

OPPORTUNISTIC INTRAOCULAR INFECTIONS IN AIDS*

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INTRODUCTION

THE ROLE OF THE OPHTHALMOLOGIST IN THE DIAGNOSIS AND TREATMENT of life-threatening, systemic opportunistic infections in patients with the acquired immunodeficiency syndrome (AIDS) has recently been emphasized.¹⁻³ The most common opportunistic infection of the eye in AIDS patients is cytomegalovirus (CMV).⁴⁻¹⁴ Autopsy studies have shown that all AIDS patients who have CMV retinopathy also have disseminated CMV infections in other organs.^{5,6} Moreover, patients with CMV retinopathy may have a greater degree of immunosuppression and thus a more limited survival.¹³ Recent studies have shown that anti-CMV treatment does prolong survival,¹²⁻¹⁴ although the mechanism for this prolonged survival is not yet known.¹³ Unfortunately, anti-CMV treatment has numerous side effects, including neutropenia and renal failure in these already immunosuppressed patients,^{8,15,16} so the decision to institute such therapy must be carefully considered.

The serologic diagnosis of CMV in patients with AIDS can be equivocal; because of the profound immunosuppression of these patients, serologic tests may be inaccurate.¹⁷ Although culture-confirmed presence of CMV in the throat, urine, and blood may be more reliable, immunosuppressed patients, including those with AIDS, are often chronic virus carriers.¹⁷ The presence of CMV by culture does not necessarily indicate significant infection. Therefore, the significance of isolating this virus from such patients requires careful interpretation. Owing to these con-

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foundings factors, the ophthalmic examination has assumed great importance, as the diagnosis of CMV infection involving the retina is easily and reliably made by routine ophthalmic examination.

We hypothesized that treatment for CMV retinitis may prolong survival by its effect on concurrent nonocular CMV infections. We tested this hypothesis by studying ocular CMV infections and systemic CMV infections in a large autopsy series of AIDS patients, after which we reviewed their medical records to determine which of these patients had or had not been treated for the CMV infections.

MATERIAL AND METHODS

A total of 412 eyes from 206 consecutive autopsies of AIDS patients (from 1983 to 1991) were included in this study; all ophthalmic pathology was performed at the A. Ray Irvine Ocular Pathology Laboratory at the Doheny Eye Institute, Los Angeles. The clinical charts and autopsy reports of all of these cases were subsequently reviewed. At autopsy, all major organs, including eye, brain and spinal cord, were studied by light microscopy using hematoxylin-eosin preparations; in selected cases, special stains were employed, including periodic acid-Schiff (PAS) reagent, Gomori methanamine silver (GMS), Ziehl-Neelsen acid-fast stain, Alcian blue, mucicarmine, Warthin-Starrey, and Brown-Hopps tissue gram stain.

A histopathologic diagnosis of CMV infection was made if typical large violaceous intranuclear inclusion bodies (Cowdry type A), enlarged cells containing basophilic cytoplasmic inclusions, were noted. In addition, in selected eyes with retinitis, the presence of CMV was confirmed by immunohistochemical methods utilizing anti-CMV antibody (Dakopatts, Carpinteria, CA), by in situ DNA hybridization, and by polymerase chain reaction using early and late primers of CMV.¹⁸

The disease activity of CMV retinitis was assessed by an ophthalmic pathologist (NAR) who was not aware of the patient's history, including whether or not anti-CMV treatment had been given. The retinitis was considered to be active when the retina showed the presence of intranuclear inclusion bodies that were surrounded by a clear halo, giant cells containing multiple intranuclear and intracytoplasmic inclusions (Fig 1). Several of these cases also showed perivascular mononuclear cell infiltration with or without hemorrhage. The retinitis was classified as inactive when the necrotic retina showed atrophy and the presence of eosinophilic staining cells but no distinct inclusion bodies. Some of these eyes were associated with perivascular fibrosis, gliosis, and/or calcification (Fig 2). Although both eyes were examined, any given patient was considered to

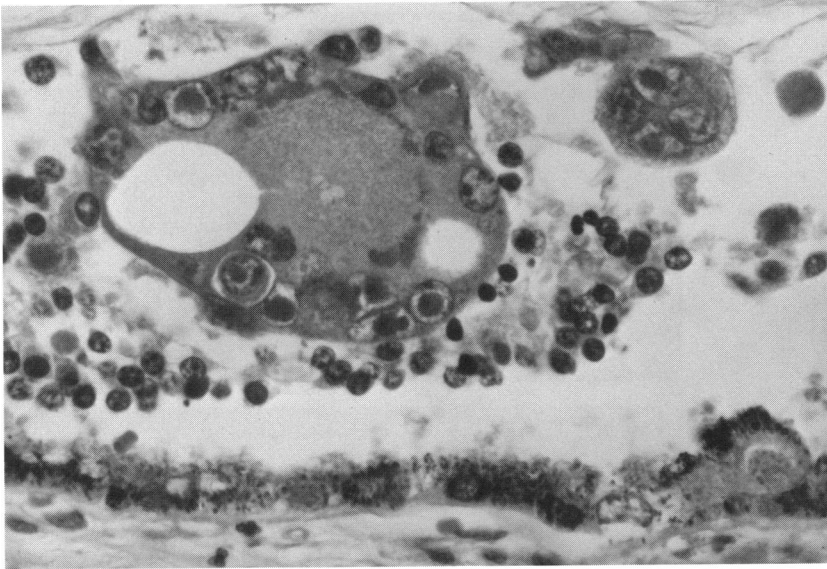


FIGURE 1

Active CMV retinitis. Note intranuclear inclusion bodies surrounded by clear halo and giant cells containing multiple intranuclear and intracytoplasmic inclusion bodies (hematoxylin-eosin, $\times 400$).

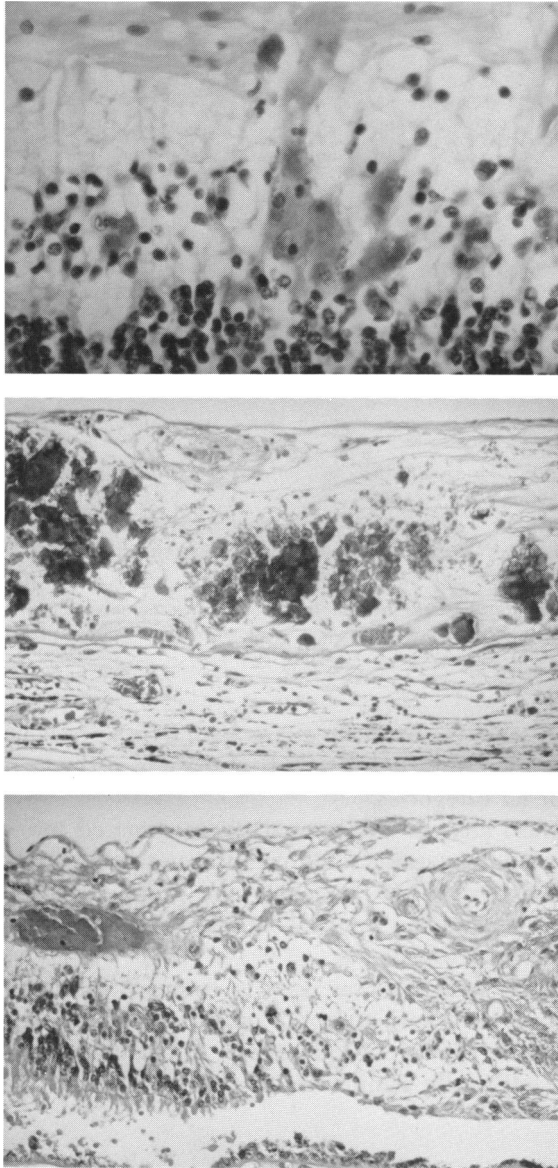
have active disease if either one eye or both eyes were found to have any active disease. For purposes of statistical analysis, patients, not eyes, were tabulated for all categories.

For statistical analysis the patients were grouped into categories by treatment as follows: treated CMV retinitis, untreated CMV retinitis, and untreated nonocular CMV. Patients were grouped by CMV organ involvement as follows: no nonocular organs, one nonocular organ, and multiple nonocular organs.

The Wilcoxon rank test was used to compare the number of organs infected between various groups. Comparison of proportions between groups was made by the chi-square test. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Of the 206 AIDS patients whose eyes we studied, 116 (56%) were found to have some organ infected with CMV, as determined by histopathologic examination. Of these 116 patients, 111 were male and 5 were female.

**FIGURE 2**

Inactive CMV retinitis. Retina shows indistinct intranuclear and intracytoplasmic inclusion bodies (a, $\times 300$), calcification (b), and perivascular fibrosis of retinal vessel (c) (hematoxylin-eosin, $\times 160$).

Ages ranged from 4 months to 62 years; excluding two infants who were less than 1 year old, the average age was 38 years. The most frequently involved organs, besides the eyes, were as follows: adrenals, 74 patients; lungs, 41 patients; colon, 17 patients; esophagus, 16 patients. Fifteen patients had CMV infection of the brain, three had involvement of the meninges, and one had involvement of the spinal cord.

Of the 116 patients with CMV infection of at least one organ, 52 eyes of 33 patients had CMV retinitis diagnosed by histopathologic examination. Of these 33 patients, 23 (70%) had received anti-CMV treatment and 10 (30%) had not. Two drugs were used in the treatment of these patients: ganciclovir sodium, (DHPG) and foscarnet sodium. Beta-interferon was used as adjunct therapy in two patients. Ganciclovir alone was used in 16 patients and foscarnet alone in 2 patients. Five patients received therapy with ganciclovir, followed by foscarnet. Five patients who had a clinical diagnosis of CMV retinitis died before ganciclovir became widely available in 1985. Four of the five patients who died between 1987 and 1991 did not receive treatment because the diagnosis of CMV retinitis was not made clinically. In one patient with the diagnosis of CMV retinitis, the patient's medical condition precluded treatment with the anti-CMV agents; this patient died 1 week after the diagnosis was made. Patients with treated CMV retinitis had significantly fewer nonocular organs infected than did patients with untreated CMV retinitis ($P = 0.005$). Moreover, patients with treated CMV retinitis had significantly fewer nonocular organs infected with CMV than did patients with untreated nonocular CMV infection ($P = 0.001$, Fig 3). Patients with untreated CMV retinitis were not statistically different from patients with untreated nonocular CMV infection ($P = 0.37$) when the number of organs infected with CMV were compared.

Of the 33 patients with CMV retinitis diagnosed by histopathologic examination, 7 of 9 (78%) untreated patients were found to have active disease, as compared with 5 of 23 (22%) treated patients. In one untreated patient the disease activity within the eye could not be determined. This difference in activity between untreated and treated patients was statistically significant ($P = 0.003$, Fig 4).

Of the 116 patients with CMV infection, 59 had involvement of one organ only. Thirteen of these patients had retinal infection only; 12 had received treatment for CMV infection, and 1 had not. Twenty-two cases showed CMV involvement of two organs; 11 of these had eye involvement along with presence of infection in the lung or adrenal or one other site. Of these 11 cases, 8 had received treatment and 3 had not. Three or more organs with CMV were seen in 35 cases, 9 of which had involvement of

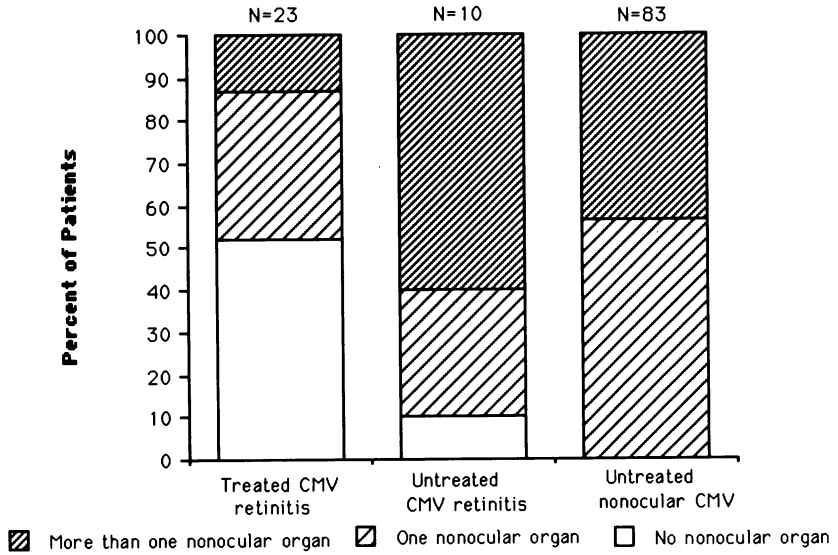


FIGURE 3

Comparison of nonocular involvement in 33 AIDS patients with ocular CMV infection. Patients with treated CMV retinitis had significantly fewer nonocular organs infected with CMV than did patients with untreated CMV retinitis ($P = 0.005$) and patients with untreated nonocular CMV infection ($P = 0.001$).

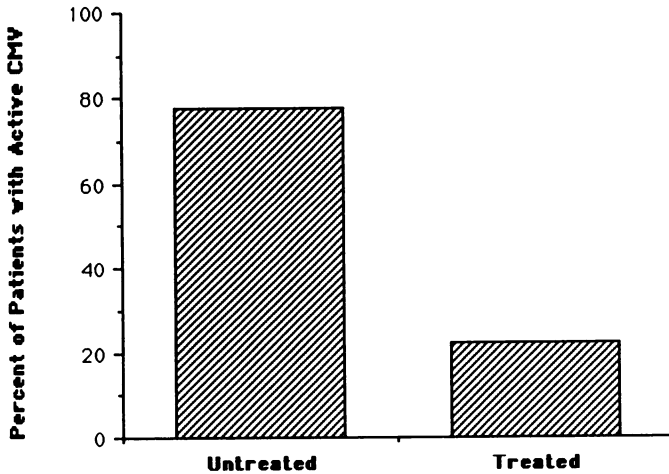


FIGURE 4

Comparison of active CMV retinitis in 33 AIDS patients. Rate of active disease was higher in untreated than in treated patients. This difference was significant ($P = 0.003$).

the retina. Of these nine cases, six had not received treatment for CMV retinitis; these data are summarized in Table I.

The relationship between CMV infection of the optic nerve and of the brain was studied. Of the 23 patients with CMV retinitis who had received treatment, 4 had optic nerve involvement. However, only one of these four had infection involving the cerebrum. Of the 10 untreated patients with CMV retinitis, 2 had optic nerve involvement; 1 of these patients did have CMV infection of the brain. In all cases the CMV infection in the nerve was limited to the preliminary portion.

Among the other intraocular opportunistic infections were four cases of *Pneumocystis carinii* choroiditis. All these cases showed multiple, bilateral choroidal lesions consisting of eosinophilic, amorphous foamy infiltrates, involving primarily the inner choroid and choroidal vessels. These infiltrates were PAS-positive. GMS stain revealed microorganisms with distinct cell walls. Several of these oval organisms had a folded appearance and some were crescentic; they showed focal thickening of the wall, contained silver-positive internal structures, and their size was similar to that of erythrocytes. Each of these four cases showed disseminated lesions of *P. carinii* involving thoracic lymph nodes, spleen, and other viscera. Three of these cases were included in a previous report.¹

Five other cases showed dissemination of *Cryptococcus neoformans*. In the choroid these fungal elements were distributed primarily within the choriocapillaris and inner choroidal vessels. In one of these cases organisms were seen also within the retinal capillaries. Morphologically these organisms showed an Alcian blue-positive thick capsule, and some revealed budding yeast forms with GMS preparation.

Two patients in this series had retinitis secondary to *Toxoplasma gondii*, and one had disseminated *Histoplasma capsulatum*. Two cases with disseminated *Mycobacterium avium-intracellulare* were also identified. The patient with *H. capsulatum* and those with *M. avium* each had organisms present in the choroid, predominately in the choroidal vessels. Both these organisms could be identified with the aid of GMS and acid-fast preparations, respectively.

TABLE I: CMV INFECTION OF OCULAR AND NONOCULAR ORGANS IN 116 AIDS PATIENTS

NO. OF ORGANS WITH CMV INVOLVEMENT	OCULAR CMV		NONOCULAR ORGANS
	TREATED	UNTREATED	
One	12	1	46
Two	8	3	11
Three or more	3	6	26

There were five cases that showed multiple, concurrent intraocular infections. One patient had multiple, bilateral choroidal infiltrates of *P carinii*, *M avium* in the choroidal tissue of both eyes, and cytomegalovirus retinitis in right eye. The second patient had toxoplasma retinitis and CMV retinitis. A third patient had optic neuritis secondary to *T gondii*, and the same eye showed CMV retinitis. A fourth case showed cryptococcal choroidal infiltration in the right eye and CMV in the left. The last patient in this group had cryptococcal infection involving the left choroid and CMV retinitis in the same eye. In each of these cases with choroidal infection, similar organisms were identified in the vasculature of viscera or of the central nervous system, including the subarachnoid space.

DISCUSSION

This study showed that ganciclovir or foscarnet therapy for CMV retinitis was associated with less frequent nonocular organ involvement with CMV in patients with AIDS. The nonocular organ involvement by CMV was reduced without use of additional treatment and/or diagnostic methods such as tissue biopsy, cytologic screening, serologic testing, or microbiologic culture from sampling of nonocular organ sites. Thus, the benefits of treatment for CMV retinitis appear to extend beyond control of ocular disease alone (Fig 3 and Table I).

The problem of selecting a treatment regimen for AIDS patients with CMV retinitis is a difficult albeit immediate one. For both ganciclovir and foscarnet, an initial 2-week, high-dose induction therapy must be given, usually requiring hospitalization. Thereafter, maintenance therapy via an indwelling central venous line is required for the duration of the patient's life, thereby exposing the patient to the risk of catheter-related infection, sepsis, or thrombosis. The cost of home health care must also be considered. Moreover, each of these drugs has severe toxic effects. The primary side effects of ganciclovir are bone marrow suppression, neutropenia, and thrombocytopenia.^{8,15,16} Furthermore, because zidovudine, an antiretroviral drug used often in the treatment of AIDS, also has toxic effects on bone marrow, it generally cannot be used at the full recommended dose (600 mg/d) concurrently with ganciclovir.¹⁹ Foscarnet has toxic effects on the kidneys, and can cause metabolic abnormalities of calcium and magnesium.¹⁹⁻²³ Despite these severe toxic effects, several studies have shown an increased survival in patients treated for CMV retinitis,^{6,8,13-15} although the mechanism of this prolonged survival remains unknown.

A randomized, multicenter clinical trial, Studies of Ocular Complications of AIDS (SOCA), demonstrated that median survival was 8.5 months

for patients receiving ganciclovir and 12.6 months for patients receiving foscarnet.¹⁴ Other studies have shown a survival of less than 2 months for patients with CMV retinitis who receive no treatment.^{24,25} Because of the severe systemic side effects of these drugs, recent studies have investigated the feasibility of intravitreal injections of ganciclovir and of intravitreal sustained release of this agent with polymer devices.²⁶⁻²⁸ Although in many cases these local therapies do at least temporarily control CMV retinitis, without systemic toxicity, they may not yield some of the benefits of the systemically administered drugs, primary of which may be prolonged survival because of a reduced number of nonocular organs infected, as noted in this study.

A host of systemic manifestations can result from CMV infection: pneumonitis, adrenalitis, retinitis, hepatitis, gastrointestinal hemorrhage, ulceration, or perforation, pancreatitis, and meningoencephalitis. These manifestations can occur individually or together in the course of AIDS. The clinical signs and symptoms of nonocular CMV are often subtle and can be confused with those produced by other opportunistic agents. Additional diagnostic problems are created by the presence of CMV viremia and by CMV within tissues without significant tissue alteration.²⁹ The significance of detection of CMV in material from the respiratory tract has been the subject of debate. Peripheral virus shedding or viremia may account for the detection of CMV in bronchoalveolar lavage fluid by cytologic screening or by microbiologic culture. However, detection may not correlate with clinical disease, such as pneumonia, since other opportunistic agents or neoplasms may also be present concomitantly.³⁰

From a clinical standpoint, diagnosis of nonocular CMV can be difficult. Histopathologic confirmation of CMV infection requires tissue biopsy or cytologic sampling procedures, most often obtained by endoscopy of the nonocular organs. This is limited to accessible organ sites, typically the respiratory tract and gastrointestinal tract. Techniques that utilize the polymerase chain reaction or *in situ* hybridization for greater sensitivity of CMV diagnosis in tissue specimens have been developed.³¹ In addition, microbiologic culture for diagnosis of CMV has been employed to obtain even greater sensitivity.³² However, diagnosis by these methods is complicated by sampling error from the focal nature of the lesions.³³ Moreover, culture cannot answer the question whether the detected CMV is truly the cause of clinically significant illness. This can be an important distinction when considering the use of anti-CMV drug therapies with ganciclovir or foscarnet, both of which have significant toxicities.

One of the best techniques that can be employed to assess both the presence of CMV and its relationship to clinical manifestations is retinal

examination by ophthalmoscopy. Retinitis may also be one of the earliest clinical manifestations of CMV infection.²⁴ Therefore, a decision to treat CMV retinitis is based upon clinically significant evidence for the disease. Moreover, the response of the antiviral treatment can be monitored successfully by the retinal examination.¹²

Adrenalitis due to CMV is common in AIDS patients. In the present study 64% of patients with CMV infection had adrenalitis from CMV. In another autopsy series, 21 of 41 patients had cortical as well as medullary lesions.³⁴ However, no conclusive clinical evidence of adrenal cortical insufficiency was demonstrated, even though hypotension and hyponatremia were common findings. Other CMV-associated endocrinopathy in AIDS patients include hypoparathyroidism.³⁵

Because CMV retinitis and CNS involvement by CMV are so common, we looked into the possibility of contiguous spread of CMV from the eye to the brain, via the optic nerve. If this proved to be the case, CMV optic neuropathy would have significant diagnostic and prognostic implications. However, we were unable to demonstrate this association. Although our sample size was too small to be conclusive, on the basis of this study, we do not believe that CMV retinitis spreads to the brain via the optic nerve. Moreover, in all patients with CMV optic neuropathy, the infection was confined to the prelaminar portion. This suggests that brain infection occurs by the same mechanism as do other systemic infections, namely by hematogenous dissemination.

SUMMARY

In conclusion, this clinicopathologic study has shown that CMV ocular infection is present in about 16% of terminal AIDS patients. The treatment of CMV retinitis reduces the number of CMV-infected nonocular organs and may also lessen the severity and control the spread of concurrent nonocular infection, both of which may prolong survival in AIDS patients. Other opportunistic infections, involving primarily the choroid, were also seen in a number of patients, some of whom had concurrent intraocular infections with CMV and *P carinii*, *M avium-intracellulare*, *C neoformans*. In addition, all of these choroidal infections were components of disseminated infection, underscoring the increasingly important role of the ophthalmologist in the diagnosis and treatment of disseminated opportunistic infections in AIDS.

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DISCUSSION

DR ALAN H. FRIEDMAN. Doctor Rao and co-workers have done a thoughtful study in assessing the survival of AIDS patients with CMV retinitis. They tested the hypothesis of whether treatment for the concurrent nonocular CMV infection played a role in survival. They studied 206 consecutive autopsies of AIDS patients over an 8-year period from 1983 to 1991. Their criteria for active infection versus inactivity of CMV in the retina is accepted by ophthalmic pathologists. Some important conclusions could be drawn from their observations.

Of the 206 AIDS patients autopsied, 56% had CMV infection in at least one organ. The eye is the third most commonly involved organ and was observed in 16% of the autopsies. Importantly, they found that patients who had been treated for CMV retinitis had fewer nonocular organs involved compared with patients who had nonocular CMV and were not treated with an antiviral agent. Although CMV affects a great many organs, including the eye and specifically the retina and

optic nerve, CMV involvement of the brain is rare. In comparison, toxoplasmosis involvement of the eye and brain is very common. There are other conclusions to be drawn regarding CMV retinitis and the AIDS patient. Ophthalmic screening is critically important in the care of HIV patients. All HIV-positive patients with CD4 counts of 100 or less should have a retinal examination every 2 months; those with CD4 counts of less than 50, with or without cotton-wool spots, should be seen more frequently. The Studies of Ocular Complications of AIDS study observed that median time to progression of CMV retinitis after initiation of either ganciclovir or foscarnet therapy was less than 60 days. These antiviral drugs whether used separately or together, with or without granulocyte cell stimulating factor to minimize neutropenia, merely slow down the rate of progression of CMV retinitis after an initial period of apparent remission is observed. The florid type of CMV retinitis is transformed by antiviral agents into a very low-grade infection that proceeds at a reduced rate. Thus far, for many AIDS patients, the inexorable progression of CMV retinitis leads to total blindness in the eye involved. It is also apparent, though, that in patients treated with antiviral agents for disease in one eye, CMV retinitis develops in the fellow eye at a very significantly reduced rate in the fellow eye.

Doctors Rao and co-workers are to be congratulated for bringing to our attention such timely and important information about this most devastating disease.

DR NARSING A. RAO. In closing, I would like to thank Doctor Friedman for his kind and generous review of our paper. I did appreciate his summarizing our results and emphasizing the importance of CMV infection in AIDS patients. We agree that all HIV patients with low CD₄ counts should frequently be evaluated for CMV retinitis.