpretation of serology for infectious agents?

Because of its localized nature, an active intraocular infection is not always accompanied by a significant rise in systemic antibody titers. Furthermore, serology may be unreliable in immunocompromised patients or negative in masquerade syndrome. In cases of progressive sight-threatening uveitis in one or both eyes that is unresponsive to therapy or when unusual infections or masquerade syndrome are suspected and systemic antibody titers are not diagnostic, specimens from the iris, aqueous, vitreous, retina, or choroid may be obtained for evaluation, including antibody titers, polymerase chain reaction (PCR), histopathology, and flow cytometry.

22. What is the most common cause of intermediate uveitis?

Pars planitis, an inflammation of unknown etiology, is the most common cause of intermediate uveitis. It is recognized by the typical inflammatory "snow bank" in the inferior pars plana. The clinical course is variable. Approximately 16% of patients may develop multiple sclerosis (MS). HLA-DR15 may play a role in both diseases. Granulomatous anterior uveitis may be present in MS-associated uveitis.[7,8]

23. What are the causes of vision loss in pars planitis?

Cystoid macular edema is the most common cause of vision loss. Other causes include cataract, glaucoma, vitreous hemorrhage, epiretinal membrane, and tractional retinal detachment.

24. What are the indications for treatment in pars planitis?

Indications for treatment include cystoid macular edema with associated vision loss.

25. Describe the most common causes of posterior uveitis.

Ocular toxoplasmosis is the most common cause of posterior uveitis. It is most often a recurrent infection, characterized by necrotizing retinochoroiditis, appearing as a white infiltrate adjacent to a pigmented retinal scar. A diffuse vitritis may make the retinitis appear as a "headlight in the fog." In immunocompromised patients, including the elderly, the retinitis may be multifocal and bilateral and may not be associated with a scar.[9]

26. How is the diagnosis of ocular toxoplasmosis made?

Diagnosis usually is based on clinical history and fundus examination. Positive IgG or IgM titers, even in very low concentrations (undiluted serum), are supportive of the diagnosis. IgG indicates congenital or previous infection, whereas IgM indicates recently acquired infection. Interpretation may be confounded by a high prevalence of positive titers in the population. A negative titer excludes the diagnosis except in immunosuppressed patients.[10]

27. How is ocular toxoplasmosis managed?

Treatment is recommended for active lesions that threaten the macula or optic nerve and for severe vitritis. Although sulfonamides, clindamycin, pyrimethamine, folinic acid, and corticosteroids have been used in various combinations, there is no universally accepted treatment regimen, and the effectiveness of toxoplasmosis therapy has been questioned. Duration of treatment is typically 4 to 6 weeks and treatment does not prevent recurrences. Observation is recommended for small peripheral lesions.[11,12]

28. What serious side effects may occur with oral antibiotic therapy for toxoplasmosis?

- Pseudomembranous colitis (clindamycin)
- Hematologic toxicity (pyrimethamine)
- Erythema multiforme and Stevens-Johnson's reaction (sulfonamides)

29. What are the features of ocular sarcoidosis?

The eye is involved in approximately 20% of individuals. Uveitis is the most common ocular manifestation. Anterior segment inflammation is classically bilateral, chronic, and granulomatous, although acute and asymmetric anterior uveitis may occur. Posterior segment inflammation including choroidal or optic nerve granulomas, vitritis, retinal vasculitis or vascular occlusions, and neovascularization are less common, but do threaten sight. Conjunctival and eyelid nodules and enlarged lacrimal glands may be noted and are useful tissues for confirmatory biopsy.

30. How does the presentation of sarcoidosis differ with age?

In children younger than 5 years, uveitis, arthritis, and skin rash are typical and the presentation may resemble JIA. In patients 20 to 40 years of age, bilateral chronic granulomatous iritis or panuveitis and hilar adenopathy are most common, whereas in elderly patients, lesions resembling multifocal choroiditis or birdshot chorioretinitis and interstitial lung disease may be seen.[13,14]

31. What testing may be helpful in making the diagnosis of sarcoidosis?

- Chest x-ray is positive in 90% of patients with sarcoidosis.
- Angiotensin-converting enzyme and lysozyme are sensitive but not specific indicators of sarcoidosis.
- In cases with high suspicion and a negative chest x-ray, gallium scan and computed tomographic (CT) scan of the chest may be considered.
- Biopsy of normal-appearing conjunctiva in patients with presumed sarcoidosis is positive in 12% of cases. Lacrimal biopsy in presumed sarcoidosis is positive in 22% of cases.[15]

KEY POINTS: MOST COMMON FORMS OF UVEITIS

1. Children—JIA (chronic iridocyclitis)
2. NGAU—HLA-B27
3. Granulomatous anterior uveitis—sarcoidosis
4. Intermediate uveitis—pars planitis
5. Posterior uveitis—toxoplasmosis

32. What are the features of ocular syphilis?

Salt-and-pepper chorioretinitis, vitritis, uveitis, and interstitial keratitis typify congenital syphilis. The clinical findings of acquired syphilis are protean. Anterior uveitis, vitritis, choroiditis, retinitis, retinal vasculitis, optic neuropathy, and Argyll Robertson pupils are most common. Others have been reported.[16]

33. Which diagnostic tests are used to assess syphilitic uveitis?

Nontreponemal tests, including serial venereal disease research laboratory (VDRL) titers, are useful in monitoring response to therapy but may be negative in late-stage syphilis. For this reason, syphilitic uveitis must be evaluated with specific treponemal tests, that is, FTA-ABS test or the microhemagglutination test. Examination of cerebrospinal fluid for elevated protein, lymphocytic pleocytosis, or VDRL may reveal neurosyphilis. Human immunodeficiency virus (HIV) testing should be performed in all patients with syphilis.[17]

34. How is syphilitic uveitis treated?

Ocular syphilis is treated as neurosyphilis with intravenous penicillin G, 12 to 24 million units/day for 14 days followed by intramuscular benzathine penicillin G, 2.4 million units/week for 3 weeks. Doxycycline, tetracycline, and erythromycin have been used in penicillin-allergic patients.

35. What are the most common features of ocular histoplasmosis?

The most common features (histoplasmosis triad) are peripapillary atrophy or pigmentation, peripheral chorioretinal lesions, and macular choroidal neovascular membrane.

36. What is Vogt-Koyanagi-Harada syndrome?

Vogt-Koyanagi-Harada (VKH) syndrome is an idiopathic multisystem disorder that primarily affects heavily pigmented individuals. Clinical manifestations are present in the skin (alopecia, vitiligo, poliosis), eye (granulomatous uveitis, exudative retinal detachment), and central nervous system (encephalopathy, cerebrospinal fluid lymphocytosis). Symptoms may include dysacousis, headache, and stiff neck. Fluorescein angiography is notable for a characteristic "starry sky" pattern of early hyperfluorescence. Treatment usually requires systemic immune suppression.

37. Name five other conditions that have uveitis and central nervous system manifestations.

Sarcoidosis, syphilis, Behçet's disease, acute posterior multifocal placoid pigment epitheliopathy, and multiple sclerosis all have uveitis and central nervous system (CNS) manifestations.

38. What is sympathetic ophthalmia?

This is a bilateral, diffuse granulomatous T-cell-mediated uveitis that has been reported to occur between 5 days and many years after perforating ocular injury (0.2%) or ocular surgery (0.01%). Eighty percent of cases occur within 2 weeks to 3 months after the inciting event. Clinical findings include panuveitis, papillitis, and in some cases exudative retinal detachment. Dalen-Fuchs nodules, collections of sub-retinal pigment epithelium (RPE) lymphocytes, may be recognized clinically as grayish-white lesions scattered throughout the posterior fundus. Treatment usually requires systemic immune suppression. Enucleation of the traumatized eye after the onset of the uveitis is not typically recommended.[18]

39. Describe acute retinal necrosis syndrome

Acute retinal necrosis (ARN) is a clinical syndrome caused by herpesvirus infections (varicella zoster, herpes simplex types 1 and 2). The typical triad includes peripheral retinitis, arteritis, and vitritis. Long-term complications include retinal detachment, glaucoma, cataract, and optic atrophy. Intravenous acyclovir for 14 days, followed by 3 months of oral therapy, is recommended to limit retinal necrosis, as well as the occurrence of ARN in the fellow eye. Prophylactic laser coagulation may decrease the risk of secondary retinal detachment. Acute retinal necrosis may occur in the fellow eye in approximately 30% of patients at an average interval of 4 weeks.[19]

40. What other types of retinitis may have a similar clinical presentation?

Toxoplasmosis, syphilis, Behçet's disease, *Aspergillus,* and lymphoma (masquerade syndrome) may have similar presentation.[20]

41. What are the major diagnostic characteristics of Behçet's disease?

The major characteristics are recurrent anterior and posterior uveitis, skin lesions (erythema nodosum, thrombophlebitis), genital ulcers, and painful oral ulcers.

42. What is unusual about the clinical course of Behçet's disease?

Behçet's disease is characterized by periodic relapse and spontaneous remission. Remissions may be misunderstood as a therapeutic response to intermittent steroid therapy. Unlike most other causes of retinal vasculitis, including sarcoidosis, which may have similar clinical findings, Behçet's disease requires chronic systemic immunosuppression to prevent relapses that lead to blindness.

43. Describe the ocular features of Lyme disease

Ocular Lyme disease is usually bilateral. In stage 1, conjunctivitis may occur along with a migratory rash (erythema migrans) or arthritis. In later stages, an atypical intermediate uveitis with granulomatous KPs and PS may be present. Inflammation may affect almost any ocular tissue. Diagnosis requires a history of outdoor activity in an endemic area in the late spring or summer and positive indirect immunofluorescent antibody and/or enzyme-linked immunosorbent assay. Western blot, which is very specific, may be confirmatory. False-negative results occur in the early stages or following incomplete antibiotic treatment. The spirochete may be identified in skin rash biopsy or cerebrospinal fluid.[21,22]

44. Describe the most common features of ocular tuberculosis.

The most common feature of ocular tuberculosis is choroiditis. Inflammation is typically unilateral. Associated anterior uveitis is chronic and granulomatous. Ocular involvement may occur without signs of active pulmonary involvement.[23,24]

45. What form of uveitis may present with enlarged lymph glands?

Primary inoculation with *Bartonella henselae* produces regional lymphadenopathy and conjunctivitis (Parinaud's oculoglandular syndrome). Additional findings may include Leber's neuroretinitis and a retinal white-dot syndrome. Patients with sarcoidosis may also present with lymphadenopathy.[25]

46. Why do patients with uveitis develop glaucoma?

The most common mechanism of acute glaucoma is direct inflammation of the trabecular meshwork or trabeculitis. Chronic glaucoma may result from closure of the trabecular meshwork by peripheral anterior synechiae or angle-closure glaucoma from iris bombé (360 degrees of PS). In addition, topical, intraocular, and periocular corticosteroids can cause glaucoma.[26]

47. Name the uveitis entities that are associated with an acute elevation in intraocular pressure.

- Herpes simplex and zoster
- Toxoplasmosis
- Sarcoidosis
- Syphilis

48. What is the approach to the treatment for uveitis?

1. Identify and treat the underlying causes. This is especially important in immunocompromised individuals, in whom most uveitis cases are infectious.
2. Prevent vision-threatening complications. Anti-inflammatory agents are the mainstay of treatment to prevent or reverse vision-threatening complications, including retinal ischemia, retinal scarring, cataract, and macular edema, among others.
3. Relieve ocular discomfort and improve vision. Cycloplegic agents relax the ciliary body and reduce pain. In addition, they stabilize the blood aqueous barrier and help to break or prevent PS.

49. What should be the general approach to the use of steroids to treat uveitis?

High-dose corticosteroids should be used initially until inflammation is suppressed and then tapered. A common mistake is infrequent dosing initially, which results in a smoldering, extended course. Topical corticosteroids are best suited to anterior uveitis, as they do not reach the posterior segment in therapeutic levels. Prednisolone acetate achieves the highest anterior chamber concentrations. Posterior segment disease must be treated with periocular (posterior sub-Tenon or preseptal) or intravitreal injection, or intravitreal implant, and/or systemic corticosteroids. Systemic steroids are typically reserved for severe or bilateral disease. In patients unresponsive to steroids, one must suspect an infectious or neoplastic masquerade syndrome.

50. When are alternate immunosuppressives indicated to treat autoimmune uveitis?

- When the systemic steroids required to suppress ocular inflammation are higher than can be safely administered over extended periods. In these cases a steroid-sparing agent is indicated.

- When the systemic or local steroids are causing intolerable side effects.
- When steroids do not significantly alter the nature of the uveitis or underlying condition.

51. In which conditions with uveitis or scleritis are immunosuppressive agents indicated?

They are indicated for Behçet's disease, Wegener's granulomatosis, and rheumatoid arthritis-associated vasculitis. They are often required in cases of sympathetic ophthalmia, VKH syndrome, serpiginous choroiditis, birdshot retinochoroidopathy, and multifocal choroiditis.

52. Name major categories of alternate immunosuppressives.

- Antimetabolites (e.g., methotrexate): Often used for their steroid-sparing effect
- T-cell inhibitors (e.g., cyclosporine)
- Alkylating agents (e.g., cyclophosphamide): Typically reserved for severe, sight-threatening uveitis not adequately responsive to the aforementioned agents
- Biologic agents (e.g., infliximab): Tumor necrosis factor inhibitors are one example of this expanding arsenal of immunosuppressant and anti-inflammatory agents[27]

MASQUERADE SYNDROMES

53. Define masquerade syndrome

The term *masquerade syndrome* refers to ophthalmic disorders that are not primarily inflammatory in nature but may present clinically as either anterior or posterior uveitis (Table 39-5). These entities may be mistaken for, or masquerade as, primary uveitis. Extensive evaluation is often initiated because patients manifest with atypical features, recurrent episodes of uveitis, or uveitis that is unresponsive to standard therapy.

KEY POINTS: COMMON MASQUERADE SYNDROMES

1. Retinoblastoma in children
2. Leukemia in children
3. Primary intraocular lymphoma in older adults
4. Ocular ischemic syndrome in the older adults
5. Peripheral retinal detachment in any age group

54. In what age groups should one have the highest suspicion for masquerade syndromes?

One should suspect in the very young and in the elderly.

55. Describe the clinical features of retinoblastoma.

Retinoblastoma is the most common primary intraocular malignancy in children, usually presenting before age 2. The most common signs are leukocoria (white pupillary reflex) and strabismus. Occasionally, tumor necrosis may produce significant inflammation. Tumor cells layered in the anterior chamber may produce a pseudohypopyon (Fig. 39-3). Retinoblastoma cells may enter the vitreous, as vitreous seeds, and simulate vitritis. Calcification on ultrasonography and CT scan may help to differentiate retinoblastoma from various forms of childhood uveitis, including toxoplasmosis, toxocariasis, cysticercosis, and pars planitis.[28]

56. What may present with chronic steroid-resistant panuveitis in a patient older than age 50?

Primary intraocular lymphoma (Fig. 39-4) presents in elderly individuals with bilateral vitreous cells, anterior chamber reaction, and retinal or choroidal infiltrates. The retinal infiltrates may be patchy and associated with hemorrhage and exudate. Dense vitritis may be the only presenting sign. Most patients eventually develop some form of CNS involvement. CT or magnetic resonance imaging may demonstrate CNS tumors. Vitreous aspirate or lumbar puncture may establish the diagnosis. Therapy may include ocular and CNS irradiation combined with intrathecal chemotherapy.[29]

57. Describe the ocular findings associated with leukemia.

Clinically the retina is the most often affected (Fig. 39-5). Retinal vascular dilation and tortuosity, hemorrhages, cotton-wool spots, and peripheral neovascularization occur. Roth spots are

Table 39-5. Most Common Masquerade Syndromes That May Mimic Uveitis

DISEASE	LOCATION	AGE (YEARS)	SIGNS OF INFLAMMATION	DIAGNOSTIC TESTS
Retinoblastoma	Anterior	<15	Flare, cells, pseudohypopyon	Aqueous tap for LDH levels and cytology
Leukemia	Anterior	<15	Flare, cells, heterochromia	Bone marrow, peripheral blood smear, aqueous cytology
Intraocular foreign body	Anterior	Any age	Flare, cells	X-ray, ultrasound, CT scan
Malignant melanoma	Anterior	Any age	Flare, cells	Angiography (fluorescein, ICG), ultrasound, MRI
Ocular ischemic syndrome	Anterior	50+	Cell, flare, redness	IVFA, carotid Doppler
Peripheral retinal detachment	Anterior	Any age	Flare, cells	Ophthalmoscopy, ultrasound
Retinitis pigmentosa	Posterior	Any age	Cells in vitreous	ERG, EOG, visual fields
Primary intraocular lymphoma	Posterior	15+	Vitreous cells, retinal hemorrhage or exudates, RPE infiltrates	Cytology of aqueous/vitreous fluid
Lymphoma	Posterior	15+	Retinal hemorrhage, exudates, vitreous cells	Biopsy of lymph node/bone marrow, physical examination
Retinoblastoma	Posterior	<15	Vitreous cells, retinal exudate	Ultrasound, aqueous tap
Malignant melanoma	Posterior	15+	Vitreous cells	Fluorescein ultrasound

Adapted from American Academy of Ophthalmology: Ophthalmology Basic and Clinical Science Course, Section 6, San Francisco, American Academy of Ophthalmology, 1997.

CT, Computed tomography; *ERG*, electroretinogram; *EOG*, electro-oculogram; *ICG*, indocyanine green; *IVFA*, fluorescein angiography; *LDH*, lactate dehydrogenase; *MRI*, magnetic resonance imaging; *RPE*, retinal pigment epithelium.

hemorrhages with white centers composed of leukemic cells or platelet–fibrin aggregates. Histopathologically, the choroid is the most commonly involved and may cause exudative retinal detachment. Intravenous fluorescein angiogram (IVFA) demonstrates multiple areas of hyperfluorescence similar to that found in VKH syndrome. Anterior segment findings include conjunctival mass, iris heterochromia, anterior chamber cell and flare, pseudohypopyon, spontaneous hyphema, and elevated intraocular pressure. Optic nerve infiltration and orbital involvement are common.[30]

58. How can a malignant melanoma produce inflammatory signs?

Necrotic tumors may elicit an intense inflammatory response associated with seeding of tumor cells into the vitreous cavity and anterior segment. Occasionally, melanophages or tumor cells that contain melanin produce a brown pseudohypopyon. Blockage of the trabecular meshwork by tumor cells may result in elevated intraocular pressure (melanomalytic glaucoma). Necrosis of the tumor may result in spontaneous vitreous hemorrhage. Other clinical findings include iris heterochromia and exudative retinal detachment with shifting subretinal fluid. Ultrasound examination and IVFA help to establish the diagnosis.[31]

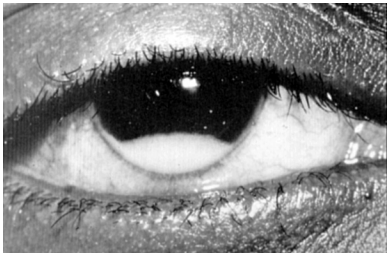

Figure 39-3. Pseudohypopyon caused by seeding of retinoblastoma cells in the anterior chamber. *(From Shields JA, Shields CL: Intraocular Tumors: A Text and Atlas, Philadelphia, W.B. Saunders, 1992.)*

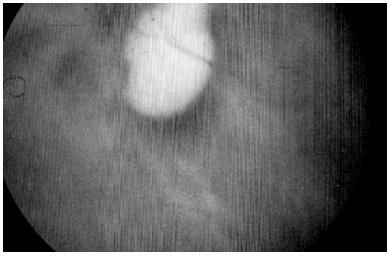

Figure 39-4. Yellow-white chorioretinal infiltrates in intraocular lymphoma. *(From Shields JA, Shields CL: Intraocular Tumors: A Text and Atlas, Philadelphia, W.B. Saunders, 1992.)*

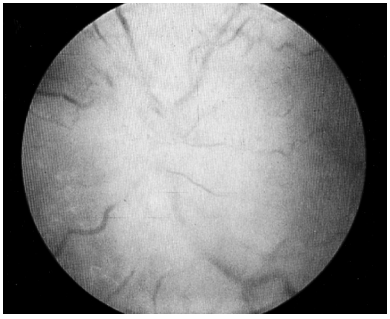

Figure 39-5. Leukemic infiltration of the optic nerve head, retina, and choroid in an 8-year-old child. *(From Shields JA, Shields CL: Intraocular Tumors: A Text and Atlas, Philadelphia, W.B. Saunders, 1992.)*

59. Describe other entities that may simulate anterior and/or posterior uveitis.

- **Long-standing peripheral rhegmatogenous retinal detachment** may produce a cellular reaction in the anterior or posterior chamber as well as PS.
- **Retained intraocular foreign body** associated with trauma may cause persistent anterior and/or posterior segment inflammation. CT or ultrasonography results should demonstrate the abnormality. Retained iron foreign bodies may lead to siderosis, retinal degeneration with an abnormal electroretinogram.
- **Retinitis pigmentosa** may present with vitreous cells and posterior subcapsular cataract. The "bone spicule" pigment deposition in the retina, attenuated retinal vessels, mottling and atrophy of the RPE, and waxy pallor of the optic nerve help to distinguish this disease from other disorders. The diagnosis can be confirmed with an extinguished electroretinogram and ring scotoma on visual field testing.[32]

OCULAR MANIFESTATIONS OF ACQUIRED IMMUNE DEFICIENCY SYNDROME

60. Who is at greatest risk for developing acquired immune deficiency syndrome-related eye disease?

Patients with severely reduced $CD4^+$ T-lymphocyte counts and associated immunosuppression are most likely to develop acquired immune deficiency syndrome (AIDS)-related eye disease. For this reason, screening for opportunistic infections with dilated fundus examination is recommended every 3 months in patients with $CD4^+$ counts less than 100 cells/μL.[33]

61. What is the most common ocular manifestation of AIDS?

Retinal microvasculopathy that manifests clinically as cotton-wool spots (CWSs) (Fig. 39-6). Retinal microaneurysms and hemorrhages may be present. Most patients are asymptomatic. CWSs become more common as the $CD4^+$ T-lymphocyte count declines, reaching a prevalence of 45% in patients with counts <50 cells/μL.[34]

62. What is the most common ocular opportunistic infection in patients with AIDS?

Cytomegalovirus (CMV) is by far the most common cause of opportunistic ocular infection and most frequently results in necrotizing retinitis (Fig. 39-7). Varicella zoster, toxoplasmosis, and *Mycobacterium avium* occur less frequently.

63. What is the incidence of cytomegalovirus retinitis?

Among patients whose $CD4^+$ count is less than 50 cells/μL, 20% per year develop CMV retinitis.

64. Describe the early symptoms of cytomegalovirus retinitis

Floaters that appear as numerous tiny black specks are often present early in the course of CMV retinitis. Pain and redness are not associated. Scotomas (blind spots) or visual loss may develop with more advanced stages of the disease.

65. How does cytomegalovirus retinitis present clinically?

Classic ophthalmologic findings of fulminant CMV retinitis include white areas of retinal necrosis with associated hemorrhage and minimal vitreous inflammation (see Fig. 39-7). The indolent or granular

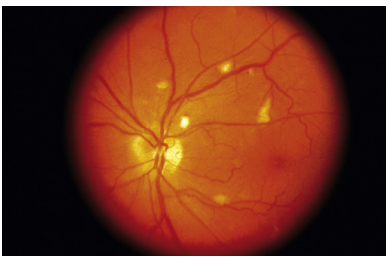

Figure 39-6. Cotton-wool spots are infarcts of the nerve fiber layer. Unlike early infiltrates of cytomegalovirus retinitis, they do not enlarge, do not have associated hemorrhage, and may resolve in several weeks.

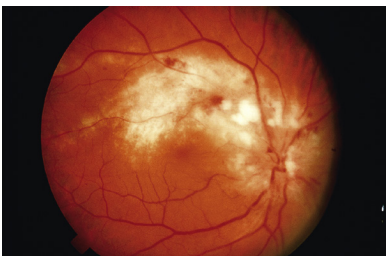

Figure 39-7. Cytomegalovirus retinitis is characterized by areas of retinal infiltrate with associated hemorrhage. Note the optic nerve involvement.

form, which is often less symptomatic, is characterized by peripheral retinal whitening with minimal associated hemorrhage.[35]

66. What are the more common entities in the differential diagnosis of cytomegalovirus retinitis?

The more common entities are progressive outer retinal necrosis, toxoplasmosis, syphilis, HIV retinitis, and cotton wool spots.

67. How is the diagnosis of cytomegalovirus retinitis made?

The diagnosis of CMV retinitis is made clinically when characteristic findings of fulminant or indolent retinitis are found in an immunosuppressed patient with $CD4^+$ count <100 cells/μL. In the unusual case in which the diagnosis is in question, a vitreous biopsy with or without retinal biopsy for PCR analysis may be performed.

68. What is the initial treatment strategy for cytomegalovirus retinitis?

Treatment of CMV retinitis is given in two stages. The first stage is 2 to 6 weeks of induction therapy with ganciclovir (Fig. 39-8), valganciclovir, foscarnet, or cidofovir. These are antiviral agents that inhibit the viral DNA polymerase. Induction is discontinued after a healing response (consolidation or stabilization of the margins) begins. The second stage, maintenance therapy, consists of a lower dose of the medication that is continued until relapse occurs.

69. What is the strategy in the event of a relapse?

Despite maintenance therapy, CMV retinitis may relapse in persons who remain immunosuppressed. The mean interval to relapse varies from 2 to 8 months and depends on the medication used and the route of administration. If relapse occurs in patients taking oral or intravenous (IV) medication, reinduction with the same medication (2 to 6 weeks of high-dose IV or multiple intraocular injections) is indicated. When relapse develops in patients with ganciclovir implants, the implant is replaced.

70. Does resistance to antiviral medication develop?

Drug resistance is an emerging problem of great concern because of the limited number of available agents that are effective against CMV. Ganciclovir-resistant CMV has been reported in 27.5% of urine samples at 9 months. CMV UL97 mutation (a CMV DNA polymerase mutation that confers ganciclovir resistance) was detected in 30.8% of patients treated with ganciclovir over 3 months and in none treated less than 3 months. Resistance to foscarnet and cidofovir has also been reported. Owing to similarities in the mechanism of action, cross-resistance may develop with cidofovir and ganciclovir. Clinical resistance is defined as a lack of response to 6 weeks of induction therapy. A change in medication or combination therapy is indicated.[36,37]

71. How long should treatment be continued in patients with cytomegalovirus retinitis?

Length of therapy depends on the immune status of the patient. For patients who remain severely immunosuppressed ($CD4^+$ count <100 cells/μL), treatment must be continued indefinitely. In patients whose immune status is improved by highly active antiretroviral therapy (HAART) (see question 73), maintenance therapy may be discontinued if the retinitis is completely quiescent and $CD4^+$ counts are >100 cells/μL.

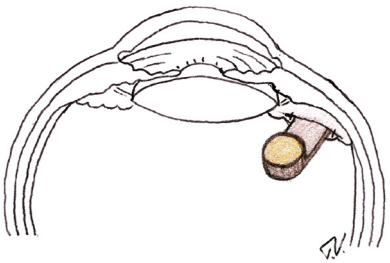

Figure 39-8. The intraocular ganciclovir implant is sutured to the sclera and extends into the vitreous cavity. The drug delivery system slowly releases ganciclovir over 8 months. It may be replaced when the drug supply is exhausted. Although it is not associated with the systemic toxicity seen with oral or intravenous therapy, the implant provides no prophylaxis against systemic cytomegalovirus (CMV) or CMV retinitis in the fellow eye.

72. Name the main toxicities of the antiviral therapies

Ganciclovir: bone marrow toxicity with neutropenia and/or thrombocytopenia.

Foscarnet: nephrotoxicity.

Cidofovir: nephrotoxicity, which may be ameliorated by concurrent probenecid and hypotony after either intravenous or intravitreal administration.

73. How has highly active antiretroviral therapy affected the natural history and treatment of cytomegalovirus retinitis?

HAART causes significant and sustained increases in $CD4^+$ counts and remission of CMV retinitis. Discontinuation of maintenance therapy has been recommended for patients with completely quiescent retinitis and $CD4^+$ count greater than 100 cells/μL. Other criteria include $CD4^+$ elevation for at least 3 months, prolonged relapse-free intervals, HAART longer than 18 months, and reduced HIV and CMV viremia.[38,39]

74. What is immune recovery uveitis?

Immune recovery uveitis (IRU) is intraocular inflammation that develops as systemic immunity recovers. It is hypothesized that immunologic improvement leads to an inflammatory response directed at the CMV antigen. IRU typically develops in 10 to 20% of eyes with CMV within 1 month after HAART is initiated, but may occur up to 3 years later. Treatment of CMV retinitis with intravenous cidofovir and large CMV lesion size increase the risk. Vision-threatening complications include macular edema, epiretinal membrane, cataract, optic disc edema, retinal neovascularization, and neovascular glaucoma. Treatment depends on the location and severity of inflammation and the presence of complications and usually requires local and or systemic corticosteroids. On occasion, observation or antiviral therapy may be indicated.[40]

75. What is progressive outer retinal necrosis?

Progressive outer retinal necrosis is an extremely aggressive form of retinitis in the AIDS population (Fig. 39-9). It primarily affects persons with CD4 counts less than 50 cell/μL. Caused by herpes zoster virus, it is temporally associated with herpes zoster skin lesions, which may or may not be in the periocular region. Prompt diagnosis and treatment are imperative to prevent blindness, which develops in >80% of patients because of either relentless progression of infection or secondary retinal detachment.[41]

76. Why do retinal detachments develop in cases of infectious retinitis? Who is at risk?

Retinal infections may cause multiple necrotic retinal holes that over time lead to retinal detachment. Most AIDS-related retinal detachments develop as a complication of CMV retinitis and occur in 34% of patients with CMV. However, patients with progressive outer retinal necrosis are at highest risk; retinal detachments occur in 60 to 70% of these cases.

77. How are most AIDS-related retinal detachments repaired?

Lasers may be used to demarcate or wall off macula-sparing retinal detachments, especially in patients who are not well enough to tolerate surgery. Vitrectomy with silicone oil injection is often required in cases in which the macula is detached or retinitis is active. The silicone oil replaces the vitreous and tamponades the multiple necrotic holes to prevent redetachment.[42,43]

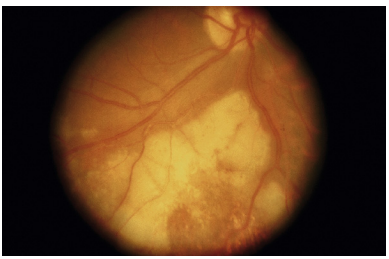

Figure 39-9. Progressive outer retinal necrosis typically affects the outer retina with sparing of the retinal vessels. Note the areas of perivascular clearing and absence of associated hemorrhage.

78. Describe the unique characteristics of ocular syphilis in patients with AIDS.

Syphilis is not considered an opportunistic infection by definition, because most patients have $CD4^+$ T-cell counts >250 cell/μL. Ocular findings range from iritis to necrotizing retinitis. CNS syphilis is present in 85% of HIV-positive patients with ocular syphilis. Hence, evaluation of cerebrospinal fluid is mandated for all HIV-positive patients with ocular syphilis. Syphilis may be seronegative (negative RPR despite active infection) in the AIDS population. Regardless of clinical findings, syphilis in patients with AIDS should be treated as tertiary disease with a 10-day course of intravenous antibiotics. Although recurrent infection may occur, maintenance therapy is not currently recommended.[44]

KEY POINTS: OCULAR MANIFESTATIONS OF AIDS

1. Microvasculopathy is the most common ocular manifestation.
2. CMV is the most common ocular opportunistic infection.
3. Progressive outer retinal necrosis is the most potentially blinding ocular complication.
4. Kaposi's sarcoma is the most common periocular malignancy.
5. *Cryptococcus* is the most common cause of neuro-ophthalmologic abnormalities in ambulatory patients.

79. What is the most common cause of neuro-ophthalmologic abnormalities in the ambulatory AIDS population, and what are the clinical findings?

Cryptococcal meningitis causes papilledema and cranial nerve palsies (Fig. 39-10). Papilledema is defined as disc swelling that is secondary to increased intracranial pressure. The central disc tissue remains pink. Early optic nerve dysfunction is minimal, and vision is usually preserved, in contrast to papillitis (see question 81). Other more common causes of papilledema include CNS infection by toxoplasmosis or malignancy (lymphoma).

80. How should retrobulbar optic neuritis be diagnosed and managed in AIDS patients?

The etiology of retrobulbar optic neuritis in an AIDS patient is almost always infectious. Idiopathic optic neuritis is a diagnosis of exclusion. Prompt evaluation must include serology for *Cryptococcus,* syphilis, and varicella zoster virus. A lumbar puncture is also indicated. Patients should be questioned about history of syphilis or previous varicella zoster infection, and a review of medications should be done. Ethambutol and didanosine may cause toxic optic neuropathy. Treatment with corticosteroids is contraindicated.

81. What is papillitis?

Papillitis is direct infection of the visible intraocular portion of the optic nerve. The optic nerve appears white and necrotic (Fig. 39-11), and vision is severely compromised. CMV may cause papillitis, often in association with adjacent retinitis. Vision may improve after treatment with antiviral medications.

82. What is the most common malignancy in the periocular region in AIDS patients?

Kaposi's sarcoma is the most common periocular malignancy (Fig. 39-12). This aggressive tumor affects 35% of bisexual HIV-positive males and is viscerally disseminated in 70% of cases. Ocular

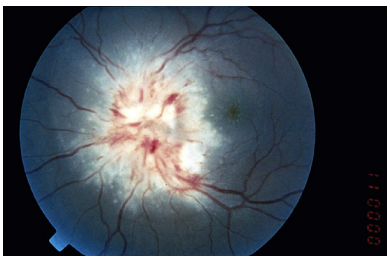

Figure 39-10. Papilledema caused by cryptococcal meningitis is characterized by optic disc swelling and blurring of the disc margins.

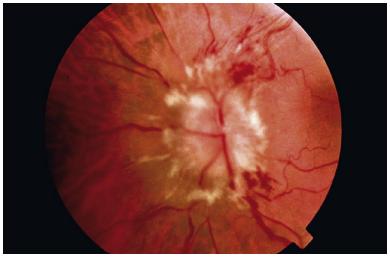

Figure 39-11. Note white, necrotic appearance and associated hemorrhage of entire optic disc in this example of papillitis secondary to cytomegalovirus.

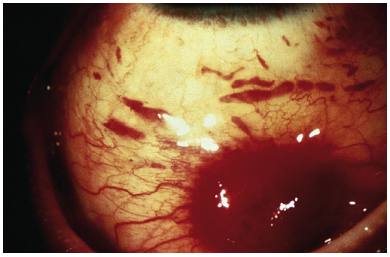

Figure 39-12. Kaposi's sarcoma of the conjunctiva most often occurs in the inferior cul-de-sac. Flat lesions may be easily mistaken for subconjunctival hemorrhage. *(Courtesy Drs. Carol and Jerry Shields.)*

findings are observed in 20% of patients with visceral disease. Skin lesions are more common than conjunctival lesions. Orbital tumors are rare. Treatment is indicated in patients with cosmetic or functional problems. Local ocular treatment is reserved for lesions that persist following systemic therapy. Conjunctival lesions may be excised, and skin lesions may be treated with cryotherapy (flat lesions) or external beam radiation (nodular lesions).[45,46]

83. What other periocular malignancies may develop?

Squamous cell carcinoma of the conjunctiva has been reported with increasing frequency in patients with AIDS. The lesions may mimic papillomas or be more characteristic masses with associated leukoplakia. Young patients with conjunctival squamous cell carcinoma should be tested for HIV.[47]

84. Which medications may be associated with ocular toxicity?

Rifabutin, when used in combination with clarithromycin and fluconazole, has been reported to cause severe hypopyon iritis and, in rare instances, sterile endophthalmitis. Ethambutol may cause optic neuropathy. Side effects of cidofovir include uveitis, hypotony, and nephrotoxicity.[48]

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CHAPTER 40

TOXIC RETINOPATHIES

Chrysoula Koutsiouki, Sobha Sivaprasad, and Philip G. Hykin

1. **Describe the clinical features of chloroquine retinopathy.**
Patients are usually asymptomatic but some may experience difficulties with reading due to paracentral scotomas or metamorphopsia. Because the initial retinal changes are in the parafoveal area, the visual acuity is typically normal in the early stages of retinopathy. Nyctalopia, color vision defects, and blurred vision occur when the retinal epithelial atrophy extends to involve the fovea. In the early stages of toxicity, mild mottling of the perifoveal retinal pigment epithelium is seen in conjunction with a reduced foveal reflex. Peripheral pigmentary changes often occur at this stage but may be overlooked. Macular pigmentary changes progress to a classic bull's eye maculopathy (Fig. 40-1). In the later stages, generalized retinal pigmentary changes occur with vascular attenuation and optic disc pallor.

2. **What doses of chloroquine and hydroxychloroquine cause retinopathy?**
Retinopathy is unlikely with a daily dose of <4 mg/kg/day chloroquine (CQ) or <6.5 mg/kg/day hydroxychloroquine (HCQ). A daily dose of >8 mg/kg/day hydroxychloroquine produces retinopathy in 40% of cases. Retinopathy is extremely unlikely with a total dose <100 g of chloroquine or <300 g of hydroxychloroquine and rare with total doses of <300 and <700 g, respectively.

3. **What are the risk factors for chloroquine and hydroxychloroquine retinopathy?**
The cumulative dose is believed to be the most important risk factor. A cumulative dose of 1000 g of HCQ is reached in 7 years with a typical daily dose of 400 mg, and a cumulative dose of 460 g of CQ is reached in 5 years with a typical daily dose of 250 mg. With daily doses of >6.5 mg/kg for HCQ and >3.0 mg/kg for CQ accumulation of the drug may enhance the rate or degree of toxic retinopathy. CQ and HCQ are excreted by the kidney and liver. Therefore, hepatic and renal failure/disease are risk factors, because they may contribute to increased blood levels of the drug. Other risk factors are age, genetic factors, and preexisting macular disease.

4. **How should patients taking chloroquine and hydroxychloroquine be monitored?**
All patients starting CQ or HCQ therapy should have a baseline examination within the first year of the treatment. The baseline examination should include careful biomicroscopy, automated threshold visual-field testing with a white 10-2 protocol for the detection of paracentral scotomas, and one or more further subjective tests for screening: spectral domain optical coherence tomography (SD-OCT) showing disorganization or loss of the ellipsoid layer in the parafoveal region of the macula is an early objective sign. Similarly, the multifocal electroretinogram (mfERG) is more sensitive in documenting localized paracentral functional loss compared to the white 10-2 visual field. Fundus autofluorescence (FAF) imaging may reveal paracentral foci of hyperfluorescence due to accumulation of outer segment debris within the retinal pigment epithelium (RPE) and hypofluorescent areas in the later stages due to RPE loss. Baseline color fundus photography may be useful for documentation. Annual screening should be performed after 5 years of treatment with CQ and HCQ as described above.

5. **What management is advised for chloroquine retinopathy?**
If retinal toxicity is present, hydroxychloroquine or chloroquine should be stopped immediately. There is a stage of very early functional loss when the cessation of the drug will reverse the toxicity, but progression typically continues although it is not clear if it is related to low excretion of the drug or to gradual decompensation of cells that were damaged during the period of drug exposure. If suggestive findings/visual symptoms occur, subjective tests should be repeated (automated fields, mfERG, SD-OCT, FAF). If toxicity is suspected, cessation of the CQ and HCQ followed by 3- to 6-monthly review is advised. Patients with probable toxicity (bilateral bull's eye scotoma, bilateral paracentral mfERG, SD-OCT/FAF abnormalities) should be closely monitored every 3 months.

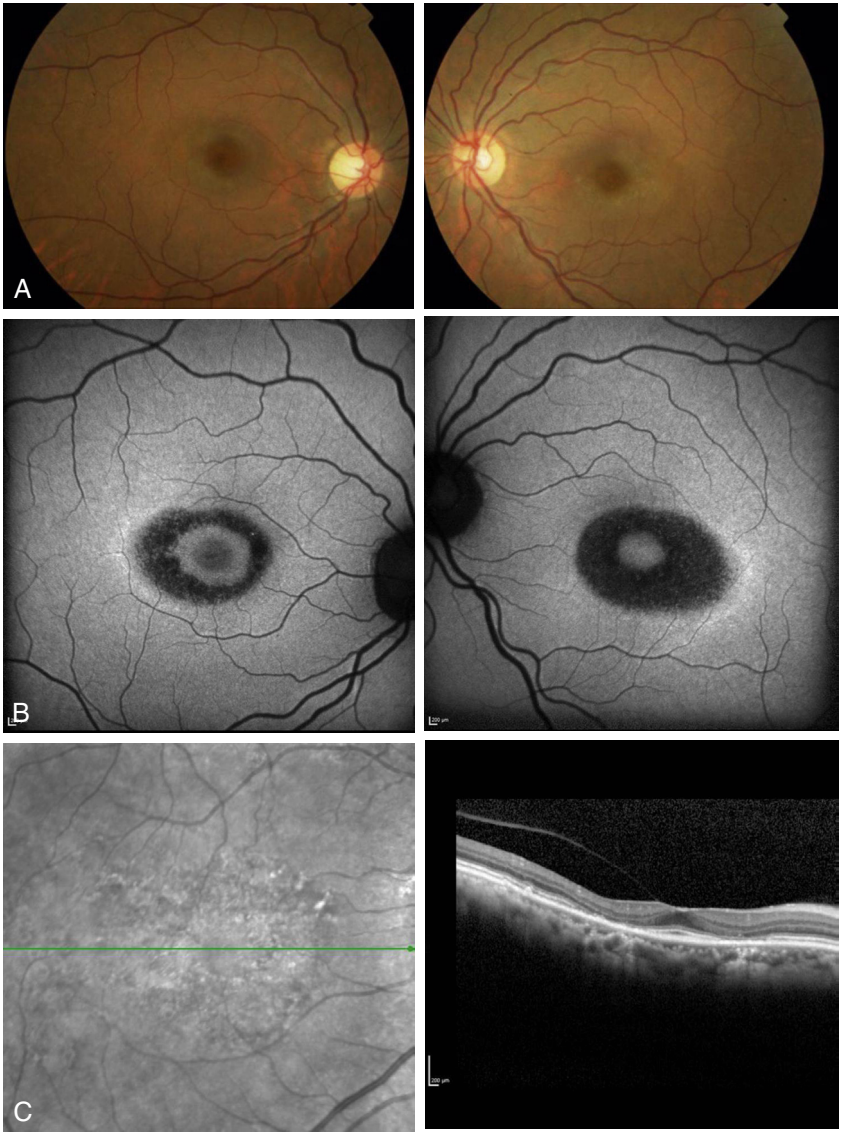

Figure 40-1. Bull's eye lesion due to chloroquine retinopathy: color photograph **(A),** autofluorescence image **(B),** magnified photograph of macula with associated spectral domain optical coherence tomography **(C).**

6. Is the pathogenesis of chloroquine and hydroxychloroquine retinopathy understood?

The earliest histopathologic changes of chloroquine retinopathy include membranous cytoplasmic bodies in ganglion cells and degenerative changes in the outer segments of the photoreceptors. However, chloroquine has a selective affinity for melanin, and it has been suggested that this affinity reduces the ability of melanin to combine with free radicals and protect visual cells from light and radiation toxicity. Other authors believe that the drug may directly damage photoreceptors.

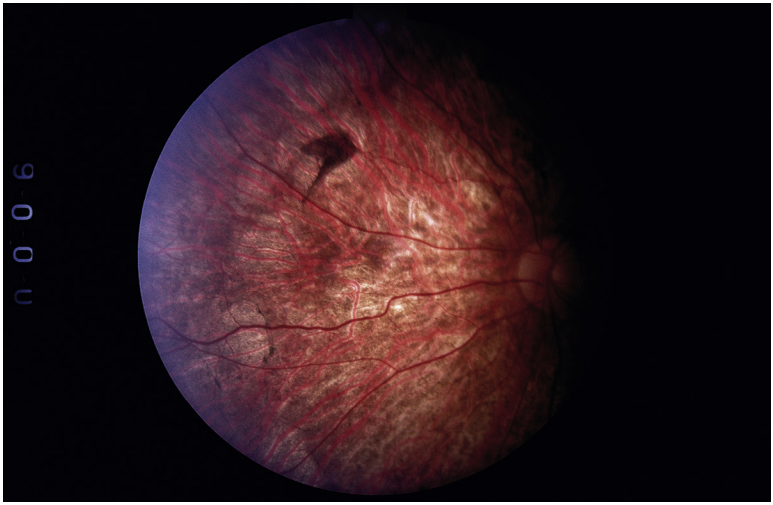

Figure 40-2. Thioridazine retinopathy.

7. How may thioridazine affect the retina?

Thioridazine (Mellaril) may cause nyctalopia, dyschromatopsia, and blurred vision. The earliest retinal changes are a fine mottling or granularity to the retinal pigment epithelium posterior to the equator, which may progress to marked pigmentary atrophy and hypertrophic pigment plaques (Fig. 40-2). Vascular attenuation and optic atrophy may follow. Toxicity is said to be uncommon with daily doses <800 mg/day but may develop rapidly with doses over 1200 mg/day. Toxicity is more dependent on total daily dose than on cumulative dose. In perimetry, a nonspecific but most characteristic finding is a paracentral or ring scotoma. Fluorescein angiography reveals the loss of RPE and choriocapillaris within the areas of depigmentation.

8. What other phenothiazines cause retinopathy?

Retinal toxicity has been reported with other phenothiazines, including chlorpromazine. However, these compounds are less likely to cause retinopathy, probably because they lack the piperidinylethyl side group of thioridazine. It is thought that 1200 to 2400 g/day chlorpromazine for at least 12 months is required before toxicity occurs.

9. How may quinine sulfate cause retinopathy?

Quinine sulfate is used for nocturnal cramps and as a malarial prophylaxis. It may cause retinal toxicity after a single large ingestion (4 g). The therapeutic window is narrow, with some patients taking a daily dose of 2 g. Patients develop blurred vision, nyctalopia, nausea, tinnitus, dysacusis, and even coma within 2 to 4 hours of ingestion. The acute findings include dilated pupils, loss of retinal transparency caused by ganglion cell toxicity (Fig. 40-3), and dilated retinal vessels. As the acute phase resolves, vessel attenuation and optic disc pallor result. Visual acuity may improve after the acute phase.

10. What are the similarities and differences in electrophysiologic tests between chloroquine and phenothiazine retinopathy?

The ERG in chloroquine toxicity may show an enlarged a wave and depressed b wave, whereas it is generally depressed in phenothiazine toxicity. The electro-oculogram (EOG) is decreased in both, but only progressive disease is significant in chloroquine retinopathy because some decrease is common shortly after starting chloroquine therapy. Dark adaptation may remain normal in chloroquine toxicity even in late cases, whereas it is typically delayed in phenothiazine toxicity.

11. What are the retinal toxic effects of sildenafil (Viagra)?

Sildenafil is an effective drug for erectile dysfunction, acting to inhibit phosphodiesterase type 5 (PDE-5) isoenzyme. It can also inhibit PDE-6 isoenzyme, an important enzyme in the retinal

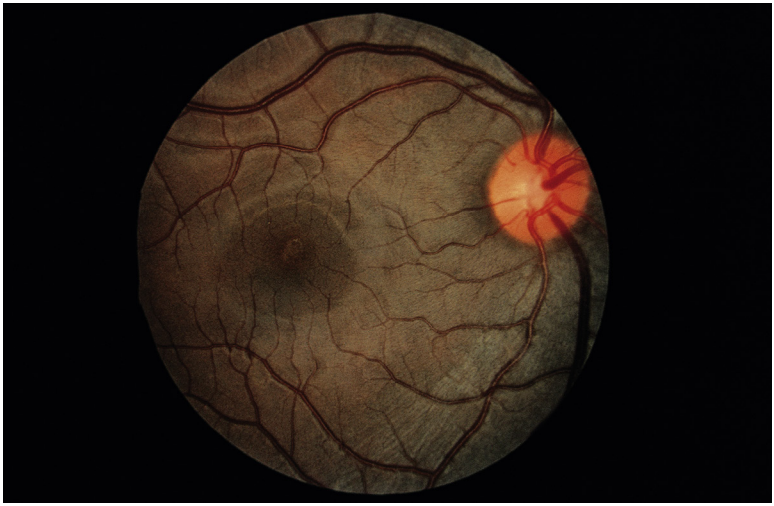

Figure 40-3. Mild loss of retinal transparency caused by quinine sulfate toxicity.

phototransduction cascade, and can cause reversible reduced amplitude of the a and b waves in an ERG. Overall 3 to 11% of patients may experience transient visual changes such as tinting of vision or photosensitivity lasting minutes to hours after the ingestion of the drug. Serious and permanent side effects have been described, including retinal hemorrhages, branch retinal vein and artery occlusion, anterior ischemic optic neuropathy, and acceleration of proliferative diabetic retinopathy.

12. How does cocaine abuse affect the retina?

Cocaine has both dopaminergic and adrenomimetic effects. Dopamine is found in high concentrations in the retina and plays an important role in color vision. Cocaine-withdrawn patients have significantly reduced blue cone b-wave amplitude responses on the electroretinogram and blue–yellow color vision defects. The adrenomimetic response and sudden increase in blood pressure associated with the intranasal use of cocaine may also cause retinal arterial occlusions.

13. What is vigabatrin retinotoxicity?

Vigabatrin (VGB) is an irreversible inhibitor of γ-aminobutyric acid transaminase and is a highly effective antiepileptic drug for treating partial-onset seizures and infantile spasms. It causes a characteristic form of peripheral retinal atrophy and nasal or "inverse" optic disc atrophy in approximately 10% of children being treated with VGB, resulting in severely constricted visual fields. Discontinuation of VGB should be strongly considered in these children.

14. How does fetal alcohol syndrome affect the retina?

Alcohol-induced malformations include hypoplastic optic discs and tortuous retinal vessels.

15. What is unusual about cystoid macular edema caused by nicotinic acid?

Nicotinic acid is used to reduce serum lipid and cholesterol levels for the treatment of hyperlipidemia. In doses of >1.5 g/day patients will report blurred vision sometimes associated with paracentral scotoma or metamorphopsia. Although typical cystoid macular edema is seen clinically, fluorescein angiography shows no leakage, suggesting that the edema is caused by a toxic effect on Müller cells resulting in intracellular edema. The incidence is low (0.67%) and dose related. The cystoid macular edema is reversible.

16. Name the substances that may cause crystalline retinopathy.

- Tamoxifen
- Canthaxanthin
- Talc (often used with intravenous drug abuse) (Fig. 40-4)

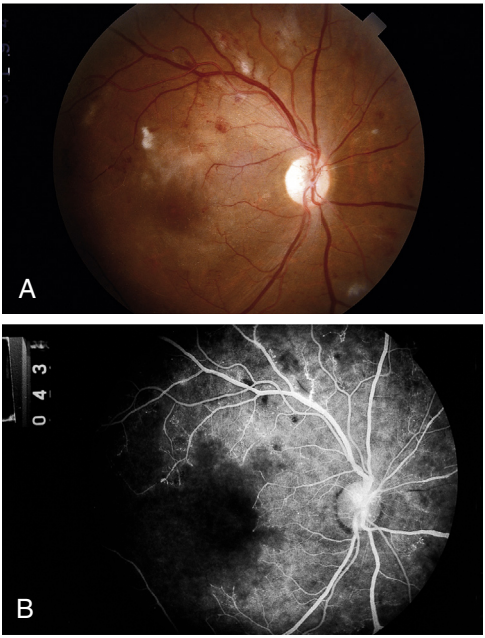

Figure 40-4. Talc retinopathy showing fine perifoveal talc particles **(A)** and extensive resultant posterior pole retinal vascular closure on fluorescein angiography **(B)**.

- Drugs that cause secondary oxalosis
  - Methoxyflurane anesthesia
  - Ethylene glycol
  - Salicylate ingestion in the presence of renal failure

17. What is the mechanism of the retinopathy caused by talc?

Talc is used as filler in methylphenidate hydrochloride (Ritalin) pills that drug addicts may crush and inject intravenously. Initially, the talc particles embolize the lungs, but after prolonged abuse (=12,000 pills), pulmonary arteriovenous shunts allow talc into the systemic circulation. Emboli to the retinal arterioles may lead to marked peripheral and posterior closure, resulting in retinal neovascularization, vitreous hemorrhage, and ischemic maculopathy.

18. How should talc retinopathy be managed?

Immediate cessation of Ritalin abuse is essential. If retinal neovascularization and vitreous hemorrhage are present, peripheral panretinal photocoagulation should be considered. There is no effective treatment for ischemic maculopathy.

19. What is xanthopsia? Which drug may cause it?

Xanthopsia is the unusual symptom of yellow vision. Along with hemeralopia (reduced visual acuity in the presence of increased background illumination), blurred vision, poor color vision, and paracentral scotomas, it is caused by digitalis toxicity.

20. What are the clinical features of tamoxifen retinopathy? How much drug is necessary to cause symptoms?

Patients are typically asymptomatic, although significantly reduced visual acuity has been reported in a subset of cases. Irreversible dot-like or refractile crystals are seen deposited in the inner retina and located predominately in the paramacular region and often associated with macular edema. The cumulative dose of tamoxifen seems to be important, with retinal deposits occurring more frequently after a 100-g lifetime dose. The overall prevalence is 1 to 6%.

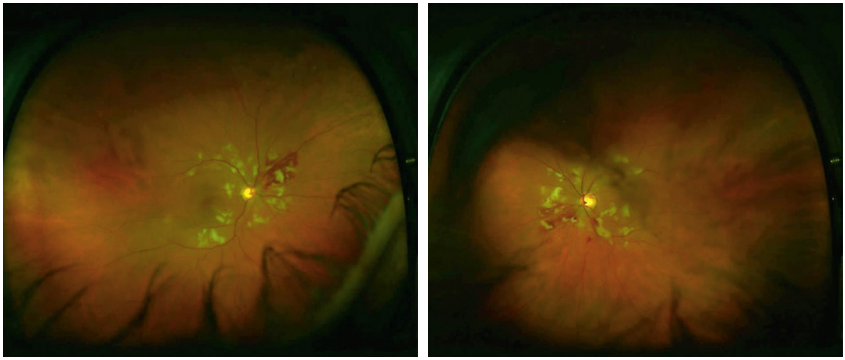

Figure 40-5. Tacrolimus-associated retinopathy.

No consistent ERG changes are seen. SD-OCT may prove to be a sensitive diagnostic tool in the future and may identify cases with macular hole, the risk of which appears to be increased in patients taking tamoxifen. Patients with documented visual loss or macular edema should discontinue the drug. Although vision may recover and macular edema resolve after cessation of tamoxifen, the retinal deposits will persist.

21. Can intraocular injection of antibiotics cause retinopathy?

Inadvertent intraocular injection of gentamicin may result in rapid onset of retinal whitening in the macular area, superficial and intraretinal hemorrhages, retinal edema cotton-wool spots, arteriolar narrowing, and venous beading. Optic atrophy and retinal pigment epithelial changes develop later. The visual prognosis is poor and neovascular glaucoma may develop. Fluorescein angiography will reveal severe vascular nonperfusion in the acute stages. Macular infarction has been reported after intravitreal injection of 400 μg. Similar problems may occur with tobramycin and amikacin.

22. What is interferon retinopathy?

Interferon-associated retinopathy is dose related and occurs in healthy patients 12% of the time. Sixty-five percent of diabetic patients and 50% of hypertensive patients taking interferon may develop retinopathy or have exacerbated current retinopathy. Ischemic retinopathy includes cotton-wool spots, retinal hemorrhages, cystoid macular edema, vascular occlusions, epiretinal membrane development, and optic disc edema. The mechanism may include immune complex deposition in the retinal vasculature and activated complement C5a followed by leukocyte infiltration and vascular closure. The EOG may become abnormal in early toxicity. Fluorescein angiography demonstrates poorly perfused areas of retina.

23. What is tacrolimus-associated retinopathy?

Tacrolimus is an effective immunosuppressive agent that inhibits cytokine synthesis and blocks T-cell development. Bilateral optic neuropathy and ischemic maculopathy were reported in patients after the use of tacrolimus. Rarely, tacrolimus toxicity may manifest as cotton-wool spots and superficial hemorrhages (Fig. 40-5). A direct neurotoxic effect on the RPE, cones, or rods has been hypothesized. The presentation is a gradual onset of bilateral blurred vision associated with nonspecific findings on OCT and fluorescein angiography but with a central scotoma on 10-2 threshold visual-field testing. Multifocal ERG has demonstrated foveal suppression in both eyes.

24. What effects may iron overload have on the retina?

A retained iron intraocular foreign body may lead to darkening of the iris, orange deposits in the anterior subcapsular region of the lens, anterior and posterior vitritis, pigmentary retinopathy, and progressive loss of visual field. The intraocular foreign body should be removed as soon as possible.

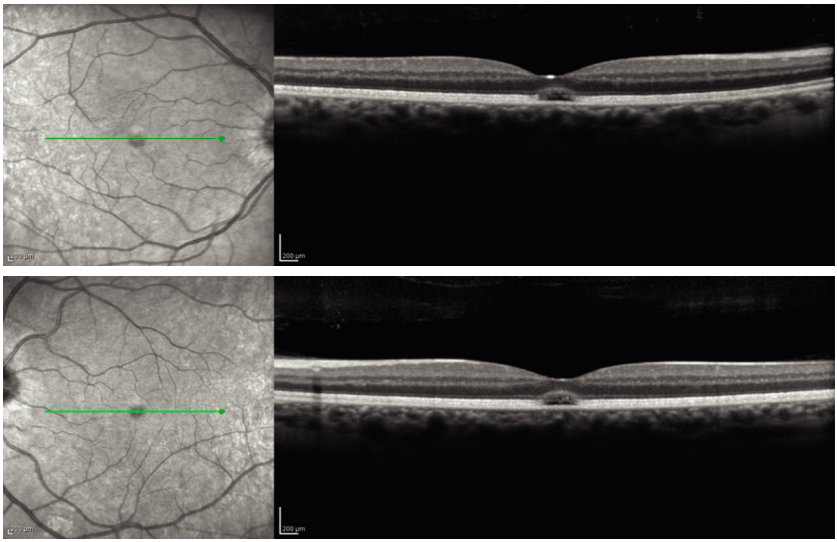

Figure 40-6. SD-OCT of poppers maculopathy.

25. What drugs can cause retinal thromboembolic events?

Oral contraceptives have been associated with central, branch, and cilioretinal artery occlusions and central retinal vein occlusion. Considerable controversy surrounds the role of oral contraceptives in causing these events, but stopping the oral contraceptive seems advisable. Talc retinal emboli are discussed in questions 17 and 18. Periorbital steroid injection with inadvertent arterial penetration may result in extensive embolization of the retinal circulation.

26. What chelating agents may cause maculopathy?

The chelating agents deferoxamine and deferasirox are used routinely for iron overload, particularly in thalassemia major. Deferoxamine is a siderophore that has been commercially available for over 30 years and may cause blurred vision, nyctalopia, and ring scotoma. The fundus may show bilateral widespread retinal pigment derangement. Deferasirox is a highly protein-bound synthetic chelator that became available in 2005. Preclinical and clinical trials of deferasirox reported it is well tolerated and does not cause toxic retinopathy, although one possible deferasirox-related retinopathy has been reported.

27. What is poppers maculopathy?

Poppers are a recreational substance of abuse belonging to the alkyl nitrite family of compounds. In the United Kingdom, the most commonly used compound is isopropyl nitrite, which can be purchased legally, but is illegal to sell for human consumption. The exact mechanism of central photoreceptor damage is unknown. The patient presents with the symptoms of a central scotoma, distortion of vision, and phosphenes. Clinical signs range from a normal foveal appearance to yellow, dome-shaped lesions at the fovea. Disruption or loss of the presumed ellipsoid layer on SD-OCT is the characteristic feature (Fig. 40-6).

28. Which cancer therapy drugs can cause toxic retinopathies?

The retina is among the most metabolically active tissues in the body, making it vulnerable to unwanted side effects of chemotherapeutic agents. Biologic agents, small-molecule inhibitors, and chemotherapies can all cause toxic retinopathies. Clinical findings noted with monoclonal antibodies include choroidal neovascularization (Ipilimumab) and macular edema, hemorrhages, and hard exudates (Trastuzamab). Chemotherapies such as cisplatin may cause retinal/macular pigment changes or, rarely, retinal ischemia, neovascularization, intraretinal hemorrhages, and exudates. Retinoid acid derivatives such as isotretinoin may cause nyctalopia.

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CHAPTER 41

COATS DISEASE

William Tasman

1. **What is Coats disease?**
   Exudation, retinal telangiectasia, and retinal aneurysms are hallmarks of the disorder, named for the British ophthalmologist George Coats, who first described this condition in 1908. It comes on painlessly and may be slow and insidious in its development. In many instances, Coats disease is not discovered until the patient is beyond childhood.

2. **List the clinical characteristics of Coats disease.**
   - It is a lifetime disease.
   - It occurs 80% to 90% of the time in young boys.
   - It is usually unilateral.
   - It is not familial.
   - Characteristic retinal vascular lesions are telangiectatic-like "light bulb" aneurysms that are associated with capillary dropout in the fundus periphery (Fig. 41-1, *B* and *D*).
   - Intraretinal and subretinal exudation, a prominent feature, has a predilection to accumulate in the macular area (Fig. 41-1, *A* and *C*); the exudate contains cholesterol crystals.
   - Coats disease may lead to exudative retinal detachment, cataract, neovascular glaucoma, and phthisis bulbi.

3. **What percentage of patients are girls?**
   Between 8% and 10% of patients are girls.

4. **What is the most common age at which Coats disease becomes apparent?**
   Coats disease usually becomes apparent between 8 and 10 years of age. However, it can present in infancy and later in life. It is often much more severe when noted in infancy.

5. **What percentage of cases are unilateral versus bilateral?**
   Approximately 80% to 90% of the cases are unilateral. When bilateral cases do develop, there is usually asymmetry, with one eye being much more involved than the other.

6. **Are the retinal vascular changes easy to detect?**
   If the patient is cooperative, it is not hard to diagnose the peripheral retinal vascular changes. However, examination under general anesthesia may be necessary in younger patients.

7. **How does this condition differ from Leber's miliary aneurysms?**
   In 1912, Leber described retinal miliary aneurysms. He suggested that the conditions were one and the same as that reported by Coats, and that is the generally accepted thinking at the present time.

8. **Do we know the etiology of Coats disease?**
   The precise etiology for Coats disease has not been determined.

9. **Are there any conditions with which Coats disease can be confused?**
   When there is exudation in the macula and peripheral telangiectasia, and no retinal detachment, the Coats disease can be diagnosed with confidence. There are a number of conditions to rule out, most notably retinoblastoma, the malignant intraocular tumor that occurs in infancy and childhood. It has been estimated that approximately 3.9% of eyes originally diagnosed as harboring retinoblastoma were subsequently discovered to have Coats disease. See Table 41-1.

10. **Can conditions other than retinoblastoma simulate Coats disease?**
    Angiomatosis retinae (von Hippel-Lindau syndrome), one of the phakomatoses, can cause exudation in the macula. This condition is inherited in an autosomal dominant fashion and has visceral and central nervous system hemangioblastomas as part of the syndrome. In addition, visceral cysts and tumors, including renal cell carcinoma, may occur. Early in its onset, the fundus picture is different from that of Coats disease in that angiomatosis retinae demonstrates a dilated and

tortuous afferent arteriole and an efferent draining venule that enters and leaves a reddish balloon-like mass, usually in the fundus periphery. If the capillary angioma is on the disc, it may be associated with macular exudation, making the differential diagnosis from Coats disease more difficult. Other conditions to be considered in the diagnosis are familial exudative vitreoretinopathy (FEVR), persistent fetal vasculature (PVF), and retinopathy of prematurity (ROP). FEVR is a dominantly inherited condition that may have a Coats-like response. PVF was previously known as persistent hyperplastic primary vitreous. It is usually unilateral and occurs in a microphthalmic eye. ROP may present with retinal detachment but usually occurs in patients with a history of significant prematurity.

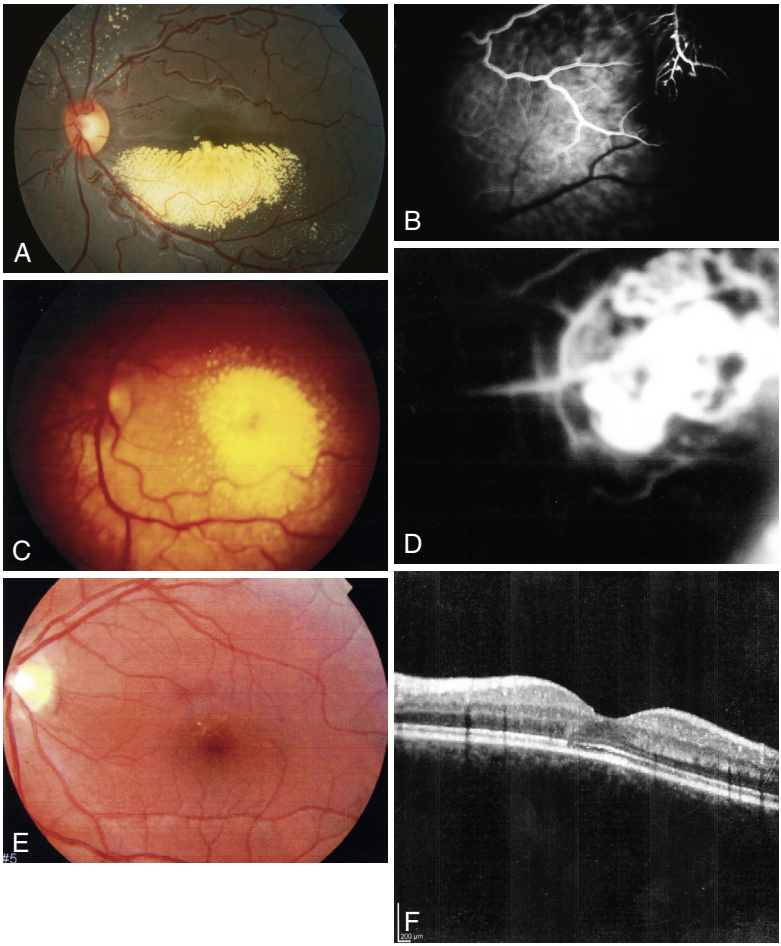

Figure 41-1. A, Pretreatment photograph of exudate in the posterior pole of a 10-year-old male with Coats disease. **B,** Peripheral vascular retinal changes of patient shown in A. **C,** Although Coats disease predominantly affects males, females may also develop the disease, as seen in this 9-month-old girl. **D,** Peripheral retinal vascular changes are present in the temporal periphery of the patient shown in C. **E,** The 9-month-old baby girl is now 22 years of age and has not had a recurrence. **F,** After resorption of the exudate in the patient shown in E the OCT shows a normal macular appearance, but best corrected vision is only 20/200 despite patching in childhood.

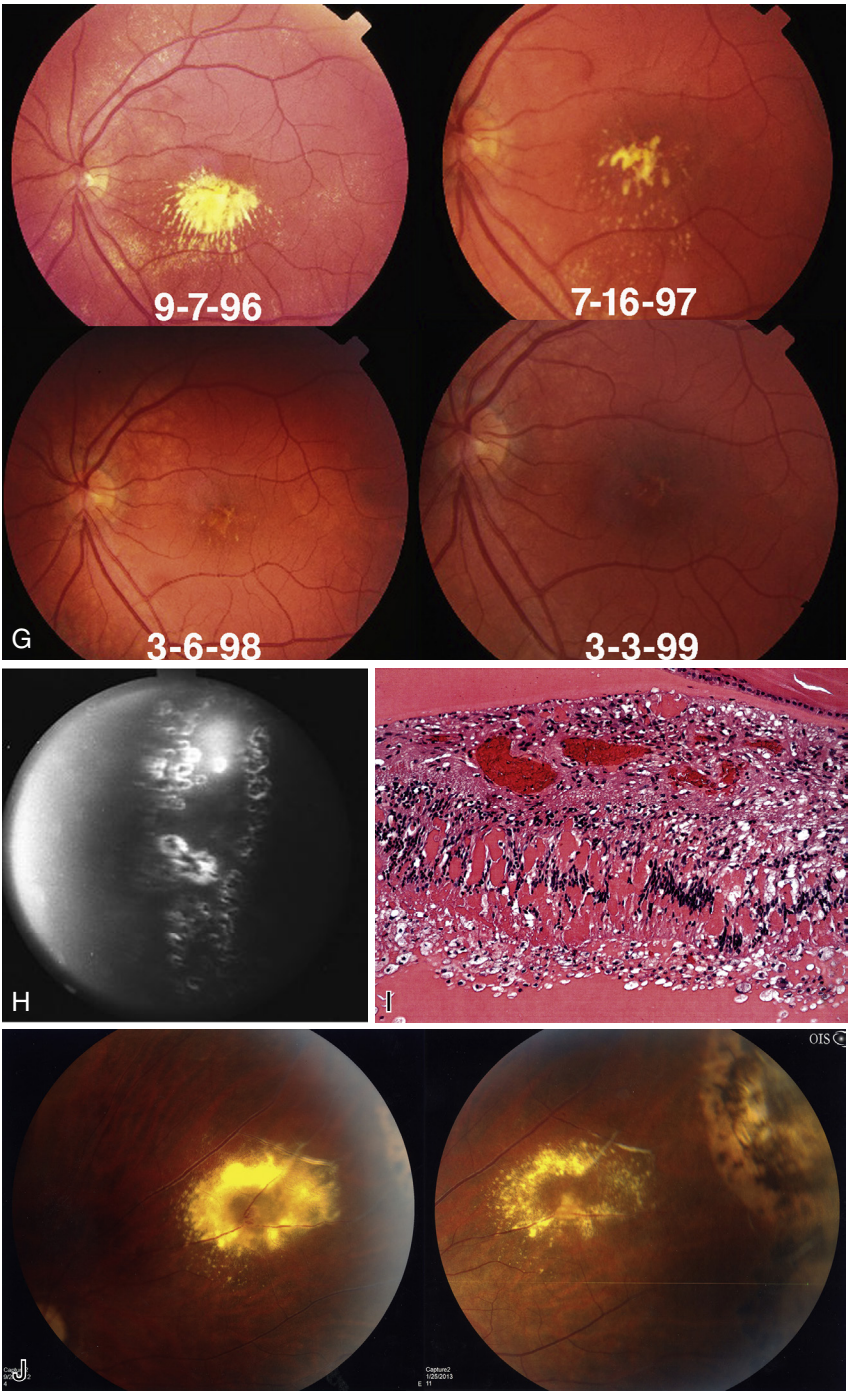

Figure 41-1, cont'd G, Exudate disappearing after laser treatment. **H,** Microaneurysmal changes in a patient with Coats disease. **I,** Histopathologic section of the retina in a patient with Coats disease with bullous retinal detachment almost touching the posterior lens capsule secondary. Aneurysmal changes can be seen in the nerve fiber layer. *(Courtesy of Dr. Ralph Eagle.)* **J,** Recurrent Coats in a 26-year-old male diagnosed at 5 years of age. Exudate is beginning to diminish 3 months after retreatment.

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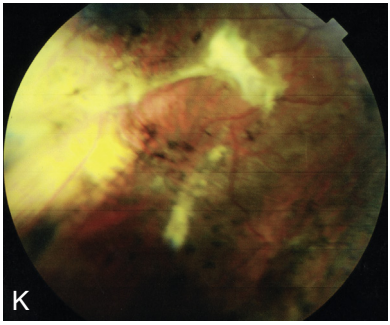

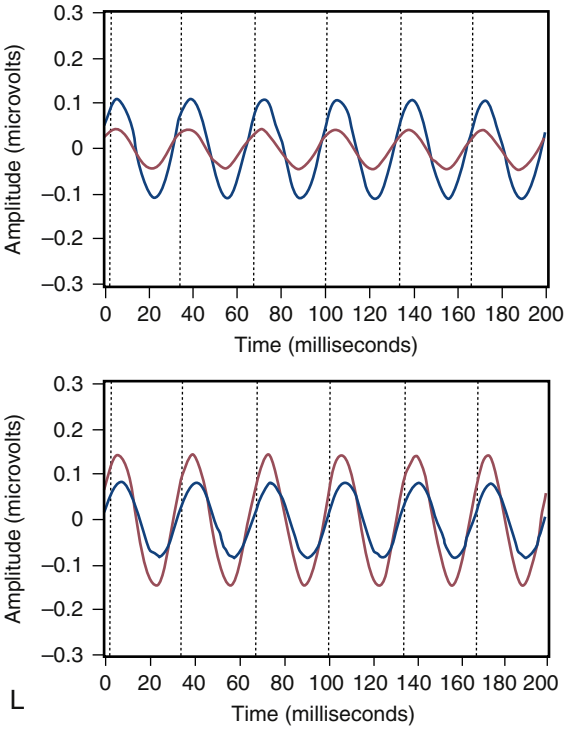

Figure 41-1, cont'd K, 27-year-old male with retinitis pigmentosa and Coats disease. **L,** The patient in J has reduced and delayed hertz (hz) cone electroretinogram both eyes compatible with retinitis pigmentosa.

Table 41-1. Differential Diagnosis of Coats Disease

1. Retinoblastoma
2. Familial exudative vitreoretinopathy
3. Von Hippel-Lindau disease
4. Retinopathy of prematurity
5. Persistent fetal vasculature

11. Other than fluorescein angiography, what may be helpful in confirming the diagnosis?

Ultrasonography and computed tomographic (CT) scans may help to differentiate between Coats disease and retinoblastoma by detecting the presence or absence of subretinal calcifications. Calcification is found in retinoblastoma, but it is extremely rare in Coats disease.

12. Is it advisable to obtain a computed tomographic scan?

CT scanning is perhaps the single most valuable test in diagnosing Coats disease because of its ability to delineate intraocular morphology, to qualify retinal densities, and to detect associated orbital or intracranial abnormalities. However, this does expose a young patient to low levels of radiation, especially if studies are repeated periodically.

13. Can aspiration of subretinal exudates aid in diagnosis?

The key diagnostic findings in the analysis of subretinal aspirates are the presence of cholesterol crystals and pigment-laden macrophages and the absence of tumor cells. This technique should be reserved for patients in whom retinoblastoma has been ruled out by all other noninvasive means, because tumor seeding may occur.

14. How is Coats disease managed?

If possible, it is desirable to treat the condition before exudate accumulates in the macular area. Treatment is directed at the peripheral vascular abnormalities. Photocoagulation can be used to eliminate these abnormal vessels. In patients with exudation under the peripheral vascular telangiectasia, cryotherapy may be preferable (Fig. 41-1, *D*). Elimination of the defective vessels prevents further leakage and is followed by resorption of the exudate over ensuing months. Because patients have been found to have elevated levels of vascular endothelial growth factor (VEGF), bevacizumab, triamcinolone, and dexamethasone have been injected intravitreally. Most of the time these drugs have been used as adjuvants to laser or cryotherapy. However, dramatic improvement has occasionally been reported when bevacizumab has been used as the primary mode of therapy. With the use of steroids, cataract has to be considered as a potential complication.

15. How long does it take for the exudate to disappear?

Resorption of the exudate may take up to a year or more before it is completely gone. Its disappearance becomes apparent in the first few months after treatment. Solid masses of exudate take on a more speckled appearance as the exudate goes away.

16. Is more than one treatment necessary?

If more than two quadrants have retinal telangiectasia, two or three treatments may be required.

17. Once the abnormal vessels are gone, is the patient considered cured?

Recurrence, which is usually heralded by the reappearance of exudate and is almost always associated with new vascular abnormalities, can occur even many years later. It is recommended that patients be scheduled for follow-up appointments at 6- to 12-month intervals throughout their lifetime. See Table 41-2.

18. Can this condition be managed once the retina has detached?

Vitreoretinal surgery may, in some cases, help to reattach the retina. At the time of surgery, it is necessary to treat the abnormal vessels by laser photocoagulation or cryotherapy. The vision in these eyes,

Table 41-2. Recurrence of Coats

Number of patients: 13
• Males: 11 (85%)
• Females: 2 (15%)
Average follow-up: 12.4 years
• Range: 4 to 58 years
Average number of recurrences: 3.3
Oldest patient at time of recurrence: 58 years

however, is usually quite limited, and sometimes, despite reattachment of the retina, there is no light perception.

19. If left untreated, what is the outcome?

Untreated Coats disease does not invariably lead to intractable glaucoma. However, retinal detachment and neovascular glaucoma are the ultimate complications that may precede phthisis and loss of the globe.

20. When should an eye with Coats disease be enucleated?

When retinoblastoma cannot be ruled out or when neovascular glaucoma is present in blind, painful eyes, enucleation is the best option.

21. Can Coats disease occur with any other retinal conditions?

Coats disease may occur in conjunction with retinitis pigmentosa. Retinal antigen autoimmune reactivity may play a role in specific types of retinitis pigmentosa. In addition, retinitis pigmentosa has been noted to be associated with muscular dystrophy, and the son of a mother with retinal telangiectasis had Norrie disease.

KEY POINTS OF COATS DISEASE

1. Affected patients are predominantly male of ages 8 to 12, but may present in infancy as well.
2. Exudate often accumulates in the macular area owing to abnormal peripheral telangiectatic and aneurysmal changes.
3. Retinoblastoma is important to rule out noninvasively with ultrasound and sometimes CT scan because of its malignant nature.
4. Primary treatment is usually laser or cryotherapy. Anti-VEGF treatment can be helpful.
5. It is a lifetime disease because multiple recurrences may occur in about one of three patients, 3 to 4 years or more after what appears to be successful resolution of the disease.

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FUNDUS TRAUMA

Jeffrey P. Blice

CHAPTER 42

1. What are the mechanisms of injury to the fundus in blunt trauma?

Blunt trauma to the sclera can produce a direct effect on the underlying choroid and retina. In addition, a concussive effect from force transmitted through the vitreous may be seen away from the initial point of impact. The sudden deformation of the globe may cause stretching of the retina and retinal pigment epithelium (RPE) and traction on the vitreous base. The shearing forces generated by this traction may tear the retina in the area of the vitreous base or result in avulsion of the vitreous base. Forces can be severe enough to avulse the optic nerve (Fig. 42-1).[1]

2. What clinical entity is caused by the contrecoup mechanism?

Indirect damage from the concussive effect of an injury tends to occur at the interfaces of tissue with the greatest differences in density, most commonly the lens–vitreous interface and the posterior vitreoretinal interface. The transmitted force may cause fragmentation of photoreceptor outer segments and damage to the receptor cell bodies. Clinically, these areas appear as opacified retina and are termed *commotio retinae*. Although the retinal whitening is only temporary, resolving over 3 to 4 weeks, permanent damage may occur. Loss of vision depends on the amount and location of early photoreceptor loss. The RPE underlying an area of commotio may develop a granular hyperpigmentation or atrophic appearance and lead to decreased vision. The eponym associated with this entity is Berlin's edema; however, there is no true intracellular or extracellular edema, and no fluorescein leakage is seen.

3. Name the five types of retinal breaks seen in fundus trauma.

- Retinal dialyses
- Horseshoe tears
- Operculated holes
- Macular holes
- Retinal dissolution (necrosis)[2]

4. Where are retinal dialyses most commonly seen?

Retinal dialyses are usually located in the superonasal or inferotemporal quadrants (Fig. 42-2). Trauma is more clearly related to superonasal than to inferotemporal dialyses. Dialyses may be associated with avulsion of the vitreous base. Because they can lead to retinal detachment, a careful depressed exam of all patients with a history of blunt trauma is essential. Prophylactic treatment of all dialyses with cryopexy or laser photocoagulation is recommended in the hope of decreasing the likelihood of future retinal detachments.[3]

5. When do retinal detachments occur with dialyses?

Retinal detachments present at variable intervals after injury; however, the dialysis is usually detectable early or immediately at the time of injury. Approximately 10% of dialysis-related detachments present immediately, 30% within 1 month, 50% within 8 months, and 80% within 2 years. Most trauma victims are young, with a formed vitreous that tamponades a break or dialysis, but as the vitreous eventually liquefies, fluid passes through retinal breaks causing detachments. The nature of the vitreous in such cases may explain the delay in presentation of the detachments.[4]

6. In addition to retinal dialyses, do other trauma-related breaks need to be treated prophylactically?

Horseshoe tears and operculated holes in the setting of acute trauma are usually treated by cryopexy or laser photocoagulation. Macular holes require pars plana vitrectomy with gas exchange if closure of the hole is attempted; however, macular holes usually do not progress to retinal detachments. Surgery is not performed for the purposes of prophylactic closure. Direct injury with necrosis of the retina is usually associated with underlying choroidal injury so that a chorioretinal adhesion may be formed spontaneously. However, any accumulation of subretinal fluid or persistent traction on damaged retina makes prophylactic treatment reasonable.

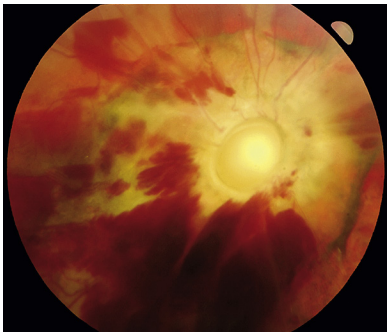

Figure 42-1. Optic nerve avulsion after severe blunt trauma.

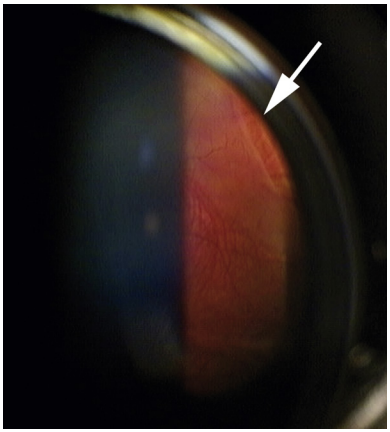

Figure 42-2. Retinal dialysis *(arrow)* with associated chronic retinal detachment through contact lens.

7. What is the prognosis for repair of a retinal detachment associated with a dialysis?

Dialysis-related detachments are usually smooth, thin, and transparent. Intraretinal cysts are common, and half have demarcation lines. In addition, proliferative vitreoretinopathy is rare. The characteristics of the detachment are suggestive of its chronic nature and insidious onset; however, the prognosis for repair with conventional scleral buckling techniques is good.

8. Are traumatic macular holes the same as typical macular holes?

Traumatic macular holes often behave differently compared to a typical macular hole formed as a result of vitreoretinal interface disease. Traumatic macular holes that form immediately at the time of initial injury may close spontaneously. Those that fail to close after a few months of observation can be anatomically improved by surgical intervention. However, the improvement in vision may be disappointing. The initial trauma can result in retinal damage that is incompatible with good vision. Careful consideration by the surgeon in discussions with the patient is required before considering surgical intervention.

9. Describe the clinical features of a choroidal rupture.

The retina is relatively elastic, and the sclera is mechanically strong. The Bruch's membrane, the structure between the retinal pigment epithelium and the choriocapillaris, is neither elastic nor strong. Consequently, it is susceptible to the stretching forces exerted on the globe in blunt trauma. The Bruch's membrane usually tears along with the choriocapillaris and RPE. Choroidal ruptures may be

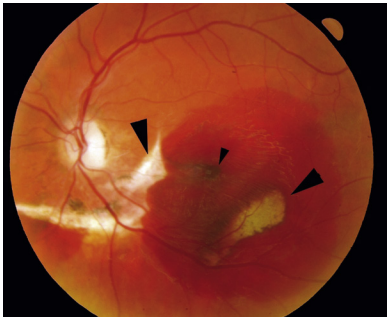

Figure 42-3. Choroidal ruptures *(large arrowheads)* located concentric to the optic nerve. The *small arrowhead* indicates the center of the associated subretinal hemorrhage.

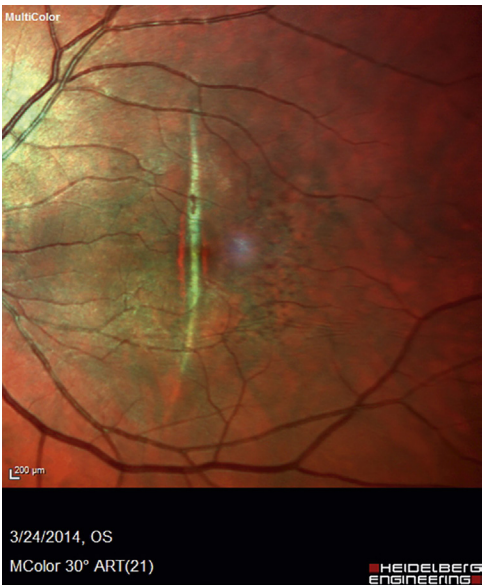

Figure 42-4. Choroidal rupture color photograph corresponding to OCT scan in Fig. 42-5.

found at the point of contact with the globe or in the posterior pole as a result of indirect forces. Clinically, choroidal rupture appears as a single area or multiple areas of subretinal hemorrhage, usually concentric and temporal to the optic nerve (Fig. 42-3). The hemorrhage may dissect into the vitreous. As the blood resolves, a crescent-shaped or linear white area is seen where the rupture occurred. With time, surrounding RPE hyperplasia or atrophy may be seen. Linear white areas are most consistent with a fibrotic response following the resolution of the hemorrhage. This can be seen on optical coherence tomography (OCT) (Figs. 42-4 and 42-5).[5]

10. Are there any long-term complications of choroidal ruptures?

The visual consequences of a choroidal rupture depend on its location with respect to the fovea. A patient with a choroidal rupture near the fovea may have good vision; however, the break in the Bruch's membrane predisposes him or her to the development of a choroidal neovascular membrane, which may threaten vision long after the initial injury. Therefore, patients at risk should be followed regularly and advised of the potential complication.

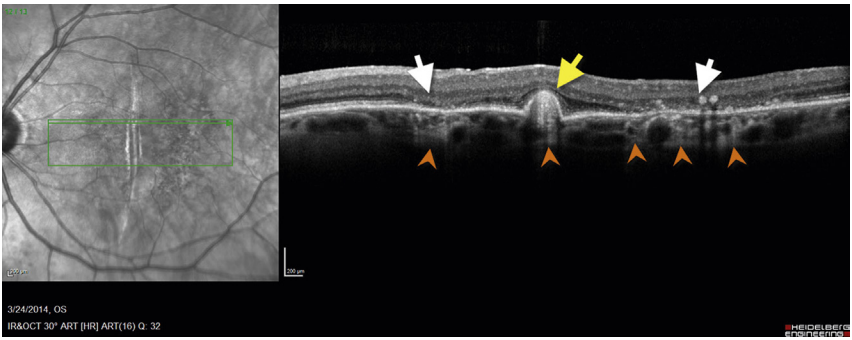

Figure 42-5. An OCT scan through the choroidal rupture in color photograph Fig. 42-4. There is an elevated mound of fibrosis visible at the level of the choroid *(yellow arrow)* with an absence of normal retinal architecture. Areas of disrupted outer retinal anatomy with absence of the ellipsoid line are shown by the *white arrows.* The *orange arrowheads* indicate increased transmission through the damaged RPE.

11. Can orbital adnexal trauma result in fundus abnormalities?

High-velocity missile injuries may cause an indirect concussive injury to the globe, resulting in retinal breaks and ruptures in the Bruch's membrane that resemble a claw. A fibroglial scar with pigment proliferation forms, but retinal detachment is rare, possibly because a firm adhesion develops, acting as a retinopexy. Chorioretinitis sclopetaria is the name given to this clinical entity.

KEY POINTS: RETINAL BREAKS IN BLUNT TRAUMA

1. The five types of breaks are horseshoe tears, operculated tears, dialyses, retinal dissolution, and macular holes.
2. Retinal dialyses usually occur superonasally in trauma.
3. A total of 50% of dialysis-related detachments present within 8 months.
4. A dialysis-related detachment has a very high success rate with treatment by scleral buckling.

12. What are the signs of a scleral rupture?

When a laceration or obvious deformation of the globe is not visible, other findings raise the index of suspicion that an injury may be more serious than initially thought. The presence of an afferent pupillary defect (APD), poor motility, marked chemosis, and vitreous hemorrhage raise the suspicion of an open globe. Other findings that may be helpful include a deeper than normal anterior chamber and a low intraocular pressure; however, in an eye with a posterior rupture and incarcerated uvea the intraocular pressure may be normal.

13. Why is the initial exam of a severely traumatized eye important?

A poor outcome is associated with initially poor visual acuity, presence of an APD, large wounds (>10 mm) or wounds extending posteriorly to the rectus muscles, and vitreous hemorrhage. The first person to evaluate the traumatized eye may have the only opportunity to assess the best visual acuity. The delay often associated with referral to other institutions or dealing with life-threatening complications may result in diffusion of vitreous hemorrhage and corneal or other anterior segment abnormalities that preclude an adequate view of the posterior segment. The first look may be the only look at a traumatized eye.[6]

14. Where is the most likely place for a globe to rupture?

The globe may rupture anywhere, depending on the nature of the injury. However, the globe most often ruptures at the limbus, beneath the rectus muscles, or at a surgical scar. The sclera is thinnest and therefore weakest behind the insertions of the rectus muscles. The site of a previous cataract extraction or glaucoma procedure is weaker than normal sclera.

15. Outline the goals of managing a ruptured globe.

1. Identify the extent of the injury. Perform a 360-degree peritomy, inspecting all quadrants. If necessary, disinsert a muscle to determine the extent of a laceration.
2. Rule out a retained foreign body. In any case of projectile injury, sharp lacerations, uncertain history, or questionable mechanism of injury, consider a computed tomographic (CT) scan to detect a foreign body.
3. Close the wound, and limit reconstruction as much as possible. Close the sclera with a relatively large suture (e.g., 8-0 or 9-0 nylon), and reposit any protruding uvea. If vitreous is protruding, cut it flush with the choroidal tissues, using fine scissors and a cellulose sponge or automated vitreous cutter.
4. Guard against infection. Start prophylactic systemic antibiotic treatment. An intravenous (IV) aminoglycoside or third-generation cephalosporin in combination with vancomycin (e.g., ceftriaxone, 1 to 2 mg every 12 hours, and vancomycin, 1 mg every 12 hours) is acceptable. Alternatively, a systemic fluoroquinolone may be used initially IV with an oral regimen for outpatient care (e.g., levofloxacin 500 or 750 mg daily). Clindamycin can be added if coverage for *Bacillus* spp. is desired.
5. Protect the remaining eye. Place a shield over the fellow eye during the repair procedure to prevent accidental injury. Counsel the patient at the earliest opportunity about the need for protective eyewear to prevent future injury.

KEY POINTS: GLOBE RUPTURES

1. Vitreous hemorrhage, poor vision, APD, and massive chemosis/subconjunctival hemorrhage are the hallmarks of a ruptured globe.
2. The globe is most likely to rupture at the limbus, underneath a rectus muscle, or at a previous surgical site.
3. Large ruptures (>10 mm) are associated with a poor prognosis.
4. Sympathetic ophthalmia is an exceedingly rare complication.
5. Remember to protect the remaining eye during repair and afterward.

16. Discuss the role of CT and magnetic resonance imaging (MRI) in the detection of intraocular foreign bodies.

The best method of detecting intraocular foreign bodies is indirect ophthalmoscopy (Fig. 42-6). If a view of the posterior segment is impossible, CT is the next best alternative. A CT scan is excellent for the detection of metallic foreign bodies but also detects glass or even plastic foreign bodies in some instances (Fig. 42-7). When an organic foreign body is suspected, MRI offers the advantage of better soft-tissue discrimination and is an excellent supplement to CT. However, any suspicion of a metallic foreign body prevents the use of MRI. Ultrasonography also supplements the information provided by a CT, possibly detecting a radiolucent foreign body as well as providing information about the status of the retina and vitreous. Plain films of the orbit are still useful for the detection of a foreign body if a CT scanner is not available; however, the ability to localize and detect nonmetallic foreign bodies is more limited.

17. What ultrasound artifacts are important to recognize in the evaluation of a traumatized globe?

The appearances of intraocular foreign bodies on ultrasonography are related to the nature, shape, and size of the foreign body, in addition to the angle of incidence of the sound waves. Reverberations and shadowing are characteristic ultrasound artifacts seen with intraocular foreign bodies. Reverberations are the multiple echoes that appear behind the initial reflection from a foreign body. Shadowing is the absence of echoes seen behind the initial reflection from a foreign body. Both of these artifacts may be demonstrable on the same patient by altering the angle of incidence of the ultrasound.

18. Do all intraocular foreign bodies need to be removed immediately? Which ones require early vitrectomy for removal?

Not all foreign bodies do not require immediate removal. The decision to remove a foreign body at the time of initial repair is complex and depends somewhat on the preferences of the surgeon and

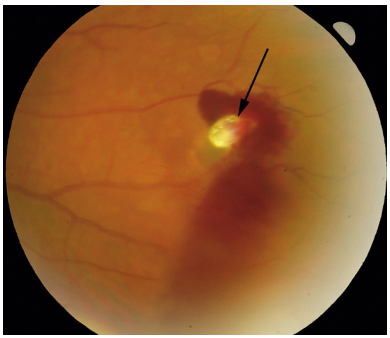

Figure 42-6. Fundus photograph of intraocular foreign body *(arrow)* resting on the surface of the retina.

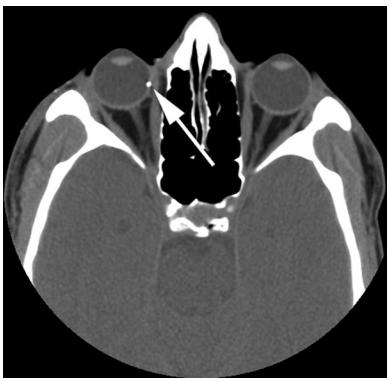

Figure 42-7. Computed tomographic scan demonstrating the presence of a small intraocular foreign body *(arrow)* located nasally.

the specific situation. However, in a patient with acute traumatic endophthalmitis or a known toxic or reactive foreign body, vitrectomy with removal of any intraocular foreign bodies at the time of initial repair, or soon after, is a reasonable option.[7]

19. Which metals are toxic to the eye?

The toxicity of a metal is related to the reduction–oxidation potential (redox potential). Metals such as copper and iron have a low redox potential and tend to dissociate into their respective ionic forms, which makes them more toxic. Pure forms are more reactive than alloys. The ocular toxicity from an iron foreign body is called *siderosis*. When copper is the offending agent, the condition is *chalcosis*. Other metals such as gold, platinum, silver, and aluminum are relatively inert. Nonmetallic substances such as glass, plastic, porcelain, and rubber are also relatively inert and pose no threat of toxicity on the basis of their chemical composition.

20. List the clinical findings in siderosis bulbi.

Iron tends to be deposited in epithelial tissues. An affected eye has hyperchromic heterochromia of the iris and a middilated, minimally reactive pupil. Brownish dots are visible in the lens from iron deposition in the lens epithelium, along with generalized yellowing of the lens from involvement of the cortex. The retinal effects of iron toxicity can be detected and followed by electroretinography (ERG). Pure iron particles may cause a flat ERG in 100 days. Clinically, a pigmentary degeneration with sclerosis of vessels, retinal thinning, and, later, atrophy develops in the periphery and progresses posteriorly. If not removed initially, the potential toxic effects of a foreign body can be monitored by clinical exam and serial ERG. However, siderosis generally causes progressive gradual permanent visual loss unless the foreign body is removed.

21. Do all copper foreign bodies cause chalcosis?

Foreign bodies composed of less than 85% pure copper cause chalcosis; greater than 85% pure copper foreign bodies cause sterile endophthalmitis. Copper ions are deposited in basement membranes. In the peripheral cornea, a Kaiser Fleischer ring is a brownish discoloration of the Descemet's membrane. The iris may be sluggishly reactive to light and have a greenish color. Deposition of copper in the anterior capsule results in a "sunflower" cataract, and the vitreous may become opacified. ERG findings are similar to those found in siderosis but may improve if the foreign body is removed.

KEY POINTS: INTRAOCULAR FOREIGN BODIES

1. The best method of detection is indirect ophthalmoscopy whenever possible.
2. An intraocular foreign body does not usually require immediate removal.
3. Topical and systemic antibiotics are required as prophylaxis against endophthalmitis.
4. MRI is contraindicated in any patient with a suspected metallic intraocular foreign body.
5. Iron can cause siderosis and copper can cause chalcosis or sterile endophthalmitis.

22. Which organisms most commonly cause posttraumatic endophthalmitis?

The most common organism associated with endophthalmitis in the setting of acute trauma is *Staphylococcus aureus*. Skin flora are the most likely source of contamination of a traumatic ocular wound. Infections caused by *Bacillus cereus*, although much less common (estimates range from 8% to 25%), are important because of the severity and damage caused by the infection. In any ocular injury contaminated by soil, the possibility of infection with *B. cereus* needs to be considered and the regimen of prophylactic antibiotics adjusted accordingly.

23. Outline the role of prophylactic antibiotics.

Posttraumatic endophthalmitis is a relatively rare complication of penetrating ocular trauma, occurring in only 7% of cases; however, the potential for devastation to the eye warrants prophylactic treatment. In cases of obvious endophthalmitis, a grossly contaminated wound, or contaminated foreign body, initial intravitreal antibiotic injection may be considered. Although no definitive evidence exists for a clinical benefit, all ruptured or lacerated globes are usually treated with prophylactic topical and systemic antibiotics for 3 to 5 days postoperatively. Although the Endophthalmitis Vitrectomy Study showed no benefit to systemic antibiotic treatment in postoperative endophthalmitis, the issue of prophylaxis in trauma was not specifically addressed.

Recent experiences of U.S. military physicians with severely injured and grossly contaminated ocular wounds have seen almost no endophthalmitis with timely antibiotics prophylaxis, usually with an oral fluoroquinolone.[8-10]

24. What regimen of antibiotics is used to treat posttraumatic endophthalmitis?

The choice of intravitreal injections is directed at covering a broad spectrum of organisms. Although a number of combinations are possible, a regimen with coverage for typical pathogens is vancomycin, 1 mg/0.1 mL, in combination with amikacin, 0.2 to 0.4 mg/0.1 mL. Concerns for aminoglycoside toxicity often drive a choice to substitute ceftazadime 2.25 mg/0.1 mL for amikacin. Clindamycin, 1 mg/0.1 mL, is considered an additional agent for any suspicion of *Bacillus* species. Frequently applied topical treatment with a fluoroquinolone should be initiated postoperatively in addition to systemic antibiotics for 7 to 10 days.

25. Does injury to one eye place the other eye at risk for visual loss?

Granulomatous inflammation may affect both the uninjured and the injured eye weeks to years after a penetrating injury. Sympathetic ophthalmia (SO) is a bilateral granulomatous uveitis manifested by anterior segment inflammation and multiple yellow-white lesions in the peripheral fundus. Complications include cataract, glaucoma, optic atrophy, exudative retinal detachments, and subretinal fibrosis. Exposure of the immune system to a previously immunologically isolated antigen in the uvea probably triggers the response. Eighty percent of cases develop within 3 months of injury, and 90% develop within 1 year. Rare cases of SO have occurred after ocular surgery. Therapy is directed at immunosuppression with steroids, cyclosporine, and/or cytotoxic agents. Most patients retain 20/60 vision or better at 10-year follow-up, but complications limit vision in many patients.

26. How can the uninjured eye be protected from the long-term sequelae of penetrating ocular injury?

The incidence of SO is extremely rare (<0.5% of penetrating trauma). The only known way to absolutely prevent the disease is enucleation of the injured eye 10 to 14 days after the injury. With modern repair techniques, the potential for vision in severely injured eyes has improved; therefore, enucleation as a prophylactic treatment for SO should be reserved only *for eyes confirmed to have no visual potential.* Removal of the inciting eye after inflammation has developed may improve the final acuity of the uninjured eye, but the inciting eye may eventually retain the best visual acuity. Enucleation as a treatment is reserved for inciting eyes with *no visual potential.*[11]

27. Can trauma elsewhere in the body cause fundus abnormalities?

Cotton-wool spots, usually in the peripapillary distribution, retinal hemorrhages, and optic disc edema have been described after severe head injury or compressive chest trauma. Purtscher's retinopathy, the name given to this entity, is a result of microvascular occlusion presumed to be embolic in nature and related to complement activation; however, the true pathogenesis is unknown. A similar appearance in other conditions, such as acute pancreatitis, collagen vascular disease, renal dialysis, and eclampsia, suggests a systemic process with secondary retinal capillary occlusion. The fundus manifestations in severe trauma may be related to the generally poor condition of patients who sustained such trauma rather than the trauma itself. Vitreous, preretinal, and retinal hemorrhages may be seen in birth trauma; however, if seen in the absence of such trauma or other causes (leukemia or bleeding diathesis), nonaccidental trauma should be suspected. Ocular manifestations are present in 40% of abused children, and the ophthalmologist is first to recognize the abuse in 6% of cases. Suspicious injuries need to be reported to protect children from further abuse.

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AGE-RELATED MACULAR DEGENERATION

Joseph I. Maguire II

CHAPTER 43

1. What is age-related macular degeneration?

Age-related macular degeneration (ARMD) is the leading cause of significant, irreversible central visual loss in the Western world. It is characterized by age-dependent alterations in the sensory retina, retinal pigment epithelium, and choriocapillaris complex in the central retina (macula). The macula is defined clinically by the area within the major temporal vascular arcades and provides our sharp, discriminating vision (Fig. 43-1). The incidence of this disease is age dependent, and prevalence steadily increases past age 55. A common international classification exists, but most clinicians still divide ARMD into exudative (wet) and nonexudative (dry) forms.

2. Who develops age-related macular degeneration?

Anyone can. The greatest statistical association with macular degeneration development is increasing age. All long-term epidemiologic studies indicate an increasing prevalence of exudative and nonexudative macular changes, as well as visual loss, with increasing age. Most reports point to a greater incidence of disease in women over men. In addition, skin pigmentation plays an important role in exudative disease; African Americans have a significantly smaller incidence of choroidal neovascularization compared with Caucasians.[1]

3. Why is age-related macular degeneration such an enormous challenge?

The number of Americans age 65 and over continues to accelerate with maturation of the baby boomers. The visual morbidity and mortality associated with ARMD potentially will affect a large number of elderly Americans socially, emotionally, and economically. The loss of reading and driving vision, the increased need for social and familial support, the cost of treatment, and the resultant emotional consequences have a significant impact on increasingly limited resources.

4. Describe the etiologic factors involved in the development of age-related macular degeneration.

The exact cause of ARMD is unknown, but multifactorial. In addition to increasing age, smoking is a consistent risk predictor. Individuals with a family history of ARMD have a fivefold increased risk of developing macular degeneration themselves. Genetic predisposition is an increasingly active area of research. The discovery of a genetic link in the complement factor H *(CFH)* gene has exposed a single nuclear polymorphism responsible for nearly 50% of ARMD risk. This supports ARMD being an inflammatory disease. Other associated gene variations in the *HTRA1/ARMS2* locus on chromosome 10, hepatic lipase C *(LIPC)*, and tissue inhibitor of metalloproteinase 3 *(TIMP3)* are found in large genome-wide studies.

Female gender, white race, smoking, poor nutrition, scleral rigidity, photic exposure, previous cataract surgery, and hypertension have been implicated as well.[2-5]

5. Name common visual symptoms in age-related macular degeneration patients.

- Visual blur
- Central scotomas
- Metamorphopsia

Metamorphopsia is visual distortion. Images may appear smaller (micropsia) or larger (macropsia) than they really are. Patients frequently comment that straight lines such as door jams, tile patterns, telephone poles, or other straight-edged surfaces appear curved. Special graphs, *Amsler grids*, test the central 20 degrees of vision and are effective home-testing devices for eyes at higher risk for development of exudative ARMD. Recent results from hyperacuity home monitoring devices have shown increased sensitivity in early exudative macular disease detection.[6]

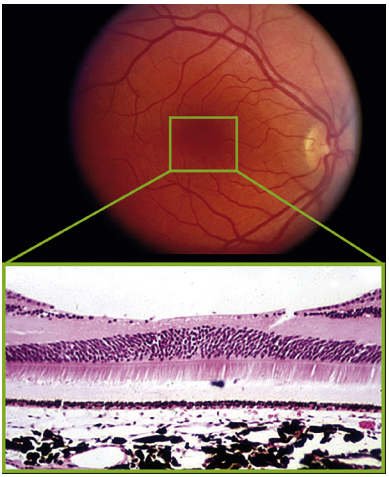

Figure 43-1. The clinical macula describes that area of the retina encompassed by the temporal arcade vessels.

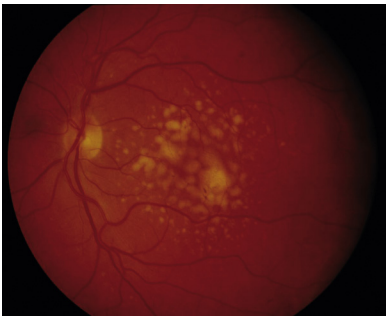

Figure 43-2. Drusen are the by-product of retinal metabolism and manifest as focal yellow-white deposits deep to the retinal pigment epithelium. They serve as markers of nonexudative age-related macular degeneration.

6. What is dry or nonexudative age-related macular degeneration?

Nonexudative ARMD is characterized by drusen, pigmentary changes, and atrophy. Drusen are the most common and earliest dry ARMD changes (Fig. 43-2). Drusen represent metabolic byproducts of retinal pigment epithelial cell metabolism. They vary in shape, size, and color. Hard drusen are small, discrete, yellow-to-white nodules, whereas soft drusen tend to be larger and more amorphous. Soft drusen may coalesce with neighboring drusen and are frequently associated with overlying pigmentary changes either from photoreceptor dysfunction or from retinal pigment epithelial demise. Progressive retinal pigment epithelial disruption eventually causes loss of overlying sensory retina and underlying choriocapillaris. Such developments result in localized atrophic regions that extend and coalesce around the fovea, eventually involving the fovea itself.

7. What is wet or exudative age-related macular degeneration?

Exudative ARMD is characterized by the development of neovascular changes and fluid in and under the sensory retina and retinal pigment epithelium (RPE). Choroidal neovascular membranes progressing to end-stage disciform macular scarring are the typical outcome of untreated exudative ARMD. Variations in age-related neovascular disease include type 1 (occult), type 2 (classic), and type 3 (retinal angiomatous proliferation). All can be associated with pigment epithelial detachments. Clinically, choroidal neovascular membranes are slate green-hued

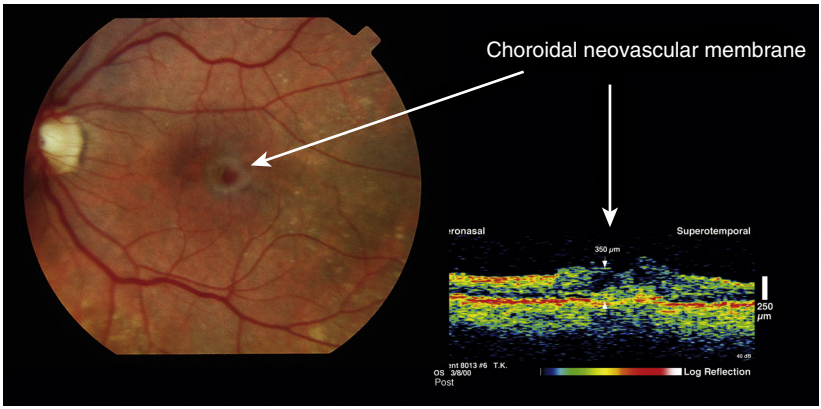

Figure 43-3. Choroidal neovascular membranes gain access to the subretinal space via defects in the Bruch's membrane *(arrow)*. Once there, these vessels may cause bleeding and disciform scar formation, resulting in overlying retinal dysfunction.

subretinal lesions associated with hard exudates, hemorrhage, or fluid. These vessels commonly originate from the normal choriocapillaris and enter the subretinal space through defects in the Bruch's membrane, a collagenous layer separating the choroidal circulation from the retina (Fig. 43-3). Pigment epithelial detachments are dome-shaped clear, turbid, or blood-filled elevations of the retinal pigment epithelium; they may or may not be associated with choroidal neovascular ingrowth.[7,8]

KEY POINTS: CLINICAL FINDINGS ASSOCIATED WITH ARMD

1. Nonexudative changes
   a. Drusen
   b. Pigmentary alterations
   c. Atrophy: Incipient, geographic
2. Exudative changes
   a. Hemorrhage
   b. Hard exudate
   c. Subretinal, sub-RPE, and intraretinal fluid

8. Name the three processes necessary for choroidal neovascular membrane development.

- Increased vascular permeability
- Extracellular matrix breakdown
- Endothelial budding and vascular proliferation

9. Describe the difference between occult and classic choroidal neovascularization.

Classic choroidal neovascularization is clinically well defined. Fluorescein angiography demonstrates a discrete hyperfluorescent lesion with a cartwheel configuration that increases in intensity over the course of the study (Fig. 43-4). Occult neovascularization usually demonstrates a poorly defined, stippled, pigmented appearance with associated retinal thickening. It is not well localized with fluorescein angiography, exhibiting diffuse punctate hyperfluorescence (Fig. 43-5).

10. How does age-related macular degeneration cause visual loss?

ARMD ultimately leads to visual loss via permanent alterations in the sensory retina, retinal pigment epithelium, and choroid within the macula. These changes may arise from the development of disciform scarring secondary to choroidal neovascularization or atrophy in which areas of retina cease to exist.

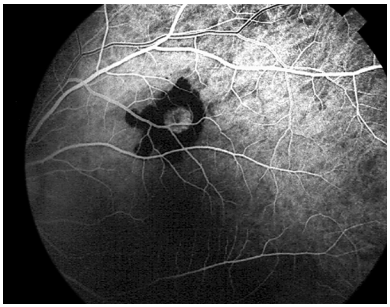

Figure 43-4. Angiographically, classic neovascular membranes appear as focal hyperfluorescent lesions deep to the retina. This example shows a corona of hypofluorescence, which is associated with hemorrhage.

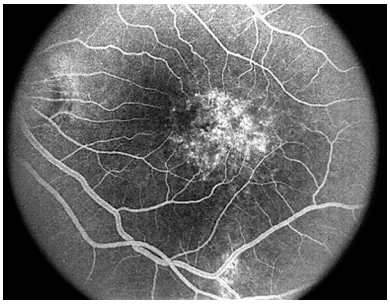

Figure 43-5. Unfortunately, the majority of choroidal neovascularization is nondiscrete or occult in character. This presentation is often not fully localized with fluorescein angiography. It has a punctate hyperfluorescent pattern with nondiscrete borders.

11. What is fluorescein angiography?

Fluorescein angiography is a photographic test used in the diagnosis and treatment of ARMD. Fluorescein dye is injected via an antecubital vein while simultaneous photographs of the macula are taken with a fundus camera. Fluorescein dye demonstrates fluorescence when stimulated with visible light in the blue frequency range. This property, along with anatomic constraints in the retinal and choroidal circulations, allows the identification and localization of abnormal vascular processes, such as choroidal neovascularization, that are found frequently in ARMD.

12. What is indocyanine green video-angiography?

Indocyanine green (ICG) videoangiography is a photographic technique similar to fluorescein angiography. The major difference is the use of ICG dye, which has a peak absorption and emission in the infrared range, whereas the spectral qualities of fluorescein dye are in the visible range. ICG angiography's advantage is allowing visualization through pigment and thin blood, which facilitates viewing of the choroid.[9]

13. What is optical coherence tomography?

Optical coherence tomography uses the property of optical coherence to give a cross-sectional representation of the macula. Its high resolution allows localization of choroidal neovascular processes and secondary effects such as retinal edema, sensory retinal detachment, and atrophy. Its articulation of retinal edema may make it an equal or even a superior diagnostic test in eliciting and following choroidal neovascular membrane activity.[10]

14. Name proven therapies for exudative age-related macular degeneration.

Current proven therapies for ARMD involve thermal laser photocoagulation, photodynamic therapy (PDT), and intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors. Intravitreal anti-VEGF injections are currently the preeminent treatment for exudative ARMD.[11]

15. What is the role of pharmacologic management in age-related macular degeneration?

Currently, medical management involves the inhibition of angiogenic growth factors and associated modulators. Inhibition of VEGF has assumed primary importance. These agents can cause successful regression or inhibition of neovascular membranes in selected vascular neoplasms and animal models of neovascularization. Several vascular inhibitors and their delivery systems are available.

Although Food and Drug Administration (FDA)–approved and off-label intravitreal anti-VEGF injections have assumed primary importance in the treatment of exudative ARMD, the aging of our population has increased the incidence of visual loss from nonexudative ARMD. Although AREDS2 vitamin supplements are the only available form of prophylaxis, multiple investigational protocols attacking other mechanisms of atrophic macular disease evolution are undergoing trials. These include complement inhibition, vitamin A analogs, interdiction of other inflammatory pathways, and addition of neurotrophic factors.[12,13]

16. Describe vascular endothelial growth factor and its role in ocular neovascularization.

VEGF is a homodimeric glycoprotein with multiple isomers, split products, and receptor sites. It is essential in the development and proper maintenance of normal body vasculature. It is influenced by multiple growth factors, cofactors, and environmental influences such as ischemia. Loss of normal VEGF homeostasis can result in its upregulation with resultant neovascularization.[14]

17. What are the advantages of current anti-vascular endothelial growth factor therapy in the treatment of exudative age-related macular degeneration compared to previous therapies such as thermal laser and photodynamic therapy?

Previous laser-based therapies created thermal or photodynamic tissue damage. This treatment for exudative ARMD lesions is based on either location or type. Although these treatments might slow the process, most patients progress to end-stage foveal involvement and visual decline is the rule. Anti-VEGF therapies have the advantage of being effective on nearly all subtypes of ARMD especially in subfoveal lesions. Their track record for visual stability and improvement is extremely good over time and their mechanism of effect is physiologic, not tissue destructive.

18. What are disadvantages of current anti-vascular endothelial growth factor therapy for exudative age-related macular degeneration?

Unfortunately, anti-VEGF agents must currently be delivered intravitreally via pars plana injection. They are effective for approximately 1 month after injection; thus recurrence is noted in nearly all eyes over time. This necessitates the need for multiple visits both for active treatment and for surveillance. Patients are seen every 4 to 8 weeks. Intravitreal injections have secondary risks including endophthalmitis, intraocular pressure elevation, and possible progression of atrophic macular disease.[15]

19. Describe the role of vitamins in the treatment and prophylaxis of age-related macular degeneration.

The Age-Related Eye Disease Study (AREDS) is sponsored jointly by the National Institutes of Health and the National Eye Institute and has proved the benefit of high-dose vitamins in the prophylaxis of ARMD. Individuals with intermediate or high risk of developing ARMD had a 25% reduction in developing visual loss from either exudative or nonexudative forms of ARMD. Theoretically, the intake of certain vitamins and trace elements acts directly or indirectly through association with certain enzymes in free radical scavenging, thereby modulating the aging process.

AREDS vitamins include high concentrations of vitamins C and E, lutein/zeoxanthine, zinc, and copper. Release of the AREDS2 study demonstrated no benefit from ω-3 fatty acids and potential increased risk of lung cancer in previous smokers taking β-carotene, prompting elimination of β-carotene from current AREDS2 formulations and replacement with lutein/zeoxanthine.[16]

AREDS summary: www.nei.nih.gov/amd/summary.asp.

20. What is photodynamic therapy? How does it differ from laser photocoagulation?

PDT is an FDA-approved intervention for predominantly discrete subfoveal choroidal neovascular membranes secondary to ARMD. It involves the intravenous administration of a porphyrin-based medication that is absorbed by abnormal subretinal vessels. The drug is activated by wavelength-specific, low-energy, nonthermal infrared laser exposure. Activation of the photosensitizing compounds produces localized vascular damage via generation of free radicals. Because its action is local, the overlying sensory retina is spared while abnormal neovascularization is destroyed. Because so many exudative lesions in ARMD are foveal, PDT has the ability to eliminate subfoveal choroidal neovascular changes while preserving fixation.[17]

21. What is the role of surgery in age-related macular degeneration?

The Submacular Surgery Trial was a prospective randomized trial that evaluated the benefits of invasive surgical techniques in the treatment of ARMD. For ARMD, removal of choroidal neovascular membranes was not found beneficial. Removal or displacement of submacular hemorrhage was found to be helpful in selected cases in which visual acuity was less than 20/200.

22. What is macular translocation?

Macular translocation surgery is performed for exudative foveal ARMD. It has not been evaluated in prospective clinical trials. It involves physically "picking up" and moving macular retina away from the underlying choroidal neovascularization. This allows placement of the fovea in areas of healthy retinal pigment epithelium and choroid. Currently, there are two methods of translocation—limited translocation and 360-degree macular translocation.

23. What is combination therapy?

Combination therapy involves the use of more than one treatment regimen or treatment modality. Similar to the evolution of oncologic therapeutics, treatment of ARMD may come to involve laser, photodynamic therapy, and/or combinations of vascular growth inhibitors (Box 43-1). A current example involves the use of PDT with anti-VEGF agents in polypoidal variants of exudative ARMD and investigative anti-platelet–derived growth factors in association with anti-VEGF agents.

24. What are low-vision aids?

Low-vision support involves the use of devices that maximize a visually deficient eye's visual function through magnification, lighting, and training. It allows patients to take advantage of near peripheral vision. Such aids take many forms, including special spectacles, magnifiers, closed-circuit television devices, digitally enhanced cameras, and overhead viewers. People often can read print and carry out important functions not possible without such support. In patients with untreatable bilateral visual loss, evaluation for low-vision support is critical.

Box 43-1. Additional ARMD Treatment Strategies Previously or Currently Under Investigation

1. Radiation therapy
   a. External beam
   b. Radioactive plaque therapy
   c. External probe application
2. Submacular surgery
   a. Removal of choroidal neovascular membranes
   b. Removal of submacular hemorrhage
3. Laser treatment
   a. Prophylactic laser for drusen in nonexudative disease
   b. Transpupillary thermotherapy for treatment of occult choroidal neovascularization
   c. High-speed ICG-guided laser therapy for feeder vessels in occult and classic choroidal neovascularization
4. Pharmacologic management with inhibitors of angiogenesis
   a. Anti-VEGF agents
   b. Anti-PDGF agents
   c. Steroids
   d. Angiostatic steroids
5. Combination therapies
6. Inhibitors of nonexudative ARMD progression
   a. Complement inhibitors
   b. Neurotrophic factors
   c. Vitamin A analogs
   d. Non-complement-related anti-inflammatory medications
7. Stem cell replacement
8. Gene therapy

ICG, Indocyanine green; *VEGF,* vascular endothelial growth factor; *PDGF,* platelet-derived growth factor.

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CHAPTER 44

RETINOPATHY OF PREMATURITY

James F. Vander

1. What is retinopathy of prematurity?

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disease that affects infants born prematurely. It has two phases. In the acute phase, normal vascular development goes awry with the development of abnormal vessels that proliferate, occasionally with associated fibrous proliferation. In the chronic or late proliferation phase, retinal detachment, macular ectopia, and severe visual loss may occur. More than 90% of cases of acute ROP go on to spontaneous regression.

2. Who is at risk for retinopathy of prematurity?

Infants weighing less than 1500 grams at birth and those born at a gestational age of 32 weeks or less are at risk for developing ROP. The disease is more likely to affect the smallest and most premature of infants. The incidence of acute ROP in infants weighing less than 1 kg at birth is three times greater than that of infants weighing between 1 and 1.5 kg. Infants born at 23 to 27 weeks of gestation have a particularly high chance of developing ROP.

3. Who should be screened for retinopathy of prematurity?

Guidelines published by the American Academy of Pediatrics, Section on Ophthalmology; the American Association of Pediatric Ophthalmology and Strabismus; and the American Academy of Ophthalmology recommend that all infants weighing less than 1500 grams at birth or those with a gestational age of 28 weeks or less should be examined. Selected infants with a birth weight between 1500 and 2000 grams with an unstable clinical course should also be examined.

4. Which infants are at highest risk for retinopathy of prematurity?

Infants at particularly high risk are those who weigh less than 1000 grams at birth and those born at less than 27 weeks' gestation. The first exam should take place 4 to 6 weeks after birth or between 31 and 33 weeks of postconceptional or postmenstrual age.

5. When should follow-up exams be done when screening for retinopathy of prematurity?

The frequency of follow-up examinations is based on the retinal status at the time of the first exam. Exams should be done every 1 to 2 weeks, either until there is complete retinal vascularization or until two successive 2-week examinations show stage 2 ROP in zone III (more on staging is discussed later in this chapter). Infants should then be examined every 4 to 6 weeks until the retina is fully vascularized. If there is prethreshold disease (see further discussion), examinations should be done every week until threshold disease occurs (at which point treatment should be offered) or until the disease regresses.

KEY POINTS: INDICATIONS FOR SCREENING INFANTS FOR ROP

1. All infants weighing less than 1500 grams at birth
2. All infants with a gestational age of 28 weeks
3. Infants with a birth weight between 1500 and 2000 grams with an unstable clinical course
4. Any infant that the neonatologist considers at risk because of an unstable clinical course

6. How is retinopathy of prematurity classified?

The International Classification of Retinopathy of Prematurity (ICROP) is the system used for describing the findings in ROP. ICROP defines the location of disease in the retina and the extent of involvement of the developing vasculature. It also specifies the stage of involvement with levels of severity ranging from 1 (least affected) to 5 (severe disease).

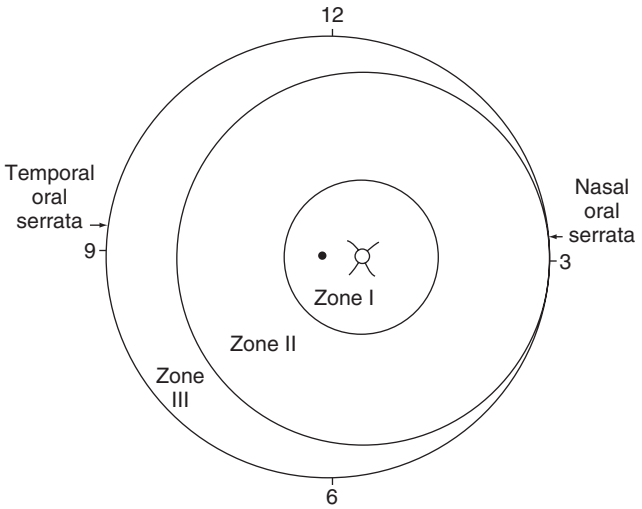

Figure 44-1. The zones of retinopathy of prematurity are shown schematically.

7. What are the zones of retinopathy of prematurity?

For the purpose of defining location, the retina is divided into three zones, with the optic nerve as the center because vascularization starts from the optic nerve and progresses peripherally (Fig. 44-1). Zone I consists of a circle, the radius of which subtends an angle of 30 degrees and extends from the disc to twice the distance from the disc to the center of the macula (twice the disc-to-fovea distance in all directions from the optic disc). Zone II extends from the edge of zone I peripherally to a point tangential to the nasal ora serrata and around to an area near the temporal anatomic equator. Zone III is the residual temporal crescent of retina anterior to zone II.

8. Describe the stages of retinopathy of prematurity.

Staging pertains to the degree of abnormal vascular response observed. Staging of the eye as a whole receives the stage of the most severe manifestation present.

Stage 1 is a demarcation line. It is a thin but definite structure that separates avascular retina anteriorly from the vascularized retina posteriorly. Abnormal branching of vessels can be seen leading up to the line. It is flat and white and is in the plane of the retina.

Stage 2 is a ridge. The line of stage 1 has height and width and occupies a volume extending out of the plane of the retina. The ridge may be pink or white. Vessels may leave the plane of the retina to enter it. Small tufts of new vessels may be seen on the surface of the retina posterior to the ridge. These vessels do not constitute fibrovascular growth.

Stage 3 is the ridge of stage 2 with extraretinal fibrovascular proliferation (Fig. 44-2). Stage 4 ROP is a subtotal retinal detachment. Retinal detachments in ROP are concave, tractional retinal detachments. Stage 4A ROP is a subtotal retinal detachment that does not involve the central macula. Typically, it is present in the temporal region of zones II and III. Stage 4B ROP is a subtotal retinal detachment that involves the central macula.

Last, stage 5 ROP is a total retinal detachment. These retinal detachments are funnel-shaped but may have an open or closed configuration in their anterior and posterior areas.

9. What is plus disease?

Plus disease is indicative of progressive vascular incompetence and is a strong risk factor for the development of more severe ROP. Anteriorly, plus disease is iris vascular engorgement and pupillary rigidity. Posteriorly, plus disease appears as retinal venous dilation and arterial tortuosity in the posterior pole. It is graded as mild, moderate, or severe (Fig. 44-3). When plus disease is present in the posterior pole, a plus sign (i.e., +) is added to the number stage of the disease, i.e., stage 3+.

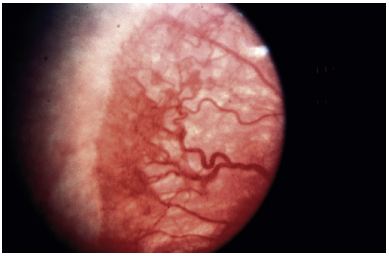

Figure 44-2. Stage 3 retinopathy of prematurity.

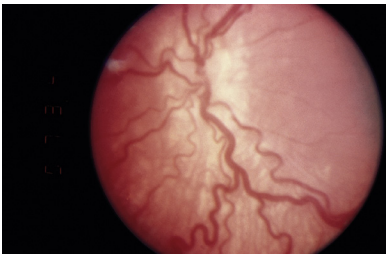

Figure 44-3. Moderately severe plus disease.

Before the appearance of plus disease, increasing dilation and tortuosity of the posterior vessels signify increased activity of ROP. Pre-plus disease is present when there are vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease, but that demonstrate more venous dilation and arterial tortuosity than normal.

10. What is the worst form of acute retinopathy of prematurity?

There is a more virulent retinopathy usually observed in the lowest-birth-weight infants that is called aggressive posterior ROP (AP-ROP). This form of ROP is posteriorly located and has prominent plus disease with ill-defined retinopathy. The plus disease is out of proportion to the peripheral retinopathy and usually progresses rapidly to stage 5 disease. AP-ROP typically extends circumferentially and is associated with a circumferential vessel.

11. What is the rationale for treating acute retinopathy of prematurity?

Because ROP can lead to blindness from retinal detachment, treatment to prevent progression to retinal detachment is indicated. However, 90% of infants who develop acute ROP undergo spontaneous regression. Treatment should therefore be performed only for those infants who have a high risk of developing retinal detachment.

12. What did the Cryotherapy for Retinopathy of Prematurity study teach us?

The Cryotherapy for Retinopathy of Prematurity (Cryo-ROP) study set out to determine whether treatment for ROP would prevent poor outcomes. For the purposes of that study, a level of disease (called *threshold disease*) was chosen at which 50% of infants were predicted to go blind without treatment. This prediction was appropriate for the Cryo-ROP study and remains the level of clinical disease at which treatment is recommended.

Threshold disease is defined as the presence of at least five contiguous or eight cumulative 30-degree sectors (clock hours) of stage 3 ROP in zone I or II, in the presence of plus disease (Fig. 44-4). Thus, prethreshold ROP is defined as zone I, any stage; zone II, stage 2 with plus disease; or zone II with extraretinal fibrovascular proliferation less than threshold. When ROP reaches prethreshold, examinations should be performed weekly.

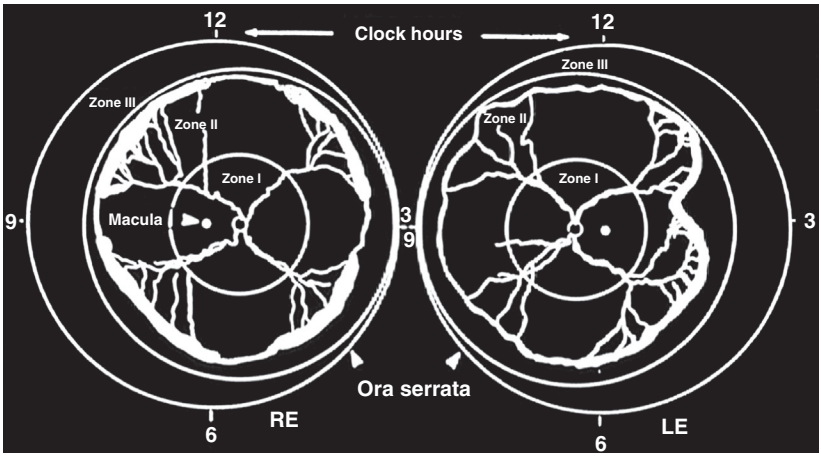

Figure 44-4. The Cryo-ROP definition of threshold disease is shown schematically.

13. Do all treated infants do well?

Analysis of natural history data from the Cryo-ROP study indicated that certain infants are at high risk for an unfavorable outcome. Infants with zone I ROP are included as infants at high risk for an unfavorable outcome. The Early Treatment for Retinopathy of Prematurity (ETROP) study used a risk model (RM-ROP2) based on the natural history data from the Cryo-ROP study to identify infants at high risk for an unfavorable outcome. The model used demographic characteristics of the infants and clinical features of ROP to classify eyes with prethreshold ROP at high or low risk. High-risk prethreshold eyes that received conventional management had a much higher likelihood of unfavorable structural outcome (10% versus 1% at 6 months).

14. What did the ETROP study teach us?

The ETROP study described a clinical algorithm for which eyes should be treated. High-risk eyes (termed *type 1 ROP*) were those with the following findings: zone I, any stage ROP with plus disease; zone I, stage 3 ROP with or without plus disease; and zone II, stage 2 or 3 ROP with plus disease. Plus disease requires that there be at least two quadrants of dilation and tortuosity of the posterior pole vessels. With these criteria to apply laser treatment to the anterior avascular zone of affected high-risk prethreshold eyes, there was a reduction from 19.5% to 14.5% in an unfavorable grating visual acuity measurement and from 15.6% to 9.1% in an unfavorable structural outcome at 9 months compared to the control group, which was not treated until threshold was reached. Less severely advanced, low-risk prethreshold eyes (termed *type 2 ROP*) included the following: zone I, stage 1 or 2 ROP without plus disease, and zone II, stage 3 ROP without plus disease. It was recommended that infants with type 2 ROP should be monitored closely and treated if they progress to type 1 ROP or to threshold disease. The recommendation to treat type 1 eyes and adopt a "wait-and-watch" approach for type 2 eyes (treat if the eyes progress to type 1 or threshold) was supported by the final results of the ETROP study.

15. How do you treat acute retinopathy of prematurity?

Cryotherapy was the standard of care for treating acute ROP. More recently, multiple studies have reported on the efficacy of treating ROP with laser photocoagulation delivered by the indirect ophthalmoscope. Indirect laser has become the most common form of treatment for acute ROP.

Indirect laser can be delivered in the intensive care nursery without having to take the infant to an operating room. Intravenous sedation is administered at the discretion of a neonatologist, who should be immediately available to manage any possible systemic complications. Laser is applied to the entire peripheral avascular zone, with the use of a laser indirect ophthalmoscope. The laser spot desired is a dull white or gray spot, and the spots are placed approximately 1 to 1.25 lesion-widths apart (Fig. 44-5). Critical focus on the retina is essential.

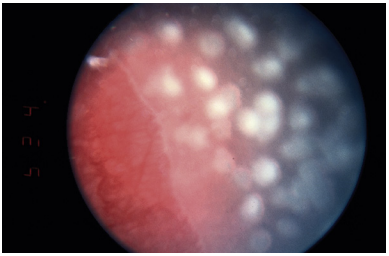

Figure 44-5. Appearance of the peripheral fundus immediately after laser treatment.

16. How is cryotherapy applied?

Cryotherapy is still preferred by some ophthalmologists for managing acute ROP. As with laser treatment, intravenous sedation can be administered at the discretion of the neonatologist. Some ophthalmologists prefer general anesthesia because of the greater stress on the infant and the greater risk of cardiopulmonary complications with cryotherapy than with laser photocoagulation. Cryotherapy is applied to the entire peripheral avascular zone using a handheld cryo-pencil. The peripheral retina is brought into view using the cryo-pencil as a scleral depressor. A white freeze spot seen for 1 to 2 seconds is the desired endpoint. The lesions are placed contiguously.

17. Does posterior retinopathy of prematurity respond to treatment?

Zone I and posterior zone II disease have a worse prognosis than more anterior ROP. Cryotherapy is often ineffective in posterior ROP. Investigations have shown that laser photocoagulation for posterior disease can limit the likelihood of an unfavorable anatomic outcome to approximately 20%. Applying the criteria of the ETROP noted previously will result in a better prognosis for zone I disease.

18. What is the expected result after laser treatment for retinopathy of prematurity?

Various reports have quoted a regression rate of approximately 90% after laser photocoagulation for threshold ROP. If regression is to occur, plus disease is usually less on the first week's follow-up visit. There may not be much change in the extraretinal fibrovascular proliferation (ERFP). By 2 weeks, one should start to see a reduction in the ERFP.

19. When should you consider retreatment for retinopathy of prematurity?

Laser photocoagulation for threshold ROP is successful at inducing regression of the acute disease in approximately 90% of cases. Occasionally supplemental treatment after the initial session is necessary to induce regression. Retreatment should be considered if there is worse disease (worse plus disease and increased extraretinal fibrovascular proliferation) at the 1-week visit or persistently active disease (ERFP with plus disease) and the presence of "skip lesions" (areas of apparently missed treatment) or widely spaced laser lesions at the 2-week follow-up visit. Additional treatment should be applied to previously untreated areas rather than treating over old laser spots. In a similar fashion, supplemental cryotherapy can be applied to "skip areas" if there has not been an adequate response to initial cryotherapy treatment.

KEY POINTS: INDICATIONS FOR LASER TREATMENT OF ROP

1. Eyes with type 1 ROP
2. Zone I, any stage ROP with plus disease
3. Zone II, stage 2 or 3 ROP with plus disease
4. Eyes with threshold ROP: At least five contiguous or eight cumulative 30-degree sectors (clock hours) of stage 3 ROP in zone I or II, in the presence of plus disease

20. Are there any options other than laser for acute retinopathy of prematurity?

Many ophthalmologists are now using an intravitreal anti-vascular endothelial growth factor injection (usually bevacizumab) to induce regression of plus disease and ERFP. There is evidence that this

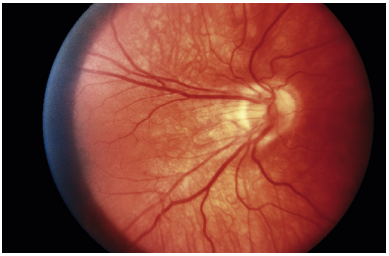

Figure 44-6. Moderate temporal dragging of the macula caused by regressed retinopathy of prematurity.

Table 44-1. Differential Diagnosis of Retinopathy of Prematurity

LESS SEVERE DISEASE	MORE SEVERE DISEASE
Familial exudative vitreoretinopathy	Congenital cataract
Incontinentia pigmenti (Bloch-Sulzberger syndrome)	Persistent hyperplastic primary vitreous/persistent fetal vasculature
X-linked retinoschisis	Retinoblastoma
—	Ocular toxocariasis
—	Intermediate uveitis
—	Coats disease
—	Advanced X-linked retinoschisis
—	Vitreous hemorrhage

treatment may be particularly helpful with posterior ROP. To date, no large randomized studies have been able to demonstrate systemic safety with this treatment, which is concerning with fragile, growing infants. These injections may reduce or eliminate the need for destructive retinal ablation and further evaluation is warranted.

21. What can be done for more advanced stages of retinopathy of prematurity?
Stage 4B and progressive stage 4A retinal detachments may be managed with lens-sparing vitrectomy. There is a 70% to 85% rate of retinal reattachment. Vitrectomy surgery may be tried for more advanced stage 5 ROP. However, the anatomic and visual success rates are extremely poor.

22. What are some of the late complications of retinopathy of prematurity?
The late complications of ROP include myopia, retinal pigmentation, dragging of the retina (Fig. 44-6), lattice-like vitreoretinal degeneration, retinal holes, retinal detachment, and angle-closure glaucoma. Obviously, these children need long-term follow-up by both a retina specialist and a pediatric ophthalmologist. Amblyopia and strabismus are also common.

23. What is the differential diagnosis for retinopathy of prematurity?
The differential diagnosis differs depending on the extent of the disease (Table 44-1). In less severe ROP, conditions that lead to peripheral retinal vascular changes and retinal dragging should be considered. In more severe disease the differential diagnosis of a white pupillary reflex must be considered.

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DIABETIC RETINOPATHY

James F. Vander

CHAPTER 45

1. **How is diabetic retinopathy classified? What fundus features are characteristic of each category?**
   - **Nonproliferative diabetic retinopathy (NPDR):** This form is arbitrarily divided into three categories based on severity: mild, moderate, and severe. Features of mild and moderate nonproliferative retinopathy result predominantly from loss of capillary integrity (i.e., microaneurysms, dot-and-blot hemorrhages, hard yellow exudates, and macular edema) (Fig. 45-1). Cotton-wool spots are also seen. Features of more severe NPDR are related to early signs of ischemia. In addition to the features found in mild nonproliferative disease, the fundus shows venous beading and intraretinal microvascular abnormalities (IRMAs) as well as more extensive intraretinal hemorrhages (Fig. 45-2).
   - **Proliferative diabetic retinopathy (PDR):** Typical features are related to the consequences of extensive retinal capillary nonperfusion. Fundus findings include those of NPDR as well as the development of neovascularization of the disc (NVD; Fig. 45-3), neovascularization elsewhere in the retina (NVE), preretinal and/or vitreous hemorrhage, and vitreoretinal traction with tractional retinal detachment.
2. **What is the most common cause of vision loss in diabetic retinopathy?**
   The most common cause of vision loss in diabetic retinopathy is macular edema.
3. **Who is at risk for the development of diabetic retinopathy?**
   All patients with diabetes mellitus are at risk for diabetic retinopathy. Relative risk factors include the following:
   - **Duration of diabetes:** The longer diabetes has been present, the greater the risk of some manifestation of diabetic retinopathy. After 10 to 15 years, more than 75% of patients show some signs of retinopathy.
   - **Age:** Diabetic retinopathy is uncommon before puberty even in patients who were diagnosed shortly after birth. NPDR appears sooner in patients diagnosed with diabetes after the age of 40. This may be related to duration of disease before diagnosis.
   - **Diabetic control:** The Diabetic Control and Complications Trial (DCCT) clearly demonstrated a correlation between poor long-term glucose control and subsequent development of diabetic retinopathy as well as other complications of diabetes.
   - **Renal disease:** Proteinuria is a particularly good marker for the development of diabetic retinopathy. This association may not be causal, but a patient with renal dysfunction should be followed more closely.
   - **Systemic hypertension:** Again, the causal nature of the relationship is not certain.
   - **Pregnancy:** Diabetic retinopathy may progress rapidly in patients who are pregnant. Patients with preexisting retinopathy are at particular risk.

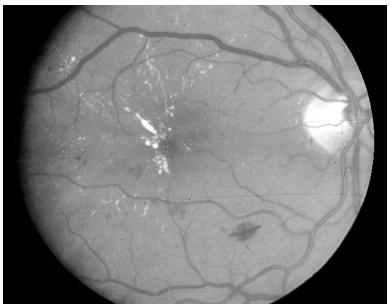

Figure 45-1. Nonproliferative diabetic retinopathy with exudates, hemorrhages, and edema.

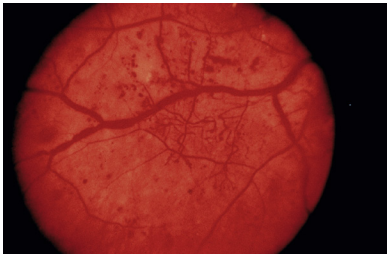

Figure 45-2. Severe nonproliferative retinopathy with venous beading and intraretinal microvascular abnormalities.

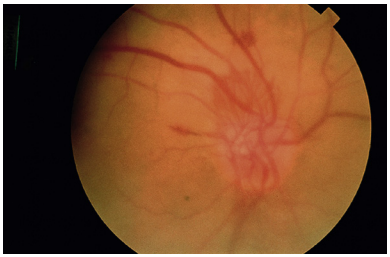

Figure 45-3. Neovascularization of the disc in proliferative retinopathy.

KEY POINTS: MECHANISMS OF VISION LOSS IN DIABETES

1. Macular edema
2. Macular ischemia
3. Vitreous hemorrhage
4. Macular traction detachment
5. Combined rhegmatogenous/tractional retinal detachment

4. What is the significance of the hemoglobin A_1C? What is its correlation with the development of diabetic retinopathy?

Hemoglobin A_1C is serum glycosylated hemoglobin. It is an indicator of the average level of serum glucose for the preceding 3 months. Thus it provides a report card of the adequacy of glucose control for the preceding 3 months without identifying peaks, valleys, or timing of glucose fluctuation. The hemoglobin A_1C has been found to correlate most closely with the development of diabetic retinopathy. Nondiabetic patients typically have a level of 6 or less. The DCCT demonstrated that hemoglobin A_1C of less than 8 was associated with a significantly reduced risk of retinopathy compared with a value greater than 8.

5. What is the recommendation for screening patients with diabetes?

Patients with juvenile insulin-dependent diabetes should have a dilated ophthalmologic examination 5 years after diagnosis. Patients with type II adult-onset diabetes should be examined at diagnosis. All diabetic patients should have an annual dilated funduscopic examination; more frequent examinations depend on the findings.

6. What are the fluorescein angiographic features of nonproliferative and proliferative diabetic retinopathy?

- In **mild-to-moderate nonproliferative retinopathy** the large vessels fill normally. Pinpoint areas of early hyperfluorescence correspond to microaneurysms, whereas dot-and-blot hemorrhages are hypofluorescent. Microaneurysms leak in the later frames with blurring of margins and diffusion of fluorescein dye, whereas hemorrhages remain hypofluorescent throughout the study. Telangiectasis hyperfluoresces with late leakage. Hard yellow exudate generally does not appear on a fluorescein angiogram unless it is extremely thick, in which case it is hypofluorescent. Macular edema usually is apparent as fluorescein leaks into the retina as the angiogram progresses (Figs. 45-4 and 45-5).

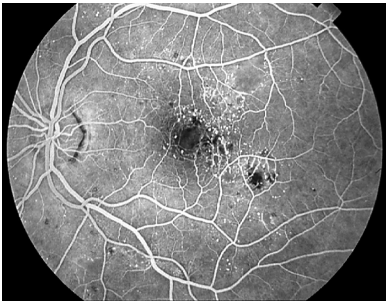

Figure 45-4. Early phase fluorescein angiogram shows pinpoint hyperfluorescence corresponding to microaneurysms.

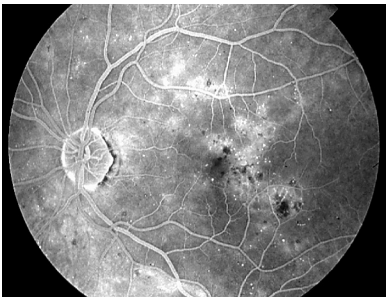

Figure 45-5. Later phase fluorescein angiogram shows leakage with diffusion of dye and blurring of the microaneurysms.

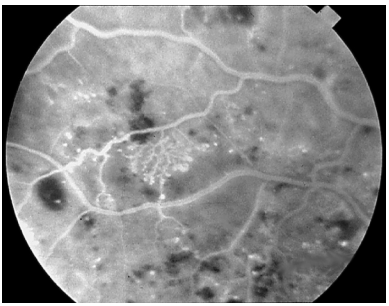

Figure 45-6. Neovascularization *(arrow)* is markedly hyperfluorescent early and develops at the border of perfused and nonperfused retina.

- **More severe nonproliferative retinopathy** has the features noted above as well as evidence of retinal capillary loss. Cotton-wool spots are usually hypofluorescent, sometimes with late hyperfluorescence along the margins. Areas of capillary dropout appear as smooth, hypofluorescent "ground-glass" patches, with staining at the margins in the later frames of the angiogram. IRMAs fill in the arterial phase of the angiogram and does not leak significantly in the later frames (Fig. 45-6).
- **Proliferative retinopathy.** Extensive retinal capillary loss is seen early in the angiogram with diffuse leakage at the edges of the ischemic areas in the later frames. NVD and NVE show intense early hyperfluorescence with marked leakage developing rapidly (Fig. 45-7).

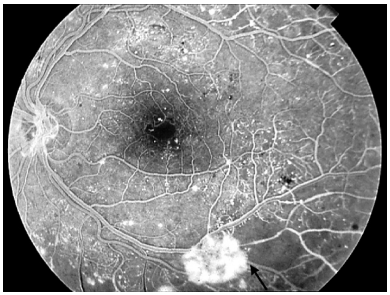

Figure 45-7. Intraretinal microvascular abnormalities do not leak on fluorescein angiography.

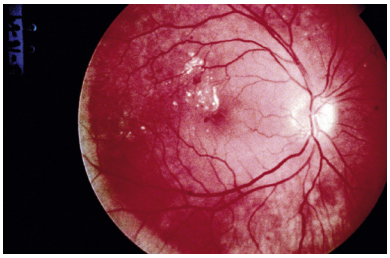

Figure 45-8. Four months after focal laser, the edema and exudate are gone.

7. What is the definition of clinically significant macular edema?

Clinically significant macular edema (CSME), as defined in the Early Treatment Diabetic Retinopathy Study (ETDRS), is present in patients with any one of the following:

- Retinal thickening within 500 microns of the center of the fovea
- Hard yellow exudate within 500 microns of the center of the fovea with adjacent retinal thickening (Fig. 45-8)
- At least one disc area of retinal thickening, any part of which is within one disc diameter of the center of the fovea

CSME describes the fundus features as seen on stereoscopic high-magnification viewing of the macula. Visual acuity is not relevant; a patient with 20/20 vision may still have CSME. The fluorescein angiographic appearance is not relevant for the definition of CSME. Monocular viewing of the macula with a direct ophthalmoscope or a solitary color photograph is not adequate for diagnosing CSME, nor is the low-magnification view provided by the indirect ophthalmoscope.

KEY POINTS: CLINICAL FEATURES OF CLINICALLY SIGNIFICANT MACULAR EDEMA

1. Macular thickening within 500 microns of the center of the fovea **or**
2. Hard exudates within 500 microns of the center of the fovea with adjacent thickening **or**
3. Macular thickening of one disc area, any part of which is within one disc diameter of the center of fovea

8. What are the results of the ETDRS concerning treatment of diabetic macular edema?

The ETDRS showed that macular laser treatment for patients with CSME reduced the risk of doubling of the visual angle (for example, 20/40 worsening to 20/80) from 24% to 12% over a 3-year period. This benefit was detected over all levels of visual acuity. Significant visual improvement is uncommon after macular laser treatment. The goal is to prevent worse vision in the future. Treatment is directed at areas of diffuse leakage by using a grid pattern and at areas of focal leakage by direct treatment of the leaking abnormality (Fig. 45-9). Resolution of macular edema may take several months and re-treatment is occasionally necessary.

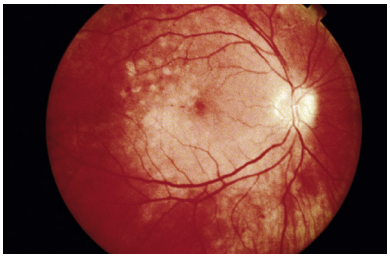

Figure 45-9. Clinically significant macular edema with thickening and exudate within 500 microns of the center of the fovea.

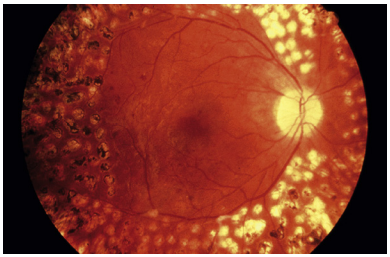

Figure 45-10. Panretinal photocoagulation several months after treatment.

9. What other findings did the ETDRS report?

The ETDRS also was designed to determine whether aspirin use was helpful or harmful in patients with diabetic retinopathy; the study concluded that it was neither. The study also assessed the role of early panretinal laser treatment for proliferative disease (see further discussion).

10. What is the definition of high-risk characteristics?

High-risk characteristics (HRC) was used by the Diabetic Retinopathy Study (DRS) to describe patients at a high risk of severe vision loss from PDR. The study found that patients with (1) NVE and vitreous hemorrhage, (2) mild NVD and vitreous hemorrhage, and (3) moderate or severe NVD with or without vitreous hemorrhage are at high risk for severe vision loss over the ensuing 3 years. Initiation of full-scatter panretinal photocoagulation (PRP) greatly reduced the risk of severe vision loss in patients with HRC (Fig. 45-10). Subsequently, the EDTRS found that for patients with severe nonproliferative retinopathy and/or early proliferative retinopathy without HRC, there was no clear-cut benefit to initiation of full-scatter PRP. As long as careful follow-up can be ensured, PRP may be safely withheld in such cases.

KEY POINTS: DRS HIGH-RISK CHARACTERISTICS

1. Neovascularization of the disc of ¼ to ⅓ of the disc area
2. NVD of <¼ of the disc area with any vitreous hemorrhage
3. Neovascularization elsewhere in the retina with any vitreous hemorrhage

11. What are the side effects of PRP?

PRP does not improve vision but is performed to prevent the blinding complication of proliferative retinopathy. Loss of peripheral vision and night vision are the major concerns. Loss of central vision also may result from exacerbation of macular edema. Thus, if possible, macular focal laser should be performed before PRP when both are indicated. Other complications include impaired accommodation, papillary dilation, and inadvertent macular burns.

12. Do all patients treated with PRP show resolution of HRC?

No. As many as one-third of patients do not show resolution of NVD or NVE, and in some cases there will be no apparent regression.

13. What is the role of supplemental PRP?

The DRS evaluated the placement of 2000 spots of PRP. For patients who do not show regression of high-risk characteristics or who have persistent vitreous hemorrhage, it is not clear whether additional PRP improves the long-term visual prognosis. Patients have been reported with 7000 or more spots of PRP, and in some cases recurrent vitreous hemorrhage persists.

14. What are the indications for fluorescein angiography in diabetic retinopathy?

Fluorescein angiography is not part of the definition of either clinically significant macular edema for patients with nonproliferative retinopathy or HRC for patients with proliferative disease. The indications for treatment are based on clinical rather than angiographic features. Nevertheless, fluorescein angiography is important, particularly for patients with diabetic maculopathy. Most patients considered for treatment of macular edema should have a fluorescein angiogram to determine the focal and diffuse areas of leakage and thus to guide the treating physician during placement of the laser. Areas of capillary nonperfusion also are treated with a grid pattern, which can be determined angiographically. The proximity of focal areas of leakage to the foveal avascular zone (FAZ) also can be demonstrated on fluorescein angiography. Treatment too close to the FAZ carries a higher risk of vision loss and therefore should be done with caution. In patients with unexplained vision loss, the cause may be macular ischemia, which is nicely demonstrated on fluorescein angiography. Finally, patients with a vitreous hemorrhage of uncertain etiology may benefit from a fluorescein angiogram. In patients with significant media opacity a fluorescein angiogram may demonstrate retinal neovascularization that was not apparent clinically.

15. What are the possible uses of optical coherence tomography in the management of diabetic retinopathy?

Optical coherence tomography (OCT) provides a noninvasive, photographic method for obtaining a cross-sectional view of the macula. Macular thickness and volume may be quantified, providing an objective measurement that is especially useful when serial studies are available and progression or response to treatment can be evaluated. Significant vitreomacular traction, if present, lends insight into a possible mechanism for the presence of macular edema and points toward vitrectomy as a therapeutic option. OCT may also show significant macular thinning as can sometimes occur after treatment of macular edema. This may explain a poor visual result in an eye after resolution of intraretinal fluid.

16. What is the differential diagnosis of diabetic retinopathy?

The differential diagnosis includes branch or central retinal vein obstruction, ocular ischemic syndrome, radiation retinopathy, hypertensive retinopathy, and miscellaneous proliferative retinopathies such as sarcoidosis, sickle cell hemoglobinopathy, and other less common causes. In patients with typical macular features of nonproliferative retinopathy such as microaneurysms and macular edema, but no evidence of diabetes mellitus, the disease usually is categorized as idiopathic juxtafoveal telangiectasia.

17. What is the significance of neovascularization of the iris in diabetes?

Neovascularization of the iris (NVI) is an ominous sign of severe PDR and generally requires urgent treatment. NVI may progress to occlude the trabecular meshwork in a relatively short period, leading to severe neovascular glaucoma. This dreaded complication of proliferative disease usually can be avoided if heavy PRP can be placed before the angle has become occluded.

18. What are the indications for vitrectomy in diabetic retinopathy?

- **Vitreous hemorrhage:** Vitreous hemorrhage obscuring the visual axis causes severe vision loss. Although it generally clears spontaneously, for patients with more extensive hemorrhage, vitrectomy may be indicated. The Diabetic Retinopathy Vitrectomy Study concentrated on eyes with vitreous hemorrhage reducing vision to 5/200 or worse. The study demonstrated a strong benefit for patients with type I diabetes, perhaps related to extensive fibrovascular proliferation. Guidelines are variable, but most surgeons wait at least 3 months for patients to clear spontaneously unless occupational or personal needs demand early intervention or extensive untreated fibrovascular proliferation is known to be present. The development of NVI also may prompt earlier vitrectomy.
- **Tractional retinal detachment:** Most surgeons agree that tractional retinal detachment involving the macula is an indication for diabetic vitrectomy. If the vitreoretinal traction can be relieved within weeks or a few months of onset, visual results are excellent. Long-standing tractional retinal detachments generally do not respond favorably in terms of visual recovery. Progressive extramacular tractional retinal detachment moving toward the fovea is occasionally an indication for surgery, although this is controversial.

- **Combined tractional–rhegmatogenous retinal detachment:** The development of combined retinal detachment with an open retinal break is an indication for vitrectomy. Such detachments are notoriously difficult to fix and patients are usually taken to surgery shortly after diagnosis.
- **Refractory macular edema:** Patients with a taut posterior hyaloid face producing chronic macular edema that is not responsive to focal laser therapy can undergo surgery, sometimes with significant visual improvement. It is believed that the chronic traction of the vitreous face on the macula produces persistent leakage and that the edema can resolve only after traction is released.

19. What are the complications of vitrectomy for diabetes?

- **Progression of cataract:** Progressive nuclear sclerotic or posterior subcapsular cataracts occur frequently after vitrectomy. The risk of secondary neovascular glaucoma may be higher in patients in whom the lens is removed intraoperatively.
- **Nonhealing corneal epithelial defects:** The cornea may swell, and the surface may break down during vitrectomy. Diabetic patients are prone to poor healing of corneal epithelial defects.
- **Retinal detachment:** Retinal detachment may be related to a peripheral tear near one of the sclerotomy sites or posteriorly as a result of persistent or recurrent vitreoretinal traction.
- **Vitreous hemorrhage:** Some degree of vitreous hemorrhage is frequently present postoperatively. It generally clears quickly.

20. Are there any other options for the treatment of diabetic macular edema beyond laser and, occasionally, vitrectomy?

Within the past few years there have been numerous reports regarding the use of various intravitreal injections to manage macular edema due to diabetes as well as other causes.

21. Does injection of steroids help diabetic macular edema?

The initial intravitreal medication was triamcinolone (Fig. 45-11). Many cases will show prompt resolution of macular thickening, even if long-standing edema has been present. Complications such as cataract, elevated intraocular pressure, infection, and retinal detachment may occur. Although severe complications are infrequent, they can be devastating. The beneficial effect is generally not maintained. Randomized trials have shown that steroids are not better than focal laser as primary therapy for most cases of diabetic macular edema (DME).

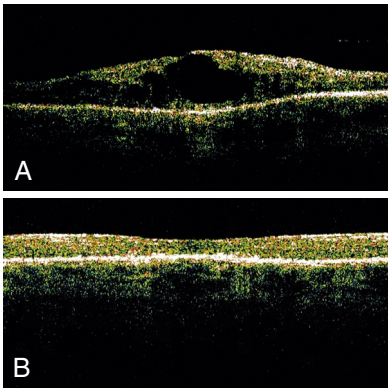

Figure 45-11. A, OCT shows marked macular edema with cystic spaces. **B,** Repeat OCT taken 3 weeks after injection of intravitreal steroids shows resolution of edema.

22. What about anti-vascular endothelial growth factor agents for diabetic macular edema?

Ranibizumab (Lucentis) has been shown in a series of clinical trials to be efficacious in treatment of DME. In most cases the edema responds quickly and visual acuity results are favorable. Repeated injections are generally necessary although the need for injections often diminishes 1 to 2 years after initiating treatment. There is some evidence that this may be superior to focal laser as primary therapy, at least for diffuse, center-involving edema. Bevacizumab (Avastin) is an off-label alternative that is also generally effective.

23. Are there any other uses for anti-vascular endothelial growth factor agents in diabetic retinopathy?

Intravitreal anti-vascular endothelial growth factor drugs will produce a dramatic reduction in the activity of neovascularization in PDR. They are often used, off-label, for treatment of vitreous hemorrhage in PDR, sometimes in conjunction with PRP or in anticipation of vitrectomy. They can be very helpful in inducing regression of NVI for treatment or prevention of neovascular glaucoma (NVG).

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RETINAL ARTERIAL OBSTRUCTION

Rebecca Droms and Jay S. Duker

CHAPTER 46

1. What types of retinal arterial obstructions can occur?

Retinal arterial obstructions are generally divided into branch retinal arterial obstructions and central retinal arterial obstructions, depending on the precise site of obstruction:

- A **branch retinal arterial obstruction** (BRAO) occurs when the blockage is distal to the lamina cribrosa of the optic nerve; in other words, within the visible vasculature of the retina. A BRAO can involve as large an area as three-quarters of the retina or as small an area as just a few micrometers.
- A **central retinal arterial obstruction** (CRAO) occurs when the blockage is within the optic nerve substance itself. The site of obstruction is therefore not generally visible on ophthalmoscopy. In a CRAO most, if not all, of the retina is affected.

Obstructions more proximal to the central retinal artery, in the ophthalmic artery, or even in the internal carotid artery can cause visual loss as well. Ophthalmic arterial obstructions can be difficult to differentiate from CRAO on a clinical basis.

2. What causes a retinal artery to become blocked?

The typical causes differ for CRAO and BRAO. Because the site of obstruction is not visible on clinical examination and, in general, the central retinal artery is too small to image with most techniques, the precise cause of most CRAOs cannot be definitely determined. It is currently believed that most CRAOs are caused by thrombus formation. Localized intimal damage from atherosclerosis probably incites the thrombus in most cases. In approximately 20% of cases an embolus is visible in the central retinal artery or one of its branches, suggesting an embolic cause (Fig. 46-1). Rarely, extrinsic mechanical compression is caused by an orbital or an optic nerve tumor, hemorrhage, or inflammation. Inflammation due to vasculitis, optic neuritis, or even orbital disease (e.g., mucormycosis) can cause a CRAO as well. Trauma with direct damage to the optic nerve or blood vessels can lead to CRAO. In addition, systemic coagulopathies can also be associated with both CRAO and BRAO.

Emboli are the cause of more than 90% of BRAOs. Cholesterol, calcium, fibrin, and platelets have all been implicated individually or together. Emboli are usually visible in the retinal arterial tree. In an older individual the most common source of emboli is the ipsilateral carotid artery. In a younger

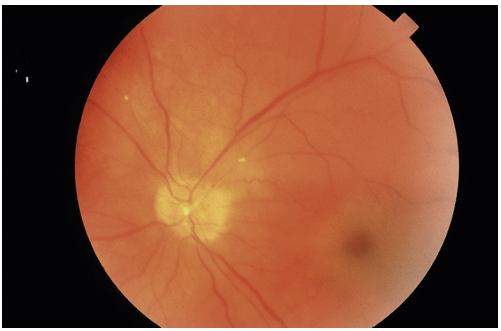

Figure 46-1. A central retinal arterial obstruction caused emboli in this patient. Note the refractile particles in the central retinal artery in the center of the optic disc, as well as in two branch retinal arteries superior to the optic disc.

person it is more likely to be cardiac in origin. Rarely, retinal vasculitis or intraocular inflammation such as toxoplasmosis or herpes retinitis (acute retinal necrosis) can lead to BRAO.

3. Describe the typical symptoms of a retinal arterial obstruction.

The hallmark symptom of an acute retinal arterial obstruction is abrupt, painless loss of sight in the visual field that corresponds to the territory of the obstructed artery. In a CRAO this would be most, if not all, of the visual field. In some patients an artery derived from the choroidal circulation, called a *cilioretinal artery*, may perfuse a small amount of the central retina. The cilioretinal artery, which is present in up to 20% of individuals, remains patent when the site of obstruction is the central retinal artery. Some of the visual field corresponding to the territory of the patent cilioretinal vessel can be spared in select individuals. Cilioretinal artery sparing can rarely leave a patient with 20/20 (normal) central vision, albeit with a very constricted visual field (Fig. 46-2).

Occasionally, patients report stuttering visual loss or episodes of amaurosis fugax before arterial obstruction. Pain is not generally a part of retinal arterial obstruction unless some other underlying disease is present (e.g., giant cell arteritis, ocular ischemia).

In a BRAO the visual field loss can vary from up to three-quarters of the visual field to as little as a few degrees, depending on the territory of the obstructed vessel. Often, the central vision will be 20/20, therefore sparing the macular area.

4. What do you see on examination when a retinal arterial obstruction has occurred?

The decreased blood flow results in ischemic whitening of the retina in the territory of the obstructed artery. Because the retinal vasculature supplies circulation only to the inner retina (the outer retina gets its circulation from the choroid), the ischemia is limited to the inner retina. The retinal whitening is most pronounced in the posterior pole where the nerve fiber layer (NFL) is thickest.

In an arterial obstruction the retinal arteries distal to the blockage appear thin and attenuated. The blood column may be interrupted in both the distal arteries and the corresponding draining veins. This phenomenon has been labeled "boxcarring." Splinter retinal hemorrhages on the disc are common. Embolic material may be visible in the central retinal artery, where it exits the disc, or in one of the branches of the central retinal artery. In most instances a cherry-red spot will be visible in the macular area.

The most common sites of obstruction in a BRAO are the retinal arterial bifurcations. Because there are more bifurcations and more retinal vessels in the temporal retina, temporal BRAOs are more common than nasal BRAOs.

In a CRAO the visual acuity is usually quite poor. The patient typically can only discern motion or, perhaps, count fingers from a distance of several feet. Many episodes of BRAO result in only peripheral visual loss with intact central acuity.

5. What is a cherry-red spot?

A cherry-red spot represents a pathologic appearance of the macula, the center of the retina. There are two main causes: ischemia and abnormal NFL deposits. A cherry-red spot occurs in CRAO because of the retinal whitening of the surrounding nerve fiber layer. The fovea itself has no nerve

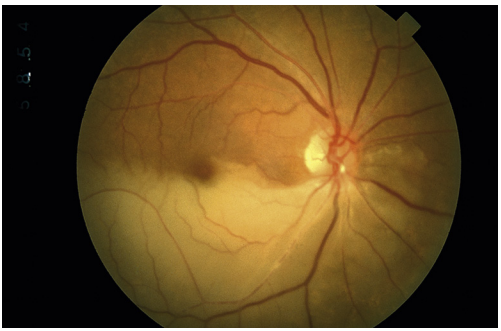

Figure 46-2. Typical inferior hemispheric branch retinal arterial obstruction. The visual acuity was 20/20, but there was a marked superior visual field defect.

fibers, so its appearance does not change significantly from normal. The retinal whitening surrounding the normal reddish tint of the macular area produces the cherry-red spot.

6. What other conditions result in a cherry-red spot of the retina? How can you differentiate these from an arterial obstruction?

In addition to CRAO, a cherry-red spot may be seen in conditions in which abnormal deposits accumulate in cells of the retinal nerve fiber layer. The classic example is Tay-Sachs disease, which is a sphingolipidosis. A cherry-red spot has been reported in other sphingolipidoses, such as Farber syndrome, Sandhoff's disease, Niemann-Pick disease, Goldberg's syndrome, Gaucher's disease, and gangliosidase GM1, type 2. A cherry-red spot has also been described in Hurler's syndrome (MPS I-H), β-galactosidase deficiency (MPS VII), Hallervorden-Spatz disease, and Batten-Mayou (Vogt-Spielmeyer) disease.

An ischemic cherry-red spot can be differentiated from these other entities by a history of visual loss, concurrent systemic disease, the age of the patient, and the appearance of the surrounding retinal blood vessels and retina.

7. Is there any ancillary testing that can be done to confirm the diagnosis?

In most cases an experienced observer can accurately diagnose CRAO and BRAO. In cases in which the diagnosis is in doubt, an intravenous fluorescein angiogram can be performed. This will show a significant diminution in dye flow through the obstructed vessels. A color Doppler ultrasound evaluation of the orbital circulation can also be used to determine the degree of obstruction and to differentiate an ophthalmic artery obstruction from CRAO.

8. Which systemic diseases are associated with retinal arterial obstruction?

Although many systemic diseases are associated with retinal arterial obstruction, more than 50% of all affected patients will manifest no apparent systemic or local cause for their retinal disease. The most common association is ipsilateral carotid artery disease, which is present in approximately one-third of affected patients. Approximately 10% of arterial obstructions in patients over 50 years of age are associated with giant cell arteritis. This is a critical association because visual loss can occur rapidly in the fellow eye in these patients. Prompt administration of high doses of corticosteroids may prevent the contralateral visual loss.

In both CRAO and BRAO, all patients should be evaluated for embolic sources from the carotid artery system and the heart with carotid noninvasive testing and echocardiogram. In some instances, esophageal echocardiography is necessary to detect embolic sources. Holter monitoring to detect a cardiac arrhythmia may be appropriate in select patients.

9. Do you always have to test for giant cell arteritis?

It is of paramount importance that giant cell arteritis be ruled out in all patients older than age 50 with a CRAO. A stat erythrocyte sedimentation rate, C-reactive protein, and platelet count should be ordered and, if the results are high, or if there is a strong clinical suspicion of giant cell arteritis, a biopsy should be considered along with high-dose corticosteroids until definitive biopsy results are known. BRAO associated with giant cell arteritis is exceedingly uncommon.

KEY POINTS: GIANT CELL ARTERITIS

1. Must be considered in all patients over age 50 with amaurosis.
2. Order a stat erythrocyte sedimentation rate, C-reactive protein, and platelet count.
3. Temporal arteritis may occur in patients with normal blood tests. Clinical suspicion is important.
4. High-dose steroids must be started immediately. A biopsy should be done within a week, but may be positive up to a month after steroids are initiated.

10. Which patients are at risk to get a retinal arterial obstruction?

Patients who have suffered an arterial obstruction in one eye are at a higher risk for developing an obstruction in the contralateral eye. Ten percent of patients have bilateral retinal arterial obstructions. Patients with known carotid artery disease, diseased heart valves, or cardiac arrhythmias are also at increased risk. In addition, conditions that result in abnormal rheologic parameters such as pancreatitis, lupus, pregnancy, and amniotic fluid emboli can result in artery obstructions.

11. Can any prophylactic treatment be given?

With the exception of corticosteroid treatment for giant cell arteritis, prophylaxis against arterial obstructions is not generally given. The utility of anticoagulation to prevent retinal arterial obstructions in the setting of known carotid disease is not definitively proven. Extrapolation from studies showing a benefit of lowering the risk of subsequent stroke in this situation suggests that anticoagulation is useful to lower the risk of arterial obstruction as well. The same conclusion may be extrapolated from the studies proving a benefit for carotid endarterectomy for appropriate patients with carotid arterial disease.

12. What is the incidence of bilateral retinal arterial obstructions?

Ten percent.

13. Is there any proven treatment for retinal arterial obstruction?

There is no proven treatment for either CRAO or BRAO. Some investigators feel that none of the currently recommended treatments have any value. Because the inner retina is highly sensitive to loss of perfusion, intervention is rarely, if ever, attempted in anyone with an obstruction more than 72 hours old. Proposed therapies for retinal arterial obstructions are as follows:

- Dislodging emboli to a more distal location
- Dissolving thrombi
- Increasing oxygenation to the retina
- Protecting surviving retinal cells from ischemic damage

The traditional approach to CRAO includes paracentesis, ocular massage, and medications to lower the intraocular pressure. All three of these interventions are an attempt to dislodge any embolus that may be present. A paracentesis is the removal of a small amount of aqueous humor via a small needle (30 or 27 gauge). This can be done in an office setting. Although generally simple and safe, it has rarely been reported to cause endophthalmitis.

Increasing oxygenation to the retina is attempted by having patients inhale a mixture of 95% oxygen and 5% carbon dioxide (carbogen) for 10 minutes every 2 hours for 24 to 48 hours after the blockage. Carbon dioxide counteracts the normal retinal arterial vasoconstriction that occurs when pure oxygen is inhaled. However, there is no clinical evidence of any beneficial effect. Carbogen should not be used to treat any patient suffering from chronic obstructive pulmonary disease. Hyperbaric oxygen therapy is another approach intended to increase oxygenation to the ischemic inner retina. This may be considered for patients seeking treatment within 24 hours of onset.

More recently, both systemic (via intravenous infusion) and local (directly into the ophthalmic artery via an arterial catheter) infusions of clot-dissolving medications (streptokinase, tissue plasminogen activator, urokinase, heparin) have been tried for retinal arterial obstruction. However, a randomized clinical trial found no difference in visual outcome between intra-arterial thrombolysis (IAT) via local infusion of tissue plasminogen activator and traditional CRAO treatments at 1 month follow-up, although IAT was associated with more adverse reactions. The long-term procedural results and potential favorable anatomic outcomes of IAT, such as central retinal artery reperfusion, have not yet been determined. IAT is not without risk and should be contemplated only for obstructions less than 48 hours old. Because branch retinal arterial obstructions do not usually affect central vision, such invasive procedures probably should not be attempted in these cases.

At present, there are no means to "rescue" ischemic retinal tissue. This is an area of active research and it may be possible in the future.

KEY POINTS: RETINAL ARTERIAL OBSTRUCTION

1. Systemic disease must be ruled out in any retinal artery obstruction.
2. Giant cell arteritis should be considered and ruled out in any patient older than age 60 with a central retinal artery obstruction.
3. No proven treatment exists for retinal artery obstruction.

14. Why is the retina so sensitive to arterial inflow problems?

The retina is a highly metabolic organ and is therefore sensitive to ischemia. The central retinal artery is an end artery with no true normal anastomosis. As part of the central nervous system, the retina is unable to regenerate if damaged.

15. How do you tell a retinal arterial obstruction from a retinal venous obstruction?

It is simple—white versus red. The hallmark of retinal arterial obstructions is ischemic retinal whitening. The hallmark of retinal venous obstruction is retinal hemorrhage in the territory of the obstructed vessel. In addition, the retinal veins will appear dilated and tortuous as opposed to thin and attenuated.

Warning: Rarely, a patient may present with a combined obstruction. Obstructions of a branch retinal artery or the central retinal artery in conjunction with a central retinal venous obstruction have been reported. This produces a combined fundus picture (i.e., whitening from ischemia with red from retinal hemorrhage).

16. Is acute obstruction of a retinal artery an emergency?

CRAO is considered a true ophthalmic emergency, even though there is no proven treatment. Because the retina is highly sensitive to ischemia, treatment should be initiated as quickly as possible if contemplated. Although animal studies indicate that more than 90 minutes of ischemia produce irreversible retinal cell death, clinical experience suggests that some eyes can tolerate ischemia for up to 72 hours and still recover. If a potentially risky intervention such as anticoagulation is contemplated, the visual loss should be no more than 48 hours old to maximize the possibility of recovery and the overall risk-to-benefit ratio. Optimal timing for anticoagulation is within 6 to 8 hours of visual loss. In addition, concurrent systemic diseases need to be ruled out.

17. What does the retina look like months or years after an arterial obstruction?

The retinal vessels look attenuated and the optic disc is often pale, owing to the loss of the retinal nerve fiber layer. Because the retina itself is transparent and the underlying retinal pigment epithelium and choroid are unaffected by a pure CRAO or BRAO, the retina itself looks normal.

18. Are there any other late complications after retinal arterial obstructions?

Neovascularization of the iris occurs in approximately 15% of patients with CRAO. It is usually seen within 3 months of the CRAO and can result in a severe type of glaucoma called *neovascular glaucoma* (NVI). If NVI is detected, a laser treatment to the ischemic retina, panretinal photocoagulation, is usually performed. Neovascularization is extremely rare after BRAO.

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CHAPTER 47

RETINAL VENOUS OCCLUSIVE DISEASE

Ehsan Rahimy

BRANCH RETINAL VEIN OCCLUSION

1. **What are the symptoms of a branch retinal vein occlusion?**
   Patients may notice an acute, painless loss of vision if there is macular edema, ischemic maculopathy, or intraretinal hemorrhage involving the fovea. A branch retinal vein occlusion (BRVO) in a nasal quadrant may be asymptomatic. A long-standing BRVO can present with floaters or an abrupt decrease in vision from vitreous hemorrhage secondary to retinal neovascularization.

2. **What are the clinical signs of a branch retinal vein occlusion?**
   The acute funduscopic findings of BRVO include a wedge-shaped segmental pattern of intraretinal hemorrhages with its apex near the site of occlusion, tortuous and dilated veins, cotton-wool spots, and macular edema (Fig. 47-1). In a chronic BRVO, collateral vessels on the disc or bridging the horizontal raphe, macular retinal pigment epithelium changes, or neovascularization of the retina (NVE) or disc can develop.

3. **Are there systemic associations in patients with a branch retinal vein occlusion?**
   The Eye Disease Case–Control Study Group identified a number of risk factors for BRVO: hypertension, cardiovascular disease, increased body mass index, and glaucoma. Interestingly, diabetes mellitus was not found to be a major independent risk factor for BRVO. Bilaterality, young age, or other atypical features should prompt further investigation for an underlying systemic disease (hypercoagulable state, autoimmune/inflammatory condition, or infectious disease).[1]

4. **Where does a branch retinal vein occlusion most commonly occur?**
   The superotemporal quadrant is the most common location for a BRVO, representing approximately 60% of observed cases. Inferotemporal BRVOs account for an additional 30% of cases, while nasally distributed ones represent the remaining 10%. However, these numbers may be misrepresented, because most patients with nasal BRVOs do not have visual complaints and are often found only incidentally. Approximately 10% of patients with a BRVO will develop a retinal vein occlusion in the fellow eye.

KEY POINTS: COMMON CHARACTERISTICS OF A BRANCH RETINAL VEIN OCCLUSION

1. Occurs at arteriovenous crossing
2. Segmental pattern of intraretinal hemorrhages
3. Macular edema
4. Majority occur in the superotemporal quadrant

5. **How is a branch retinal vein occlusion categorized?**
   A BRVO is classified as either ischemic or nonischemic. A nonischemic BRVO is defined as having fewer than five disc areas of retinal capillary nonperfusion, as documented by fluorescein angiography. An ischemic BRVO is defined as having more than five disc areas of retinal capillary nonperfusion.

6. **What are the complications of a branch retinal vein occlusion?**
   Patients with a nonischemic BRVO may lose vision secondary to macular edema, which may be appreciated clinically and confirmed with ancillary imaging studies, such as fluorescein angiography

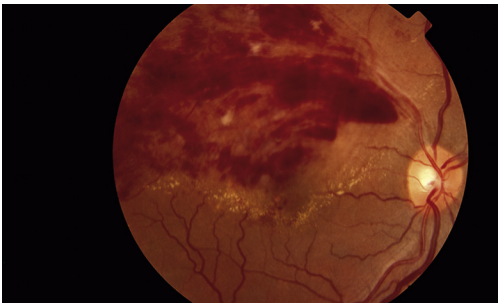

Figure 47-1. Superotemporal branch retinal vein occlusion with intraretinal hemorrhages, cotton-wool spots, hard exudates, and macular edema.

or, more commonly, optical coherence tomography. Patients with an ischemic BRVO most commonly lose vision from macular edema, ischemic maculopathy, or vitreous hemorrhage (VH). Fluorescein angiography is useful in detecting macular ischemia, revealing an enlarged and irregular foveal avascular zone. Depending on the degree of macular ischemia present, permanent visual loss is common. Additional sequelae of BRVO include retinal neovascularization (25%), which can result in vitreous hemorrhage from traction on the neovascular fronds, and epiretinal membrane formation (20%).

7. What is the treatment for an uncomplicated branch retinal vein occlusion?

Patients with a nonischemic BRVO without macular edema are followed clinically for the development of macular edema and for potential progression into an ischemic BRVO and its complications, which include ischemic maculopathy, NVE, and VH.

8. What is the first-line treatment for macular edema secondary to branch retinal vein occlusion?

The introduction of anti-vascular endothelial growth factor (VEGF) therapy has revolutionized the management of macular edema associated with retinal vascular disease. The BRAVO study was a large, multicenter, phase 3, randomized study that evaluated monthly ranibizumab (Lucentis, Genentech, South San Francisco, CA, USA) versus sham injections in treating acute macular edema secondary to BRVO. After 6 months, patients who received 0.3 mg ranibizumab had a mean gain from baseline of 16.6 letters, those who received 0.5 mg ranibizumab gained 18.3 letters, and the sham group gained 7.3 letters. Many clinicians have extrapolated these results to bevacizumab (Avastin, Genentech), a cheaper off-label alternative, which has been shown to substantially reduce macular edema in a number of smaller uncontrolled studies.[2]

9. What is the role of intravitreal steroids in the treatment of macular edema secondary to branch retinal vein occlusion?

The Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) BRVO study compared the safety and efficacy of macular grid laser treatment versus intravitreal triamcinolone corticosteroid injections (1 and 4 mg doses) to treat vision loss from macular edema associated with BRVO. After 1 year, a comparable percentage of patients experienced a substantial gain of three or more lines of vision across all three groups (29% in the laser group, 26% in the 1 mg triamcinolone group, and 27% in the 4 mg triamcinolone group). However, patients who received either dose of steroid were more likely to develop a cataract or elevated intraocular pressure than those who received laser treatment. In the GENEVA study, a biodegradable dexamethasone intravitreal implant (Ozurdex, Allergan, Irvine, CA, USA) demonstrated efficacy in treating macular edema from BRVO with much less intraocular pressure elevation or cataract progression than was reported with triamcinolone.[3,4]

10. What is the role of macular grid laser in the treatment of macular edema secondary to branch retinal vein occlusion?

The Branch Vein Occlusion Study was a historic multicenter, randomized, controlled clinical trial designed to answer whether argon macular grid laser photocoagulation is useful in improving visual acuity in eyes with a BRVO and macular edema that reduced vision to 20/40 or worse. The study found 65% of eyes treated with macular grid laser compared to 37% of control eyes gained two or

more lines of vision. The investigators recommended macular grid laser for patients with a BRVO of at least 3 months' duration and vision 20/40 or worse secondary to macular edema. Although the results of this study may seem outdated in the modern era of anti-VEGF pharmacotherapy, there is still a distinct role for macular grid laser treatment, either alone or as an adjunct to intravitreal therapy.[3,5]

11. What is the treatment for a patient with an ischemic branch retinal vein occlusion before the development of neovascularization?

A second arm of the Branch Vein Occlusion Study was designed to determine whether peripheral sectoral scatter argon laser photocoagulation in the distribution of the vein occlusion can prevent the development of retinal neovascularization and vitreous hemorrhage. Significantly less neovascularization developed in patients treated with laser (19%) than in control patients (31%). Although the Branch Vein Occlusion Study was not designed to determine whether peripheral scatter laser treatment should be applied before rather than after the development of neovascularization, data accumulated in the study suggested there was minimal risk for severe vision loss if laser treatment was performed after the development of neovascularization. Thus, the authors did not advocate for prophylactic laser.[6]

12. What is the treatment for a patient with an ischemic branch retinal vein occlusion after the development of neovascularization?

The Branch Vein Occlusion Study determined that peripheral sectoral scatter argon laser photocoagulation in the distribution of the vein occlusion can prevent vitreous hemorrhage in patients who have already developed neovascularization (Fig. 47-2). Patients treated with laser developed vitreous hemorrhage significantly less often (29%) compared to the control patients (61%).[6]

KEY POINTS: WORKUP TO CONSIDER IN PATIENTS WITH BRVO

1. Blood pressure
2. Hemoglobin A1c, fasting blood glucose
3. Lipid profile
4. Prothrombin time/partial thromboplastin time
5. Hypercoagulable panel (e.g., protein C activity, protein S activity, homocysteine, antiphospholipid antibody, antithrombin III, factor V Leiden)

CENTRAL RETINAL VEIN OCCLUSION

13. What are the symptoms of a central retinal vein occlusion?

Patients may complain of sudden, painless loss of vision. A patient who has developed neovascular glaucoma secondary to ischemic central retinal vein occlusion (CRVO) may present with complaints of a painful red eye.

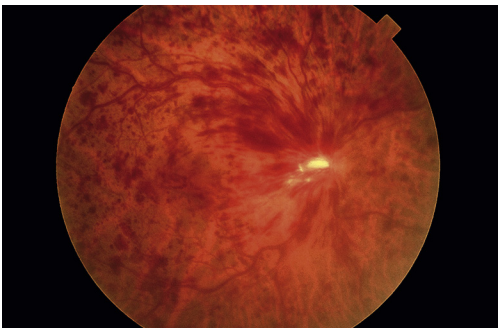

Figure 47-2. Fluorescein angiogram of a superotemporal branch retinal vein occlusion after receiving sectoral scatter argon laser photocoagulation after developing neovascularization of the retina.

14. What are the clinical signs of a central retinal vein occlusion?

In an acute CRVO, dilated fundus examination reveals certain characteristic findings: tortuosity and dilation of the central retinal vein, intraretinal hemorrhages throughout all four quadrants, cotton-wool spots, optic disc edema, and/or macular edema (Figs 47-3 and 47-4). Increased intraocular pressure or even frank open-angle glaucoma may be noted in a patient presenting with an acute CRVO. Cases of ischemic CRVO can develop anterior-segment or posterior-segment neovascularization, which manifests as proliferating new vessels on the iris, angle, disc, or retina. In a long-standing CRVO, patients may develop disc or retinal venous collaterals (Fig. 47-5).

KEY POINTS: COMMON CHARACTERISTICS OF A CENTRAL RETINAL VEIN OCCLUSION

1. Intraretinal hemorrhages in all four quadrants
2. Dilated tortuous retinal veins
3. Cotton-wool spots
4. Disc edema
5. Macular edema

15. What are the risk factors for a central retinal vein occlusion?

The Eye Disease Case–Control Study Group identified a number of risk factors for CRVO: hypertension, diabetes mellitus, and glaucoma. Oral contraceptives and diuretics have also been

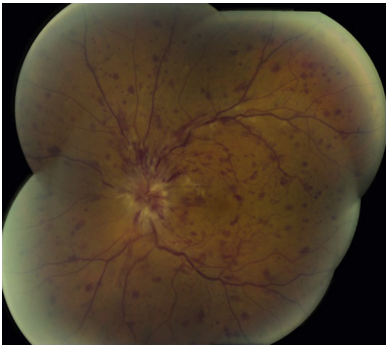

Figure 47-3. Nonischemic central retinal vein occlusion with dilated tortuous veins, prominent disc edema, intraretinal hemorrhages in four quadrants, and macular edema.

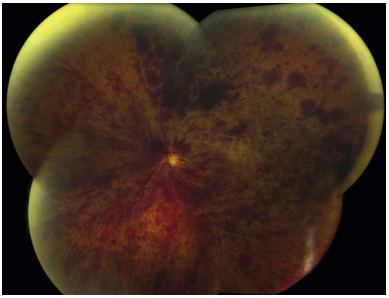

Figure 47-4. Ischemic central retinal vein occlusion with dilated tortuous veins, extensive intraretinal hemorrhages in four quadrants, and macular edema.

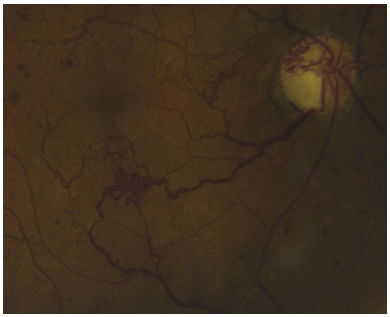

Figure 47-5. Disc and retinal collaterals that have formed in the setting of a long-standing central retinal vein occlusion.

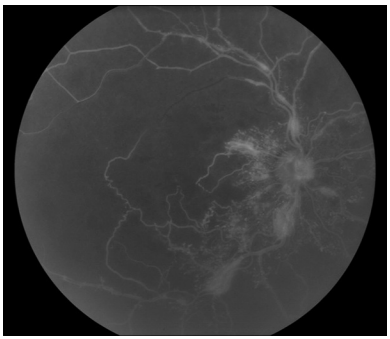

Figure 47-6. Fluorescein angiogram of an ischemic central retinal vein occlusion demonstrating extensive retinal nonperfusion involving the macula.

implicated in causing CRVO. Other systemic conditions that affect the retinal vasculature or clotting mechanisms may also be associated with CRVO: blood dyscrasias (i.e., polycythemia vera), hypercoagulable states (i.e., protein C/S deficiencies), or autoimmune/inflammatory diseases. Notably, hyperviscosity retinopathy is a bilateral condition that can mimic CRVO; however, it is due to an underlying systemic dysproteinemia, such as Waldenstrom macroglobulinemia or multiple myeloma.[7]

16. How is a central retinal vein occlusion categorized?

A CRVO is classified as either ischemic or nonischemic. A nonischemic CRVO is defined as having fewer than 10 disc areas of capillary nonperfusion as demonstrated by fluorescein angiography, whereas an ischemic CRVO is defined as having more than 10 disc areas of capillary nonperfusion (Fig. 47-6). Clinically, ischemic CRVO tends to be associated with poor vision, an afferent pupillary defect, and dense central scotoma.[8]

17. What are the complications of a central retinal vein occlusion?

Patients with a nonischemic CRVO can lose vision secondary to macular edema (Fig. 47-7). Patients with an ischemic CRVO can lose vision from macular edema, ischemic maculopathy, neovascular glaucoma (NVG), and vitreous hemorrhage. If ischemia occurs in the macula, the patient complains of central vision loss, and a fluorescein angiogram will demonstrate an enlarged and irregular foveal avascular zone. The most feared complication of an ischemic CRVO is anterior-segment neovascularization, which can lead to NVG. Approximately 15% of patients with an ischemic CRVO develop neovascularization of the retina or disc. Traction from the vitreous may cause these new vessels to bleed, leading to VH and decreased vision (Fig. 47-8).[9]

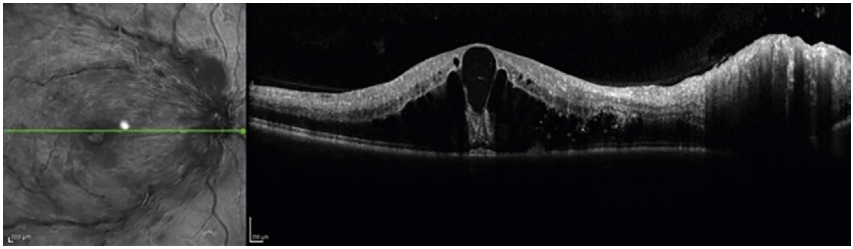

Figure 47-7. Spectral-domain optical coherence tomography scan demonstrating macular and disc edema associated with central retinal vein occlusion.

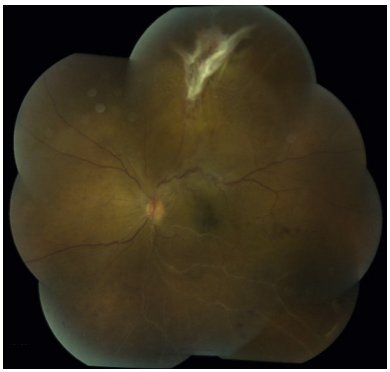

Figure 47-8. Ischemic central retinal vein occlusion that has developed secondary neovascular membranes superiorly with associated traction and early vitreous hemorrhage.

18. What is the most important risk factor for development of iris neovascularization in central retinal vein occlusion?

The Central Vein Occlusion Study (CVOS) determined that poor presenting visual acuity is the most important risk factor predictive of iris neovascularization.[10]

19. What is the proposed pathophysiologic basis for development of a combined cilioretinal artery occlusion and central retinal vein occlusion?

In an acute CRVO, increased venous intraluminal pressure is transmitted upstream to the feeding capillary bed. This increase in pressure carries over to the typically low-pressure cilioretinal artery system (which is unable to autoregulate), resulting in a transient blockage and thus a cilioretinal artery occlusion (Fig. 47-9).

20. What is the treatment for an uncomplicated central retinal vein occlusion?

Patients with a nonischemic CRVO without macular edema are followed clinically for the development of macular edema and for progression into an ischemic CRVO and its complications, including ischemic maculopathy, NVG, and VH. These patients should be monitored at monthly intervals for potential progression and for at least 6 months for the development of anterior-segment neovascularization/neovascular glaucoma.

21. What is the first-line treatment for a patient with a central retinal vein occlusion and macular edema?

Like with BRVO, intravitreal anti-VEGF injections are the mainstay treatment for macular edema secondary to CRVO. In the CRUISE study (counterpart to the BRAVO study), patients were randomized to receive monthly injections of either 0.3 or 0.5 mg ranibizumab for 6 months versus sham injections. After 6 months, patients who received 0.3 mg ranibizumab had a mean gain from baseline of 12.7 letters, those who received 0.5 mg ranibizumab gained 14.9 letters, and the sham group gained

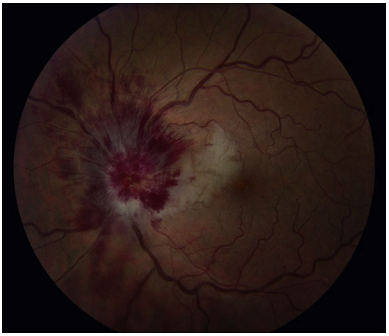

Figure 47-9. Combined central retinal vein occlusion and cilioretinal artery occlusion.

0.8 letters. Ophthalmologists have extrapolated these results to bevacizumab (Avastin, Genentech), a cheaper off-label alternative, which has been demonstrated to reduce macular edema in a number of smaller uncontrolled studies. More recently, a third anti-VEGF drug, aflibercept (Eylea, Regeneron, Tarrytown, NY, USA), has been approved for the indication of macular edema secondary to CRVO. In the nearly identical COPERNICUS and GALILEO studies, patients received 6-monthly injections of aflibercept at a dose of 2 mg versus sham injections. In the COPERNICUS trial, 56.1% of patients receiving aflibercept gained at least 15 letters of vision from baseline, compared with 12.3% of patients receiving sham injections. In the GALILEO study, 60.2% of patients receiving aflibercept gained at least 15 letters of vision from baseline, compared with 22.1% of patients receiving sham injections.[11-13]

22. What is the role of intravitreal steroids in the treatment of macular edema secondary to central retinal vein occlusion?

In the SCORE-CRVO study, more patients experienced an improvement of 15 ETDRS letters or more after 1 year in the 1 mg triamcinolone (27% of patients) and 4 mg triamcinolone (26%) groups compared to only 7% of patients in the observation group, In the GENEVA study, a biodegradable dexamethasone intravitreal implant (Ozurdex, Allergan) demonstrated efficacy in improving visual acuity outcomes and reducing macular edema from CRVO with a lower incidence of elevated intraocular pressure or cataract progression than was previously reported with triamcinolone.[4,14]

23. What is the role of macular grid laser in the treatment of macular edema secondary to central retinal vein occlusion?

The CVOS was a multicentered, randomized, controlled clinical trial designed to answer whether argon macular grid laser photocoagulation was useful in improving visual acuity in eyes with a CRVO and macular edema that reduced vision to 20/50 or worse. Patients were randomized to macular grid photocoagulation or no treatment. Although the grid laser treatment reduced angiographic evidence of macular edema, there was no improvement in final visual acuity compared to untreated eyes. However, a trend was observed that revealed that grid laser treatment may be beneficial in younger patients. Taking the results together, the study investigators did not recommend routine macular grid photocoagulation for patients with macular edema secondary to CRVO.[15]

KEY POINTS: WORKUP TO CONSIDER IN PATIENTS WITH CRVO

1. Blood pressure
2. Hemoglobin A1c, fasting blood glucose
3. Lipid profile
4. Prothrombin time/partial thromboplastin time
5. Hypercoagulable panel (e.g., protein C activity, protein S activity, homocysteine, antiphospholipid antibody, lupus anticoagulant, antithrombin III, factor V Leiden)
6. Consider hemoglobin electrophoresis, cryoglobulins, and serum protein electrophoresis if clinically indicated

24. What is the treatment for a patient with an ischemic central retinal vein occlusion?

The CVOS was also designed to answer whether scatter panretinal argon laser photocoagulation could prevent the development of anterior-segment neovascularization and NVG. Although prophylactic laser decreased the incidence of anterior-segment neovascularization, 20% of study participants still developed neovascularization despite the prophylactic treatment. Additionally, waiting to perform laser until the time of development of anterior-segment neovascularization was shown to be effective in preventing subsequent NVG. Thus, the study investigators recommended careful follow-up of patients with an ischemic CRVO and panretinal photocoagulation only once a patient develops two clock hours of iris neovascularization or any angle neovascularization. In modern clinical practice, however, panretinal photocoagulation is often performed at the first sign of iris neovascularization.[9,16]

Acknowledgments

We acknowledge Vernon K. W. Wong, chapter author from the previous edition.

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CHAPTER 48

RETINAL DETACHMENT

Michael J. Borne and James F. Vander

1. What is retinal detachment?

Retinal detachment (RD) is separation of the neurosensory retina from the underlying retinal pigment epithelium with accumulation of fluid in the potential space between the two layers. The types of retinal detachment include rhegmatogenous, tractional, and exudative.

- In **rhegmatogenous retinal detachment (RRD)**, a break in the retina allows fluid from the vitreous cavity access to the potential space between the retina and the retinal pigment epithelium.
- **Tractional retinal detachment** occurs when epiretinal tissue forms and contracts, pulling the retina away from the pigment epithelial layer. Occasionally the severe traction caused by epiretinal membranes may cause a tear in the retina, creating a combined rhegmatogenous–tractional detachment.
- **Exudative retinal detachment** is produced by retinal and choroidal conditions that damage the blood–retina barrier and allow fluid to accumulate in the subretinal space (the potential space between the retina and the retinal pigment epithelium).

2. What are the major characteristics of each type of retinal detachment?

- **Rhegmatogenous retinal detachments** typically have a corrugated appearance caused by intraretinal edema (Fig. 48-1). Obviously, they are associated with a retinal break, although in a small percentage of cases the break is not easily identifiable. Decreased intraocular pressure, pigmented cells in the vitreous cavity, and vitreous hemorrhage are also associated with RRDs. Fixed folds and other signs of proliferative vitreoretinopathy (PVR) strongly suggest an RRD. Extension of fluid through the macula is a poor prognostic sign. The intraocular pressure is usually low.
- **Tractional retinal detachments** are characterized by a smooth and stiff-appearing retinal surface. In most cases the epiretinal membranes that cause the traction may be ophthalmoscopically observed. The detachment is usually concave toward the front of the eye. The most common location of the tractional membranes is in the postequatorial region; the traction detachment rarely extends to the ora serrata.
- **Exudative retinal detachments** are characterized by shifting subretinal fluid. The subretinal fluid accumulates according to gravitational forces and detaches the retina in the area where it accumulates. Thus, the fluid is noted to shift when the patient is viewed in an upright compared with a supine position. The surface of the retina is usually smooth in exudative detachments, compared with the corrugated appearance of an RRD. Occasionally the retina may be seen directly behind the lens in exudative detachments. This rarely occurs in RRDs, unless severe vitreoretinal traction is present.

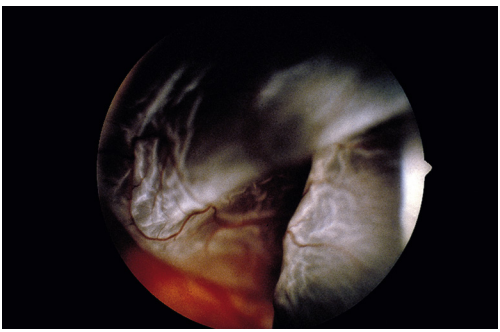

Figure 48-1. Bullous rhegmatogenous retinal detachment with mobile, corrugated appearance.

3. What are the major causes of exudative retinal detachments?

The major causes of exudative RDs are intraocular tumors, intraocular inflammatory diseases, and congenital abnormalities. Intraocular neoplasms, such as choroidal melanomas, choroidal hemangiomas, and metastatic choroidal tumors, are most likely to produce serous RDs. Intraocular inflammation, such as posterior scleritis, Harada's disease, severe posterior uveitis, and central serous chorioretinopathy, occasionally produce shifting subretinal fluid. The most common congenital abnormalities known to produce exudative RDs are optic pits, nanophthalmos, and the morning glory disc syndrome.

4. How does the retina remain attached?

The retinal photoreceptors and retinal pigment epithelial (RPE) cells are oriented with the apices of the cells in apposition. An interphotoreceptor matrix between the cells forms a "glue" that helps to maintain cellular apposition. It also has been postulated that the RPE functions as a cellular pump to remove ions and water from the interphotoreceptor matrix, providing a "suction force" that helps to keep the retina attached.

5. What are the major predisposing factors for rhegmatogenous retinal detachments?

The main predisposing factors for RRDs are previous cataract surgery, lattice degeneration, and myopia. The incidence of RRD after cataract surgery is approximately 2 in 1000. The incidence becomes much higher after complicated cataract surgery, including posterior capsule rupture, vitreous loss, and retained lens fragments. Some studies have shown an incidence of RRD after complicated cataract surgery as high as 15%. Currently, approximately half of all primary RRDs occur in patients with a history of cataract surgery.

Lattice degeneration (Fig. 48-2) is a peripheral retinal degeneration characterized by thinning of the retina with liquefaction of the overlying vitreous, which results in a high risk for retinal tears and breaks. Lattice degeneration is found in 6% to 7% of the population and is often bilateral. Lattice degeneration is the direct cause of primary RRD in approximately 25% of eyes.

High myopes have a high risk of RD for several reasons. First, the incidence of lattice degeneration is higher in myopes. Second, myopes tend to have a higher rate of posterior vitreous detachment. Of greater importance, myopic eyes have a higher rate of retinal breaks because of the thin peripheral retina. The rate of retinal breaks tends to be higher with increasing myopia.

6. What are the signs and symptoms of a retinal break?

Flashes and floaters are the classic symptoms. Pigmented cells or blood in the vitreous strongly suggests the possibility of a retinal break.

7. What are the types of retinal breaks?

- **Horseshoe tear:** A flap of retina created by vitreous traction gives the appearance of a horseshoe. The open end of the horseshoe is anterior. A retinal vessel may bridge the gap of the tear (Figs 48-3 and 48-4). The risk of subsequent RD is high, especially with acute tears.
- **Operculated tear:** When a piece of retina is completely torn away by vitreous traction, the fragment is seen floating over the retinal defect. The risk of RD is lower than with a horseshoe tear.

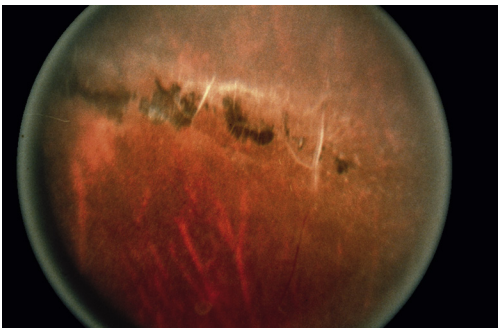

Figure 48-2. Lattice degeneration.

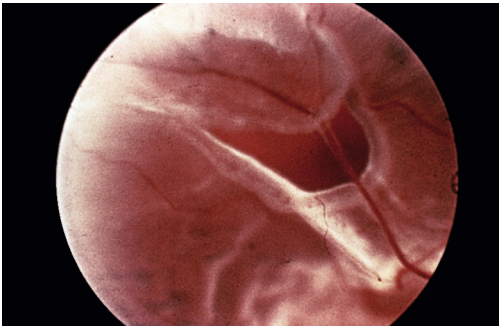

Figure 48-3. Horseshoe retinal tear with a bridging vessel.

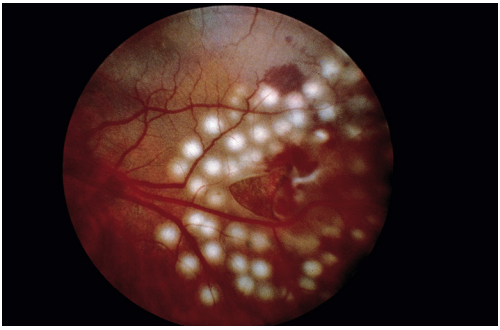

Figure 48-4. Horseshoe retinal tear after laser photocoagulation.

- **Atrophic hole:** A round hole without evidence of retinal traction is often associated with lattice degeneration. The risk of RD is low.
- **Dialysis** (Fig. 48-5): A disinsertion of the retina at the ora serrata, this is most common in the inferotemporal quadrant. The second most common site is superonasal. A frequent cause is trauma.

KEY POINTS: SYMPTOMS AND SIGNS OF RHEGMATOGENOUS RETINAL DETACHMENT

1. Flashes
2. Floaters
3. Pigment in the vitreous
4. Posterior vitreous detachment (usually)
5. Elevated mobile retina
6. Corrugations
7. Loss of retinal transparency
8. Presence of a retinal break
9. Retinal pigment epithelial alterations under detachment, i.e., a demarcation line
10. Fixed folds
11. Peripheral visual field loss
12. Loss of central vision (with macular involvement)

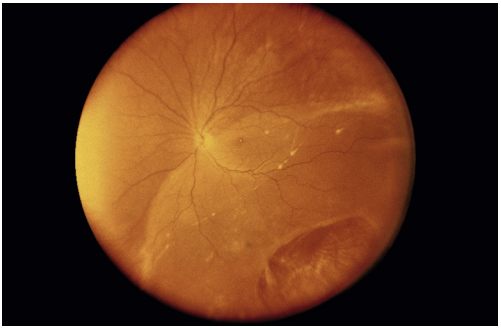

Figure 48-5. Retinal detachment resulting from inferotemporal dialysis.

8. What are the signs of a chronic rhegmatogenous retinal detachment?

The retina is more transparent than in an acute RD, and the corrugations are minimal or absent. Pigmentary alterations are more prominent, including hyperpigmented demarcation lines (indicative of progression if multiple), RPE atrophy in the bed of the detachment, and abundant pigment in the vitreous. Retinal cysts, sometimes very large, may develop. The causative retinal break may be difficult to identify. PVR may also be present. The intraocular pressure may be low, normal, or high.

9. What is degenerative retinoschisis?

Sometimes called senile retinoschisis, this is a dome-shaped elevation of the inner retina caused by a splitting within the outer plexiform layer. In contrast to an RRD, this rarely progresses and is usually observed. Occasionally, outer wall holes will form and create a progressive retinoschisis-related RRD. The inferotemporal quadrant is most commonly affected, and 80% are bilateral.

KEY POINTS: SIGNS OF CHRONIC RETINAL DETACHMENT VERSUS RETINOSCHISIS

1. Presence of retinal break most reliable method to distinguish the two but is often difficult to find
2. Pigment in the vitreous
3. Pigment alterations in the retinal pigment epithelium
4. Retinal folds
5. Absence of schisis in the fellow eye

10. What are the options for repair of retinal detachment?

First, determining the type of RD is important before identifying the modality of treatment. Exudative RDs are approached differently compared to rhegmatogenous or traction detachments. Exudative detachments are repaired by treating the primary cause of the fluid extravasation into the subretinal space. For example, an RD associated with choroidal melanoma is addressed by treating the tumor with radiation, thermotherapy, or resection. Exudative RDs related to intraocular inflammatory conditions are generally treated by aggressive anti-inflammatory regimens. Rarely does an exudative detachment require primary surgical repair.

On the other hand, treatment of rhegmatogenous and tractional RD is primarily surgical. Tractional RDs caused by diabetes or proliferative vitreoretinopathy require relief of all traction membranes before the retina will remain reattached.

Small, localized RRDs are usually treated by cryotherapy or barrier laser photocoagulation. Rarely, an asymptomatic localized detachment may be treated with close observation only. If significant vitreous traction is present on the retinal tear, especially if the tear is superior in location, or if a large amount of subretinal fluid is found, more definitive treatment is usually indicated. Options include pneumatic retinopexy, Lincoff balloon, scleral buckling, and pars plana vitrectomy. Scleral buckling surgery is the time-honored approach and has been applied routinely since the 1950s. Pars plana

vitrectomy was first performed in the late 1960s and has become the operation of choice for some surgeons. Pneumatic retinopexy has gained popularity since the early 1980s.

11. What is pneumatic retinopexy?

To perform a pneumatic retinopexy, an inert gas or sterile air is injected into the vitreous cavity. Strict positioning is required to place the gas bubble in contact with the retinal break. If the break is closed by the surface tension from the gas bubble, the retinal pigment epithelium can pump the subretinal fluid back into the choroid and allow the retina to reattach. The break is sealed either with cryotherapy at the time of gas injection or with laser photocoagulation after the retina is flattened.

12. Which patients are the best candidates for pneumatic retinopexy?

The ideal candidates are patients with a detachment caused by a single retinal break in the superior eight clock hours or multiple breaks if all of the tears are within one to two clock hours of one another. Obviously the patient must not have a systemic disease or mechanical problem that precludes the positioning requirements. Phakic patients tend to fare slightly better than patients with a history of cataract surgery.

13. Which patients are poor candidates for pneumatic retinopexy?

Patients with RDs caused by multiple tears in several locations are poor candidates, as well as patients with a detachment resulting from a single tear but with tears in other areas of attached retina. Proliferative vitreoretinopathy, especially if fixed folds are present, lessens the chances for reattachment with pneumatic retinopexy. And, as previously stated, patients who are unable to obey the strict postoperative positioning requirements are poor candidates.

KEY POINTS: FACTORS THAT INFLUENCE THE DECISION TO TREAT RETINAL BREAKS PROPHYLACTICALLY

1. Type of break.
2. Presence of symptoms of vitreoretinal traction.
3. Horseshoe tears are usually treated, especially if symptomatic.
4. Operculated tears are generally not treated unless symptomatic.
5. History of retinal detachment in the fellow eye.
6. Family history of retinal detachment.
7. Anticipated prolonged inaccessibility to care.

14. What are the advantages of scleral buckling and pars plana vitrectomy?

Scleral buckling and pars plana vitrectomy reduce vitreous traction mechanically. Scleral buckling involves the surgical placement of a silicone band or sponge, either sewn to the sclera as an exoplant or implanted in the sclera after a partial-thickness scleral bed is surgically created (Fig. 48-6). Scleral buckles provide smooth, broad relief of vitreous traction. Subretinal fluid may be drained at the time of placement of the scleral buckle via an external sclerostomy, and intraocular gas may be injected into the vitreous cavity as an adjunct to aid in retinal reattachment. Scleral buckles are especially effective in anterior retinal breaks. This is the most common site for postcataract retinal breaks. Another advantage of scleral buckling is the opportunity to repair the RD from a purely external approach with no intraocular invasion.

With vitrectomy, it is possible to relieve vitreous traction directly with the vitrectomy cutter. This technique is especially useful in cases with very posterior breaks. Vitrectomy is advantageous in cases of RD with vitreous hemorrhage or vitreous opacities that obscure a view of the retinal breaks. Vitrectomy also allows the surgeon to remove epiretinal membranes when proliferative vitreoretinopathy is present. When vitrectomy is performed, the vitreous cavity must be filled with gas to reattach the retina. The presence of intravitreal gas hastens the development of cataract in phakic patients.

15. What are the major risks and complications with scleral buckling and pars plana vitrectomy?

Risks of infection and hemorrhage are found with any invasive ocular procedure. The risk of an infection with a scleral buckle is less than 3%. Other risks and complications from scleral buckles include angle-closure glaucoma, acute glaucoma from intraocular gas injection, intraocular hemorrhage from

perforation during drainage of subretinal fluid, and anterior-segment ischemia and necrosis. The surgically placed buckles may cause extrusion or intrusion over time, and, if the buckle is placed under an extraocular muscle, strabismus may result.

Vitrectomy involves the risks of endophthalmitis, iatrogenic retinal breaks, retinal or vitreous incarceration in the sclerostomy sites, and glaucoma from the use of intraocular gases.

16. What intraoperative findings should be confirmed at the time of scleral buckle placement?

The most important intraoperative decisions at the time of scleral buckling procedures are to find and treat all retinal tears and place the scleral buckle in a position to support all retinal breaks. After the buckle has been temporarily placed, the surgeon should confirm that the tears are flat on the buckle. If the tears are not flat, the placement of the buckle should be checked with scleral depression. If the buckle is in the appropriate position but fluid still exists between the retina and the buckle, the decision to drain subretinal fluid or to inject an intravitreal gas bubble should be made. If the detachment is primarily inferior in location, most surgeons prefer to have the retina completely attached before leaving the operating room. Superior detachments may flatten with gas injection and postoperative positioning; the decision to drain subretinal fluid adds potential complications.

17. What three factors should be confirmed with indirect ophthalmoscopy at the conclusion of scleral buckling surgery?

Apposition of the scleral buckle to the retinal breaks, absence of complications at the drainage site, and absence of central retinal artery pulsations should be confirmed before final closure. If pulsations are present, the intraocular pressure is high enough to cause a central retinal artery obstruction. The pressure should be lowered by loosening the buckle, removing intraocular fluid or gas until pulsations are no longer seen.

18. How should cases of rhegmatogenous retinal detachment be approached if pars plana vitrectomy is the chosen treatment?

Vitreous traction on all retinal breaks should be relieved if possible. Care must be taken to avoid damaging retinal blood vessels if they are coursing across the retinal tears. A complete posterior vitreous detachment and meticulous removal of peripheral vitreous should be ensured using wide-field illumination. All retinal tears should be treated completely with laser.

19. Which gases may be used inside the eye? In what concentrations?

The inert gases sulfur hexafluoride (SF_6) and perfluoropropane (C_3F_8), along with sterile air, are the most commonly used intraocular gases. Nonexpansile mixtures are composed of approximately 20% sulfur hexafluoride and 14% perfluoropropane. These are the most commonly used mixtures when the vitreous cavity is filled with gas, as in vitrectomy. Pure 100% gas injection allows a larger bubble to form with a smaller volume of injection. This technique is advantageous in patients with pneumatic retinopexy and scleral buckles. Typically, sulfur hexafluoride expands to two to three times its initial volume, and perfluoropropane expands to approximately four times its initial volume. Thus, injection of 0.4 mL of each gas produces a 20% to 40% intravitreal gas bubble when they are injected as a pure concentration.

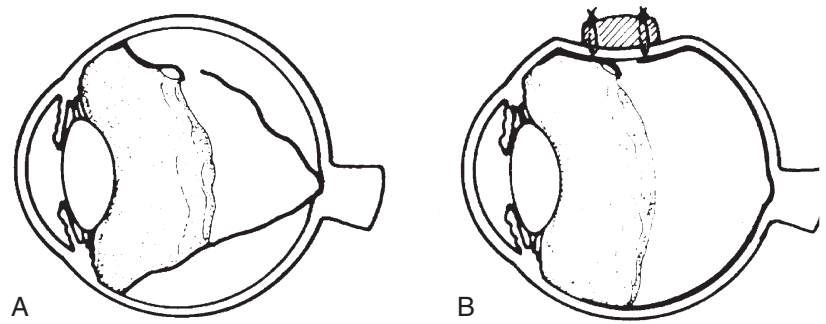

Figure 48-6. Placement of a scleral buckle. **A,** Rhegmatogenous retinal detachment. **B,** The retina is attached after placement of a scleral buckle supenaly.

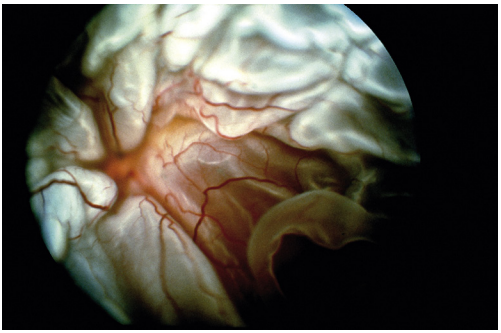

Figure 48-7. Severe proliferative vitreoretinopathy with total retinal detachment.

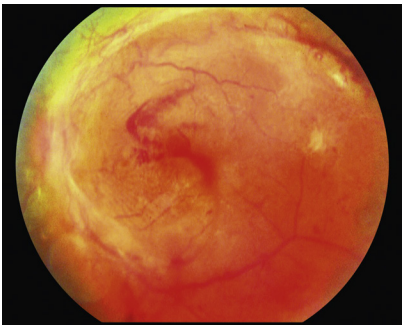

Figure 48-8. Proliferative diabetic retinopathy causing localized tractional retinal detachment.

20. What are the primary causes of failure of initial retinal detachment repair?

Except for cases of severe PVR, in which epiretinal membranes cause traction retinal detachments (Fig. 48-7), failures of RD repair are caused by an open retinal break. With pneumatic retinopexy, the most common reasons for failure include poor patient compliance with positioning requirements, inadequate identification of all retinal breaks, and development of new retinal tears from vitreous traction related to intravitreal gas. After scleral buckling surgery, failure to flatten the retina or to keep it attached results most often from undetected retinal breaks; continued vitreous traction with new, extended, or reopened retinal breaks; or a misplaced scleral buckle. Inadequate photocoagulation, continued vitreous traction, and new or missed breaks are the most common reasons for failure after pars plana vitrectomy. Ten percent of retinal reattachments have evidence of PVR. However, only 10% to 25% of these progress to require treatment for detachment.

21. What are the major objectives in repair of tractional retinal detachment?

When tractional retinal detachments are caused by proliferative diabetic retinopathy (Fig. 48-8), one of the major aims is to relieve all anteroposterior traction. A complete posterior vitreous separation must be created to remove or segment all retinal traction. Segmentation of diabetic tractional membranes is effective if no anterior traction remains (Fig. 48-9). Delamination of traction membranes is accomplished by carefully identifying the plane between the epiretinal tissue and the retina and by lysing all adhesions. In advanced PVR, retinal traction may be so severe that the retina must be cut to relieve all retinal traction. In cases with such severe traction, especially when a retinotomy must be created, silicone oil is often useful as a long-acting tamponade. The silicone oil is usually removed after 3 to 6 months but may be left in place longer if the retina appears unstable.

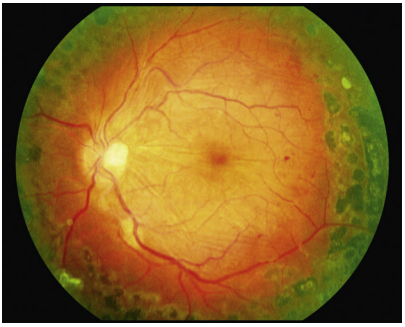

Figure 48-9. Postoperative appearance of patient shown in Fig. 48-8 after repair of traction RD.

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CHAPTER 49

RETINOBLASTOMA

Carol L. Shields

1. **What is retinoblastoma?**
   Retinoblastoma is the most common eye cancer in children. It arises from primitive cells destined to be retinal tissue. Generally, it is found in babies from birth to approximately 3 years of age.

2. **How common is retinoblastoma?**
   Retinoblastoma occurs with a frequency of about 1 in 14,000 live births. Approximately 250 to 300 children in the United States each year are diagnosed with retinoblastoma. Worldwide, it is estimated that there are approximately 7000 children with this cancer yearly.

3. **What causes retinoblastoma?**
   Retinoblastoma is the result of a genetic mutation on chromosome 13. If the mutation is somatic, then the child can develop one tumor in one eye. If the mutation is in the germ line, the child is at risk for multifocal tumors in both eyes, with an average total of five retinoblastomas. There are no specific exposures that lead to this mutation, but research has identified advanced paternal age and possible paternal radiotherapy exposure as risks.

4. **On what chromosome is the genetic mutation associated with retinoblastoma?**
   The genetic mutation associated with retinoblastoma is found on chromosome 13 in the region 13q14. It is believed that this single locus exists for most forms of retinoblastoma. The esterase D gene is closely linked to this site.

5. **What syndrome is associated with retinoblastoma?**
   Retinoblastoma is a manifestation of the 13q deletion syndrome. The characteristic findings include:
   - microcephaly
   - broad prominent nasal bridge
   - hypertelorism
   - microphthalmos
   - epicanthus
   - ptosis
   - protruding upper incisors
   - micrognathia
   - short neck with lateral folds
   - large low-set ears
   - facial asymmetry
   - imperforate anus
   - genital malformations
   - perineal fistula
   - hypoplastic or absent thumbs
   - toe abnormalities
   - psychomotor delay
   - mental delay

6. **What is the laterality of retinoblastoma?**
   Retinoblastoma is unilateral in approximately 67% of cases and bilateral in 33% of cases. All bilateral cases have germ-line mutation. Approximately 15% of unilateral cases have germ-line mutation, whereas 85% have somatic mutation.

7. **What is germ-line mutation retinoblastoma?**
   Germ-line mutation retinoblastoma is the occurrence of the retinoblastoma (Rb) mutation on all cells in the body, including the retina and systemic sites. These patients typically develop bilateral retinoblastoma and are at risk for pinealoblastoma and second cancers.

8. **Who manifests germ-line mutation retinoblastoma?**
All bilateral and all familial retinoblastomas by definition have germ-line mutation. About 10% to 15% of unilateral sporadic retinoblastomas have germ-line mutation.

9. **What is somatic mutation retinoblastoma?**
Somatic mutation retinoblastoma is the occurrence of the Rb mutation only in the retina in one clone of cells. Hence these patients typically develop unilateral sporadic retinoblastoma. These patients are generally not at increased risk for pinealoblastoma or second cancers.

10. **Who manifests somatic mutation retinoblastoma?**
Only unilateral sporadic retinoblastomas carry a somatic mutation.

11. **What are the most common presenting findings of retinoblastoma (Fig. 49-1)?**
In the United States, leukocoria is the presenting feature in nearly 50% of cases and strabismus in 20%. Other less common presenting features include poor vision, red eye, glaucoma, and orbital cellulitis. In less developed nations, these children often present with proptosis from tumor extension into the orbit.

12. **What are the most common lesions simulating retinoblastoma?**
Of all patients referred to an experienced ocular oncology center with the diagnosis of possible retinoblastoma, about 80% prove to have retinoblastoma and 20% have pseudoretinoblastoma. The most common pseudoretinoblastomas include Coats disease (40%), persistent hyperplastic primary vitreous (28%), and vitreous hemorrhage of infancy (16%).

13. **At what age does retinoblastoma typically present?**
Retinoblastoma is diagnosed typically in the first 1 to 2 years of life. Bilateral cases are recognized at an earlier average age of 1 year, whereas unilateral cases are typically older, at 2 years. In 5% of cases, the tumor is first diagnosed over age 5 years.

14. **What is trilateral retinoblastoma?**
Trilateral retinoblastoma is the association of bilateral retinoblastoma with midline brain tumors, especially pinealoblastoma. Trilateral disease represents 3% of all retinoblastoma cases and typically occurs before the age of 5 years.

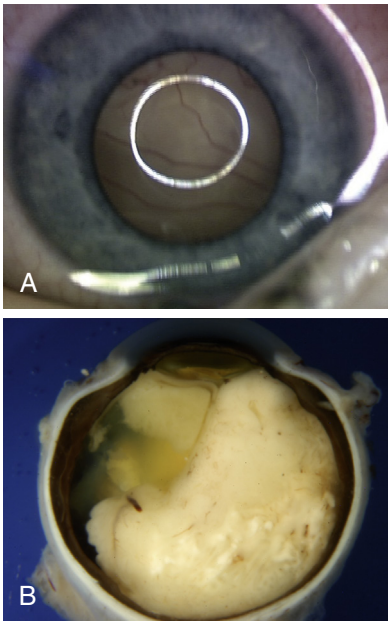

Figure 49-1. A, Leukocoria from retinoblastoma. **B,** Enucleated globe showing large white retinoblastoma within the eye.

15. When is pinealoblastoma diagnosed?

Pinealoblastoma is generally diagnosed within 1 year of retinoblastoma diagnosis. In fact, most cases are found before the age of 5 years. Keep in mind that benign pineal cyst can resemble malignant pinealoblastoma and magnetic resonance imaging is necessary to differentiate these two conditions.

16. What second cancers are associated with retinoblastoma?

The most common second cancers associated with retinoblastoma include osteosarcoma (especially of the femur), cutaneous melanoma, and other sarcomas. Second cancers are believed to be related to germ-line mutation of chromosome 13. Second cancers present in 20% of germ-line mutation patients by 20 years and 50% by 50 years.

17. How often do eyes with retinoblastoma present with glaucoma?

From a clinical standpoint, about 17% of eyes with retinoblastoma have glaucoma, most often neovascular or angle closure glaucoma. From a pathology standpoint, glaucoma is present in 40% of eyes that come to enucleation.

18. How often does retinoblastoma invade the optic nerve?

In the United States, optic nerve invasion by retinoblastoma occurs in 29% of eyes that come to enucleation. Usually it occurs in the prelaminar area. Risks for optic nerve invasion by retinoblastoma include a large exophytic tumor measuring greater than 15 mm and secondary glaucoma.

19. What is high-risk retinoblastoma?

High-risk retinoblastoma is retinoblastoma that has invaded:

- the optic nerve beyond the lamina cribrosa
- the uvea, with greatest dimension of at least 3 mm
- any combination of the optic nerve and uvea

High-risk retinoblastoma requires systemic chemotherapy.

20. What is the survival rate with retinoblastoma?

Currently in the United States, Europe, and Japan, nearly 98% of children with retinoblastoma survive this cancer. Less developed nations carry a relatively high risk for metastasis and death. The rate for death in South America is approximately 40% and in Africa it is 70%. Risks for metastatic disease include substantial optic nerve, choroidal, or orbital invasion by the tumor.

21. What are the clinical growth patterns of retinoblastoma?

The growth patterns are endophytic and exophytic. Endophytic retinoblastoma arises from the inner retina and seeds the vitreous. Exophytic retinoblastoma arises from outer retinal layers and causes a solid retinal detachment. A variant of endophytic retinoblastoma is the diffuse infiltrating retinoblastoma. These patterns impart no difference to the patient's life prognosis.

22. What is the differential diagnosis of endophytic retinoblastoma?

The differential diagnosis of endophytic retinoblastoma includes various inflammatory or infectious processes of the eye in children, such as toxocariasis, endophthalmitis, or advanced uveitis.

23. What is the differential diagnosis of exophytic retinoblastoma?

The differential diagnosis of exophytic retinoblastoma includes Coats disease, retinal capillary hemangioma, familial exudative vitreoretinopathy, and other causes of rhegmatogenous or nonrhegmatogenous retinal detachment in children.

KEY POINTS: RETINOBLASTOMA

- Retinoblastoma is an ocular cancer of childhood, usually detected before age 3 years. However, about 5% of newly diagnosed cases are in children over 5 years of age.
- The diagnosis of retinoblastoma must be excluded in any child, even a teenager or young adult, who manifests atypical uveitis, vitreous hemorrhage, or nonrhegmatogenous retinal detachment.
- Do not perform a vitrectomy or intraocular needle aspiration biopsy on an eye with retinoblastoma. This could seed the tumor.
- Any child with spontaneous hyphema or vitreous hemorrhage should be evaluated for trauma, retinoblastoma, and other intraocular tumors and inflammations.

KEY POINTS: RETINOBLASTOMA—CONT'D

- The best way to diagnose retinoblastoma is with indirect ophthalmoscopy by an experienced observer. If uncertain, ultrasonography, fluorescein angiography, and computed tomography can be useful tests. Magnetic resonance imaging is most useful for evaluation of tumor invasion into the optic nerve or orbit, as well as assessment of the brain for related intracranial neuroblastic malignancy (trilateral retinoblastoma; pinealoblastoma).

24. Can retinoblastoma spontaneously regress?

Yes, about 3% of all cases of retinoblastoma are classified as spontaneously regressed or arrested. They are also termed "retinoma" and "retinocytoma." These tumors do carry a 5% risk of recurrence and becoming active, requiring therapy.

25. When is genetic testing appropriate?

All children with retinoblastoma have genetic testing to ascertain whether they carry germ-line or somatic mutation. This affects their follow-up, because germ-line mutation children are at risk for pinealoblastoma and second cancers, unlike somatic mutation children.

26. How do we classify retinoblastoma?

In the past, the Reese Ellsworth classification scheme was used, but it is now outdated. Currently, the International Classification of Retinoblastoma is used worldwide (Table 49-1). This classification is simple and practical and pertinent for current therapies.

27. How does retinoblastoma appear on ultrasound?

On ultrasound, retinoblastoma appears as a mass originating from the retina with acoustic solidity and high internal reflectivity. Foci of calcium can be seen as dense echoes.

28. How does retinoblastoma appear on computed tomography?

On computed tomography, retinoblastoma appears as a solid mass within the globe with foci of bone density, representing calcium. Often retinal detachment can be detected.

29. How does retinoblastoma appear on magnetic resonance imaging?

On magnetic resonance imaging, retinoblastoma shows a hyperintense signal to the vitreous on T1-weighted images and a hypointense signal on T2. Contrast enhancement of the tumor is bright. The foci of calcium remain hypointense on both T1 and T2 without enhancement. Areas of necrosis appear similar to calcium except that they can show enhancement.

Table 49-1. International Classification of Retinoblastoma

GROUP	QUICK REMEMBER BY LETTER	DETAILS
A	Sm**A**ll	Small Rb (≤3 mm diameter)
B	**B**igger	Bigger Rb (>3 mm diameter) or • any Rb in macula • any Rb with subretinal fluid
C	**C**ontained seeds	Localized subretinal or vitreous seeds (≤3 mm from Rb)
D	**D**iffuse seeds	Diffuse subretinal or vitreous seeds (≤3 mm from Rb)
E	**E**xtensive	Extensive Rb involving over 50% of the fundus • opaque media • neovascularization of iris • suspicion of invasion of optic nerve, choroid, or orbit

30. Should pars plana vitrectomy or biopsy be performed to obtain tissue to confirm the diagnosis of retinoblastoma?

No. Biopsy is not indicated and should not be performed in any eye with retinoblastoma because it can potentially seed the tumor into the orbit and may lead to metastasis.

31. What are the pathology features of a well-differentiated retinoblastoma (Fig. 49-2)?

Flexner-Wintersteiner rosettes and fleurettes represent well-differentiated retinoblastoma.

32. List the options for management of an eye with intraocular retinoblastoma.

The options for management include:

- enucleation
- intravenous chemotherapy (chemoreduction)
- intra-arterial chemotherapy
- intravitreal chemotherapy
- thermotherapy
- cryotherapy
- laser photocoagulation
- plaque radiotherapy
- external beam radiotherapy

33. What are the conservative options for management of a small retinoblastoma posterior to the equator of the eye?

Intravenous chemotherapy, intra-arterial chemotherapy, or plaque radiotherapy are the most appropriate therapies for this tumor. Cryotherapy is generally limited to small tumors anterior to the equator of the eye.

34. What are the conservative options for management of a small retinoblastoma (<3 mm) anterior to the equator of the eye?

Chemoreduction combined with thermotherapy, laser photocoagulation, cryotherapy, or plaque radiotherapy are the most conservative options.

KEY POINTS: MANAGEMENT OF RETINOBLASTOMA

- The goal in management of retinoblastoma is, first and most important, to save the patient's life; then consideration for globe salvage and vision preservation is made.
- The most common method for management of unilateral advanced retinoblastoma (group D or E) is enucleation or intra-arterial chemotherapy.
- Most bilateral retinoblastomas can be treated with intravenous chemotherapy. However, enucleation of one eye or intra-arterial chemotherapy is often necessary.
- Intravitreal chemotherapy injected directly into the vitreous cavity is useful for active vitreous seeds.
- Fresh retinoblastoma tissue should be harvested for DNA analysis and family genetic counseling.

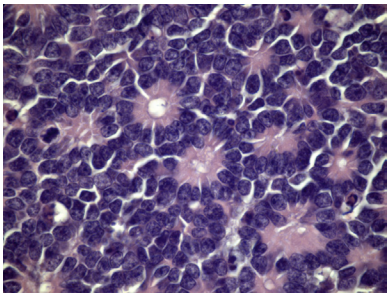

Figure 49-2. Flexner-Wintersteiner rosettes in well-differentiated retinoblastoma.

35. When do we use intravenous chemotherapy (chemoreduction) (Fig. 49-3)?
Chemoreduction is generally used for patients with bilateral retinoblastoma to cure the eyes, protect the patient from pinealoblastoma, and minimize long-term second cancers.

36. When do we use intra-arterial chemotherapy (Fig. 49-4)?
Intra-arterial chemotherapy is usually used for unilateral advanced retinoblastoma or those that fail intravenous chemotherapy.

37. When do we use intravitreal chemotherapy?
Intravitreal chemotherapy is used for eyes with viable vitreous retinoblastoma seeding following failure of standard intravenous or intra-arterial chemotherapy.

38. When do we use external beam radiotherapy and what are the risks?
External beam radiotherapy is used for children with retinoblastoma that have failed all standard methods and could potentially lose both eyes. We try to avoid this therapy because of its risks for short-term and long-term effects. The short-term effects include:

- dry eye
- cilia loss
- cutaneous erythema.

The long-term effects include:

- persistent dry eye
- cataract
- retinopathy
- papillopathy
- orbital fat atrophy
- maldevelopment of the orbital bones
- second cancers

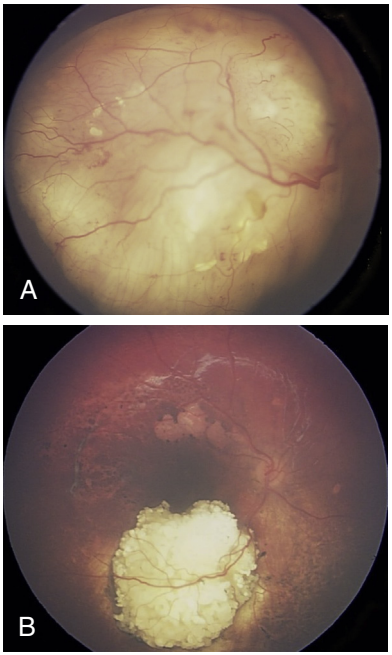

Figure 49-3. Retinoblastoma. **A,** before and **B,** after intravenous chemotherapy.

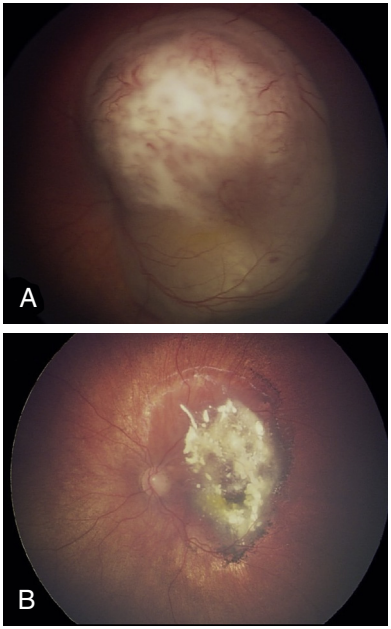

Figure 49-4. Retinoblastoma. **A,** before and **B,** after intra-arterial chemotherapy.

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PIGMENTED LESIONS OF THE OCULAR FUNDUS

Jerry A. Shields and Carol L. Shields

CHAPTER 50

1. **What is the main differential diagnosis of a relatively flat pigmented fundus lesion?**
   1. Choroidal nevus (Fig. 50-1)
   2. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) (Fig. 50-2)
   3. Combined hamartoma
2. **What ophthalmoscopic features help to differentiate choroidal nevus, CHRPE, and combined hamartoma?**
   Choroidal nevus is generally a slate-gray lesion with a slightly ill-defined border. Drusen may be present on the surface of the lesion. CHRPE is usually black, has a sharply demarcated border, and may have depigmented lacunae through which the underlying choroid can be visualized. Combined hamartoma shows vitreoretinal traction that is not seen with the other two conditions.
3. **Do both choroidal nevus and CHRPE have malignant potential?**
   Although both lesions are benign and usually stationary, nevus can give rise to melanoma and most melanomas probably arise from a preexisting nevus. CHRPE was once believed to be stationary with no malignant potential. However, it has recently been recognized to show enlargement in diameter in

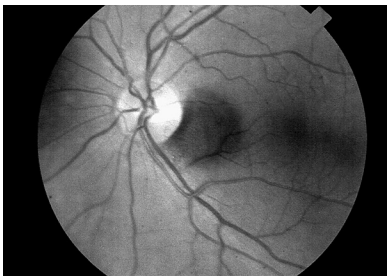

Figure 50-1. Typical choroidal nevus adjacent to the optic disc.

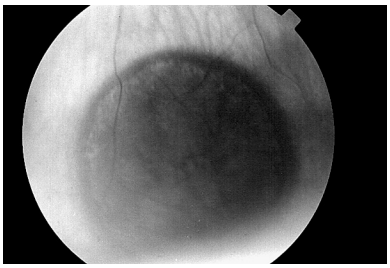

Figure 50-2. Congenital hypertrophy of the retinal pigment epithelium.

80% of cases and to rarely become elevated and evolve into adenocarcinoma of the retinal pigment epithelium.

4. What is the main differential diagnosis of an elevated pigmented fundus lesion?

1. Choroidal melanoma
2. Subretinal hemorrhage
3. Tumor of the retinal pigment epithelium
4. Bilateral diffuse uveal melanocytic proliferation

5. What ophthalmoscopic features help to differentiate a choroidal melanoma from a subretinal hemorrhage?

Choroidal melanoma usually is a rather homogeneous brown-to-black lesion with a smooth surface. Subretinal hemorrhage in the macular area (age-related macular degeneration) or in the peripheral fundus (peripheral disciform degeneration) initially has a reddish-blue color; because it undergoes resolution, it has a more heterogeneous color with areas of fresh red blood and older yellow blood.

6. What is the most practical ancillary test for differentiating choroidal melanoma from subretinal blood?

The most practical test is fluorescein angiography. Most melanomas show hyperfluorescence, and most hemorrhages are hypofluorescent.

7. What is the significance of a mushroom-shaped fundus lesion?

A mushroom-shaped fundus lesion is strongly suggestive of choroidal melanoma (Fig. 50-3). Even when the mushroom-shaped lesion is nonpigmented, melanoma is still the most likely diagnosis. It is very unusual for other fundus lesions to assume a mushroom shape.

8. What is the best way to diagnose choroidal melanoma?

The best way is the use of binocular indirect ophthalmoscopy by an experienced ophthalmologist who is familiar with the characteristic features of choroidal melanoma and other lesions that simulate choroidal melanoma. Most melanomas can be readily diagnosed by indirect ophthalmoscopy alone. However, ancillary studies such as fluorescein angiography and ultrasonography are also quite reliable.

9. When the diagnosis is uncertain after ophthalmoscopy, what are the four most helpful ancillary tests in the diagnosis of uveal melanoma?

1. Transillumination
2. Fluorescein angiography
3. Ultrasonography
4. Fine-needle aspiration biopsy

Most melanomas cast a shadow with transillumination, are hyperfluorescent with angiography, and show low internal reflectivity with ultrasonography. Most simulating lesions show different patterns with these modalities. Fine-needle aspiration biopsy is perhaps the most reliable method, but it is an invasive procedure that requires a skilled and experienced physician.

10. What clinical signs suggest that a benign choroidal nevus is likely to grow and eventually evolve into a malignant choroidal melanoma?

Elevation of the lesion, orange pigment on the surface of the lesion, secondary retinal detachment, proximity of the lesion to the optic disc, and presence of visual symptoms.

KEY POINTS: RISK FACTORS FOR GROWTH OF CHOROID NEVUS

1. **T**hickness greater than 2 mm
2. Associated retinal detachment (subretinal **F**luid)
3. Visual **S**ymptoms due to the tumor
4. **O**range pigment
5. **M**argin within 3 mm of the optic disc

The mnemonic "To Find Small Ocular Melanoma" is used clinically to estimate the possibility of growth of the nevus.

11. What clinical signs suggest that a small, suspicious pigmented fundus lesion may eventually metastasize?

1. Elevation of the lesion >2 mm
2. Proximity to the optic disc
3. Visual symptoms
4. Documentation of growth

It is important that documented growth is a risk factor for metastasis. Therefore, if other risk factors for growth and metastasis are present, the ophthalmologist should consider treatment without waiting for growth.

12. What congenital ocular conditions are associated with a higher incidence of uveal melanoma?

Congenital ocular melanocytosis and oculodermal melanocytosis (nevus of Ota) are the main conditions, perhaps because of the excessive melanocytes in their uveal tract, that predispose to a greater chance of developing uveal melanoma.

13. Does uveal melanoma have a predilection for gender, age, or race?

Uveal melanoma has no significant predilection for gender. It generally occurs in patients between 40 and 70 years of age and is relatively uncommon in patients younger than age 20. It has a definite predilection for Caucasians; only 1% to 2% of cases occur in African Americans and Asians.

14. What external ocular signs suggest the possibility of an underlying ciliary body or peripheral choroidal melanoma?

1. One or more dilated, tortuous episcleral blood vessels in the ciliary body region (sentinel vessels; Fig. 50-4).
2. A black focus of pigment on the sclera, indicative of extraocular extension of the melanoma.

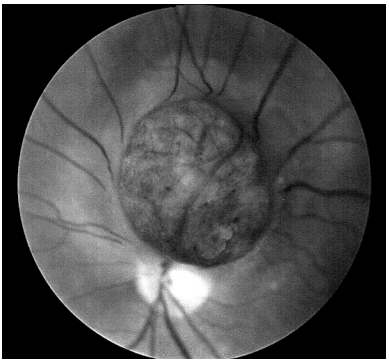

Figure 50-3. Mushroom-shaped choroidal melanoma.

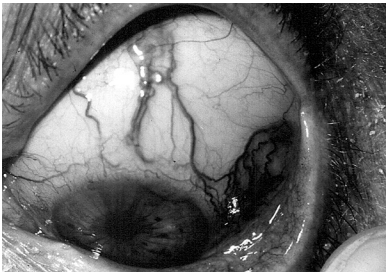

Figure 50-4. Sentinel vessel over a ciliary body melanoma.

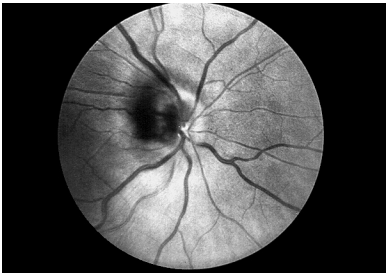

Figure 50-5. Melanocytoma of the optic nerve.

15. What is the main route of distant spread of uveal melanoma?
Melanoma spreads to extraocular locations primarily by hematogenous metastasis to liver. Metastatic uveal melanoma to skin, lung, and other organs is less common but often occurs. Because there are no lymphatic channels in the eye, lymphogenous metastasis does not occur.

16. What is a melanocytoma?
A melanocytoma is a variant of benign nevus that has distinct clinical and histopathologic features. Clinically, it is usually detected on and next to the optic disc as a deeply pigmented lesion that may have a feathery border because of involvement of the nerve fiber layer of the retina (Fig. 50-5). It also can occur as a deeply pigmented lesion in the ciliary body or choroid. Histopathologically, it is composed of round-to-oval cells that have densely packed cytoplasmic melanosomes, small uniform nuclei, and few prominent nucleoli. Like other uveal nevi, it rarely gives rise to uveal melanoma.

17. What is the most acceptable method of treating a choroidal melanoma that occupies more than half of the globe and has produced severe visual loss?
Enucleation, because there is little hope for useful vision and the patient's quality of life would be better, and extensive ocular follow-up would not be so necessary.

18. What is the most often used alternative to enucleation for a medium-sized melanoma located posterior to the equator?
Brachytherapy with a radioactive plaque is most common, and irradiation and proton beam irradiation is the second most common.

19. What is the most common treatment for a melanoma that occupies two clock hours of the ciliary body?
The most common treatment is resection of the tumor by iridocyclectomy or application of radioactive plaque, depending on several clinical circumstances.

20. What is the most acceptable method of management for an asymptomatic pigmented lesion that measures 3 mm in diameter and 1 mm in thickness and has fine drusen on its surface?
It is managed with baseline fundus photographs and examination every 6 to 12 months. Most such lesions are benign nevi that remain stationary.

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CHAPTER 51

OCULAR TUMORS

Ralph C. Eagle, Jr.

1. What is the most common malignant intraocular neoplasm?

Uveal metastasis, usually from a distant primary carcinoma, is thought to be the most common malignant intraocular neoplasm. An estimated 66,000 patients develop uveal metastases each year. However, most are terminally ill patients, few of whom are evaluated ophthalmologically or pathologically. In contrast, only 1800 cases of uveal melanoma and 300 cases of retinoblastoma occur yearly in the United States.

Many textbooks state that uveal malignant melanoma is the most common primary intraocular tumor, but this statement actually applies only to the United States and Europe, because uveal melanoma has a propensity for fair-skinned, blue-eyed persons. Throughout Africa, Asia, and South America, where melanoma is relatively rare, retinoblastoma is the most common primary intraocular tumor. Kivelä has estimated that approximately 1000 more retinoblastomas than uveal melanomas occur yearly in the world.[1,2]

2. What is the characteristic shape of choroidal malignant melanoma?

Approximately 60% of choroidal malignant melanomas have a mushroom or collar-button configuration (Fig. 51-1). Melanomas initially have a dome or almond shape when they arise in the choroid. The mushroom or collar-button configuration develops after the tumor ruptures or erodes through the Bruch's membrane and invades the subretinal space, where it forms a round or ovoid nodule.

3. Is a mushroom configuration pathognomonic for choroidal melanoma?

A mushroom or collar-button configuration almost always signifies that a choroidal tumor is a malignant melanoma. Few things in medicine are pathognomonic, however. Exceedingly rare mushroom-shaped choroidal metastases, hemangiomas, and schwannomas have been reported.[3-5]

4. What important prognostic features of uveal melanoma can be assessed during routine histopathologic examination?

Tumor size and cell type are two of the most important prognostic factors that can be assessed during routine histopathologic evaluation of uveal melanoma. Larger tumors and tumors that contain epithelioid cells have a poorer prognosis. Tumor size generally is expressed in millimeters as the largest basal tumor diameter. Other prognostic features include mitotic activity (expressed as the number of mitoses in 40 high-power fields), the presence of extrascleral extension, extracellular matrix patterns called vascular loops and networks, lymphocytic infiltration, and involvement of the ciliary body.[6-8]

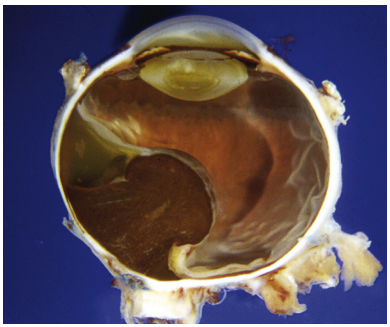

Figure 51-1. Mushroom-shaped choroidal melanoma.

5. What factors does the American Joint Commission on Cancer (AJCC) *Cancer Staging Manual* use to stage uveal melanoma?

Tumor size, ciliary body involvement, and extraocular extension are important factors used to prognostically stratify uveal melanomas in the AJCC's TNM classification (T is the size of the tumor, N denotes lymph node involvement, M is for metastasis). The staging manual includes a chart that uses both the tumor's largest basal diameter and its largest thickness to assign tumors to size categories. Tumors greater that 18 mm in diameter are in size category 4. Tumors that involve the ciliary body and/or show extraocular extension have a poorer prognosis.[9]

6. What is the Callender classification?

In 1931, Major George Russell Callender reported that there was an association between survival and histologic characteristics of uveal melanomas called *cell type*. Callender showed that uveal melanomas may contain two types of spindle cells (spindle A and spindle B cells) and less-differentiated epithelioid cells. Dr. Ian McLean modified Callender's classification in 1978. Spindle A and spindle B melanomas were lumped together as spindle melanomas in the modified classification, and necrotic and fascicular variants were deleted.[10,11]

7. What is the most common cell type?

Most medium or large melanomas that are enucleated and examined histopathologically are mixed-cell tumors that contain a mixture of spindle and epithelioid cells. Eighty-nine percent of the melanomas that were enucleated in the Collaborative Ocular Melanoma Study (COMS) were mixed-cell tumors.

8. How are melanoma cell types distinguished histopathologically?

Melanoma cells are readily differentiated by the characteristics of their nuclei. Spindle A cells have long, tapering cigar-like nuclei, an absent or indistinct nucleolus, and a characteristic longitudinal stripe caused by a fold in the nuclear membrane. Spindle B nuclei are oval and plumper and have less finely dispersed chromatin and a distinct nucleolus (Fig. 51-2). Epithelioid cell nuclei are typically round and vesicular and have a prominent reddish-purple nucleolus (Fig. 51-3). The chromatin is coarse and often clumps along the inside of the nuclear membrane (peripheral margination of chromatin). Spindle melanoma cells grow as a syncytium, making it difficult to discern the cytoplasmic margins of the bipolar fusiform cells. Epithelioid cells are poorly cohesive and their cytoplasmic margins are readily discernible.[12]

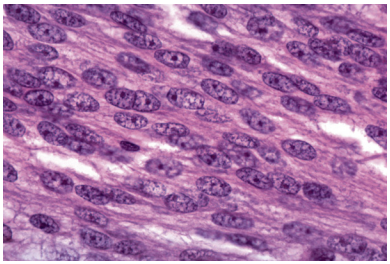

Figure 51-2. Spindle B melanoma cells.

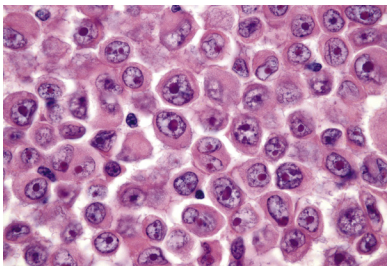

Figure 51-3. Epithelioid melanoma cells.

9. Which cell type has the worst prognosis?

The presence or absence of epithelioid cells in a uveal melanoma has an important effect on prognosis. If no epithelioid cells are present, the expected survival at 15 years is 72%. If epithelioid cells are present (mixed, epithelioid, or necrotic cell type), the survival at 15 years drops to 37%. A tumor composed entirely of spindle A cells is now considered to be a benign nevus incapable of metastasis. Tumors composed entirely of epithelioid cells have the worst prognosis. Overall, approximately 50% of patients with uveal melanoma will die from their tumors.[8]

10. What special new tests are powerful prognostic indicators for patients with uveal melanoma?

Special new tests that are powerful prognostic predictors for patients with uveal melanoma include:

1. Assessment for nonrandom chromosomal anomalies in the tumor cells;
2. Gene expression profiling.

Nonrandom chromosomal abnormalities including loss of chromosome 3 and gains in chromosome 8 are associated with metastatic death. Monosomy 3 is a significant predictor of poor prognosis in uveal melanoma. In one study, 57% of patients with monosomy 3 had developed metastases at 3 years, compared to none of the patients with disomy 3. Chromosomal 3 abnormalities can be identified using a variety of techniques including fluorescence in situ hybridization and DNA amplification and microsatellite assay.

Gene expression profiling (GEP) of uveal melanomas by microarray analysis has disclosed two classes of tumors that differ markedly in their potential for metastasis. Class I melanomas are low-grade tumors with less than 5% risk for metastasis. In contrast, patients with class II melanomas have a greater than 90% risk for metastasis. The GEP of class II melanomas resembles primitive neural/ectodermal stem cells. They typically have other high-risk features including epithelioid cells, vascular mimicry patterns, and monosomy 3. GEP is available as a proprietary commercial test.[13-15]

KEY POINTS: PROGNOSTIC FACTORS IN UVEAL MELANOMA

Size
Ciliary body involvement
Cell type
Extraocular extension
Mitotic activity
Lymphocytic infiltration
Vascular mimicry patterns
Nonrandom chromosomal abnormalities (monosomy 3—poor prognosis)
Gene expression profile (class 2—poor prognosis)

11. What is the most common site of metastatic uveal melanoma?

The liver is the most common site. Liver metastases occur in 93% of patients who develop metastatic uveal melanoma. Other sites include the lungs (24%) and bone (16%).[16]

12. What was the Collaborative Ocular Melanoma Study?

The COMS was a large prospective, randomized, multicentered study funded by the National Eye Institute that investigated the treatment of choroidal malignant melanoma. The arm of the study that focused on medium-sized tumors compared survival after enucleation and radioactive iodine 125 (^{125}I) plaque brachytherapy. The large tumor study compared survival after standard enucleation and enucleation preceded by external beam radiotherapy.[17]

13. What were the results of the COMS?

The medium-sized tumor arm of the COMS showed that survival was similar after both enucleation and plaque brachytherapy. The large tumor arm showed that "sterilization" of large melanomas with preenucleation external-beam radiotherapy did not improve survival.[18,19]

14. How are most uveal melanomas treated?

Today, most posterior uveal melanomas are treated with radioactive plaques. Plaque-treatment failures and eyes with larger tumors and/or tumor-related complications, such as secondary glaucoma or

extrascleral extension, are still enucleated. Some smaller tumors are locally resected or treated with transpupillary thermotherapy (TTT). In some cases TTT is used to supplement plaque therapy.[20]

15. How effective is treatment of posterior uveal melanoma?

Treatment of uveal melanoma merely achieves local control and is relatively ineffective from the standpoint of survival. All forms of treatment seem to have little effect on decreasing subsequent death from metastases. It is thought that, unfortunately, most tumors already have metastasized before they are treated. Treatment for metastatic melanoma also is ineffective. Smaller tumors have a better prognosis and a lower incidence of monosomy 3 and class 2 GEP. Hence, the treatment of tumors while they are still small theoretically might be efficacious.[21]

16. What clinical features suggest that a small pigmented choroidal tumor is a melanoma?

The mnemonic "To Find Small Ocular Melanoma Using Helpful Hints Daily" refers to the clinical factors that suggest that a small pigmented tumor is a melanoma that is likely to grow, therefore putting the patient at greater risk for metastasis:

T for thickness greater than 3 mm
F for subretinal fluid
S for symptoms
O for orange pigment
M for margin touching optic disc
UH for ultrasound hollow
H for no halo
D for drusen absent

Choroidal melanocytic tumors that display none of these factors have only a 3% risk of growth at 5 years and most likely represent choroidal nevi. More than 50% of tumors with two or more risk factors grow, and they probably represent small choroidal melanomas. Early treatment of such lesions generally is indicated.[22]

KEY POINTS: OVERVIEW OF UVEAL MELANOMA

1. Caucasian patients at greater risk
2. Mushroom shape
3. Spindle and epithelioid cells
4. Liver metastases
5. A 50% mortality rate

17. Do iris melanomas behave differently?

The prognosis of iris melanoma generally is excellent (4 to 10% mortality). Most pigmented tumors of the iris are benign spindle-cell nevi. Overall, only 6.5% will enlarge during a 5-year period of observation. Most are low-grade spindle cell tumors, although iris melanomas do contain epithelioid cells occasionally.

Clinical features that suggest that a pigmented iris tumor is a melanoma include documented tumor growth, elevated intraocular pressure, hyphema, large tumor size, and tumor vascularity. Although they can occur anywhere, melanomas arise most frequently in the inferior sun-exposed part of the iris.[23,24]

18. What clinical features suggest that a uveal tumor is a metastasis?

Uveal metastases usually are creamy yellow amelanotic tumors that have a placoid or nummular configuration. Pigment mottling may occur on the tumor apex. Metastases are often multiple but can be solitary. Metastases usually cause a nonrhegmatogenous serous detachment of the retina with shifting subretinal fluid.[25]

19. What is the most common site of uveal metastasis?

Uveal metastases involve the choroid 81% of the time. They typically are found in the region of the macula where the choroidal blood supply is richest.[25]

20. What primary tumors are responsible for most uveal metastases?

Most uveal metastases come from breast carcinoma in women and lung carcinoma in men. Breast carcinoma is responsible for more than half of all ocular metastases. Nearly one-fifth are caused by lung cancer. Most women with uveal metastases from breast tumors have a history of breast carcinoma. In contrast, uveal metastasis may herald the presence of an occult lung cancer.[25]

21. How is immunohistochemistry (IHC) used to assess uveal metastases?

Primary uveal melanomas usually can be distinguished from uveal metastases using routine light microscopy. When a metastasis is found in a patient with no prior history of cancer, IHC often can suggest the identity of the primary tumor. For example, breast and lung cancers frequently stain positively (i.e., are immunoreactive) for cytokeratin 7 (CK7) and are negative for CK20. In contrast, most gastrointestinal cancers are CK20 positive. Immunoreactivity for specific markers that are expressed only by certain cancers is particularly helpful. Examples include the BRST2 marker in breast carcinoma, the TTF1 marker in lung cancer, and PSA and PSAP in prostate cancers.

IHC also is used as a prognostic marker and a guide to therapy. For example, breast carcinomas that express estrogen receptors can be treated with tamoxifen and aromatase inhibitors, whereas tumors that express HER/2neu can be treated with trastuzumab (Herceptin).[26]

22. What types of hemangiomas occur in the choroid?

Choroidal hemangiomas are classified as capillary, cavernous, or mixed. They are composed of thin-walled vessels and have little stroma (Fig. 51-4). Sporadic hemangiomas tend to be discrete, localized, elevated reddish-orange tumors. The choroidal hemangiomas that occur in patients with Sturge-Weber syndrome are typically diffuse with indistinct tapering margins. These obscure the underlying choroidal architecture and impart a "tomato ketchup" appearance to the fundus.[27]

23. If choroidal hemangiomas are benign, why are they treated?

Choroidal hemangiomas are treated to save vision or the eye itself. Although they are benign from a systemic standpoint, choroidal hemangiomas cause retinal detachment and secondary glaucoma via iris neovascularization and/or a papillary block mechanism. The latter can lead to loss of the globe. Hemangiomas usually are treated with photodynamic therapy or laser photocoagulation.[28,29]

24. How does retinoblastoma typically present in the United States and Europe?

In the United States and Europe, retinoblastoma typically presents with leukocoria (a white pupillary reflex). Smaller tumors that involve the macula initially may present with strabismus. All children with strabismus should have a careful fundus examination to exclude retinoblastoma or other significant macular pathology. In developing countries, children often present in an advanced stage of the disease with a large orbital tumor secondary to extraocular extension.[30]

25. How old are patients when diagnosed with retinoblastoma?

The mean age at diagnosis is 18 months. Patients who have the familial form of the disease (i.e., who have germ-line mutations) are diagnosed earlier (mean age 12 months), probably because only a solitary "hit" or gene inactivation is required. Sporadic somatic cases occur in slightly older patients; they are diagnosed at a mean age of 24 months.[30]

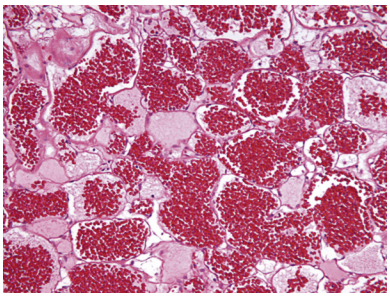

Figure 51-4. Choroidal hemangioma.

26. What does retinoblastoma look like grossly?

Grossly, retinoblastoma has a distinctly encephaloid or brainlike appearance. This is not surprising because the tumor arises from the retina, which is a peripheral colony of brain cells. Foci of dystrophic calcification occur in many retinoblastomas. These foci of calcification are evident grossly as lighter flecks.

27. What is an exophytic retinoblastoma?

Retinoblastoma shows several growth patterns. Exophytic retinoblastoma arises from the outer retina and grows in the subretinal space, causing retinal detachment (Fig. 51-5). Endophytic retinoblastoma arises from the inner layers of the retina, which remains attached (Fig. 51-6). Endophytic tumors invade the vitreous and may seed the anterior chamber, forming a pseudohypopyon of tumor cells. Most large retinoblastomas exhibit a combined endophytic/exophytic growth pattern. The diffuse infiltrative growth pattern is relatively rare and occurs in older children. The retina in such cases is diffusely thickened without a distinct tumefaction.[30]

28. Why does retinoblastoma appear blue, pink, and purple under low-magnification light microscopy?

The blue, pink, and purple areas evident on low-magnification light microscopy of retinoblastoma represent zones of viable, necrotic, and calcified tumor, respectively. Areas of viable tumor are basophilic. Retinoblastoma is composed of poorly differentiated neuroblastic cells that have intensely basophilic nuclei and scanty cytoplasm. Retinoblastoma cells tend to outgrow their blood supply rapidly and undergo spontaneous necrosis. The necrotic parts of the tumor are eosinophilic because the dead cells lose their basophilic nuclear DNA. Dystrophic calcification often occurs in necrotic parts of the tumor. The calcium has a purple hue in sections stained with hematoxylin and eosin.[31]

29. What do rosettes signify in retinoblastoma?

Rosettes are histologic markers for tumor differentiation in retinoblastoma. Homer Wright rosettes reflect low-grade neuroblastic differentiation. They are nonspecific and occur in other tumors such as

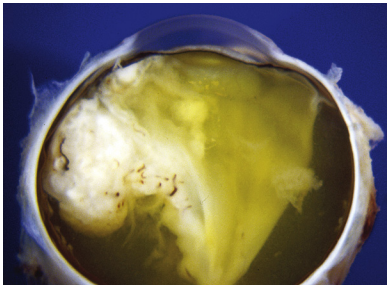

Figure 51-5. Exophytic retinoblastoma with total retinal detachment.

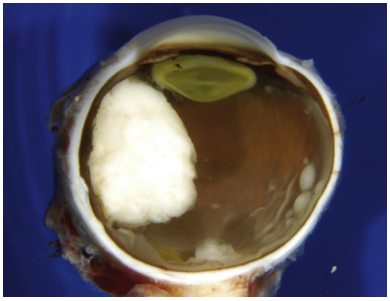

Figure 51-6. Endophytic retinoblastoma.

neuroblastoma. Flexner-Wintersteiner rosettes represent early retinal differentiation. They are highly characteristic for retinoblastoma, but they are not pathognomonic, as they are also found in some medulloepitheliomas.[30-33]

30. How are Homer Wright and Flexner-Wintersteiner rosettes distinguished histopathologically?

The nuclei of Homer Wright rosettes encircle a central tangle of neural filaments (Fig. 51-7). No lumen is present. Flexner-Wintersteiner rosettes have a central lumen that corresponds to the subretinal space (Fig. 51-8). The cells that enclose the lumen are joined by a girdle of apical intercellular connections analogous to the retinal external limiting membrane. Cilia, the precursors of photoreceptors, project into the lumen of the rosette.[32]

31. What are fleurettes?

Fleurettes are aggregates of neoplastic photoreceptors (Fig. 51-9). Photoreceptor differentiation is the highest degree of differentiation found in retinoblastoma. Fleurettes are composed of groups of bulbous eosinophilic cellular processes that correspond to photoreceptor inner segments. They are often aligned along a segment of neoplastic external limiting membrane in a bouquet-like arrangement.[30,34]

32. What is a retinoma or retinocytoma?

A retinoma or retinocytoma is a highly differentiated retinal tumor that typically contains photoreceptor differentiation. Each of the two names for this tumor has its proponents. Retinoma/retinocytoma is considered to be a benign manifestation of the retinoblastoma gene. Compared to retinoblastoma, the tumor cell nuclei are quite bland and mitoses and apoptotic cells are absent. However, both copies of the Rb1 gene are lost or mutated in these lesions as well as in retinoblastoma. This observation indicates that additional mutations other than the mutation in Rb1 are necessary for the development of retinoblastoma. Retinoma/retinocytoma is thought to be a precursor lesion for retinoblastoma, and rare cases of malignant transformation have been documented. Clinically, retinoma/retinocytoma is characterized by a translucent fish-flesh appearance; abundant calcification, which occurs within viable

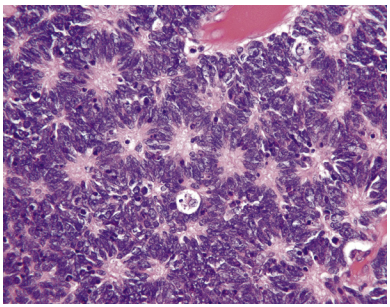

Figure 51-7. Homer Wright rosettes, retinoblastoma.

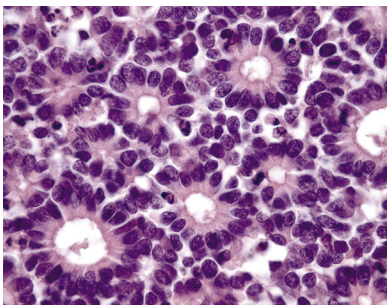

Figure 51-8. Flexner-Wintersteiner rosettes, retinoblastoma.

parts of the tumor; and an annulus of retinal pigment epithelium (RPE) depigmentation. The tumor may resemble retinoblastomas that have regressed after radio- or chemotherapy. At one time, retinomas/retinocytomas were thought to be retinoblastomas that had undergone spontaneous regression.[35,36]

33. What are the most important prognostic features of retinoblastoma?

Important prognostic features of retinoblastoma that can be assessed histopathologically include the presence and degree of optic nerve invasion, extrascleral extension, uveal invasion, and anterior segment involvement. Unlike uveal melanoma, the size of the tumor does not appear to be important. Mortality rises as the depth of tumor invasion into the optic nerve increases. Retrolaminar optic nerve invasion is equivalent to extraocular extension. Although anterior segment involvement is thought to confer poorer prognosis, its significance is uncertain because it tends to be found in eyes with other high-risk features.[37,38]

34. What histopathologic risk factors found in enucleated eyes with retinoblastoma are indications for adjuvant chemotherapy?

Certain histopathologic features are indications for adjuvant chemotherapy in most centers. These include:

1. tumor invasion of the optic nerve behind the lamina cribrosa (retrolaminar optic nerve invasion) or to the surgical margin;
2. massive invasion of the choroid;
3. any amount of concurrent prelaminar optic nerve and nonmassive choroidal invasion.

Massive choroidal invasion has been defined as greater than 3 mm in diameter or involving the full thickness of the choroid.[39,40]

35. How does retinoblastoma kill?

Many children who die from retinoblastoma have some degree of intracranial involvement. This is caused by direct extension of tumor cells along the optic nerve, subarachnoid space, or orbital foramina. Distant hematogenous metastases to bone and viscera can develop after the tumor invades the richly vascularized uvea. Anterior extrascleral extension provides access to conjunctival lymphatics and may be associated with regional lymph node metastases.[41]

36. The retinoblastoma gene is located on what chromosome?

Chromosome 13, found in the segment of the long, or "q," arm that is designated the 1 to 4 band (13q1–4).[42]

37. How is the retinoblastoma gene classified?

The retinoblastoma (Rb1) gene is the paradigmatic example of a recessive oncogene. The Rb1 gene is called a recessive oncogene because both copies of the gene must be lost or inactivated before a tumor can develop. Normal individuals have two functional copies of the Rb1 gene, although only one is needed for normal functioning. The gene's protein product, called Rb1 protein, is found in the nucleus, where it interacts with other transcription factors to control the cell cycle. Absence of Rb1 protein allows continual cell division and lack of terminal differentiation.[42]

38. If the Rb1 gene is recessive, why do cases of familial retinoblastoma appear to be inherited in an autosomal-dominant fashion?

Patients with hereditary retinoblastoma are heterozygous for the Rb1 gene. The genotype of carriers includes a single functional wild-type gene. The second copy of the Rb1 gene has been lost or

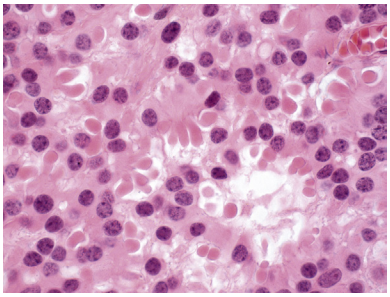

Figure 51-9. Fleurettes in retinoblastoma.

inactivated or produces a defective gene product. A retinoblastoma will develop when a retinal cell loses its single functional copy of the Rb1 gene. A mating between a normal individual ($Rb1^{+/+}$) and a heterozygous carrier ($Rb1^{+/-}$) gives rise to 50% normal offspring and 50% heterozygous carriers—a 50/50 ratio that perfectly mimics autosomal dominant transmission.

39. What does bilateral retinoblastoma signify clinically?

The presence of bilateral retinoblastoma indicates that the affected patient has a germ-line mutation in the Rb1 gene and is capable of transmitting the tumor to offspring.

40. Can a child with a unilateral retinoblastoma have a germ-line mutation?

Yes. Unfortunately, the presence of a unilateral tumor does not exclude a germ-line mutation and transmissible disease. Only approximately 60% of patients with familial retinoblastoma actually develop bilateral tumors.

41. Are most retinoblastomas familial?

No, most retinoblastomas occur sporadically in infants who have no family history of the disease. Nearly ¾ of sporadic retinoblastomas are caused by somatic mutations in retinal cells, which cannot be passed on to offspring. Such somatic sporadic tumors are invariably unilateral and unifocal. The remaining fourth of sporadic retinoblastomas are caused by germ-line mutations in the Rb1 gene (i.e., they are new familial cases). These are often bilateral and can be passed on to offspring in what appears to be autosomal dominant transmission. Only 5 to 10% of retinoblastomas occur in patients with a family history of the tumor.

42. Why are sporadic retinoblastomas caused by somatic mutations in the Rb1 gene always unilateral and unifocal?

A sporadic somatic retinoblastoma is caused by the inactivation of both Rb1 genes in a single retinal cell. The spontaneous mutation rate of the Rb1 gene is very low. Hence, the chance of this occurring in more than a single retinal cell is infinitesimally small. Therefore, sporadic somatic retinoblastomas always are unilateral and unifocal. In contrast, it is highly probable that one or more gene inactivations will occur in *both* retinas of a heterozygous carrier, because the mutation rate is substantially smaller than the number of mitoses involved in the development of the retina, and genes usually are lost during cellular division. That is why familial cases typically are bilateral and may be multifocal.

43. Are patients with hereditary retinoblastomas at risk for other nonocular tumors?

Yes. Between 20% and 50% of patients who have germ-line mutations in the retinoblastoma gene will develop a second malignant neoplasm within 20 years. One of the most interesting and characteristic secondary tumors is pineoblastoma, a retinoblastoma-like tumor of the pineal gland. The association of pineoblastoma and hereditary retinoblastoma has been termed *trilateral retinoblastoma*. There also is a 500-fold increase in the incidence of osteogenic sarcoma in retinoblastoma gene carriers. Patients also are at risk to develop radiation-induced orbital sarcomas (e.g., osteogenic sarcomas) after external-beam radiotherapy for retinoblastoma, which is why oncologists currently try to avoid this therapy.

44. Can retinoblastoma develop without mutations in the Rb1 gene?

Unusual retinoblastoma-like tumors that have no mutations in the Rb1 gene have been reported. These are characterized by high levels of amplification of the MYCN oncogene. These aggressive tumors comprise less than 3% of retinoblastomas and typically occur as unilateral tumors in young infants less than 6 months of age. They resemble neuroblastomas histopathologically and lack rosettes, which typically are numerous in retinoblastomas removed from very young infants. The cells also have prominent nucleoli. About one-fifth of unilateral retinoblastomas that occur in infants less that 6 months of age are $Rb1^{+/+}$ $MYCN^{A}$ tumors.[43]

KEY POINTS: RETINOBLASTOMA

1. Tumor suppressor gene is on chromosome 13 (13q1–4)
2. Most cases are sporadic (75% somatic, 25% germ line)
3. Bilaterality indicates transmissible germ-line mutation
4. Heritable cases pass disease to 50% of offspring (autosomal dominant pattern)
5. Heritable cases are at risk for second tumors

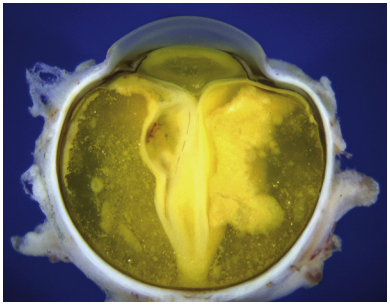

Figure 51-10. Coats disease.

45. Name the three diseases that are most often confused with retinoblastoma clinically.[44-47]

- Persistent fetal vasculature (also called persistent hyperplastic primary vitreous)
- Coats disease
- Ocular toxocariasis

46. How does Coats disease differ clinically from retinoblastoma?

Coats disease is characterized by an exudative retinal detachment caused by leaky congenital vascular anomalies in the retina (Fig. 51-10). The subretinal fluid is rich in lipid-laden macrophages and cholesterol crystals, which appear as empty clefts in microscopic sections. Histopathologically, the retina contains abnormal telangiectatic vessels, and its outer layers are massively thickened by hard exudates. A bullous retinal detachment may abut the lens, displacing it anteriorly and causing pupillary block glaucoma. Coats disease usually occurs unilaterally in boys between ages 4 and 10. It usually is confused clinically with exophytic retinoblastoma. Affected patients typically show xanthocoria rather than leukocoria.[48,49]

47. What are the characteristic features of persistent fetal vasculature (persistent hyperplastic primary vitreous?

Persistent fetal vasculature, previously called persistent hyperplastic primary vitreous, is a congenital disorder that is present at birth. It is almost always unilateral and classically is found in a microphthalmic eye. Leukocoria is caused by a plaque of fibrovascular tissue that adheres to the posterior surface of the lens. The ciliary processes typically are disclosed by dilating the pupil because their tips are attached to the edge of the retrolental plaque and are drawn centrally. Congenital retroblastomas have been reported but are exceedingly rare. On average, retinoblastomas are diagnosed at age 18 months.[45,46,50]

48. What is the second most common primary intraocular tumor of childhood?

Embryonal medulloepithelioma is the second most common primary intraocular tumor of childhood. Medulloepitheliomas probably are derived from anlagen of the embryonic medullary epithelium, which lines the forebrain and optic vesicle. Most of these rare tumors become symptomatic around age 4 years and are diagnosed at 5 years of age.[33,51,52]

49. Where are most medulloepitheliomas located?

Most medulloepitheliomas are ciliary body tumors that arise from the neuroepithelial layers on its inner surface. Rare medulloepitheliomas of the optic nerve have been reported, however.[53,54]

50. What is a teratoid medulloepithelioma?

In addition to bands, cords, and rosettes of neoplastic neuroepithelium and pools of hyaluronic acid, teratoid medulloepitheliomas contain foci of heteroplastic tissue including hyaline cartilage, rhabdomyoblasts, striated muscle, and/or brain. (Fig. 51-11) More than a third of medulloepitheliomas are teratoid. Nonteratoid medulloepitheliomas lack heteroplastic elements. Both benign and malignant variants of teratoid and nonteratoid tumors occur.

51. Is medulloepithelioma associated with other tumors?

Rarely, embryonal medulloepithelioma occurs in patients who have the pleuropulmonary blastoma syndrome. Pleuropulmonary blastomas are rare embryonal tumors of the lung that occur in infants.

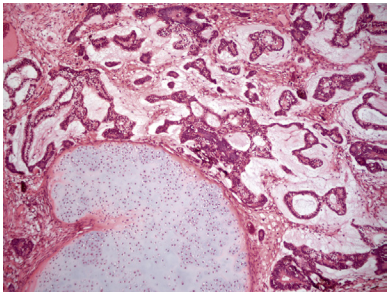

Figure 51-11. Teratoid medulloepithelioma with focus of cartilage.

They are associated with mutations in the Dicer 1 gene on 14q31. Like teratoid medulloepitheliomas, pleuropulmonary blastomas may contain cartilage.[55]

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CHAPTER 52

ORBITAL TUMORS

Jurij R. Bilyk

1. Should all orbital capillary hemangiomas be excised?

No. Orbital capillary hemangioma (hemangioma of infancy) should be treated only if there is evidence of:

- Amblyopia caused by refractive error (induced myopia or astigmatism) or
- Ptosis causing visual obstruction or head tilt.

Treatment options include the following:

- The treatment of choice at present is the use of systemic β-blockers (propranolol). Systemic monitoring should be performed during induction to ensure cardiopulmonary stability. The use of topical therapy for more superficial lesions is under investigation, with positive initial results. However, the efficacy of topical therapy for deeper orbital lesions has not yet been proven.
- Corticosteroid injections or systemic therapy. Of note, corticosteroid suspensions (e.g., triamcinolone) may rarely case vascular occlusions and visual loss when injected into the orbit. Such medications now come with a black-box warning from the manufacturer warning against their use in the periocular region. The clinician should either obtain a clear consent from the parents or guardians or use a nonsuspension corticosteroid injection or systemic therapy.
- Excision is usually reserved for cases unresponsive to more conservative therapy.
- Interferon α-2 therapy, especially in large localized or systemic cases. This option is becoming more of a rarity with the advent of β-blocker therapy. Interferon α-2 therapy in children is also associated with a risk of spastic diplegia.[1-4]

2. What orbital tumors can mimic orbital cellulitis?

In both adults and children, the differential includes noninfectious inflammation (idiopathic orbital inflammatory syndrome (inflammatory orbital pseudotumor), sarcoidosis, thyroid eye disease (Graves' orbitopathy), and granulomatosis with polyangiitis (Wegener granulomatosis)).

In children, also consider:

- Ruptured dermoid cyst. This causes a fulminant soft tissue inflammation.
- Rhabdomyosarcoma. Usually, this is painless.
- Lymphangioma, especially with rapid expansion from a blood-filled "chocolate cyst."
- Neuroblastoma. This can present with a rapid onset of proptosis and ecchymosis.

In adults, also consider:

- Ruptured dermoid cyst.
- Lymphangioma.
- Extrascleral spread and/or necrosis of an intraocular melanoma.
- Metastatic disease to the orbit.

3. What are the most common causes of childhood proptosis?

- Orbital cellulitis
- Capillary hemangioma (hemangioma of infancy)
- Idiopathic orbital inflammatory syndrome (inflammatory orbital pseudotumor)
- Dermoid cyst
- Rhabdomyosarcoma
- Lymphangioma

4. When and how does cavernous hemangioma usually present?

- Cavernous hemangioma is the most common vascular orbital tumor in adults and the most common benign orbital tumor.
- Typically presents in the 4th and 5th decades.
- Well-circumscribed on imaging (see question 16).
- It is *not* the adult equivalent of capillary hemangioma. Not only are the lesions distinct histopathologically, but cavernous hemangioma is a slowly proliferating entity.

- Because of its slow growth, it is usually a well-tolerated lesion, causing few symptoms. Visual loss, if any, is slow and limited to lesions of the orbital apex.
- Excision is curative.[5-9]

5. List some basic facts about fibrous histiocytoma and hemangiopericytoma.

- Fibrous histiocytoma, malignant fibrous histiocytoma, and hemangiopericytoma have been characterized as subtypes of *solitary fibrous tumor.* Because all of these entities are spindle-cell tumors, histopathologic diagnosis may be difficult.

Fibrous histiocytoma:

- Fibrous histiocytoma is the most common mesenchymal tumor of adults.
- Excision is curative.
- Malignant transformation is rare, but possible.

Hemangiopericytoma:

- A tumor of pericytes.
- Histopathologic appearance has little correlation with clinical behavior. In other words, a histologically benign lesion may behave aggressively and recur after excision, whereas a tumor with aggressive features on microscopic examination may never recur.
- Patients need to be followed clinically even after excision for possible recurrence or aggressive behavior.[10-16]

6. What about orbital schwannoma?

- A tumor of the Schwann cells, which form the lining of peripheral nerves.
- Schwannomas typically arise from sensory nerves, although motor and parasympathetic nerve involvement within the orbit has also been reported.
- N.B. Schwannomas do *not* arise from the optic nerve sheath (the optic nerve is lined with meninges; a tumor arising from the optic nerve sheath is a meningioma, not a schwannoma.
- Within the orbit, most schwannomas arise from sensory nerve sheaths, which may explain their predilection for the superior orbit.
- The Antoni A and B patterns are the classic histologic findings in schwannoma. The A pattern is characterized by abundant, tightly packed spindle cells, whereas the B pattern exhibits fewer cells within a myxoid matrix.[17,18]

7. How does one order an orbital computed tomography (CT) scan?

- Order axial and coronal cuts in all cases. The newest multiscan CTs typically image in the axial plane only and are then reconstructed as coronal and parasagittal images without loss of resolution or need for patient repositioning.
- If direct coronals cannot be obtained, coronal reconstructions usually suffice, but this is really an issue only with older scanners.
- Always review both soft tissue and bone windows.
- Never order cuts greater than 3 mm.
- Intravenous contrast is helpful in cases of infection or inflammation. It is not necessary for trauma or thyroid eye disease.
- In deep orbital and skull base processes, consider ordering the scan with intraoperative guidance protocols. This will allow a more precise localization of anatomy if subsequent intraoperative image guidance is needed during surgery.[19]

8. How does one order an orbital magnetic resonance image (MRI)?

Very carefully.

The Rules of Orbital MRI

- NEVER order MRI as the first imaging modality in trauma, for unresponsive patients, or for poor historians. Occult metal within the magnetic field can move and cause severe soft tissue damage.
- Always order axial, coronal, and parasagittal views.
- Always include the cavernous sinus and paranasal sinuses.
- Always order gadolinium and fat suppression (Fig. 52-1). Be careful ordering gadolinium in patients with known or suspected renal disease, as this may result in nephrogenic systemic fibrosis.
- In T1, orbital fat is bright and vitreous is dark.
- In T2, vitreous is brighter than fat.
- The majority of orbital masses are dark in T1 *before* gadolinium administration.

Exceptions to this rule are:

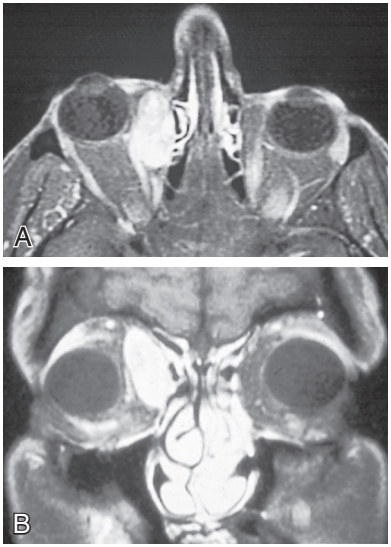

Figure 52-1. A and **B,** T1-weighted magnetic resonance images of the orbit with fat suppression.

1. Lesions containing melanin (e.g., melanoma);
2. Lesions containing fat (e.g., lipoma, liposarcoma);
3. Lesions containing mucus (mucocele, dermoid cyst);
4. Subacute blood (2 to 7 days old).[20]

9. Discuss the histologic classification of orbital rhabdomyosarcoma.

Orbital rhabdomyosarcoma (RMS) is histologically divided into three main groups (other schema are sometimes used, but this is the most basic):

1. Embryonal
2. Alveolar
3. Pleomorphic

The average age of onset is 9 years, but the span is broad. RMS is thought to arise from pleuripotential mesenchymal tissue within the orbit and *not* from extraocular muscle. Useful facts to remember about each group follow:

1. Embryonal
   - Further subdivided into classic, botryoid, spindle cell, and anaplastic
   - Most common histology in children
   - The botryoid subtype is defined as an embryonal RMS abutting a mucosal surface (e.g., conjunctiva)
2. Alveolar
   - Appears to affect the inferior orbit most frequently and carries the worst prognosis
   - Fortunately, recent findings by the Intergroup Rhabdomyosarcoma Study (IRS) indicate that with more aggressive therapy, the prognosis for alveolar RMS approaches the prognosis for the embryonal form
3. Pleomorphic
   - Occurs in older adults[16]

10. How is orbital RMS best treated? What is the prognosis?

- Much of what is known about the treatment of orbital rhabdomyosarcoma comes from the four IRSs.
- Treatment of orbital RMS consists of a combination of chemotherapy and radiation therapy.
- Radiation therapy in doses of 40 to 60 Gy definitely carries significant morbidity for the globe, but the IRS-III concluded that it is still necessary for adequate treatment. Lower doses of radiation are currently under study.

Table 52-1. Clinical Characteristics of Lacrimal Gland Lesions

	PLEOMORPHIC ADENOMA	ADENOID CYSTIC CARCINOMA
Duration	>1 year	<1 year
Pain	Rare	Common
Diplopia	Uncommon	Common
CT findings	No bony destruction. +/– fossa formation.	Bony destruction common.
Surgery	Excisional biopsy.	Incisional biopsy.
When in Doubt, Perform Total Excision of the Mass		
Postsurgical therapy	Clinical follow-up only.	Controversial: Radiation, chemotherapy (including intra-arterial therapy), radical excision.

- Orbital and genitourinary RMS carry the best prognosis for unclear reasons.
- Local spread from the orbit into the paranasal sinuses or cranial vault decreases survival rates.[21,22]

11. With regard to lacrimal gland lesions, what is the "rule of 50s"?

The rule of 50s summarizes the incidence of lacrimal gland tumors in an *orbital* referral practice:

- 50% of lacrimal gland lesions are nonepithelioid, consisting mostly of inflammatory and lymphoproliferative lesions, and 50% are of epithelial origin.
  - 50% of the epithelial tumors are benign pleomorphic adenomas (benign mixed tumor) and 50% are various malignant types.
    - 50% of the malignant tumors are adenoid cystic carcinomas.
      - 50% of the adenoid cystic carcinomas are of the basaloid variant. The final rule is important clinically, because a basaloid histopathology for adenoid cystic carcinoma carries the worst prognosis.

In a general ophthalmology practice the rule of 50s does not apply. The incidence of infectious and noninfectious inflammatory dacryoadenitis is several times higher than in an orbital referral practice.[23,24]

12. What factors help to distinguish benign and malignant epithelial lacrimal gland tumors?

See Table 52-1.[25-29]

13. What are the most common tumors to metastasize to the orbital soft tissue in men and women?

- Men, lung; women, breast carcinoma (but the incidence of lung carcinoma is increasing).
- Note that the question asks specifically about orbital soft tissue. Otherwise, prostate carcinoma, which has a propensity for bony involvement, would be an acceptable alternative in men, depending on the clinical series.[30-32]
- N.B. Metastatic lesions are about 10 times more common to the uvea than the orbit on autopsy studies. This may be due to the high blood flow through the choroid, which may allow more facile metastatic seeding of uveal tissue.

14. What is the appropriate workup for orbital lymphoma and lymphoid hyperplasia?

Regardless of the histopathology, any lymphoproliferative lesion of the orbit or ocular adnexa requires a systemic workup:

- Complete blood count.
- Serum protein electrophoresis.
- Imaging of the neck, thorax, and abdomen, which should be repeated every 6 to 12 months for at least 2 years.
- Some specialists also perform bone marrow biopsy on initial presentation.[33-35]

15. What are the important facts about orbital lymphoproliferative lesions?

- Idiopathic orbital inflammatory syndrome (inflammatory orbital pseudotumor) is *not* a lymphoproliferative disorder, because histopathologically the reaction is not limited to lymphocytes. It is *not* a precursor for orbital lymphoma.

Table 52-2. Distribution of Lymphoma Subtypes Systemically and in the Ocular Adnexa

SYSTEMIC LYMPHOMA (WHO DATA)	OCULAR ADNEXAL LYMPHOMA (OAL), N = 353
Diffuse large B cell (30.6%)	EMZL/MALT (52%)
Follicular cell (22.1%)	Follicular cell (23%)
EMZL/MALT (7.6%)	*Diffuse large B cell (8%)*
CLL (6.7%)	*Mantle cell (5%)*
Mantle cell (6.0%)	CLL (4%)

Indolent subtypes are listed in normal text. Aggressive subtypes are italicized. EMZL/MALT = extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; CLL = chronic lymphocytic leukemia.
Data modified from Ref. 36.

- The vast majority of orbital lymphomas are of B-cell origin, usually EMZL (extranodal marginal zone lymphoma), also frequently called MALT-oma (mucosa-associated lymphoid tissue lymphoma).
- Orbital B-cell lymphoma is mainly a disease of adults; it is exceedingly rare in children.
- The majority of lymphoid lesions, whether polyclonal (lymphoid hyperplasia) or monoclonal (lymphoma), are highly radiosensitive.
- The World Health Organization's reclassification of lymphoma has markedly changed the diagnosis and management of orbital lymphoma. A brief review is warranted:
  - The easiest classification schema is to simply divide ocular adnexal lymphoma (OAL) into indolent and aggressive rubrics (see Table 52-2).
  - Unlike primary systemic lymphoma, of which about 1/3 are aggressive large cell types, 75 to 80% of OALs are indolent (see Table 52-2).
  - When an aggressive subtype of OAL is encountered, it is either secondary from a different site or presents as stage III or IV disease (systemic involvement).
  - In contrast, most indolent OALs presents as stage I disease.
  - Management of OAL depends mainly on two factors: subtype of lymphoma and stage of disease. As an example, a stage I EMZL of the orbit is typically treated with 30 to 35 Gy of radiation, whereas a stage I diffuse large B-cell lymphoma would be managed with systemic chemotherapy because of its aggressive nature.
  - The goal of treatment also depends on the subtype of disease. As a sweeping statement, aggressive OALs are treated to cure, whereas indolent subtypes are usually managed as a chronic disease.
  - Transformation of an indolent OAL (e.g., EMZL/MALT) to a more aggressive type diffuse large B cell (DLBCL) can occur in a minority of patients.[36-39]

16. What is the differential diagnosis of a well-circumscribed orbital mass?

- Cavernous hemangioma
- Schwannoma
- Solitary fibrous tumor (fibrous histiocytoma)
- Neurofibroma
- Solitary fibrous tumor (hemangiopericytoma)
- Dermoid cyst
- +/– Lymphoma (about 50% of OALs will present as well circumscribed and the other half as infiltrating).

KEY POINTS

- Unilateral or bilateral proptosis usually requires imaging, especially if it is progressive.
- CT of the orbit is generally easier to obtain and interpret than MRI.
- CT is the recommended imaging modality for trauma, infection, and thyroid eye disease (Graves' orbitopathy).
- MRI is recommended for soft tissue processes, for imaging of the orbital apex/cavernous sinus, and for suspected intracranial processes.
- Orbital lymphoid hyperplasia requires systemic monitoring identical to orbital lymphoma.
- Well-tolerated, well-circumscribed lesions of the orbit can be followed conservatively with serial imaging alone in selected cases.

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