Articles

Ocular Examination and Diagnosis in Patients With the Acquired Immunodeficiency Syndrome

RAY F. GARIANO, MD, PhD; LELAND S. RICKMAN, MD; *and* WILLIAM R. FREEMAN, MD, *La Jolla, California*

Ocular involvement is seen frequently and is an important source of morbidity in patients with the acquired immunodeficiency syndrome. We outline here the general skills of physical diagnosis valuable to primary care physicians or infectious diseases specialists in recognizing and evaluating ocular complaints in patients infected with the human immunodeficiency virus. We provide an overview of common ocular diseases in these patients, with an emphasis on signs and symptoms that aid in the differential diagnosis.

(Gariano RF, Rickman LS, Freeman WR: Ocular examination and diagnosis in patients with the acquired immunodeficiency syndrome. West J Med 1993 Mar; 158:254-262)

Ocular involvement occurs in as many as 70% of patients with the acquired immunodeficiency syndrome (AIDS) and may herald numerous systemic infections.[1] Indeed, ocular symptoms are on occasion the presenting manifestations of human immunodeficiency virus (HIV) infection. We describe ocular examination findings and the differential diagnosis of patients infected with HIV, with an emphasis on physical diagnosis and treatment options. It is hoped that this review of ocular examination techniques and the overview of diagnostic possibilities will facilitate the diagnosis, referral, and treatment of patients with AIDS.

History and Physical Examination

If the chief complaint of a patient with AIDS relates to vision, the physician should ascertain whether one or both eyes are involved and should inquire whether vision loss is acute or chronic, if it occurred suddenly or gradually, and whether it is worsening or resolving. The nature of the visual change—blurring, diplopia, field defects, photopsia, or new floaters—is all important. Generally, a loss of acuity occurs if the ocular media—cornea, lens, anterior and vitreous chambers—are hazy or there is disease of the macula and optic nerve; floaters are typical of posterior uveitis, photophobia is a common sign of iritis, and visual field defects may denote peripheral retinal or central nervous system disease.

Visual acuity is the single most important piece of information required in evaluating patients. Because visual changes such as floaters, photopsia, and field defects may not be associated with changes in acuity, and because of the emotional effects of visual symptoms, the patient's subjective description of vision loss is never adequate, and only exceptionally does it correlate with objective findings. For medicolegal reasons as well, before intervention, the primary care physician must assess and quantify visual acuity for all patients with visual symptoms. If formal acuity measurement by the Snellen chart is unavailable or beyond the patient's capability, less quantitative assessments such as "counts fingers" or "no light perception" are valuable.

The testing of peripheral vision by confrontation may detect sizable field cuts such as seen in hemianopias or extensive retinal detachments, but it is unlikely to detect scotomas or smaller deficits. In these cases, formal visual field testing can be done if needed for diagnosis or for monitoring therapy.

The pupillary examination is informative in that reactivity to light depends on the number of retinal elements recruited by the stimulus. Therefore, changes in pupillary reactions indicate functional compromise of a substantial percentage of the retina or optic nerve. The most important maneuver in the pupillary examination is the detection of an afferent pupillary defect, also known as the Marcus Gunn pupil. An afferent pupillary defect generally occurs in disease of the optic nerve or with widespread retinal damage.

Generally, ocular motility problems cause symptoms of double vision and, in patients with AIDS, may reflect central nervous system disease involving the brain stem, usually a basilar meningitis, or orbital tumors that restrict the action of the extraocular muscles. Subtle displacements of the globe are indicated by asymmetry of the corneal light reflections.

Lymphatics for the external ocular structures including the lids, conjunctivae, and cornea drain into the ipsilateral preauricular and submandibular nodes. Preauricular adenopathy is an important sign of chlamydial, herpetic, adenoviral, or gonococcal keratoconjunctivitis, but may be misleading in patients with AIDS if there is diffuse lymphadenopathy. There are no lymphatic structures within the eye itself, so that intraocular infections do not produce adenopathy.

The slit lamp allows the various layers of the eye to be seen in cross-section. This instrument is generally easily accessible only to ophthalmologists. A corneal examination may reveal infectious infiltrates or inflammatory cell precipitates on the endothelium. The anterior chamber can be scrutinized for the presence of cells and protein, specifically inflammatory cells such as polymorphonuclear leukocytes, macrophages, and lymphocytes as well as fibrin and immunoglobulins, an indication of intraocular inflammation. Sim-

From the Department of Ophthalmology, Shiley Eye Center (Drs Gariano and Freeman), and the Department of Internal Medicine (Dr Rickman), University of California, San Diego, School of Medicine, La Jolla.

This work is supported in part by grant No. E707366 from the National Institutes of Health, a grant from the University of California AIDS Task Force (Dr Freeman), and the California Collaborative Treatment Group (Dr Rickman). Mr Tom Clark provided technical and photographic assistance.

Reprint requests to William R. Freeman, MD, Shiley Eye Center (0946), UCSD School of Medicine, La Jolla, CA 92093.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
HIV = human immunodeficiency virus

ilarly, the slit-lamp beam can be focused in the anterior vitreous cavity where the presence of leukocytes may indicate infection in the posterior segment, whereas pigmented cells may reflect retinal tears, detachments, or hemorrhages.

The hand-held direct ophthalmoscope provides a limited view of the posterior fundus. In most patients, only the optic nerve and macula can be seen. Ophthalmologists generally use an indirect ophthalmoscope to examine the retina and optic nerve. This technique provides stereopsis, wide-angle viewing (Figure 1), the ability to visualize peripheral retina, and the option of using a powerful light source to see the fundus when the ocular media are unclear. Because of these advantages, a clinically suspicious diagnosis or symptom should never be dismissed solely on the basis of a negative examination with the hand-held direct ophthalmoscope, particularly if the examination is done on an undilated eye. Pupillary dilation greatly eases visualization of the retina and enables a much larger retinal area to be inspected (Figure 1) when doing either direct or indirect ophthalmoscopy.

Ocular Manifestations of the Acquired Immunodeficiency Syndrome

Ocular manifestations of AIDS can be grouped into four main categories[2]: benign AIDS retinopathy or microangiopathy, opportunistic and other retinal-choroidal infections, neuro-ophthalmic lesions, and neoplasia.

Retinopathy Related to Human Immunodeficiency Virus

Retinopathy related to HIV, or microangiopathy, is found in 30% to 60% of infected patients[1-4] and may precede the occurrence of major AIDS-related infections. On funduscopic examination, small fluffy yellow-white lesions called cotton-wool spots are most often found in the posterior pole (Figure 2). These are located in the most anterior layers of the retina (the nerve fiber layer) and represent microinfarcts, caused by precapillary arteriolar occlusion, of nerve bundles coursing toward the optic nerve head. Small "dot and blot" intraretinal hemorrhages are also frequently found. Retinopathy related to HIV presumably occurs because of a microangiopathy and in appearance is similar to findings in diabetes mellitus, hypertension, and some vasculitic and rheologic disorders.

Evidence for a microangiopathy can be detected in the anterior segment of the retina of nearly all patients with AIDS. On slit-lamp examination, conjunctival vessels generally show an irregular caliber, fragmentation, microaneurysms, and sludging of blood flow similar to that seen in some patients with sickle cell disease. Although the cause of microangiopathy in AIDS is unclear, it seems to be related to the degree of immune suppression because it is seen relatively less frequently in HIV-infected persons who have not yet had major infections and is inversely related to the ratio of $CD4^+$ (helper) to $CD8^+$ (suppressor) T lymphocytes.[3] Patients with cotton-wool spots have greater weight loss, lower leukocyte counts, and a higher risk of impending infection than those without these retinal findings.[4]

Retinal microangiopathy is nonprogressive and nearly always asymptomatic[5]; its diagnostic significance lies mainly in that cotton-wool spots in the presence of dot-blot hemorrhage may mimic viral retinitis. As a rule, the spots are asymptomatic, smaller than a disc diameter, clustered in the posterior pole, and disappear over several weeks, whereas foci of cytomegalovirus or other serious retinal infections cause visual symptoms, can be much larger, may be found in any region of the retina, and do not spontaneously resolve (discussed later). Because cotton-wool spots appear at some time in the retina of most patients with AIDS, it is important that internists, infectious diseases specialists, and primary care providers become familiar with the appearance of these benign lesions.

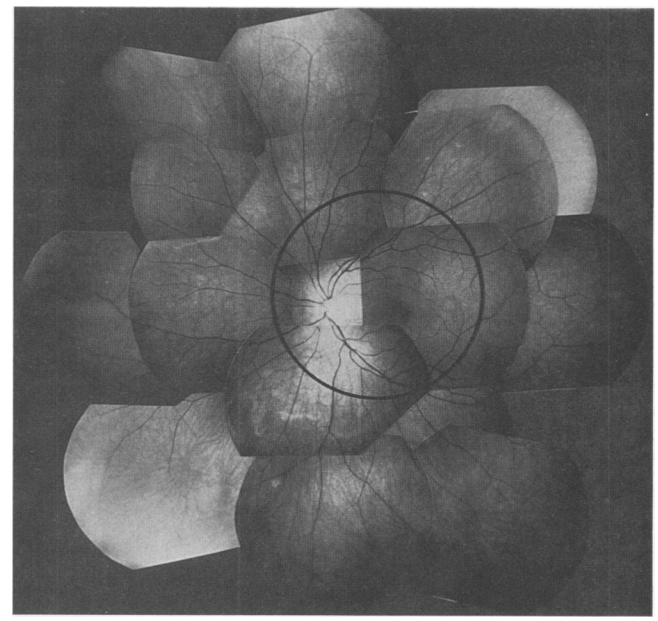

Figure 1.—The photomontage shows the retinal surface extending from the macula posteriorly to the ora serrata anteriorly. The direct ophthalmoscope gives a monocular view slightly larger than the diameter of the optic disc (1.5 mm). Indirect ophthalmoscopy with a 20-diopter lens illuminates a much larger area of retina **(circled region).** When combined with the technique of scleral depression, the indirect ophthalmoscope allows stereoscopic visualization of the entire retina.

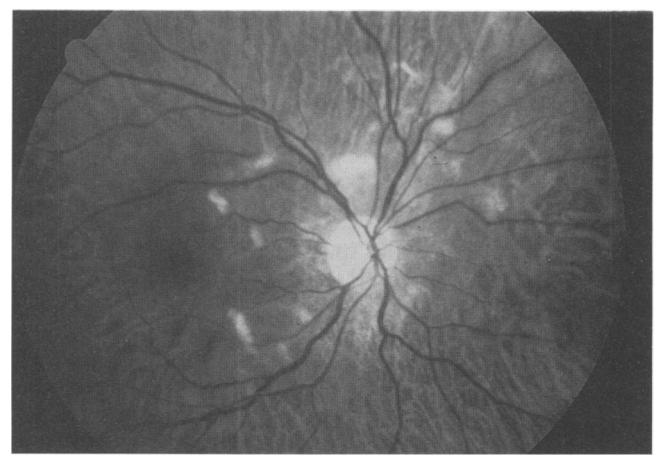

Figure 2.—The fundus of a 36-year-old man with the acquired immunodeficiency syndrome reveals scattered cotton-wool spots typical of human immunodeficiency virus (HIV) retinopathy or microangiopathy. The lesions obscure retinal vessels because of their superficial location. Small blot hemorrhages are frequently seen in HIV retinopathy as well.

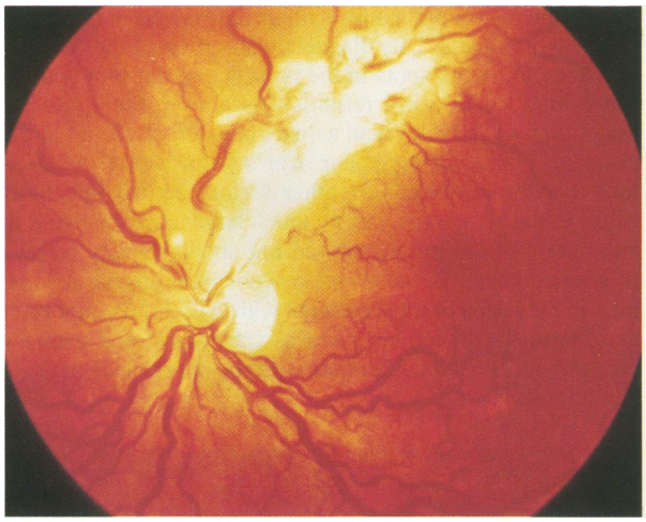

Figure 3.—A cytomegaloviral retinitis lesion involves the superior optic nerve border and threatens the fovea. Lesions located at or near the fovea or optic nerve require evaluation within days, as complete loss of vision may ensue within 1 to 2 weeks.

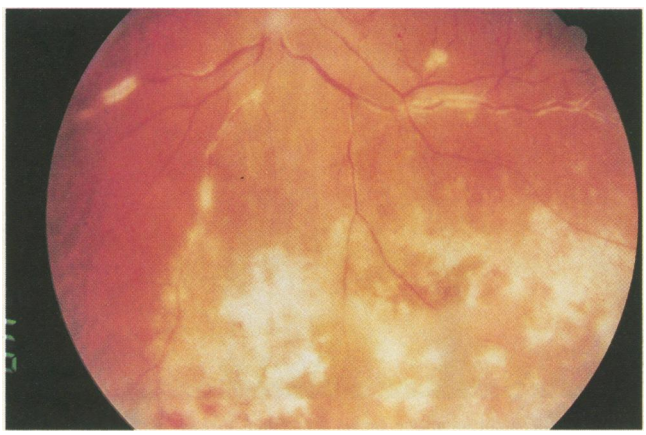

Figure 4.—Early in the course of cytomegaloviral retinitis, the retinal lesion appears white and granular and is often associated with hemorrhage. Note the vascular sheathing above this inferior peripheral lesion. Left untreated, this lesion would likely progress over several weeks to involve the macula.

Cytomegalovirus

Cytomegalovirus (CMV) is a common pathogen that usually causes asymptomatic infection in noncompromised hosts. More than 90% of patients with AIDS have evidence of recent or reactivated CMV systemic infection, and about a third of these experience severe manifestations, usually from pneumonitis, esophagitis, gastritis, hepatitis, colitis, encephalitis, and retinitis.[6]

Cytomegalovirus retinitis occurs in 15% to 40% of patients with AIDS[1,2,7,8] and, in contrast to the noninfectious ocular lesions of AIDS, demands aggressive intervention to prevent severe loss of vision.[9,10] Human CMV invades retinal cells and causes necrosis of all retinal layers. The inflammatory response to this virus in the retina is minimal, and ocular pain, redness, discharge, or intense photophobia suggest a different diagnosis; CMV retinitis is essentially painless. In nearly 95% of cases, the blood cultures are positive for the virus.[11] Because CMV viremia is present in more than 50% of AIDS patients,[12] however, the diagnosis is based entirely on the characteristic appearance of the retinal lesions. Early lesions appear as granular white patches of retinal edema,

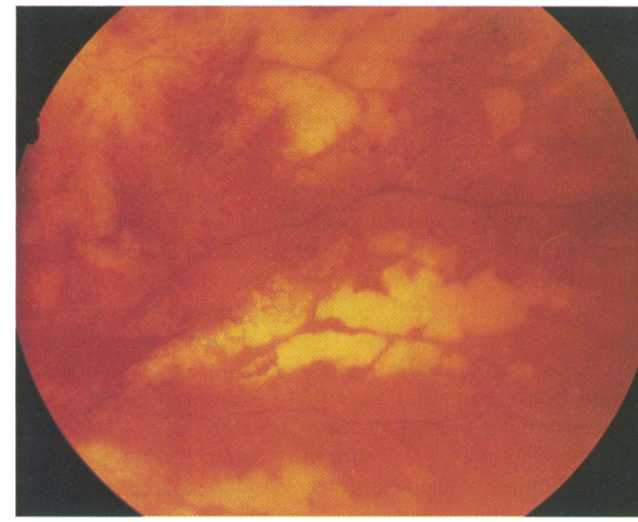

Figure 5.—The fundus photograph is taken of a patient with acute retinal necrosis. All retinal changes occurred over a 3-week period. Note the paravascular sparing and involvement of deep retinal layers—that is, beneath the retinal vessels. The peripheral retina shows small areas of whitening. These features may help to distinguish this disorder from cytomegaloviral retinitis.

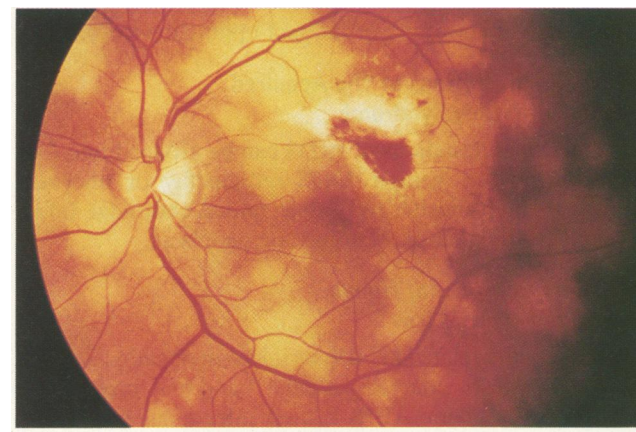

Figure 6.—The fundus photograph is taken of a patient with two ocular opportunistic infections. The superficial white hemorrhagic lesion near the fovea is active cytomegaloviral retinitis. Pale orange fluffy lesions located in the deeper choroidal layers (behind retinal vessels) contain *Pneumocystis carinii* organisms. These latter lesions do not affect vision.

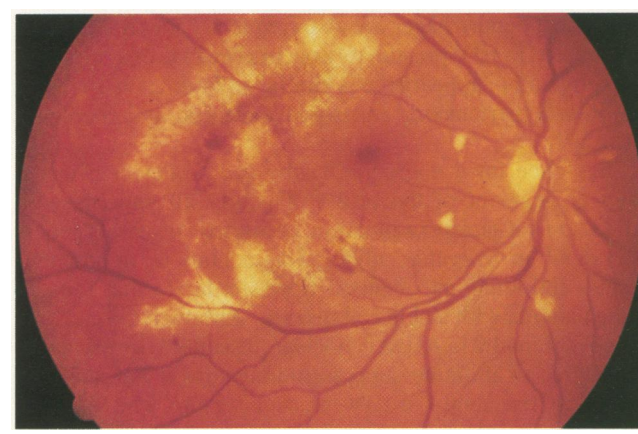

Figure 7.—The fundus photograph of a patient with the acquired immunodeficiency syndrome shows both cytomegaloviral retinitis and benign human immunodeficiency virus retinopathy. The infectious focus, located temporal to the fovea, is distinguished from the hemorrhage and circumpapillary cotton-wool spots caused by a microangiopathy, as described in the text.

often accompanied by hemorrhage (this has been likened to "cottage cheese and catsup" [Figures 3 and 4]). Often a vasculitis is present, and atrophic retina may be seen in areas affected earlier on in the course. Late in the disease, the optic nerve becomes pale owing to the extensive loss of retinal cells and axonal degeneration.

Infection may begin in the posterior pole or in the midperiphery and spreads as an advancing border, leaving an atrophic retina behind. The symptoms depend on the site of infection. If the active lesion is near the fovea or optic nerve, the patient has blurred vision. If only peripheral retina is involved, the patient may be asymptomatic or notice visual field defects or, commonly, floaters. An important feature of the disease is its relatively slow progression; measurable changes in the appearance of the lesion and symptomatic deterioration usually occur over at least one to two or more weeks. Infrequently, however, retinal detachment occurs, and extensive vision loss may ensue quickly. About two thirds of patients present with unilateral involvement, but the natural course of the disease without treatment is a progression to blindness in both eyes of all patients.

Posterior lesions, shown in Figure 3, encroach on the fovea and optic nerve and are likely within a period of several weeks to be associated with a pericentral scotoma and visual blurring. In contrast, a lesion located in the midperiphery (Figure 4) may produce less bothersome floaters or be entirely asymptomatic. A peripheral lesion may spread centrally, however; in this case, serial fundal photographs are used to document the advancing border of retinitis, leaving in its wake atrophic nonfunctional retina.

The differential diagnosis of CMV retinitis includes several fungal, parasitic, and other infections, including candidal, toxoplasmal, syphilitic, *Mycobacterium avium-intracellulare,* and *Histoplasma capsulatum* chorioretinitis. These disorders occur much less frequently than CMV retinitis, and not all are clinically important or even clinically apparent.[1,2,7,13-19] Conditions such as toxoplasmal and candidal retinitis are relatively rare in these patients despite the frequent occurrence of systemic or mucosal infection with these organisms.[1,19,20] They can be further distinguished from CMV retinitis by the typical accompanying dense vitritis that makes the ophthalmoscopic view hazy.[1,20] Disseminated tuberculosis may appear as a multifocal choroiditis but most often presents as an iritis, with photophobia the major symptom.[1,2] These other diagnoses are often greatly facilitated by specific laboratory tests.

Acute retinal necrosis is a more fulminant retinitis caused by herpes simplex virus or varicella zoster virus, is much less common in AIDS patients, and usually is more rapid in onset and progression.[1,13,16] Acute retinal necrosis may appear similar to CMV retinitis, with well-demarcated, confluent, deep retinal lesions associated with minimal hemorrhage; subtle features such as the presence of substantial intraocular inflammation (uveitis), retinal paravascular sparing, and peripheral retinal whitening favor this diagnosis (Figure 5).[13,16,21] The distinction is an important one, because acute retinal necrosis may be treated with acyclovir, thereby avoiding possible serious complications of anti-CMV therapy (discussed later). Cases of unilateral acute retinal necrosis progress to contralateral involvement in about 50% of patients, and retinal atrophy with subsequent detachment occurs commonly.

Choroidal *Pneumocystis carinii* infection has become more common with the increased use of prophylactic aerosolized pentamidine, although the actual incidence is unknown. These lesions characteristically appear as pale cream or orange space-occupying lesions beneath the retinal vessels (in the choroid, the vascular coat beneath the retina), are unilateral or bilateral, and rarely are symptomatic or reduce vision.[17,18] Other causes of opportunistic choroiditis in patients with AIDS are *Cryptococcus neoformans, Mycobacterium kansasii, Histoplasma capsulatum,* and *Candida* species.[19] Figure 6 shows a patient with both CMV and *P carinii* ocular disease; the lesions are easily differentiated

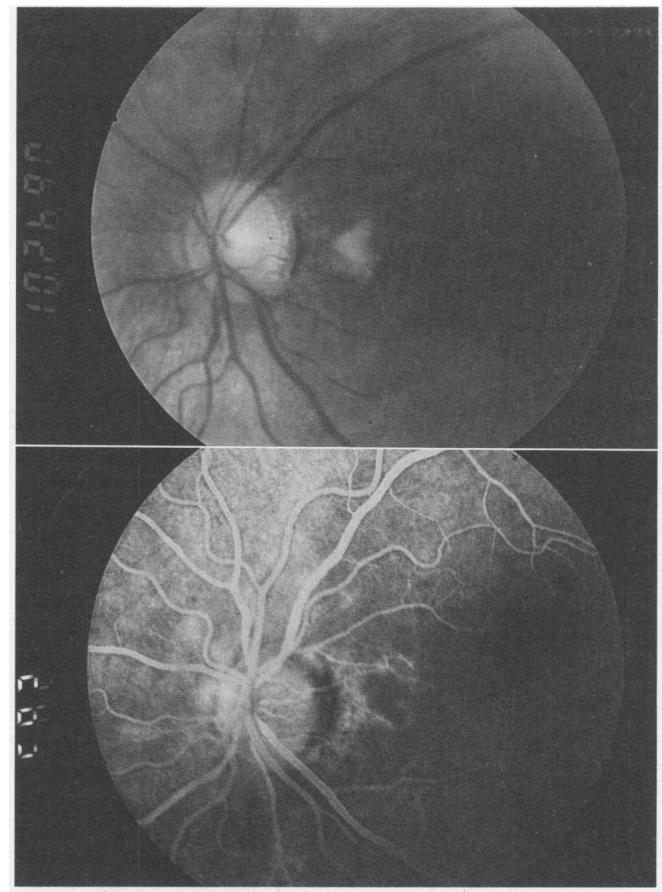

Figure 8.—Top, The patient has a small fluffy white lesion located between the fovea and optic disc. It may be difficult clinically to distinguish a cotton-wool spot from a cytomegaloviral focus of this size. **Bottom,** A fluorescein angiogram of the same lesion shows blockage of underlying choroidal fluorescence, typical of cotton-wool spots, without significant leakage of dye from the site, suggesting it is not an infectious or inflammatory lesion.

by appearance and location (superficial retinal CMV lesion versus deeper choroidal *P carinii* infection). Several reports indicate regression of the choroidal lesions following the intravenous administration of pentamidine or of trimethoprim and sulfamethoxazole (Septra),[22] yet indications for the specific treatment of asymptomatic *P carinii* choroidopathy remain uncertain. Though the diagnosis of disseminated *P carinii* infection may be suggested by the characteristic appearance of choroidopathy, and isolated ocular disease may rarely be the earliest clinical manifestation of disseminated *P carinii,* it is unclear from the literature whether early treatment with systemic therapy would alter the course of disease.[23,24]

The edema and hemorrhage of CMV retinitis may at times be difficult to differentiate from the cotton-wool spots

and small hemorrhages of HIV-related microangiopathy, especially since both conditions are relatively common. Cotton-wool spots are usually not found outside the posterior pole, rarely are larger than the optic disc, disappear spontaneously within two months, and are asymptomatic. Some of these distinguishing features can be readily appreciated in the patient shown in Figure 7, who manifests both HIV retinopathy and CMV retinitis. In cases where the two lesions are not so easily distinguished, the lesion(s) should be observed for progression over the course of several weeks. If it abuts the fovea or optic disc, such delay is inadvisable, and fluorescein angiography can be used to differentiate an active CMV lesion (leaks fluorescein) from a cotton-wool spot (no leakage). The patient shown in Figure 8 displays a lesion near the fovea that could be an early focus of retinitis. Because the lesion is in close proximity to the fovea and might threaten central visual acuity if it were infectious, a fluorescein angiogram was obtained. In this case, the angiogram showed no leakage of dye, indicating that this is probably not an infectious or inflammatory focus but probably a cotton-wool spot due to benign microangiopathy.

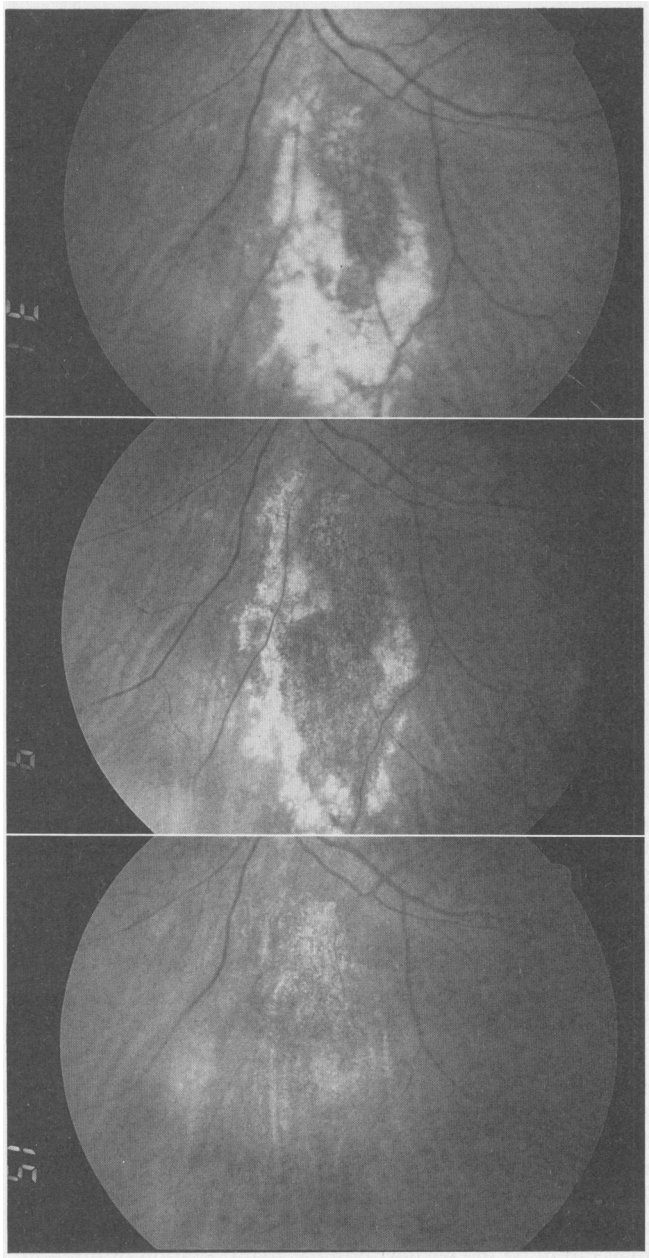

Figure 9.—A positive response of a cytomegaloviral retinal lesion to treatment with intravenous ganciclovir is demonstrated by serial fundal photography. **Top,** The pretreatment appearance of the lesion is shown. **Middle,** Two weeks after treatment was instituted, the lesion borders are less edematous and hemorrhagic and have not advanced. **Bottom,** After 6 weeks, the lesion is essentially healed; the previously involved retina is atrophic and nonfunctional.

Ganciclovir is active against all herpesviruses and is an approved agent for the treatment of CMV retinitis. The drug is taken up by host cells and phosphorylated by host-cell kinases. The phosphorylated compound then competitively inhibits only viral DNA polymerase, so that DNA synthesis in noninfected cells is spared. Ganciclovir halts progression or induces remission in 80% to 100% of patients, although recurrence and progression after several months are common, and reinduction or dose adjustments based on renal function may be required.[1,2,25]

The current use of ganciclovir usually includes a loading dose of 5 mg per kg given intravenously every 12 hours for 14 to 21 days (induction phase), followed by indefinite maintenance therapy at 5 mg per kg given once a day every day.[25-27] At many institutions, patients are instructed to administer the infusion at home through a permanent intravenous catheter typically placed at the beginning of treatment.

A clinical response is evidenced by a decreased whitening of the active lesion, usually within two to three weeks, and by failure of the border to advance. Areas of retina that have already been destroyed, and the associated vision loss, do not return with treatment. A series of photographs (Figure 9) taken over the first six weeks of ganciclovir administration shows a typical treatment response, with failure of the active border of the lesion to advance, followed by decreasing edema and hemorrhage.

The side effects of ganciclovir therapy include granulocytopenia, neurologic dysfunction, abnormal liver function test values, and, rarely, thrombocytopenia. The most serious toxic effect is neutropenia, which may occur in as many as a third of patients when defined as less than 500 neutrophils $\times 10^6$ per liter (<500 per μl).[28] Granulocytopenia is generally reversible and may dictate dose reductions or discontinuation. It is exacerbated by the concurrent use of zidovudine, which has additive bone marrow-suppressive effects.[29] The concurrent administration of granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor may protect against myelosuppression, and they are currently being evaluated in clinical trials.[30] Unfortunately, CMV retinitis is almost always reactivated within several weeks if ganciclovir therapy is discontinued; ongoing communication between the ophthalmologist and internist regarding therapeutic and unwanted effects of therapy is therefore critical.

In patients successfully treated with ganciclovir, one or more holes or tears can develop in areas of healed atrophic retina. These predispose to rhegmatogenous retinal detachments and further loss of vision. (Rhegmatogenous retinal detachments occur when fluid in the vitreous cavity enters the subretinal space through a retinal hole or tear, thereby lifting the retina from the underlying pigment epithelium.) We and others have reported incidences of retinal detachment of 15% to 30% in association with ganciclovir treatment of CMV retinitis[31,32]; detachment in CMV retinitis not treated with ganciclovir appears to be extremely rare.[33]

The repair of the detachment requires surgical therapy

(pars plana vitrectomy) with endolaser to reattach the retina, close all retinal breaks, and remove inflammatory membranes and scar tissue that place traction on the retina and the administration of a silicone oil to internally tamponade the detached retina against the eye wall.[31,32,34,35] Simpler detachment procedures, such as scleral buckling and pneumatic retinopexy, are associated with a high incidence of recurrence. Although anatomic reattachment of the retina is achieved in most instances and useful vision is often restored, postoperative visual acuity often deteriorates from progressive retinitis and recurrent or new detachments.

Foscarnet is an agent recently released for the treatment of CMV retinitis that inhibits DNA and RNA polymerases and reverse transcriptase; it thus possesses both anti-CMV and anti-HIV activity. Most patients with CMV infections will respond clinically to this drug as well.[36,37] Foscarnet also is given intravenously and, like ganciclovir, requires indefinite administration because the retinitis recurs if the drug is withdrawn. Side effects include nephrotoxicity, anemia, electrolyte disturbances, and neurotoxicity, including seizures.[36,37] Zidovudine can usually be given concurrently with foscarnet.

A recent multicenter clinical study compared ganciclovir with foscarnet in the treatment of CMV retinitis in patients with AIDS.[37] There was no difference between the treatment groups in the rate of progression of retinitis; however, the median survival was longer in the foscarnet group than in the ganciclovir group—12.6 versus 8.5 months—possibly because of foscarnet's antiretroviral activity.[38] Foscarnet is therefore gaining wider acceptance as first-line therapy for CMV retinitis in patients with normal renal function.

When discussing treatment options for CMV retinitis, the patient should be informed of the natural history of progression of the disease if left untreated, the irreversibility of vision loss from retinal necrosis, and the relatively high initial success rate of medical therapy. These factors must be weighed against the necessity for lifelong intravenous administration of medications, the placement of indwelling venous catheters, the possible incompatibility of treatment with the concurrent use of zidovudine, the risk for retinal detachment, and the myelosuppressive and other side effects that may limit therapy. Some of these concerns might be obviated by the use of intravitreal administration of ganciclovir. Multiple intraocular injections of ganciclovir have been successful in controlling CMV retinitis, but repeated injections given over several weeks are impracticable, potentially hazardous, and may cause retinal toxic effects.[25,39] Slow-release preparations for local ganciclovir delivery to the eye are under investigation, including a liposome-encapsulated drug and a surgically implanted intraocular delivery system.[40,41] Oral ganciclovir is currently being evaluated in clinical trials and may be a promising approach to the treatment of CMV infections.

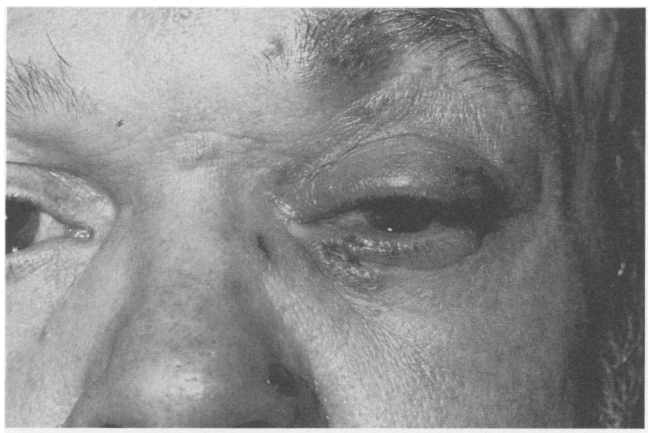

Figure 10.—Herpes zoster ophthalmicus is shown in an immunocompromised patient. Involvement of intraocular structures by the virus is especially likely when there are vesicles in the distribution of the nasociliary nerve along the anterior lateral aspect of the nose (Hutchinson's sign), as shown.

Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus is ordinarily a disease of older or debilitated patients but is seen also in younger patients with immunodeficiency. We routinely inquire regarding risk factors for HIV infection in all young patients with herpes zoster ophthalmicus and recommend HIV-antibody testing in high-risk persons.[42,43] The external disease is diagnosed, as elsewhere on the body, by an erythematous, often vesicular, eruption within a dermatomal distribution. Frequently intense pain will precede the skin changes. If the ophthalmic branch of the trigeminal nerve is affected, the patient should be referred to an ophthalmologist to rule out ocular involvement. The risk of ocular disease is especially

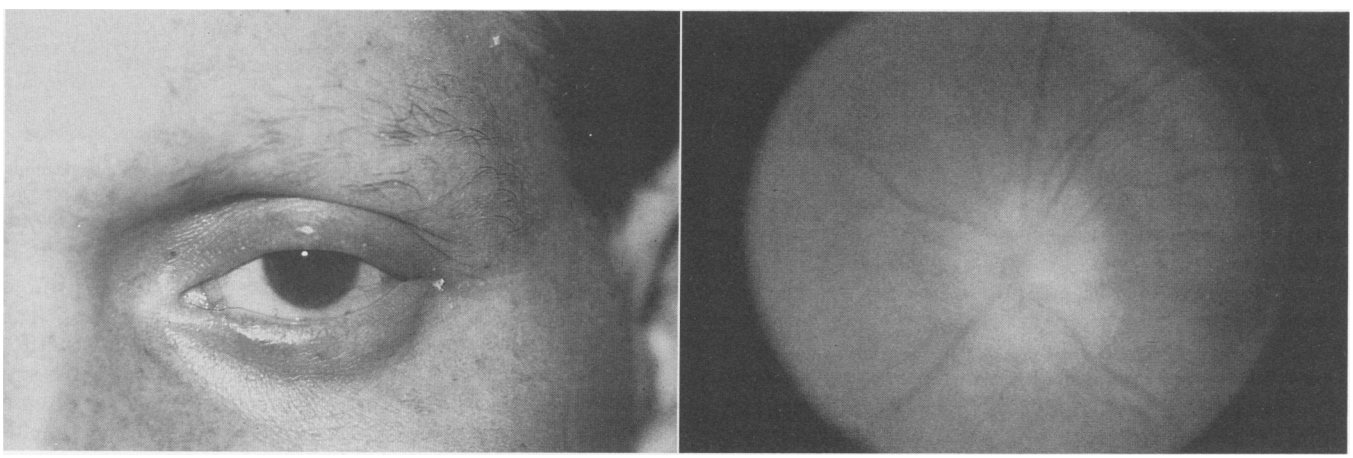

Figure 11.—Left, This 30-year-old man presented with lid erythema, loss of lashes, conjunctivitis, and a facial and palmar rash. On slit-lamp examination he had inflammatory precipitates on the posterior corneal surface and fibrinous pigmented connections between the iris and lens at the pupillary border. **Right,** Ophthalmoscopy showed vitritis, retinitis, and optic neuritis. Blood and cerebrospinal fluid specimens were positive for VDRL antigen. The patient was subsequently tested and found to be positive for the human immunodeficiency virus.

high if the nasociliary nerve is affected, indicated by lesions on the anterior lateral aspect of the nose (Figure 10). Herpes zoster ophthalmicus can affect all levels of the visual system, giving rise to dermatitis, conjunctivitis, keratitis, iritis or uveitis, vitritis, retinitis, optic neuritis, and encephalitis. Evidence of ocular zoster requires high-dose treatment with acyclovir, 10 mg per kg given intravenously three times a day for at least ten days. This disease may pursue a relatively more severe course in persons infected with HIV, and admission to hospital with intravenous therapy is recommended.[44]

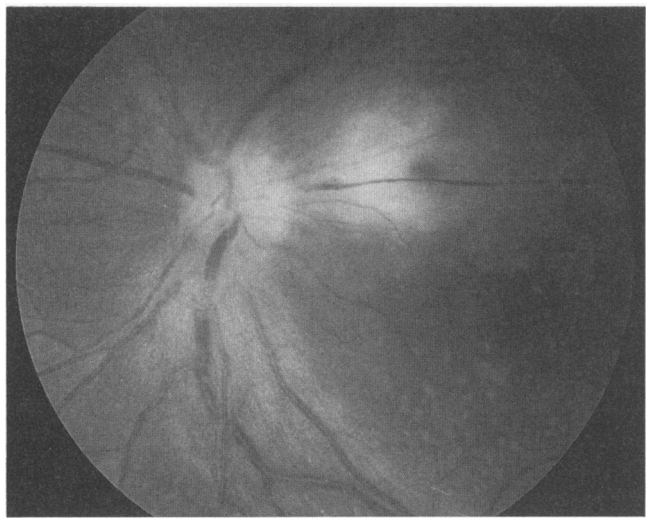

Figure 12.—A toxoplasmal retinitis lesion is shown along the superotemporal vascular arcade. The small grey choroidal scar just above the fovea suggests that the current episode involves reactivation of latent disease. There is serous retinal detachment present from extensive underlying vascular leakage. The view is hazy because of mild vitreous inflammation; severe vitritis obscures retinal detail, and the lesion appears as a "headlight in the fog." In patients with the acquired immunodeficiency syndrome, there may not be evidence of previous infection, and more extensive involvement may occur.

Syphilis

Often in the medical history of patients with AIDS, syphilis exhibits particularly severe reactivations of latent infection in immunocompromised patients.[45,46] Of note, because of the underlying disorder, serologic tests are occasionally falsely negative in these patients; biologic false-positive reactions for syphilis have rarely been reported in HIV-infected persons.[47] In the eye, syphilis may cause conjunctivitis, iritis, vitritis, retinitis, papillitis, and optic neuritis—in short, at any or all levels of the visual axis.[48,49] In some cases, the appearance of luetic retinitis as a focal expanding white lesion may simulate CMV retinitis, toxoplasmosis, or acute retinal necrosis.

In nonimmunocompromised hosts, ocular disease is usually associated with secondary syphilis, whereas in patients with AIDS, most patients with ocular symptoms harbor neurosyphilis as well[50]; thus, the presence of ocular manifestations demands a neurologic workup including lumbar puncture and therapy for neurosyphilis. The patient shown in Figure 11 had been treated by several physicians for persistent conjunctivitis; they failed to appreciate the loss of lashes typical of ocular syphilis and the palmar rash that suggests secondary syphilis. The slit-lamp examination reveals anterior chamber inflammation, and ophthalmoscopy shows an edematous retina and an inflamed optic nerve head; note also the haziness in the vitreous cavity, indicating considerable inflammation. This patient had syphilitic meningitis and was found during the hospital course to be HIV-positive.

Bacterial Infections

Bacterial conjunctivitis, keratitis, and retinitis have all been reported in patients with AIDS. Although the incidence of these infections may not be increased by concurrent infection with HIV—such infections have been generally described in case reports only—they may require more aggressive treatment. In HIV-infected patients who are also injectable drug users, severe bacterial and fungal intraocular infections may be metastatic, and systemic sources must be sought with appropriate cultures. Uncommon corneal pathogens, such as *Capnocytophaga* and *Microsporum* species have been reported to produce keratoconjunctivitis in immunocompromised patients.[51-53]

Cryptococcal Meningitis

Cryptococcal meningitis is the most common nonviral neurologic infection in patients with AIDS.[2] The visual system is commonly involved (in about 40% of patients with meningitis) by intracranial disease of the optic nerves or tracts, the third, fifth, sixth, or seventh cranial nerves, by extension of the disease process along the arachnoid sheath of the optic nerve and into the orbit,[1,2,54] and by metastatic involvement of the choroid.[10] The diagnosis of cryptococcal meningitis is suggested by the findings of visual field loss, cranial nerve palsies, or optic nerve swelling.

Toxoplasmosis

Toxoplasmosis in the eye usually occurs owing to reactivation of a latent congenital infection; in AIDS patients, however, it is generally newly acquired or newly disseminated from nonocular sites of disease.[20] It can occur alone or,

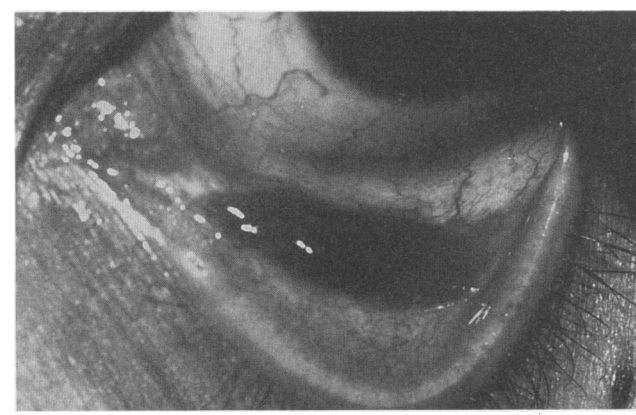

Figure 13.—Kaposi's sarcoma is a highly vascular tumor that has a predilection for the conjunctivae. The tumor typically presents as a nonclearing subconjunctival hemorrhage or as a fleshy red mass in the conjunctival fornix, as shown.

much less frequently, in association with the much more common central nervous system toxoplasmal lesions. The ocular picture, which consists of a dense vitritis and multifocal lesions of focal retinitis, has been described as a "headlight in the fog" appearance (Figure 12). The ocular disease typically resolves with the standard treatment of pyrimethamine and sulfadiazine or clindamycin.[55] Maintenance therapy is generally given because ocular toxoplasmosis in patients with AIDS frequently recurs when medical therapy is terminated.[20,55] Parenteral and topical steroids are some-

times added to reduce ocular inflammation after antibiotic administration is begun, although this should be done with caution in HIV-infected persons.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is a diffuse papovaviral leukoencephalitis that may occur in patients with AIDS. Several visual deficits have been associated with this disorder, including diffuse vision loss, homonymous hemianopia, nystagmus, ocular motility defects, and optic neuropathies.[56,57] Thus, although progressive multifocal leukoencephalopathy lacks pathognomonic ocular features, it must be considered a possible cause of vision changes in any patient with dementia and corticospinal signs.

Kaposi's Sarcoma

Kaposi's sarcoma may involve the eye in about 20% of patients who manifest this highly vascular tumor.[2,58,59] It may be found along the lids or the conjunctivae and is especially common in the fornices and the palpebral conjunctiva (Figure 13). The initial symptoms may relate to the appearance of a subconjunctival hemorrhage, diplopia, blurring due to induced astigmatism, and, rarely, pain. The lesion need not be treated unless there are substantial symptoms or cosmetic concerns, in which case excision or radiation therapy with or without chemotherapy is often palliative.

Lymphoma

Lymphoma may rarely occur in the orbit of patients with AIDS and is suggested by proptosis, diplopia, pain, or periorbital swelling.[2,58-60] Intraocular lymphoma is occasionally associated with central nervous system lymphoma and may antedate or follow the brain lesion by several months.[61] Either diagnosis must be considered in patients presenting with neuro-ophthalmic signs with or without focal neurologic deficits.[61,62] Retinal and choroidal infiltrates and vitreous seeding in intraocular lymphoma may masquerade as an inflammatory condition or an infection such as syphilitic or candidal retinochoroiditis.[62] Primary intraocular lymphoma is rarely associated with AIDS.[60]

Ophthalmologic Referral

Indications for ophthalmologic referral depend in part on the experience of the primary care physician. In general, any loss of vision demands examination by an ophthalmologist whether or not the primary physician discovers objective findings; if vision loss is acute, severe, or progressive, consultation should be on an urgent basis. Ocular examination may establish diagnoses in patients with systemic disease of an unclear origin—for example, with tuberculous uveitis or disseminated *P carinii*. Patients with visual symptoms or pupillary changes and a central nervous system infection, such as toxoplasmosis or neurosyphilis, should be referred for fundus examination. Finally, any suspicious lesions noted with a hand-held ophthalmoscope, if not readily identified, should be discussed with an ophthalmologist. Infection with HIV per se is not an indication for referral, and a patient infected with HIV without ocular complaints does not require baseline or periodic ophthalmologic examinations. Children infected with HIV are susceptible to the same ocular diseases as adults, and the considerations outlined in this article apply also to them.

Patients with known CMV disease (colitis or pneumonitis) are at increased risk for CMV retinitis,[11,63] as are patients with $CD4^+$ counts below 50×10^6 per liter (50 cells per μl).[64] Increased vigilance on the part of primary care physicians for visual signs and symptoms is thus critical in these patients; however, periodic dilated eye examinations beyond an initial screening ophthalmologic visit are probably not warranted in asymptomatic persons.

Conclusion

The acquired immunodeficiency syndrome can manifest, and on occasion present, with a wide variety of ocular diseases. The primary caretaker of patients infected with HIV, by employing basic skills in ophthalmologic examination and an increasing knowledge of ocular signs, symptoms, and disorders, can better evaluate and counsel these patients when they have visual complaints.

REFERENCES

1. Freeman WR, Helm M: Retinal and ophthalmologic manifestations of AIDS, *In* Ryan SP (Ed): Retina. St Louis, Mo, C.V. Mosby, 1989, pp 597-616
2. Jabs DA, Green R, Fox R, Polk BF, Bartlett JG: Ocular manifestations of acquired immune deficiency syndrome. Ophthalmology 1989; 96:1092-1099
3. Freeman WR, Chen A, Henderly DE, et al: Prevalence and significance of acquired immunodeficiency syndrome-related retinal microvasculopathy. Am J Ophthalmol 1989; 107:229-235
4. Brezin A, Girard B, Rosenheim M, Marcel P, Gentilini M, Le Hoang P: Cotton-wool spots and AIDS related complex. Int Ophthalmol 1990; 14:37-41
5. Quiceno JI, Capparelli E, Sadun AA, et al: Visual dysfunction without retinitis in patients with acquired immunodeficiency syndrome. Am J Ophthalmol 1992; 113:8-13
6. Jacobson MA, Mills J: Serious cytomegalovirus disease in the acquired immunodeficiency syndrome (AIDS). Ann Intern Med 1988; 108:585-594
7. Holland GN, Pepose JS, Pettit TH, Gottlieb MS, Yee RD, Foos RY: Acquired immune deficiency syndrome: Ocular manifestations. Ophthalmology 1983; 90:859-873
8. Palestine AG, Rodrigues MM, Macher AM, et al: Ophthalmic involvement in acquired immune deficiency syndrome. Ophthalmology 1984; 91:1092-1099
9. Collaborative DHPG Treatment Study Group: Treatment of serious cytomegalovirus infections with 9-(1,3-dihydroxy-2-propoxymethyl) guanine in patients with AIDS and other immunodeficiencies. N Engl J Med 1986; 314:801-805
10. Rosecan LR, Stahl-Bayliss CM, Kalman CM, Laskin OL: Antiviral therapy for cytomegalovirus retinitis in AIDS with dihydroxy propoxymethyl guanine. Am J Ophthalmol 1986; 101:405-418
11. Salmon D, Lacassin F, Harzic M, et al: Predictive value of cytomegalovirus viraemia for the occurrence of CMV organ involvement in AIDS. J Med Virol 1990; 32:160-163
12. Quinnan GV, Masur H, Rook AH, et al: Herpes infections in the acquired immune deficiency syndrome. JAMA 1984; 252:72-77
13. Chess J, Marcus DM: Zoster-related bilateral acute retinal necrosis syndrome as presenting sign in AIDS. Ann Ophthalmol 1988; 20:431-435
14. Freeman WR, Lerner CW, Mines JA, et al: A prospective study of the ophthalmologic findings in the acquired immune deficiency syndrome. Am J Opthalmol 1984; 97:133-142
15. Newman NM, Mandel MR, Gullet J, Fujikawa L: Clinical and histologic findings in opportunistic ocular infections: Part of new syndrome of acquired immunodeficiency. Arch Ophthalmol 1983; 101:396-401
16. Duker JS, Blumenkranz MS: Diagnosis and management of the acute retinal necrosis (ARN) syndrome. Surv Ophthalmol 1991; 35:327-343
17. Freeman WR, Gross JG, Labelle J, Oteken K, Katz B, Wiley CA: *Pneumocystis carinii* choroidopathy—A new clinical entity. Arch Ophthalmol 1989; 107:863-867
18. Rao NA, Zimmerman PL, Boyer D, et al: A clinical, histopathologic, and electron microscopic study of *Pneumocystis carinii* choroiditis. Am J Ophthalmol 1989; 107:218-228
19. Dugel PU, Forster DJ, Rao NA: Opportunistic choroiditis in AIDS. Ophthalmology [Suppl] 1991; 98:112
20. Holland GN, Engstrom RE, Glasgow BJ, et al: Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome. Am J Ophthalmol 1988; 106:653-667
21. Forster DJ, Dugel PU, Frangieh GT, Liggett PE, Rao NA: Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome. Am J Ophthalmol 1990; 110:341-348
22. Sha BE, Benson CA, Deutsch TA, Urbanski PA, Phair JP, Kessler HA: Suppression of cytomegalovirus retinitis in persons with AIDS with high-dose intravenous acyclovir. J Infect Dis 1991; 164:777-780
23. Northfelt DW, Clement MJ, Safrin S: Extrapulmonary pneumocystosis: Clinical features in human immunodeficiency virus infection. Medicine (Baltimore) 1990; 69:392-398
24. Raviglione MC: Extrapulmonary pneumocystosis—The first 50 cases. Rev Infect Dis 1990; 12:1127-1138
25. Henderly DE, Freeman WR, Causey DM, Rao NA: Cytomegalovirus retinitis and response to therapy with ganciclovir. Ophthalmology 1987; 94:425-434
26. Laskin OL, Stahl-Bayliss CM, Kalman CM, Rosecan LR: Use of ganciclovir to

treat serious cytomegalovirus infections in patients with AIDS. J Infect Dis 1987; 155:323-327

27. Jacobsen MA, O'Donnell JJ, Brodie HR, Wofsy C, Mills J: Randomized prospective trial of ganciclovir maintenance therapy for cytomegalovirus retinitis. J Med Virol 1988; 25:339-349

28. Jabs DA, Enger C, Bartlett JG: Cytomegalovirus retinitis and acquired immunodeficiency syndrome. Arch Ophthalmol 1989; 96:1092-1099

29. Hochster H, Dieterich D, Bozzette S, et al: Toxicity of combined ganciclovir and zidovudine for cytomegalovirus disease associated with AIDS—An AIDS Clinical Trials Group Study. Ann Intern Med 1990; 113:111-117

30. Grossberg HS, Bonnem EM, Buhles WC: GM-CSF with ganciclovir for the treatment of CMV retinitis in AIDS. N Engl J Med 1989; 320:1560-1564

31. Freeman WR, Henderly DE, Wan WL, et al: Prevalence, pathophysiology, and treatment of rhegmatogenous retinal detachment in treated cytomegalovirus retinitis. Am J Ophthalmol 1987; 103:527-536

32. Sidikaro Y, Silver L, Holland GN, Kreiger AE: Rhegmatogenous retinal detachments in patients with AIDS and necrotizing retinal infections. Ophthalmology 1991; 98:129-135

33. Broughton WL, Cupples HP, Parver LM: Bilateral retinal detachment following cytomegalovirus retinitis. Arch Ophthalmol 1978; 96:618-624

34. Freeman WR, Quicenco JI, Crapotta JA, Listhaus A, Munguia D, Aguilar MF: Surgical repair of rhegmatogenous retinal detachment in immunosuppressed patients with cytomegalovirus retinitis. Ophthalmology 1992; 99:466-474

35. Regillo CD, Vander JF, Duker JS, Fischer DH, Belmont JB, Kleiner R: Repair of retinitis-related retinal detachments with silicone oil in patients with acquired immunodeficiency syndrome. Am J Ophthalmol 1992; 113:21-27

36. Chrisp P, Clissold SP: Foscarnet—A review of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with cytomegalovirus retinitis. Drugs 1991; 41:104-129

37. Palestine AG, Polis MA, De Smet MD, et al: A randomized controlled trial of foscarnet in the treatment of cytomegalovirus retinitis in patients with AIDS. Ann Intern Med 1991; 115:665-673

38. Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group: Mortality in patients with the acquired immunodeficiency syndrome treated with either foscarnet or ganciclovir for cytomegalovirus retinitis. N Engl J Med 1992; 326:213-220

39. Heinemann MH: Long-term intravitreal ganciclovir therapy for cytomegalovirus retinopathy. Arch Ophthalmol 1989; 107:1767-1772

40. Anand R, Nightingale SD, Sanborn G, Torti RE, Smith TJ, Ashton P: Long-term ganciclovir therapy for cytomegalovirus retinitis using an intraocular sustained-release device. Ophthalmology [Suppl] 1991; 98:159-160

41. Sandorn GE, Anand R, Torti RE, Nightingale SD: Sustained-release ganciclovir therapy for treatment of cytomegalovirus retinitis—Use of an intravitreal device. Arch Ophthalmol 1992; 110:188-195

42. Sandor EV, Millman A, Croxson TS, Mildvan D: Herpes zoster ophthalmicus in patients at risk for the acquired immune deficiency syndrome (AIDS). Am J Ophthalmol 1986; 101:153-155

43. Friedman-Kien AE, Lafleur FL, Gendler E, et al: Herpes zoster—A possible early clinical sign for development of acquired immunodeficiency syndrome in high-risk individuals. J Am Acad Dermatol 1986; 14:1023-1028

44. Seiff SR, Margolis T, Graham SH, O'Donnell JJ: Use of intravenous acyclovir for treatment of herpes zoster ophthalmicus in patients at risk for AIDS. Ann Ophthalmol 1988; 20:480-482

45. Johns DR, Tierney M, Felsenstein D: Alterations in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus. N Engl J Med 1987; 316:1569-1572

46. Musher DM, Hamill RJ, Baughn RE: Effect of immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. Ann Intern Med 1990; 113:872-881

47. Rompalo AM, Cannon RO, Quinn TC, Hook EW: Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. J Infect Dis 1992; 165:1124-1126

48. McLeish WM, Pulido JS, Holland S, Culbertson WW, Winward K: The ocular manifestations of syphilis in the human immunodeficiency virus type 1-infected host. Ophthalmology 1990; 97:196-203

49. Passo MS, Rosenbaum JT: Ocular syphilis in patients with human immunodeficiency virus infection. Am J Ophthalmol 1988; 106:1-6

50. Levy JH, Liss RA, Maguire AM: Neurosyphilis and ocular syphilis in patients with concurrent human immunodeficiency virus infection. Retina 1989; 9:175-180

51. Shadduck JA, Meccoli RA, Davis R, Font RL: Isolation of a microsporidian from a human patient. J Infect Dis 1990; 162:773-776

52. Ticho BH, Urban RC Jr, Safran MJ, Saggau DD: Capnocytophaga keratitis associated with poor dentition and human immunodeficiency virus infection. Am J Ophthalmol 1990; 109:352-353

53. Cali A, Meisler DM, Rutherford I, et al: Corneal microsporidiosis in a patient with AIDS. Am J Trop Med Hyg 1991; 44:463-468

54. Lipson BK, Freeman WR, Beniz J, et al: Optic neuropathy associated with cryptococcal arachnoiditis in AIDS patients. Am J Opthalmol 1989; 107:523-527

55. Ruskin J, Remington JS: Toxoplasmosis in the compromised host. Ann Intern Med 1976; 84:193-197

56. Slavin ML, Mallin JE, Jacob HS: Isolated homonymous hemianopsia in the acquired immunodeficiency syndrome. Am J Ophthalmol 1989; 108:198-200

57. Keane JR: Neuro-ophthalmologic signs of AIDS: 50 patients. Neurology 1991; 41:841-845

58. Newsome DA: Noninfectious ocular complications of AIDS. Int Ophthalmol Clin 1989; 29:95-97

59. Shuler JK, Engstrom RE, Holland GN: External ocular disease and anterior segment disorders associated with AIDS. Int Ophthalmol Clin 1989; 29:98-104

60. Schanzer MC, Font RL, O'Malley RE: Primary ocular malignant lymphoma associated with the acquired immune deficiency syndrome. Ophthalmology 1991; 98:88-91

61. Hochberg FH, Miller DC: Primary central nervous system lymphoma. J Neurosurg 1988; 68:835-853

62. Freeman LN, Schachat AP, Knox D, et al: Clinical features, laboratory investigations, and survival in ocular reticulum cell sarcoma. Ophthalmology 1987; 94:1631-1639

63. Stewart K, Hayes K, Mijch AM, McLean H, Hoy JF: Is CMV Viremia Predictive of Subsequent CMV Retinitis? Abstracts, 6th International Conference on AIDS, San Francisco, California, 1990, No. 229

64. Kuppermann BD, Petty JG, Richman DD, Mathews WC, Fullerton SC, Freeman WR: Cross-sectional prevalence of CMV retinitis in AIDS patients: Correlation with CD4 counts. Invest Ophthalmol Vis Sci 1992; 33:750