Therapy for Ocular Toxoplasmosis

A. Rothova, M.D., C. Meenken, M.D., H. J. Buitenhuis, M.D.,
C. J. Brinkman, M.D., G. S. Baarsma, M.D., T. N. Boen-Tan, M.D.,
P. T. V. M. de Jong, M.D., N. Klaassen-Broekema, M.D., C. M. C. Schweitzer, M.D.,
Z. Timmerman, M.D., J. de Vries, M.D., M. J. W. Zaal, M.D.,
and A. Kijlstra, Ph.D.

We conducted a prospective multicenter study of the efficacy of current therapeutic strategies for ocular toxoplasmosis in 149 patients. Treatment consisted of the following three triple-drug combinations: group 1, pyrimethamine, sulfadiazine, and corticosteroids; group 2, clindamycin, sulfadiazine, and corticosteroids; and group 3, trimethoprim, sulfamethoxazole and corticosteroids. Patients with peripheral retinal lesions were not treated systemically. No difference in the duration of inflammatory activity was observed between treated and untreated patients ($P = .5$). The most important factor predicting the duration of inflammatory activity was the size of the retinal lesion itself, independent of the treatment ($P < .001$). We found a reduction in size of the retinal inflammatory lesion for 49% of the pyrimethamine-treated patients (17 of 35) compared to 20% of the untreated patients (eight of 41) ($P < .01$). However, the most frequent occurrence of side effects was also associated with pyrimethamine medication

(26%, nine of 35). The mean recurrence rate after three years of follow-up was 49% for all patients (60 of 122 patients), with no differences between treated and untreated patients ($P = .6$).

TOXOPLASMOSIS is a major and preventable cause of severe visual loss and blindness in young people. Congenital toxoplasmosis, as well as toxoplasmosis in immunocompromised patients, is a serious, sometimes fatal, disease.

Ocular toxoplasmosis is the leading cause of posterior uveitis. In most cases, it represents a late manifestation of a congenital infection.^{1,2} *Toxoplasma* organisms invade the retina of the fetus, where they may change into the cystic form. Toxoplasmic retinitis is thought to occur when the cyst ruptures and liberated parasites multiply in surrounding cells.

Because available antiparasitic agents are ineffective against the tissue cysts, the major aim of therapy is to stop multiplication of parasites during the active stage of the retinochoroiditis. Treatment includes a synergistic combination of pyrimethamine and sulfonamides.³ Concomitant with antiparasitic therapy, the administration of systemic corticosteroids is recommended to alleviate inflammatory reactions, especially when the lesions are located near or in the macula.³

Pyrimethamine, a folic acid antagonist, may cause bone marrow depression with subsequent hematologic complications. Folinic acid is used to counteract these side effects, because humans can use preformed folinic acid, whereas *T. gondii* cannot. This prophylaxis reduces the frequency of complications without interfering with the efficacy of antitoxoplasmic drugs.

The search for a less toxic method to treat toxoplasmosis is important. Clindamycin, a semisynthetic antibiotic, has a less marked an-

Accepted for publication Dec. 10, 1992.

From the Department of Ophthalmology, Academic Medical Centre (Drs. Rothova, Buitenhuis, and Brinkman) and the Department of Ophthalmology (Drs. Rothova, Meenken, and Kijlstra), Netherlands Ophthalmic Research Institute, Amsterdam, The Netherlands; the Department of Ophthalmology, Erasmus University, Rotterdam, The Netherlands (Drs. Baarsma, de Jong, and de Vries); the Department of Ophthalmology, Free University, Amsterdam, The Netherlands (Drs. Boen-Tan and Zaal); Royal Netherlands Eye Hospital, University of Utrecht, Utrecht, The Netherlands (Dr. Klaassen-Broekema); the Department of Ophthalmology, University of Leiden, Leiden, The Netherlands (Dr. Schweitzer); and the Department of Ophthalmology, University of Groningen, Groningen, The Netherlands (Dr. Timmerman).

Reprint requests to A. Rothova, M.D., Department of Ophthalmology, Netherlands Ophthalmic Research Institute, P.O. Box 12141, 1100 AC Amsterdam, The Netherlands.

titoxoplasmic effect in animals than pyrimethamine,^{4,5} but was found to be effective in the treatment of human ocular toxoplasmosis.⁶⁻¹¹ Scattered case reports have shown that co-trimoxazole (trimethoprim with sulfamethoxazole) is effective in humans.^{12,13}

Because ocular toxoplasmosis is a self-limiting disease and the diagnosis is mainly clinical, it is difficult to evaluate the efficacy of the specific therapeutic regimens as well as the various modalities used.¹⁴ We performed a prospective multicenter study to evaluate and compare the effectiveness of current therapeutic strategies in a large group of patients with ocular toxoplasmosis.

Patients and Methods

Our study included 149 consecutive patients in whom active toxoplasmic chorioretinitis was diagnosed clinically and who visited the ophthalmologic departments of six university hospitals in The Netherlands. All patients had clinical ocular toxoplasmosis at initial examination, that is, unilateral focal necrotizing retinitis, sometimes associated with typical old, pigmented scars. Toxoplasmic serologic studies were not routinely performed because most of the Dutch population have antitoxoplasmic antibodies, so that positive assays for adults have no diagnostic value.¹⁵ For six patients, the clinical diagnosis was doubtful at the time of initial examination. In these patients, the active formation of antitoxoplasmic antibodies in the eye was confirmed by the Goldmann-Witmer coefficient.¹⁶ No patients with acquired immunodeficiency syndrome (AIDS) were included. Because the tests for anti-human immunodeficiency virus (HIV) antibodies were not routinely performed, the number of HIV-infected patients without AIDS was not known. Two patients developed toxoplasmic retinitis during the treatment with immunosuppressive drugs (one patient treated for malignancy and one treated after renal transplantation); a Goldmann-Witmer coefficient was positive in both cases.

The mean age of the patients was 27 years (81 males and 68 females). The study included 46 patients (31%) who had their first ocular manifestation; 103 patients not only had active retinitis, but also had old retinal scars (sometimes in the contralateral eye). Twenty-three patients had been treated previously (15 patients re-

ceived antiparasitic drugs, eight were treated only with corticosteroids) more than three years before our study started.

Treatment lasted at least four weeks and consisted of three triple-drug combinations. Group 1 (35 patients) was treated with pyrimethamine (loading dose, 100 mg the first day, followed by 50 mg/day), sulfadiazine (4 g/day), and corticosteroids (60 mg/day from the third to seventh day, then tapered off gradually). Group 2 (46 patients) was treated with clindamycin (300 mg four times per day), sulfadiazine (4 g/day), and corticosteroids (60 mg/day from the third to seventh day, then tapered off gradually). Group 3 (27 patients) was treated with co-trimoxazole (trimethoprim and sulfamethoxazole, 960 mg two times per day during the first two weeks, then 380 mg two times per day) and corticosteroids (60 mg/day from the third to seventh day, then tapered off gradually). Time between onset of the ocular symptoms and initiation of treatment was recorded for all treated patients. Patients with peripheral retinal lesions (area extending from the major temporal vascular arcades to the ora serrata) were not treated (group 4, 41 patients). The patients of group 1 received a folic acid supplement (5 mg twice a week).

The patients were randomly assigned to treatment on the basis of clinic location. Pyrimethamine was used at the university hospitals of Amsterdam and Leiden; clindamycin was used at the university hospitals of Rotterdam and Groningen, and at the Free University of Amsterdam (previously existing therapeutic strategies at these five hospitals); co-trimoxazole was prescribed at the University Hospital of Utrecht and during the last stage of the trial at all of the previously mentioned participating hospitals.

A complete ophthalmic examination was performed at regular intervals (at least weekly for a period of six weeks); the following factors were assessed and documented according to a standardized protocol: visual acuity, inflammatory reaction in the vitreous and retina, and size and location of the retinal lesion. Repeated fundus drawings were also included. Inflammatory activity was classified according to a standard grading system.¹⁷ Fundus photographs of the central retinal area and affected retinal fields were taken before therapy and on days 7, 21, and 42. The final examination was performed by two independent ophthalmologists in a masked fashion. We considered the lesions to be healed when atrophic scars with sharp mar-

gins and eventual hyperpigmentation developed and the inflammatory activity in the vitreous disappeared. The diameter of the lesion was related to disk diameter. If the retinal lesion and the optic disk were not present on the same photograph, the diameter of the lesion was first compared to the distance of two markers on that part of the vascular tree that was present in both photographs and then related to disk size. For peripheral lesions, we had to rely on fundus drawings.

Any complications of the therapies used were carefully monitored; all patients were examined by an internist and complete blood cell counts were performed twice a week.

The patients were followed up at the respective clinics and were also asked once a year by letter for information on eventual unrecorded recurrences. Replies were obtained from all patients. Depending on the period of enrollment in the study, most patients could be followed up for three years (122 patients).

We used the chi-square test for statistical analysis. A *P* value of less than .01 was considered significant.

Results

No difference in the duration of inflammatory activity was observed between treated and untreated patients (*P* = .5) or between the separate groups of treated patients (Table 1). The most important factor predicting the duration of inflammatory activity was the size of the retinal lesion itself, independent of the treatment (*P* < .001; Table 2). Large retinal lesions were associated with longer activity and therefore prolonged recovery time. For patients who

were treated within 48 hours of the manifestation of ocular symptoms, the duration of activity was not shorter than that found for patients with a medication delay of more than 48 hours or even longer than one week. No effect of previous therapy on the recovery time could be observed among previously treated patients. The response to treatment did not differ between patients with their first manifestation and those with a recurrence (*P* = .5).

We evaluated the changes in size of the retinal lesion during treatment (Table 3). A marked decrease in the size of the lesion (decrease in diameter of the lesion of more than one half of the diameter of the optic disk) was found for 49% of the pyrimethamine-treated patients (17 of 35 patients), 28% of the clindamycin-treated patients (13 of 46 patients), 11% of the co-trimoxazole-treated patients (three of 27 patients), and 20% of the untreated patients (eight of 41 patients). Visual acuity in the affected eyes before and after treatment did not differ significantly in treated patients (*P* = .5); however, the best results were achieved with pyrimethamine-associated triple-drug therapy (Table 4).

The frequency of serious side effects that necessitated discontinuation of the drugs used was 26% for pyrimethamine triple-drug therapy (nine of 35 patients), 17% for clindamycin triple-drug therapy (eight of 47 patients), and 4% for co-trimoxazole triple-drug therapy (one of 27 patients). The most frequent occurrence of side effects was associated with pyrimethamine therapy (*P* < .05), which included hematologic complications such as thrombocytopenia and leukopenia despite prophylaxis with folinic acid. One patient was hospitalized because of a low platelet count (9,000/mm³); this condition normalized within two weeks of an increase in

TABLE 1
EFFECT OF THERAPY ON THE DURATION OF INFLAMMATORY ACTIVITY

DURATION OF INFLAMMATORY ACTIVITY	NO. OF PATIENTS (%)				
	GROUP 1 (N = 35)	GROUP 2 (N = 46)	GROUP 3 (N = 27)	GROUP 4 (N = 41)	TOTAL (N = 149)
Less than 3 wks	6 (17)	4 (9)	4 (15)	7 (17)	21 (14)
Between 3 and 6 wks	20 (57)	23 (50)	16 (59)	19 (46)	78 (52)
More than 6 wks	9* (26)	19 (41)	7 (26)	15* (37)	50 (34)

**P* = .5.

TABLE 2
SIZE OF THE RETINAL LESION AND DURATION OF THE
INFLAMMATORY ACTIVITY

DURATION OF INFLAMMATORY ACTIVITY	NO. OF PATIENTS (%)		
	RETINAL LESION < 2 DISK DIAMETERS (N = 108)	RETINAL LESION ≥ 2 DISK DIAMETERS (N = 41)	TOTAL (N = 149)
Less than 3 wks	16 (15)	6 (15)	22 (15)
Between 3 and 6 wks	65 (60)	12 (29)	77 (52)
More than 6 wks	27* (25)	23* (56)	50 (33)

*P < .001.

the dosage of folinic acid. Complications associated with clindamycin consisted of diarrhea and, in two patients, mild hepatotoxicity. Sulfadiazine-induced side effects included allergic reactions, such as rash and fever, and possibly also hematologic changes, which, however, could not be discriminated from those induced by pyrimethamine. One patient developed a peptic ulcer, which improved when the corticosteroids were quickly tapered off. All observed adverse reactions were reversible and the side effects diminished when treatment was discontinued.

One hundred thirty patients were followed up for two years and the mean recurrence rate for all patients was 41% (53 of 130 patients; Table 5). After three years, the mean recurrence rate had increased to 49% (60 of 122 patients). No significant differences in the recurrence rate were observed between treated and untreated patients ($P = .6$) or between the separate groups of treated patients. Neither the size of the retinal lesion nor previous antiparasitic therapy influenced the recurrence rate.

TABLE 4
VISUAL LOSS BEFORE AND AFTER THERAPY FOR
TOXOPLASMOSIS

VISUAL ACUITY LESS THAN 20/60	NO. OF PATIENTS (%)		
	GROUP 1 (N = 35)	GROUP 2 (N = 46)	GROUP 3 (N = 27)
Before therapy	15 (44)	16 (35)	10 (37)
After therapy	2* (9)	6* (13)	5 (19)

*P = .5.

TABLE 3
DECREASE IN SIZE OF RETINAL LESION DURING
THERAPY

DECREASE IN SIZE OF RETINAL LESION	NO. OF PATIENTS (%)				
	GROUP 1 (N = 35)	GROUP 2 (N = 46)	GROUP 3 (N = 27)	GROUP 4 (N = 41)	TOTAL (N = 149)
> 0.5 disk diameter in diameter	17* (49)	13 (28)	3 (11)	8* (20)	41 (27.5)

*P = .01.

Discussion

In this study, the duration of the inflammatory activity of ocular toxoplasmosis was not shortened by current therapies. This finding contradicts frequent published reports on the beneficial effect of these therapies in patients with ocular toxoplasmosis.^{2,18,19}

A triple-drug combination with pyrimethamine is considered the most effective treatment of toxoplasmosis,²⁰ but many toxic side effects and recurrences have been reported. A less toxic therapeutic regimen consists of clindamycin in combination with sulfadiazine and corticosteroids. Clindamycin has relatively few side effects in immunocompetent subjects, but severe diarrhea was described in patients with AIDS.²¹ Clindamycin-associated triple-drug combination therapy has repeatedly been reported to be effective in patients with ocular toxoplasmosis.⁷⁻¹¹ None of the previously mentioned studies included a control series, however, which precludes a definitive conclusion. We chose our control patients (patients with peripheral toxoplasmic retinitis) after accepting

TABLE 5
RECURRENCE OF OCULAR TOXOPLASMOSIS

FOLLOW-UP PERIOD	NO. OF PATIENTS				
	GROUP 1	GROUP 2	GROUP 3	GROUP 4	TOTAL
1 Yr	0/35	0/46	3/27	1/41	4/149
2 Yrs	10/31	20/37	8/26	15/36	53/130
3 Yrs	13/31*	21/37	8/20	18/34*	60/122

*P = .6.

the hypothesis that there is no essential difference in either pathogenesis or therapeutic response between peripheral and central toxoplasmic lesions. The inclusion of untreated control patients in our study means that a more reliable comparison of treated and untreated patients is possible and probably also explains our disappointing results. Similar findings were described in a double-masked study of a small group of patients.²² Patients with peripheral toxoplasmosis were used as untreated controls to avoid visual loss if the disease rapidly progressed. It is probable that the course of peripheral toxoplasmosis is similar to that of central toxoplasmosis, but the control patients were not randomly assigned. The randomization of treatment in our study on the basis of clinic location instead of study enrollment raises the concern of uncontrolled differences, probably of a minor concern in the small geographic area involved. The fundus photographic control and masked reading support the accuracy of registered response to different treatment modalities.

Several cases of fulminant ocular toxoplasmosis have been reported after the use of corticosteroids without antiparasitic drugs.²³ Prolongation of recovery time by corticosteroids is not probable in our study because the duration of activity did not differ between treated and untreated patients. All of our treated patients received oral corticosteroids and patients with peripheral retinal lesions (untreated patients) were not treated systemically.

This study showed that pyrimethamine-associated triple-drug therapy leads to a decrease in the size of the retinal lesion in about one half of the patients and, after the inflammation has subsided, a smaller retinal scar. This advantage for patients who received pyrimethamine compared to those treated with other drugs or those not treated at all may be important for patients with a retinal lesion near or in the fovea. However, whether the known side effects of pyrimethamine justify its use when the probable benefit is small is debatable. We found a reduction of the retinal inflammatory lesion for 49% of the pyrimethamine-treated patients (17 of 35 patients) compared to 20% of the untreated patients (eight of 41 patients). Our conclusions only apply for the dosages used in this trial and we do not know the effect of a larger dose. When deciding whether to use pyrimethamine for the individual patient, clinicians will

have to judge whether the probably small benefit outweighs the inconvenience and its side effects.²⁴

The follow-up period of three years disclosed a high recurrence rate of 49%, which was not influenced by therapy. The published recurrence rate for presumed ocular toxoplasmosis is markedly lower and varies for patients treated with pyrimethamine between 7% (follow-up, two years) and 16% (follow-up, one to 28 months)^{18,25}; for patients treated with clindamycin, the rate was 8% (follow-up, 18 months to seven years).¹⁰ The differences may be explained by several factors. First, the diagnosis of ocular toxoplasmosis used to be based on positive results of serologic testing; however, patients with nontoxoplasmic uveitis may also have positive serologic results because of a past acquired infection. The positive results in these patients are not related to ocular disease. Moreover, most of the Dutch population have antitoxoplasmic antibodies and therefore this method has, at least in The Netherlands, no diagnostic value.¹⁵ Second, recurrences in our series occurred predominantly after one year of no recurrence, so that the variable follow-up period in the previously mentioned studies may have contributed to the differences observed. Finally, real differences in the pathogenicity of causative organisms may exist in different parts of the world.

Factors other than duration of inflammatory activity and recurrence rate may have a role in the prognosis of ocular toxoplasmosis (size of the inflammatory lesion and its location and depth within the retina, the increase or decrease in the retinal lesion during treatment, and the occurrence of cystoid macular edema). It is difficult to compare the efficacy of therapeutic regimens for ocular toxoplasmosis.¹⁴ A conclusive study would require subdivision of a series of retinal lesions according to size, location, duration, first manifestation, and recurrence, which are of course difficult to realize. Because all of the previously mentioned factors could not be analyzed, the question of whether patients with ocular toxoplasmosis really do not benefit from the therapies investigated and therefore should or should not be treated cannot as yet be answered.

This study indicated that pyrimethamine-associated triple-drug therapy may be beneficial for patients with vision-threatening macular or large peripheral lesions. The size of the retinal

scar is of crucial importance for the ultimate visual function when located near or in the macula. A large peripheral lesion will not affect central visual acuity but may cause a large visual field defect; furthermore, large lesions were associated with prolonged inflammatory activity and thus potential secondary complications.

In other cases, in which corticosteroids are required because of complications of toxoplasmic uveitis (for example, cystoid macular edema or a severe vitreous reaction in patients with a lesion in a portion of the retina where an eventual scar is not sight threatening), less toxic antiparasitic drugs may possibly be preferred as a prophylaxis against fulminant ocular toxoplasmosis. Patients with small peripheral lesions, and therefore with the possibility of full visual recovery, do not seem to benefit from the therapies investigated. We could not find evidence to support the hypothesis that treatment of patients with ocular toxoplasmosis prevents reactivation of retinal activity. Development of new agents, which would destroy the cysts of *T. gondii*, as well as the free parasites, is essential. Azithromycin, a derivative of erythromycin, which was active against the cysts in vitro, is currently being tested clinically in comparison to pyrimethamine and sulfadiazine.^{26,27} The most important strategy for control of ocular toxoplasmosis is to prevent congenital infection. Because a vaccine is not yet available, the major weapon against ocular toxoplasmosis is adequate education about prevention of the infection.

Further evaluation of control studies is needed to confirm the value of therapy for ocular toxoplasmosis. Despite the lack of benefit found for our patient groups, our results do support the idea that controlled trials are helpful and provide encouragement for further efforts to identify more selective and less toxic antiparasitic drugs.

References

1. Henderly, D. E., Genstler, A. J., Smith, R. E., and Rao, N. A.: Changing patterns of uveitis. *Am. J. Ophthalmol.* 103:131, 1987.
2. Perkins, E. S.: Ocular toxoplasmosis. *Br. J. Ophthalmol.* 57:1, 1973.
3. O'Connor, G. R.: Toxoplasmosis. In Fraunfelder, F. T., and Roy, F. H. (eds.): *Current Ocular Therapy*. Philadelphia, W. B. Saunders, 1980, pp. 99-101.
4. Thiermann, E., Apt, W., Atias, A., Lorca, M., and Olguin, J.: A comparative study of some combined treatment regimens in acute toxoplasmosis in mice. *Am. J. Trop. Med. Hyg.* 27:747, 1978.
5. Harper, J. S., London, W. T., and Sever, J. L.: Five drug regimens for treatment of acute toxoplasmosis in squirrel monkeys. *Am. J. Trop. Med. Hyg.* 34:50, 1985.
6. Tate, G. W., and Martin, R. G.: Clindamycin in the treatment of human ocular toxoplasmosis. *Can. J. Ophthalmol.* 12:188, 1977.
7. Chandra, J., and Donaldson, E. J.: Clindamycin in human ocular toxoplasmosis. A preliminary report. *Aust. J. Ophthalmol.* 6:135, 1978.
8. Tabbara, K. F., and O'Connor, R. G.: Treatment of ocular toxoplasmosis with clindamycin and sulphadiazine. *Ophthalmology* 87:129, 1980.
9. Ferguson, J. G.: Clindamycin therapy for toxoplasmosis. *Ann. Ophthalmol.* 13:95, 1981.
10. Lakhanpal, V., Schocket, S. S., and Nirankari, V. S.: Clindamycin in the treatment of toxoplasmic retinochoroiditis. *Am. J. Ophthalmol.* 95:605, 1983.
11. Goldstein, H.: Clindamycin and sulphonamides in the treatment of ocular toxoplasmosis. *Acta Ophthalmol.* 61:51, 1983.
12. Norby, R., Eilard, T., Svedhem, A., and Lycke, E.: Treatment of toxoplasmosis with trimethoprim-sulphamethoxazole. *Scand. J. Infect. Dis.* 7:72, 1975.
13. Williams, M., and Savage, D. C. L.: Acquired toxoplasmosis in children. *Arch. Dis. Child.* 53:829, 1978.
14. Engstrom, R. E., Jr., Holland, G. N., Nussenblatt, R. B., and Jabs, D. A.: Current practices in the management of ocular toxoplasmosis. *Am. J. Ophthalmol.* 111:601, 1991.
15. Rothova, A., van Knapen, F., Baarsma, G. S., Kruit, P. J., Loewer-Sieger, D. H., and Kijlstra, A.: Serology in ocular toxoplasmosis. *Br. J. Ophthalmol.* 70:615, 1986.
16. Kijlstra, A., Breebaart, A. C., Baarsma, G. S., Bos, P. J. M., Rothova, A., Luyendyk, L., Fortuin, M., and Schweitzer, N. J. M.: Aqueous chamber taps in toxoplasmic chorioretinitis. *Doc. Ophthalmol.* 64:53, 1986.
17. Kimura, S. J., Thygeson, P., and Hogan, M. J.: Signs and symptoms of uveitis. II. Classification of the posterior manifestations of uveitis. *Am. J. Ophthalmol.* 47:171, 1959.
18. Ghosh, M., Levy, P. M., and Leopold, I. H.: Therapy of toxoplasmosis uveitis. *Am. J. Ophthalmol.* 59:55, 1965.
19. Schlaegel, T. F., Jr. (ed.): *Ocular Toxoplasmosis and Pars Planitis*. New York, Grune & Stratton, 1978, pp. 205-262.
20. Smith, R. E., and Nozik, R. A. (eds.): *Uveitis. A Clinical Approach to Diagnosis and Management*. Baltimore, Williams & Wilkins, 1989, pp. 128-134.
21. Jacobson, M. A., Besch, C. L., Child, C., Haf-

ner, R., Matts, J. P., Muth, K., Wentworth, D. M., Deyton, L., and Community Programs for Clinical Research on AIDS: Toxicity of clindamycin as prophylaxis for AIDS-associated toxoplasmic encephalitis. *Lancet* 339:333, 1992.

22. Acers, T. E.: Toxoplasmic retinochoroiditis. A double blind therapeutic study. *Arch. Ophthalmol.* 71:58, 1964.

23. Nicholson, D. H., and Wolchok, E. B.: Ocular toxoplasmosis in an adult receiving long-term corticosteroid therapy. *Arch. Ophthalmol.* 94:248, 1976.

24. Webster, T. L. (ed.): *The Pharmacological Basis*

of Therapeutics, ed. 8. New York, Pergamon Press, 1990, pp. 978-998.

25. Canamucio, C. J., Hallett, J. W., and Leopold, I. H.: Recurrence of treated toxoplasmic uveitis. *Am. J. Ophthalmol.* 55:1035, 1963.

26. Huskinson-Mark, J., Araujo, F. G., and Remington, J. S.: Evaluation of the effect of drugs on the cyst form of *Toxoplasma gondii*. *J. Infect. Dis.* 164:170, 1991.

27. Farthing, C., Rendel, M., Currie, B., and Seidlin, M.: Azithromycin for cerebral toxoplasmosis. *Lancet* 339:437, 1992.