8
OCULAR MANIFESTATIONS OF SYSTEMIC DISEASE

OBJECTIVES

As a primary care physician, you should be aware that many systemic diseases have ocular signs and symptoms that may result in serious ocular sequelae. You should become familiar with the important features of several of these conditions, including diabetes mellitus, hypertension, sickle cell anemia, thyroid disease, sarcoidosis and other inflammatory and autoimmune conditions, malignancy, acquired immunodeficiency syndrome, syphilis, and other systemic infections. Issues around pregnancy are also noted.

To achieve these objectives, you should learn to

- Perform a thorough eye examination (see Chapter 1)
- Recognize the characteristic features, especially the ophthalmoscopic features, of these diseases
- Determine when it is appropriate to refer a patient to an ophthalmologist for consultation or treatment

RELEVANCE

Recognition of the ocular signs, symptoms, and complications of many systemic diseases is vitally important for good medical practice. Diabetes mellitus affects more than 17 million Americans and is the leading cause of new cases of blindness in working-age Americans. Treatment of diabetic retinopathy is directed toward the prevention of visual loss. Several national clinical trials sponsored by the National Eye Institute have demonstrated that with appropriate referral and treatment the incidence of severe visual loss can be reduced

by at least 90%. Acquired immunodeficiency syndrome is a disease of epidemic proportions. More than 75% of AIDS patients have ocular involvement of some kind (from asymptomatic retinal infarctions to vision-threatening cytomegalovirus retinitis). Because ocular findings may reflect disease progression, regular ophthalmologic examination can be beneficial in initiating or modifying treatment in a timely fashion.

DIABETES MELLITUS

Although diabetes may have a number of ocular effects (eg, cataracts, changes in refractive status), the most important ocular complication is retinopathy.

The longer a person suffers from diabetes, the greater the likelihood of developing diabetic retinopathy. About 5 years after diagnosis, 23% of patients with insulin-dependent diabetes mellitus (IDDM, type 1) have diabetic retinopathy, and after 15 years, 80% have retinopathy. Diabetic patients who have non–insulin-dependent diabetes mellitus (NIDDM, type 2) have a similar but slightly lower prevalence of retinopathy. Because patients with type 2 diabetes may not be diagnosed until years after onset of their disease, many patients already have significant retinopathy at the time of diagnosis.

The Diabetes Control and Complications Trial (DCCT) showed that intensive glycemic control is associated with a reduced risk of newly diagnosed retinopathy and reduced progression of existing retinopathy in people with insulin-dependent diabetes mellitus (IDDM). Furthermore, the DCCT showed that intensive glycemic control (compared to conventional treatment) was associated with reduction in progression to severe nonproliferative and proliferative retinopathy, incidence of macular edema, and need for panretinal and focal photocoagulation. Advanced diabetic retinopathy is associated with cardiovascular disease risk factors. Patients with proliferative diabetic retinopathy are also at increased risk of heart attack, stroke, diabetic nephropathy, amputation, and death. The results of the DCCT showed that the lowering of blood glucose reduces ocular complications as well as other end-organ complications, including nephropathy, neuropathy, and cardiovascular disease. It is important that all patients with type 1 and most patients with type 2 diabetes be educated about the importance of determining and maintaining glycosylated hemoglobin levels to improve glycemic control.

The initial stage of the ocular disease is called *nonproliferative diabetic retinopathy* (NPDR). Capillaries develop leaks and later become occluded. The retinal findings of mild and moderate NPDR include microaneurysms, dot-and-blot hemorrhages, hard exudates, and macular edema (Figures 8.1 and 8.2). Patients experience visual loss only if there is clinically significant macular edema (CSME), which is present in 5% to 15% of diabetic pa-

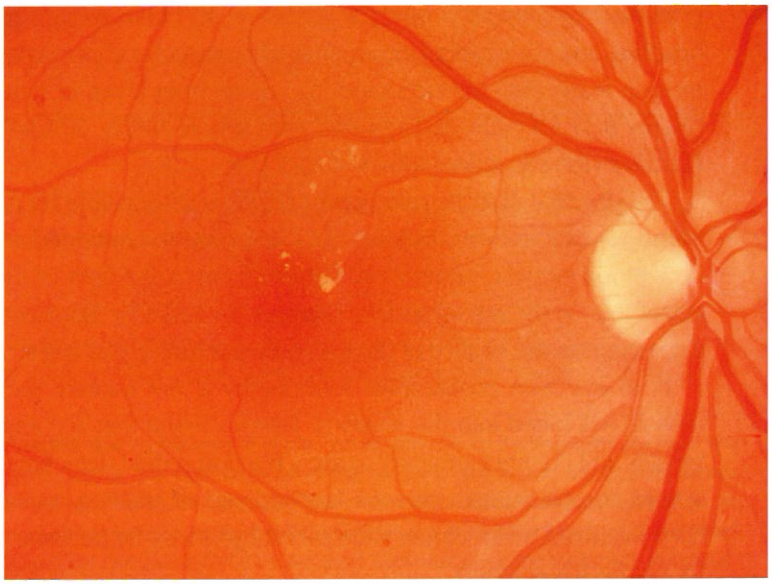

FIGURE 8.1 Nonproliferative diabetic retinopathy with clinically significant macular edema. Right macula with scattered microaneurysms and a small ring of exudate originating from small clusters of microaneurysms above the right fovea. Vascular leakage has also resulted in macular edema that cannot be visualized in this photograph. *(Courtesy Stephen Fransen, MD.)*

tients, depending on the type and duration of the disease. CSME is the most common cause of mild to moderate visual loss from diabetic retinopathy.

In time, some patients progress to severe NPDR, which heralds the onset of the most serious form of retinopathy, the proliferative stage. Severe NPDR

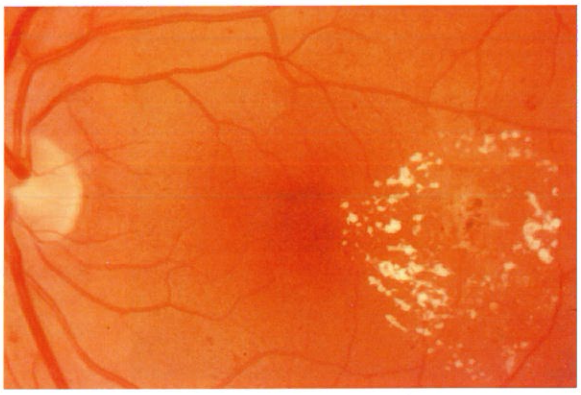

FIGURE 8.2 Nonproliferative diabetic retinopathy. Left macula with small retinal hemorrhages and ring exudates temporal to the left fovea. Prior focal laser treatment has been applied to the microaneurysms in the center of the ring. The ring will take months to resolve completely. *(Courtesy Stephen Fransen, MD.)*

is marked by increased vascular tortuosity and hemorrhagic activity, venous beading, and widespread intraretinal microvascular abnormalities; it may also include many microinfarctions of the nerve fiber layer, or cotton-wool spots (Figure 8.3). Of patients diagnosed with severe NPDR, 40% will develop proliferative diabetic retinopathy within 1 year.

Proliferative diabetic retinopathy (PDR) is responsible for most of the profound visual loss from diabetes. As a response to continued retinal ischemia, new blood vessels (neovascularization) form in the area of the optic disc or elsewhere on the retinal surface (Figures 8.4 and 8.5). Neovascularization can also occur on the surface of the iris (rubeosis iridis), causing severe glaucoma.

If an eye with proliferative retinopathy is not treated, these fragile new vessels will bleed into the vitreous. Fibrous tissue that accompanies the new vessels will contract and may cause a traction retinal detachment. Once these severe complications (vitreous hemorrhage or traction retinal detachment) have occurred, a vitrectomy with laser surgery may be necessary in the attempt to restore some vision.

PDR and CSME may remain asymptomatic well beyond the optimal stage for treatment. All patients with diabetes should be referred to an ophthalmologist for examination and annual follow up. Detection of treatable macular edema and proliferative retinopathy requires stereoscopic biomicroscopy and indirect ophthalmoscopy through dilated pupils. Examination with the handheld direct ophthalmoscope is not sufficient to rule out significant, treatable diabetic retinopathy. All patients with nonproliferative and proliferative retinopathy require frequent ophthalmoscopic examinations, and some require specialized examination techniques such as fluorescein angiography to doc-

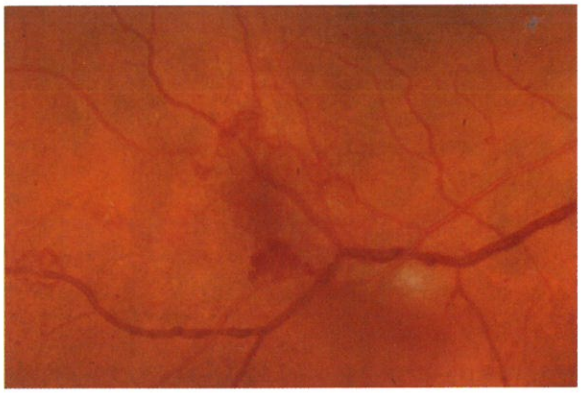

FIGURE 8.3 Early proliferative diabetic retinopathy. Venous beading (irregular caliber) along retinal vein with cotton-wool spot and neovascularization elsewhere (NVE). More subtle findings include preretinal hemorrhage and microscopic vitreous hemorrhage. *(Courtesy Stephen Fransen, MD.)*

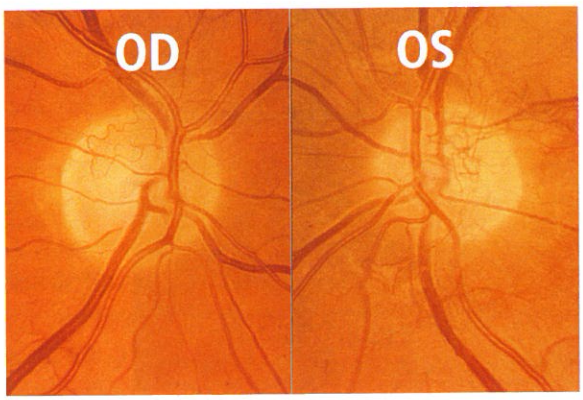

FIGURE 8.4 Proliferative diabetic retinopathy. These photographs are from the same patient. The right optic nerve has two new vessels over the superior aspect of the optic nerve. The left optic nerve has more advanced neovascularization. To prevent progression of the neovascularization and possible vitreous hemorrhage, panretinal photocoagulation is required. Early diagnosis and treatment of neovascularization is important to prevent visual disability. *(Courtesy Cynthia A. Bradford, MD.)*

ument the extent of the vascular abnormalities and to guide therapy. Some patients with macular edema will require laser surgery (focal treatment) to areas of leaking blood vessels. This treatment has been demonstrated to reduce visual loss by approximately 50%.

In treating proliferative retinopathy, the ophthalmologist scatters 1000 to 2000 laser burns over the entire surface of the retina except the macula and

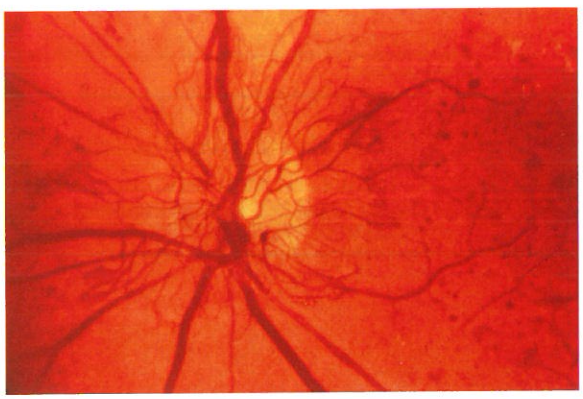

FIGURE 8.5 Proliferative diabetic retinopathy. Shown here is more advanced neovascularization of the optic nerve. These new vessels proliferate and extend into the vitreous. Later diagnosis and treatment can be more costly due to greater need for surgical intervention, and is also associated with greater visual impairment and disability.

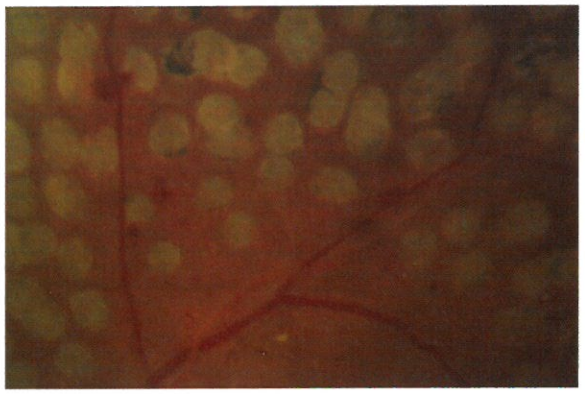

FIGURE 8.6 Panretinal argon laser photocoagulation. Shown here are old argon laser burns in a diabetic patient with proliferative retinopathy. Initially the burns are white, but with time they develop variable pigmentation from chorioretinal scarring.

the papillomacular bundle (Figure 8.6). This treatment is based on the concept that a reduction of the metabolic oxygen requirement of the retina or destruction of vascular endothelial growth factor (VEGF) promotes regression of the neovascular tissue. Appropriately timed effective panretinal laser photocoagulation surgery can reduce the incidence of severe visual loss by at least 50% and as much as 90%. Many patients require frequent treatments when the disease is actively progressing.

All individuals with type 2 diabetes should be examined at the time of diagnosis and thereafter annually by an ophthalmologist. Type 1 diabetics should be screened once they are postpubertal and have had diabetes mellitus for 5 years or longer. More frequent examinations are required for patients who have poor glycemic control, hypertension, proteinuria, or anemia, as they are at higher risk for more rapid progression of their retinopathy. Patients who have already been treated with laser surgery or vitrectomy should adhere to a follow-up schedule determined by their ophthalmologist. It is not unusual to require additional treatment.

Pregnant patients with type 1 diabetes should be examined by an ophthalmologist during the first trimester and every 3 months thereafter until completion of the pregnancy. Ideally, women who are planning a pregnancy should have a baseline ophthalmologic examination before conception, as pregnancy can severely exacerbate diabetic retinopathy.

HYPERTENSION

To understand the effects of systemic hypertension on the retinal vasculature, it is helpful to divide hypertensive retinopathy into two classifications: changes due to arteriolar sclerosis, and changes due to elevated blood pressure.

ARTERIOLAR SCLEROSIS

Although aging causes thickening and sclerosis of the arterioles, prolonged systemic hypertension (usually, diastolic pressure greater than 100 mm Hg)

accelerates this process. Thickening of the walls of the retinal arterioles results in characteristic ophthalmoscopic features of retinal arteriolar sclerosis: an increase in the light reflex of the arteriole, and changes in arteriovenous (AV) crossing. The amount of arteriolar sclerosis depends on the duration and severity of the hypertension and may reflect the condition of the arterioles elsewhere in the body.

In a normal eye, the retinal arterioles are transparent tubes with blood visible by ophthalmoscopy; a light streak is reflected from the convex wall of the arteriole. As arteriolar sclerosis causes thickening and fibrosis of the vessel wall, the central light reflex increases in width. After sclerosis progresses, the light reflex occupies most of the width of the vessels; at this point, the vessels are called *copper-wire arterioles.* As fibrosis continues, the light reflex is obscured totally. These arterioles appear whitish and are referred to as *silver-wire arterioles.*

Because the arterioles and veins share a common sheath within the retinal tissue at crossing sites, arteriovenous crossing changes can be viewed (Figure 8.7). The vein may be elevated or depressed by the arteriole and, in more severe cases, may undergo an abrupt right-angle change in course just as it reaches the arteriole. Alterations in the caliber of the vein may occur because of compression and constriction at the A/V crossing (ie, nicking) resulting in dilation of the distal portion of the vein and tapering of the vein on either side of the artery. All of these A/V crossing changes are most significant when found at or beyond the second bifurcation of the arteriole, which is about 1 disc diameter distal to the optic nerve head. Severe A/V nicking can lead to branch retinal vein occlusions, which will appear as diffuse retinal hemorrhages and cotton-wool spots in the sector of the retina that is drained by the affected vein. If accompanied by macular edema, it can decrease central visual acuity and require laser treatment in certain cases. If ischemia is present, patients are also at risk for neovascularization and vitreous hemorrhage.

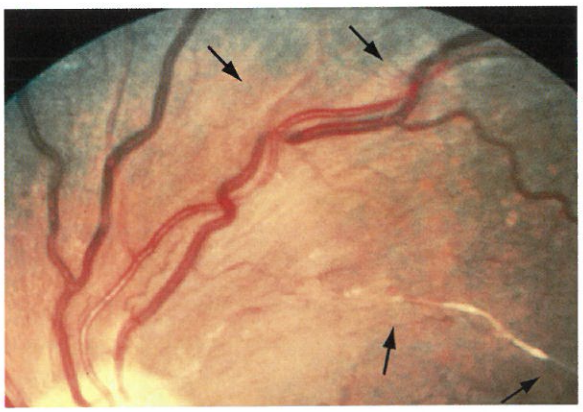

FIGURE 8.7 Hypertensive retinopathy in a patient with longstanding hypertension. Notice a single retinal vessel with areas of copper-wiring and silver wiring (lower arrows). Arteriovenous (AV) crossing changes are also visible as an abrupt right-angle change of a vein at the first AV crossing, and nicking of the vein at the second AV crossing (upper arrows).

ELEVATED BLOOD PRESSURE

A moderate acute rise in blood pressure results in constriction of the arterioles. A severe acute rise in blood pressure (usually, diastolic pressure greater than 120 mm Hg) causes fibrinoid necrosis of the vessel wall, resulting in exudates, cotton-wool spots, flame-shaped hemorrhages, and sometimes whitish swelling and edema of large portions of the retina. In the most severe form of hypertensive retinopathy, malignant hypertension (Figure 8.8), the optic disc swelling that occurs resembles the swelling seen in papilledema.

DIAGNOSTIC CONCERNS

The relationship between hypertensive vascular changes and the changes of arteriosclerotic vascular disease is complex, with great variation in the expression of these disease processes. Hence, classification of retinal vascular changes caused strictly by hypertension is difficult. One commonly used system is the Modified Scheie Classification of Hypertensive Retinopathy:

- Grade 0 No changes
- Grade 1 Barely detectable arterial narrowing
- Grade 2 Obvious arterial narrowing with focal irregularities
- Grade 3 Grade 2 plus retinal hemorrhages and/or exudate
- Grade 4 Grade 3 plus disc swelling

Hypertension is also associated with branch retinal artery occlusion (BRAO), branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), and retinal arterial macroaneurysms. In order of importance, the most sensitive ophthalmoscopic indicators of hypertension are attenuation of the retinal arterioles, focal narrowing, and A/V crossing changes.

MANAGEMENT

The primary goal in managing systemic hypertension is adequate control of the blood pressure to preserve the integrity of the cerebral, cardiac, and renal

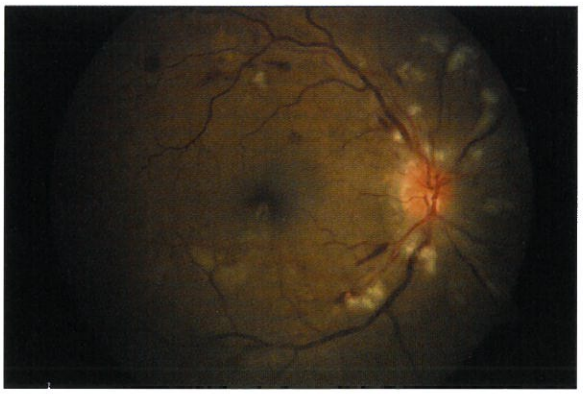

FIGURE 8.8 Malignant hypertension. This figure demonstrates the ocular findings associated with severe hypertension: optic nerve swelling, extreme arterial constriction, hemorrhages, early exudates, and cotton-wool spots. Untreated, the optic nerve swelling may progress to resemble papilledema.

circulations. A sudden, severe increase in blood pressure also can compromise the retinal and choroidal circulations, resulting in loss of vision or visual field. Under these circumstances, the blood pressure should be lowered in a controlled fashion because a sudden drop in tissue perfusion could result in optic nerve infarction and permanent loss of vision. In chronic hypertension control avoid giving the antihypertensive medication at night before sleep. Twenty-four-hour blood pressure monitoring has shown a natural, nocturnal drop in blood pressure at night, which may be compounded by the patient's antihypertensive regime and may lead to ischemic optic neuropathy or worsening of glaucomatous visual field loss.

PREGNANCY

Although pregnancy is not a disease, it can cause numerous changes in the functioning and health of the eye. Several physiologic changes occur that are not considered pathologic. These include lowering of the intraocular pressure, decrease in corneal sensitivity, and transient loss of accommodation. Pregnant women frequently suffer from dry eyes and can experience changes in their refractive error. Therefore, pregnant patients should be discouraged from changing their prescriptions for glasses or contact lenses until after delivery. In the early postpartum period and while breast feeding, the patient should not have corneal refractive surgery performed.

In addition to physiologic changes, pathologic ocular conditions may occur during pregnancy. There is an increased incidence of central serous chorioretinopathy and uveal melanomas in pregnant versus nonpregnant women. Pregnancy-induced hypertension can cause visual disturbances such as scotoma, diplopia, and dimness of vision. Visual changes may be a sign of impending seizure in a preeclamptic patient. Retinal vascular changes can occur in toxemia including focal and generalized arteriolar narrowing. Uncommonly, hemorrhages, exudates, diffuse retinal edema, and papilledema may appear. Serous exudative retinal detachments occur in 10% of patients with eclampsia.

Preexisting conditions such as diabetic retinopathy can also be affected by pregnancy. All pregnant diabetics should have a baseline exam in the first trimester. Those without retinopathy at this point are unlikely to develop it during their pregnancy. Patients who have background diabetic retinopathy at the beginning of their pregnancy often have worsening of the retinopathy during the second trimester, which may improve in the third trimester and postpartum period. An ophthalmologist should probably see these patients at least once per trimester. Proliferative retinopathy frequently progresses during pregnancy and needs to be monitored closely by an ophthalmologist. Gestational diabetics are not at risk for retinopathy.

SICKLE CELL ANEMIA

Patients with SC and S Thal disease are more likely to have ocular involvement due to sickle cell than patients with SS disease. Intravascular sickling, hemolysis, hemostasis, and then thrombosis lead to arteriolar occlusion followed by capillary nonperfusion. As with diabetes, inadequate perfusion of the retina can stimulate retinal neovascularization, which is typically more peripheral and can lead to vitreous hemorrhage and retinal detachment. Appropriately timed laser surgery can prevent many vision-threatening complications in these patients. Patients with sickle cell anemia should have baseline ophthalmologic evaluation especially with new onset floaters or vision loss.

THYROID DISEASE

Graves disease is an example of an important autoimmune disease that may have ocular manifestations. A common clinical feature of thyroid eye disease is retraction of the upper and lower eyelid, with upper-lid lag on downgaze. Thyroid eye disease is also the most common cause of unilateral or bilateral protrusion of the globes, or exophthalmos, in adults. Exophthalmos (proptosis) in combination with retraction of the eyelids may produce an appearance referred to as *thyroid stare* (Figure 8.9).

Both eyelid retraction and exophthalmos may result in corneal exposure and drying, causing the patient to complain of a foreign-body sensation and tearing. These bothersome symptoms usually can be relieved by the frequent instillation of over-the-counter artificial-tear preparations and the application of lubricating eye ointment at night. The eyelid edema and conjunctival vascular congestion that sometimes accompany thyroid eye disease usually do

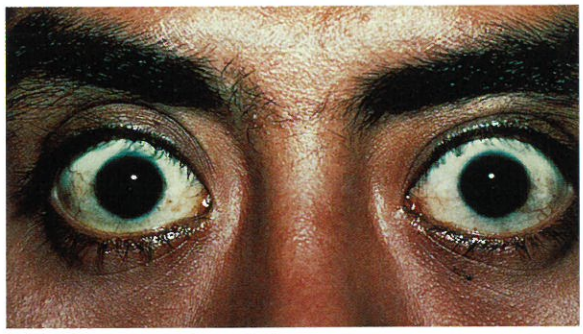

FIGURE 8.9 Thyroid stare. The staring appearance of this patient is due to forward protrusion of the eyes and retraction of the eyelids, exposing white sclera above and below the limbus.

not require therapy. If it is severe and persistent, proptosis may be surgically treated if severe and persistent.

Thyroid eye disease may cause other serious complications requiring an ophthalmologist's care. Diplopia due to extraocular muscle involvement is common and may require strabismus surgery. Compression of the optic nerve within the orbit can cause loss of vision, necessitating surgery to decompress the orbit or irradiation to reduce the inflammatory swelling of the muscles.

SARCOIDOSIS AND OTHER INFLAMMATORY AND AUTOIMMUNE CONDITIONS

Sarcoidosis is a chronic disease of uncertain derivation that affects several organ systems, including the eye. Ocular manifestations are characterized histologically by the presence of focal noncaseating granulomas. Sarcoidosis is most common in African-American women ages 20 to 40. Laboratory findings include increased serum calcium (12% of patients), elevated angiotensin-converting enzyme (75% of patients), and abnormal results on chest x-ray (80% of patients). Important histopathologic information also can be obtained from ocular tissues. The easiest tissue from which to obtain a biopsy specimen is the conjunctiva, but tissue from the lacrimal gland may be obtained as it is also a frequent locus of granulomatous infiltration. Both of these biopsy procedures can be performed under local anesthesia; these areas should be considered before performing potentially more complicated mediastinal or transbronchial biopsies of lymph nodes.

Ocular involvement from sarcoidosis may be asymptomatic, and patients suspected of sarcoidosis should have a complete ophthalmic evaluation. Sarcoidosis may cause anterior or posterior uveitis. Anterior uveitis is inflammation of the iris and ciliary body (Figure 8.10); posterior uveitis is inflammation of the choroid. Early initiation of topical or systemic corticosteroids is effective and may prevent complications, such as glaucoma, cataract, and

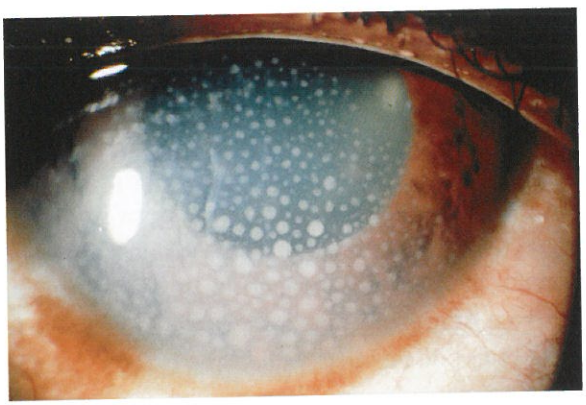

FIGURE 8.10 Anterior uveitis. Inflammatory cells collect on the inner surface of the cornea, producing opacities called keratic precipitates.

adhesions of the iris to the lens. Involvement of the retina is usually associated with posterior uveitis and may include perivasculitis, hemorrhages, and neovascularization of the peripheral retina. Involvement of the central nervous system is twice as common when the fundus is involved, increasing from 10% or 15% to between 20% and 30%. Ophthalmic manifestations of neurosarcoidosis include optic neuropathy, oculomotor abnormalities (including sixth nerve palsy), and, rarely, chiasmal and retrochiasmal visual field loss.

Dry eye caused by reduced tear production may be seen in sarcoidosis because of lacrimal gland infiltration, but it also occurs in a variety of rheumatologic conditions. The most common are systemic lupus erythematosus and rheumatoid arthritis. Dry eye also is common in a mild form in healthy individuals over age 40. Symptoms include a sensation of burning or grittiness of the eyes, especially late in the day. Accumulation of mucus on the eyelids also occurs in affected patients upon awakening. Many patients complain of tearing, presumably after the eye becomes dry enough to stimulate reflex tearing. Treatment includes the application of artificial tears and occasionally lubricating ointment at night. In the vast majority of patients, the condition is annoying, but rarely leads to serious ocular problems. Punctal occlusion by an ophthalmologist may be necessary. Occasional patients with advanced rheumatoid arthritis develop severe drying of eyes and have a greater risk of corneal melting and possible perforation. In addition, they have a greater risk of corneal infection.

Juvenile rheumatoid arthritis is an important childhood systemic condition with ocular manifestations. About 10% of all juvenile rheumatoid arthritis patients have iritis, but the inflammation is more common with the pauciarticular form of the disease (20% to 30% of patients) and much less common in the polyarticular form. Patients who have juvenile rheumatoid arthritis, especially the pauciarticular form, require visits to the ophthalmologist every 3 months because the iritis is commonly asymptomatic. If inflammation is not recognized, extensive ocular complications arise, including cataract, glaucoma, and calcification of the cornea. Iritis is also a common complication of ankylosing spondylitis (10% to 15% of affected patients), Reiter syndrome, and Behçet syndrome.

MALIGNANCY

Cancer originating within the eye or ocular adnexa is rare. More often, the eye is affected secondarily by cancer or by the various forms of cancer therapy. Ocular and orbital metastases are found in up to 5% of cancer patients at autopsy, most often from the breast or the lung. Usually, the tumors infiltrate the choroid, but the optic nerve as well as the extraocular muscles also may be affected. Systemic lymphoma affects the eye in about 3% of patients by

infiltrating the conjunctiva or the orbit and causing proptosis or limitation of extraocular movement. Primary ocular or CNS large cell lymphoma can present in the elderly patient as a chronic, often steroid-dependent uveitis. In children, leukemic infiltration of ocular tissues can occur. More than 75% of leukemia patients seen at autopsy have ocular adnexal metastases. Commonly, patients with leukemia develop superficial retinal, preretinal, or subconjunctival hemorrhages as a result of thrombocytopenia or the effects of transfusion on normal clotting. Cancer may have remote effects on the eye, including autonomic dysfunction of the pupils as well as a rare but devastating retinal degeneration that has a presumed autoimmune pathogenesis.

Radiation of tumors in the vicinity of the eye may lead to the development of cataract. The lens is susceptible to doses of radiation in the range of 2000 rads. Radiation damage causes a delayed retinal vasculopathy and optic neuropathy. A variety of cancer chemotherapeutic agents have secondary ocular effects. Superficial keratitis may be caused by cytosine arabinoside, optic neuropathy may occur with vincristine injections, and retinal artery occlusion may be caused by carotid artery injection of BCNU (carmustine). Mucosal damage from graft-vs-host disease may involve the conjunctiva, leading to dryness and corneal decompensation with subsequent infection.

ACQUIRED IMMUNODEFICIENCY SYNDROME

Acquired immunodeficiency syndrome (AIDS) is a severe disorder in which depression of the immune system results in the development of multiple opportunistic infections and malignancies. Ophthalmic examination may confirm the diagnosis. Common ophthalmic manifestations are cotton-wool spots (AIDS retinopathy), cytomegalovirus retinitis, and Kaposi's sarcoma affecting the eyelids. The less common complications include herpes zoster (shingles), herpes simplex keratitis, conjunctival microangiopathy, luetic and toxoplasmic uveitis and retinitis, and visual field defects or oculomotor dysfunction resulting from central nervous system involvement.

Retinal cotton-wool spots (Figure 8.11) are due to the focal occlusions of retinal capillaries that result in accumulation of axoplasm in the region of the retinal nerve fiber layer. In AIDS, the occlusions are thought to be due to microthrombi from antigen-antibody complexes and fibrin. These are frequently the sole ocular finding in patients with AIDS (more than 50%). Cotton-wool spots and hemorrhages with white centers are found in patients with a variety of other infectious conditions, including subacute bacterial endocarditis and systemic candidiasis.

Cytomegalovirus (CMV) retinitis (Figure 8.12) is the leading cause of visual loss in patients with AIDS. The distinctive ophthalmoscopic appearance of CMV retinitis is characterized by hemorrhagic necrosis of the retina. Areas of

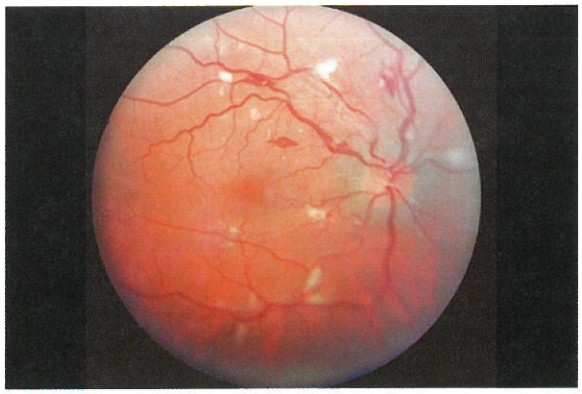

FIGURE 8.11 Cotton-wool spots in AIDS. Scattered cotton-wool spots, as well as some hemorrhages, are depicted in this retina of a patient with AIDS.

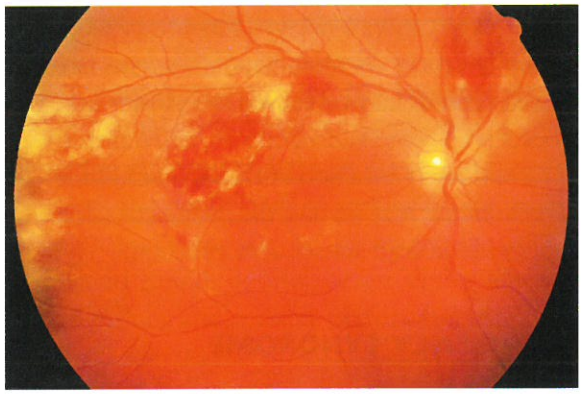

FIGURE 8.12 Cytomegalovirus retinitis in AIDS. The multicentric retinitis is characterized by discrete, fluffy, white retinal necrosis, with retinal hemorrhages and vasculitis. There is a sharp, distinct border between the diseased retina and the normal retina.

involved retina have distinct borders and abruptly abut areas of normal retina. The disease progresses over weeks to months and results in total atrophy of the affected retina. With the advent of highly active antiretroviral therapy, the incidence of opportunistic infections has decreased. Patients who can sustain a CD4 count of greater than 50 cells/mm^3 are less likely to develop CMV retinitis, although higher CD4 counts are not fully protective. Most patients who develop CMV retinitis have a poor prognosis for survival. Intravenous ganciclovir or foscarnet are effective treatments. Oral valganciclovir has improved bioavailability and may be used as induction or maintenance therapy.

Kaposi's sarcoma, characterized by multiple vascular skin malignancies, may involve the conjunctiva of either the lid or the globe. Unless suspected, this sarcoma may be misdiagnosed as a subconjunctival hemorrhage or a hemangioma.

In the past, therapeutic intervention was aimed at halting progression of the opportunistic infection. However, protease inhibitors have allowed some patients resolution of their opportunistic infection.

Any patient with a diagnosis of HIV should be referred to an ophthalmologist for a complete ophthalmologic examination. Detailed discussion of

therapeutic intervention is beyond the scope of this book. However, when such intervention is indicated, many variables must be considered, and it is important that good communication be established among the patient's other treating physicians and that therapy be determined based on a team approach.

SYPHILIS

Intraocular inflammation due to syphilis can be cured. Delay in diagnosis of syphilitic chorioretinitis can lead to permanent visual loss that might have been avoided with early treatment.

Acute interstitial keratitis with keratouveitis occurs in patients with congenital syphilis between the ages of 5 and 25 years. It is bilateral in congenital disease and unilateral if acquired. It is believed to be an allergic response to *Treponema pallidum* in the cornea. Symptoms and signs include intense pain and photophobia, and a diffusely opaque cornea with vision reduced, even to light perception. Blood vessels invade the cornea, and when they meet in the center of the cornea after several months, the inflammation subsides and the cornea partially clears. Late stages show deep ghost (nonperfused) stromal vessels and opacities. Any patient with syphilitic uveitis should have a spinal fluid examination.

Ocular involvement in secondary syphilis may feature pain, redness, or photophobia, or blurred vision and floating spots. The patient may present with iritis or choroiditis. There may be exudates around the disc and along the retinal arterioles in secondary syphilis. Arteritis and periarteritis may occur.

In latent syphilis, the presenting ocular complaint is usually blurred vision. The presence of chorioretinitis usually indicates cerebrospinal fluid involvement or neurosyphilis. Diffuse neuroretinitis with papillitis and periarterial sheathing may also occur. Systemic penicillin is curative. Patients with ocular disease should receive the neurosyphilis regimen of dosing even if the CSF is normal.

OTHER SYSTEMIC INFECTIONS

Other systemic infections may affect the eye. The most common are candidiasis and herpes zoster. The typical *Candida* lesion is a fluffy, white-yellow, superficial retinal infiltrate that may lead to the rapid development of overlying vitreous haze and eventual vitritis. Rarely, inflammation of the anterior chamber occurs. The presence of ocular candidiasis is a specific indication for systemic therapy with amphotericin B; intravitreal amphotericin may also be necessary.

Herpes zoster ophthalmicus (Figure 8.13), from varicella zoster involving the ophthalmic division of the fifth cranial nerve, may result in ocular manifestations, especially when vesicles appear on the tip of the nose from exten-

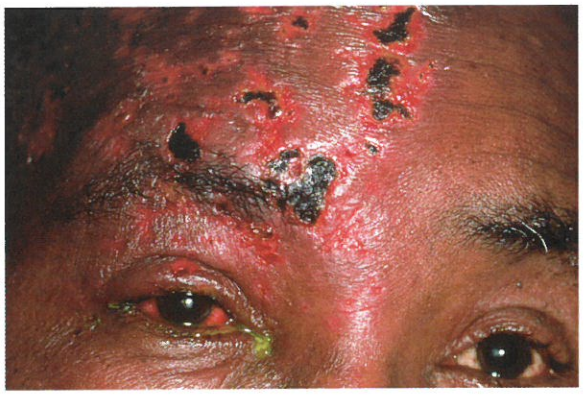

FIGURE 8.13 Herpes zoster ophthalmicus. Crusting lesions (no longer vesicles) are present in the distribution of the ophthalmic division of the fifth cranial nerve. The conjunctiva is red and the lids are swollen, indicating ocular involvement by herpes zoster. (Fluorescein has been instilled.)

sion along the nasociliary branch (Hutchinson's sign). Corneal infiltration with the virus may lead to disruption of the epithelium, best seen as fluorescein dye staining of the cornea. However, the epithelium usually heals spontaneously and rapidly.

The most important ocular side effect of herpes zoster is anterior uveitis, which can be confirmed by slit-lamp examination. The combination of anterior uveitis and keratitis, especially with loss of normal corneal sensation, is a serious vision-threatening effect. Affected patients should be referred to an ophthalmologist immediately for assistance in diagnosis and treatment. Patients can also present with anterior uveitis from herpes zoster without associated skin lesions.

Rare ocular complications of herpes zoster include optic neuritis and oculomotor nerve involvement with subsequent diplopia. Both the prevalence and the severity of postherpetic neuralgia increase with age. Evidence suggests that postherpetic neuralgia has a central rather than peripheral nervous system etiology. Early, aggressive treatment of acute pain during the vesicular eruption may decrease central hyperexcitability and the subsequent likelihood of chronic neuralgia in the elderly patient.

POINTS TO REMEMBER

- To recognize many ocular manifestations of systemic disease, the primary care physician must perform a thorough fundus examination, preferably through dilated pupils.
- Optimal blood sugar and blood pressure control may slow the development and progression of diabetic retinopathy.
- Early diagnosis of diabetic retinopathy is crucial to the ultimate success of treatment, which is effective for both nonproliferative and proliferative stages of the disease when patients are referred in a timely fashion.
- Any patient with an autoimmune disease or systemic infection who presents with a red eye, decreased vision, photophobia, or floaters should be