MANIFESTATIONS AND MANAGEMENT OF OCULAR TOXOPLASMOSIS*

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EXACTLY 50 years ago the Czechosolovakian ophthalmologist Janků[1] first described protozoa morphologically identical to *Toxoplasma gondii* in tissue sections taken from the eye of a patient who had congenital toxoplasmosis. At that time the atrophic retinal scars that we now associate with congenital toxoplasmosis (Figure 1) were thought to represent colobomata—defects associated with failure of the choroidal fissure to close in embryonic life. Janků's revolutionary discovery pointed the way to the establishment of an infectious etiology for the disease; this was later confirmed by Wolf, Cowen, and Paige[2] and others[3] who isolated living *Toxoplasma* from the affected ocular tissues, verified the infection by transmission to animals, and thus essentially fulfilled Koch's postulates.

In the half-century that has elapsed since Janku's discovery, much has been done to clarify the pathogenesis of the ocular lesions of toxoplasmosis. Correlative analysis of the clinical manifestations, the laboratory tests, the isolation data, and the histopathologic findings in a relatively large number of enucleated eyes have given us some indication of the accuracy with which we can diagnose ocular toxoplasmosis. We believe that we can make the correct diagnosis in a high percentage of the cases by ophthalmoscopic examination and dye tests alone. However, many unsolved problems remain. There is as yet no explanation for the paucity of ocular lesions among patients who are known to have acquired the disease in adult life. There is likewise no explanation for the

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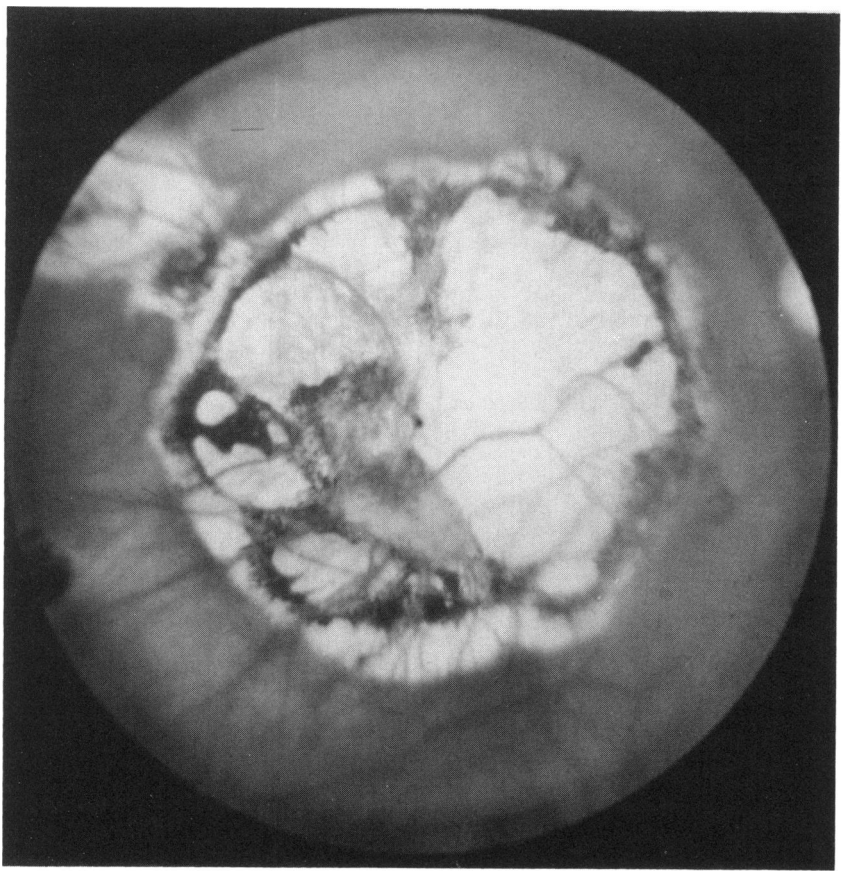

Fig. 1. Typical macular scar of congenital toxoplasmosis. Note extensive atrophy and pigment accumulation.

relatively poor, or at least unpredictable, results of Daraprim and sulfonamide therapy in the treatment of chronic, progressive inflammatory lesions of the fundus, as compared with the reportedly good results of this therapy in acutely infected animals.

The literature contains conflicting reports concerning the cause of recurrent toxoplasmic retinochoroiditis. Although toxoplasmic cysts are known to occur in the retinas of chronically infected persons, spontaneous breakdown of such cysts has never been observed in the human retina. Although it has been postulated that antigens liberated by the breakdown of such cysts may be responsible for shortlived attacks of recurrent retinochoroiditis, it is not clear that nonliving *Toxoplasma*

antigens can produce focal exudative retinochoroiditis. Indeed, some authors[4] feel that all recurrent toxoplasmic lesions in the retina, whether short-lived or long-lived, are the result of the multiplicative activity of living parasites. Whether these are released from cysts or whether they represent some unencysted but suppressed form of the organism which periodically bursts forth into reproductive activity remains to be seen.

If cell-mediated defense reactions in the host are responsible for keeping the parasite at bay, periodic lapses in the potency of these reactions may permit the parasite to proliferate in an unchecked manner in the retina as well as elsewhere in the body. This issue, if properly resolved, might influence the type of treatment administered to patients with recurrent retinochoroiditis.

The nature of recurrent *anterior* uveitis—with its attendant problems of secondary glaucoma, synechiae, and cataracts—constitutes an equally baffling though somewhat less important problem from the point of view of visual loss. Proliferating *Toxoplasma* has never been seen in the anterior uvea of man. Although Pillat and Thalhammer[5] described a case of anterior granulomatous uveitis that was allegedly due to toxoplasmosis, several authors, including Perkins,[6] have doubted the claim that the anterior uvea was primarily involved. Organisms were isolated from the enucleated eye of Pillat's patient, but the anterior uveal tissues were not separated from the posterior uvea prior to animal inoculation. Thus, it is still doubtful that *T. gondii* had actually infected the anterior uvea, as Pillat and Thalhammer inferred.

Anterior uveitis has usually been assumed to be a phenomenon of hypersensitivity, and there is good experimental evidence to support the supposition that *Toxoplasma* antigens, released into the intraocular fluids, can cause a severe anterior inflammatory reaction.[4] Such reactions are characterized by massive infiltration of the iris and ciliary body with lymphocytes and plasma cells and by the extensive release of serum proteins, including fibrinogen, into the anterior chamber.[7]

It is readily conceivable that recurrences of posterior uveitis (i.e., retinochoroiditis) might provide sufficient antigenic stimulus to trigger an anterior reaction, but it is not known why the anterior uveitis sometimes occurs in the absence of any visible recurrence of posterior disease. It has been suggested that circulating antigen or circulating antigen-antibody complexes, released from distant sities of infection, might trigger the reaction in the anterior uvea. Silverstein[6] has demonstrated this

plainly in the guinea pig by utilizing heterologous serum proteins as antigens. Whether his results apply to the situation that we face in recurrent toxoplasmic uveitis remains to be seen.

All of these observations serve to illustrate the scope and variety of the as yet unsolved problems in ocular toxoplasmosis, and this state of affairs is reflected also in the annual toll of blindness taken by this disease. Despite the use of all known forms of treatment, thousands continue to be blinded each year by toxoplasmosis. Although many of these patients retain peripheral vision and can be considered blind only in the legal sense (i.e., they have vision of 20/200 or less in the better of their two eyes), the disability occasioned by the loss of central vision is great, especially when it affects patients before or during their educational years.

Diagnosis of Ocular Toxoplasmosis

The diagnosis is made by finding a morphologically acceptable lesion in the fundus and by obtaining a positive result from any one of a number of laboratory tests that are available to physicians. A reasonable effort must be made to exclude infectious diseases other than toxoplasmosis which might be responsible for the ocular lesion observed.

The characteristic lesion of ocular toxoplasmosis is a focal necrotizing retinitis. Such lesions in the acute or subacute stage of inflammation appear as yellowish-white, cotton-like patches in the fundus. They may appear as solitary lesions that are about the same size as the optic disc or a little larger. More often, however, they appear in small clusters, among which lesions of various ages can be discerned. The more acute lesions are soft and cotton-like with indistinct borders; the older lesions are whitish-gray, sharply outlined, and spotted by accumulations of choroidal pigment (Figure 2). Often the inflammatory exudate that is cast off from the surface of the acute lesions is so dense as to preclude accurate visualization of the fundus. In such cases the most that can be discerned is a whitish mass against the pale orange background of the fundus. In such cases the posterior hyaloid membrane is often detached, and precipitates of inflammatory cells—the equivalents of keratic precipitates in the anterior segment of the eye—are seen on the posterior face of the vitreous. Cuffs of inflammatory cells are also seen along the retinal blood vessels, both the arteries and the veins. This manifestation may well be ascribed to a reaction between local antigen

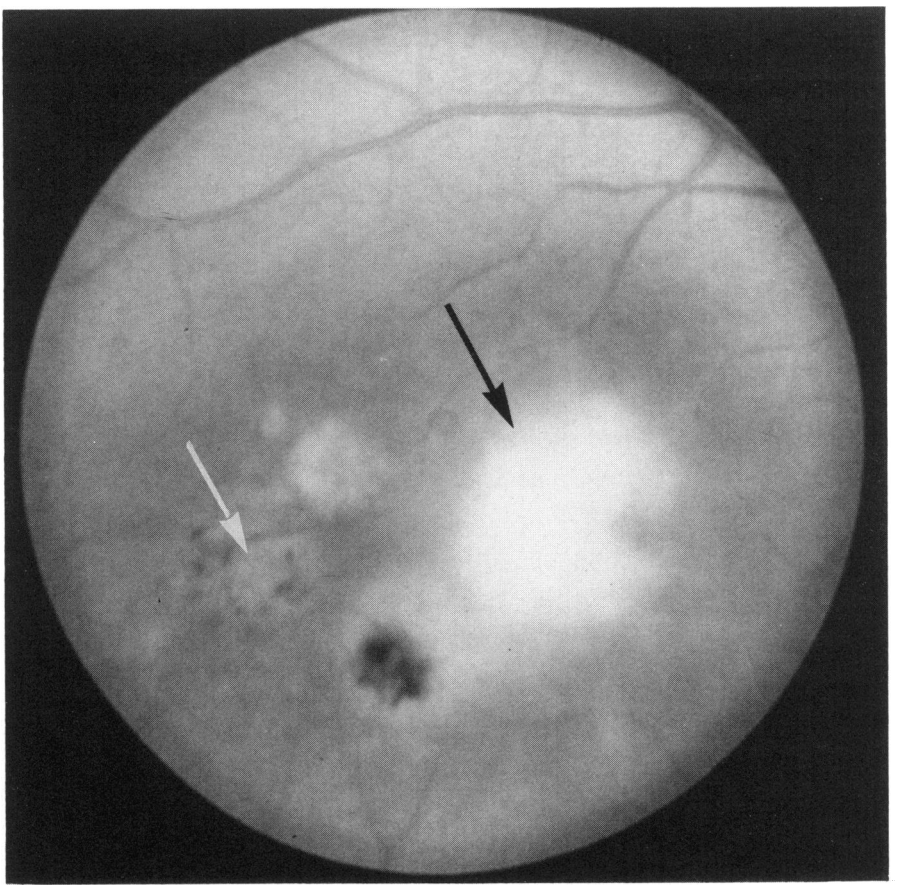

Fig. 2. The characteristic lesions of acute toxoplasmic retinochoroiditis in the adult fundus. Black arrow denotes active lesion with indistinct borders. White arrow denotes healed "satellite lesion." Reproduced by permission from O'Connor, G. R.: Ocular Toxoplasmosis. In: *Microbiology of the Eye,* Locatcher-Khorazo, D. and Seegal, B. C., editors. St. Louis, Mosby, 1972.

and circulating antibody, for it has been duplicated experimentally in chronically-infected rabbits subjected to the intravitreal inoculation of soluble, cell-free toxoplasmic antigens.[4]

Retinal edema, affecting especially the macular and peripapillary areas, is commonly observed in the subacute phase of inflammation. Edema of the macula is present almost universally in cases in which acute inflammatory foci in the retina are situated above the macula. This

edema is the principal cause of blurred vision in those cases where other causes such as a central retinal lesion, involvement of the optic nerve, or extensive clouding of the vitreous can be excluded. It is usually temporary, although cystic changes in the fovea sometimes occur as the result of long-standing edema. In this instance central visual acuity may be permanently altered despite the absence of central lesions or involvement of the optic nerve.

The optic nerve may be affected either primarily or secondarily. Manschot[9] and others have described *Toxoplasma* in the optic nerve itself; and one school of ophthalmologists, led by Berengo and Frezzotti[10] in Siena, feels that the optic nerve is the principal route by which the organisms gain access to the retina. By injecting living *Toxoplasma* into the cerebrospinal fluid they produced retinal lesions characteristic of those seen in human subjects. If their theory is correct, it might help to explain the characteristic location of toxoplasmic lesions at or near the posterior pole of the eye. It would also mesh nicely with Perkins'[6] statement that nearly all ocular toxoplasmosis is congenital in origin. We must remember that the stalk of the optic nerve and the retina represent a common outpocketing of the brain at one point in embryonic life, and that the potential space between the sensory retina and the pigment epithelium is really nothing more than an extension of the primitive ventricular system of the brain.

What appears to be primary involvement of the optic nerve head with papilledema and exudation of cells into the overlying vitreous often turns out to be a juxtapapillary lesion. A retinal lesion contiguous to the head of the optic nerve can produce swelling and inflammation in the nerve; but when the acute lesion subsides it becomes clear that the optic nerve itself has been spared and that a narrow rim of normal tissue separates the lesion from the nerve head. When Jensen[11] originally described juxtapapillary chorioretinitis, he assumed that most of the cases were due to tuberculosis. It is more than likely that a large number were due to toxoplasmosis.

Segmental atrophy of the optic nerve, characterized by pallor and loss of substance, especially of the temporal portion of the nerve head, often occurs in the wake of a macular lesion. This is due to retrograde degeneration of significant numbers of nerve fibers after the death of ganglion cells in the retina. In these cases the prognosis for vision is, of course, limited.

While the vast majority of lesions are at or near the posterior pole of the retina, peripheral lesions most probably due to toxoplasmosis have been described by Chesterton[12] and others. Although these have roughly the same morphology as the more central lesions, they tend to be less significant as a cause of visual loss unless they are accompanied by massive contractures of the overlying vitreous and subsequent retinal detachment.

The anterior uvea is often the site of intense inflammation characterized by redness of the external eye, cells and protein in the anterior chamber, large keratic precipitates, posterior synechiae, nodules on the iris, and occasionally neovascular formations on the surface of the iris. This reaction may be accompanied by high rises of the intraocular pressure and by cataract. Although Piper[13] has demonstrated *Toxoplasma* in the iris of numerous domestic animals, proof of the existence of parasites in the anterior uvea of human subjects has never been obtained. For this reason, isolated iritis should not be taken as an indication of toxoplasmosis. It should be preceded or at least accompanied by a posterior lesion to be considered as a manifestation of toxoplasmosis. The same can be said of scleritis, which may be observed external to a focus of toxoplasmic retinochoroiditis, but which has no significance by itself as a sign of toxoplasmosis.

From the foregoing it can be seen that the clinical picture of ocular toxoplasmosis is virtually specific. Coupled with laboratory evidence of systemic toxoplasmosis, the clinical picture alone is sufficient to suggest the diagnosis rather strongly. The diagnosis cannot be made in an absolute sense, of course, unless organisms are isolated from the eye itself. Short of that, we are forced to rely on indirect evidence. Serologic confirmation of systemic toxoplasmosis, as provided by the dye test, the hemagglutination test, the indirect fluorescent antibody test, or the precipitin test, is sufficient and necessary for the diagnosis of ocular toxoplasmosis. It should be stressed, however, that serum antibody titers are often very low in cases where ocular inflammation appears to be the only overt manifestation of disease. The patients originally described by Wilder[14] and subsequently studied by Jacobs, Cook, and Wilder[15] had low dye-test titers for the most part. Other patients, in whom the diagnosis was confirmed, are reported to have had high titers.[16] In general, there seems to be no correlation between the level of the dye-test titer and the activity of the ocular disease. It would seem the fluctuations in

the dye-test titer are more likely to be related to changes in the severity of the disease elsewhere in the body, particularly in the reticuloendothelial organs, than to changes in the eye.

A positive dye test at any titer, as long as it can be related to a morphologically compatible lesion in the fundus, is diagnostic. I should like to stress this point, for we are often asked: "What is a significant titer?" Our answer is than *any* titer is significant if the patient has an ocular lesion characteristic of toxoplasmosis. This point is amply illustrated by a case described by Zscheile.[17] His patient had been seen in our clinic on numerous occasions for complaints referable to typical recurrent toxoplasmosis of the retina. On several occasions the referring physician had been told that the ocular lesions resembled those of toxoplasmosis but that that disease could not be present, since the dye test was negative.

In the late 1950s we were still in the habit of referring to any dye test below a titer of 1:16 as negative. The reason was that too large a segment of the general population would have to be considered positive if we were to accept all of the lower titers as significant. When Zscheile's patient, mentioned above, subsequently died of causes unrelated to toxoplasmosis, his eyes were removed. Virtually every section of his necrotic retina contained cysts of *Toxoplasma*. At that point we removed the patient's serially collected serum specimens from our deep-freeze unit and retested all of them. Most of them showed dye-test positivity in undiluted serum only. This showed us that the sera of all patients with suspected ocular toxoplasmosis had to be tested undiluted as well as in serially diluted form. We accept no result from another laboratory as negative until we know the lowest dilution at which the test has been done.

In cases in which the form of the patient's lesions is not absolutely typical or in which other infectious diseases must be considered as possible etiologic factors, studies of the aqueous humor may be helpful. Precipitating antibodies, detected in specimens of aqueous humor withdrawn by paracentesis of the anterior chamber,[18] may provide evidence of specific antibody formation by lymphoid cells within the uveal tract. This is especially true if more specific antibody per unit of gamma globulin can be detected in the acqueous humor than in the serum. Desmonts[7] has described a series of calculations on the amounts of dye-test antibody detectable in the aqueous and has suggested that by this

technique recurrent lesions due to hypersensitivity could be differentiated from lesions caused by proliferating organisms. Since the exact pathogenesis of recurrent lesions is still open to question, and since studies performed on the aqueous humor principally reflect events that are taking place in the anterior uvea alone, I prefer to reserve judgment on this issue. Spurious results might also be obtained on hypotonous or prephthisical eyes in which protein accumulates in the anterior chamber as the result of faulty circulation of the aqueous and complete breakdown of the barrier between the blood and the aqueous.

Consideration must always be given to other diseases which might produce necrotizing retinochoroiditis. This precaution must be taken even if the patient's dye test is strongly positive. In temperate climates tuberculosis and syphilis are the two principal diseases with which we need to be concerned. I feel that a serological test for syphilis should be performed on every patient with necrotizing retinitis; if it is positive, the patient should be treated for syphilis. Similarly a roentgen examination of the chest and a tuberculin skin test should be performed on every patient under consideration. Despite the greatest care, we may be misled occasionally. In Darrell's[19] case of a necrotizing granuloma of the retina, for example, the first-strength tuberculin reaction was negative and films of the chest showed only old fibrocalcific disease. The second-strength tuberculin test was positive. When the eye was enucleated, sections of the retinal granuloma showed that it was swarming with tubercle bacilli.

Most of the other infections of the posterior eye present little or no problem in differential diagnosis. Histoplasmic choroiditis can be distinguished easily from toxoplasmosis on morphologic grounds. Friedmann and Knox[20] have described a "deep punctate" retinochoroiditis that does not becloud the vitreous as attributable to toxoplasmosis. I prefer to reserve judgement in such cases until confirmatory histopathologic or cultural data become available. Occasionally *Candida* endophthalmitis has been confused with toxoplasmosis, as has herpetic retinitis in the newborn. In compromised hosts: i.e., individuals who have received immunosuppressive therapy to prevent the rejection of grafts, or in patients who suffer from overwhelming malignant lymphomas, cytomegalic inclusion disease has caused necrotizing retinitis. Indeed, cytomegalovirus and *Toxoplasma* have been known to infect the same person.[21] Ocular granulomas associated with infestation by nematode

larvae such as *Toxocara canis* usually present as gliotic mounds with little vitreous reaction over them. In general, they, as well as the preceding entities, present little difficulty in differential diagnosis. They are mentioned here for completeness only.

Treatment of Ocular Toxoplasmosis

Treatment of ocular lesions with pyrimethamine and the sulfonamides has, in general, produced unpredictable and disappointing results. This is especially noteworthy when the relative ineffectiveness of these drugs on ocular toxoplasmosis is compared with their effectiveness in acute systemic disease in man and in experimentally-induced disease in laboratory animals. Nevertheless, the theoretical basis for treatment with these synergistic agents is sound, and many opththalmologists, including members of our own group, have returned to Daraprim and sulfonamide therapy after a period of disillusionment.

These drugs seem to exert their best effect on small, acute lesions of the retina which are less than a week old. Following the precepts annunciated by Kaufman[22] and by Choi,[23] we have attempted to give such patients a loading oral dose (100 to 150 mg.) of pyrimethamine, followed by 25 to 50 mg. of the drug daily for a period of four to six weeks. We have combined this therapy with triple sulfonamides, 2.0 gm. initially, followed by 1.0 gm. four times a day. We have monitored the peripheral leukocyte counts and platelet counts at least once a week and in some instances have injected 10 mg. folinic acid two to three times a week. Patients with small, fresh lesions have often benefitted from this treatment and have shown signs of healing within two or three weeks.

Patients with chronic elevated lesions seem to show little or no effect from this treatment. Massive granulomas of this kind seem to take their own inexorable course; they require from six to 18 months to heal, regardless of treatment. Often the reaction in the vitreous is so intense that the lesion cannot be seen for months at a time. Vitreal hemorrhages as well as retinal detachments sometimes occur in these patients, and intractible glaucoma has represented a difficult problem on more than one occasion. Patients with blind, painful eyes occasionally request enucleation of the affected eye after all attempts at treatment have failed. We have attempted to isolate the organism from the minced soft tissues of these eyes, and we have examined them all histologically. The fact that we have been able to identify and recover *Toxoplasma* from many

of these eyes makes us believe that failure of treatment rather than erroneous diagnosis is the main issue.

What is the source of the difference between eyes that heal quickly under treatment with pyrimethamine and sulfanamides and eyes that run a steady downhill course? I believe that the geometry of the lesion is an important factor. The elevated necrotic granuloma that is characteristic of the chronic progressive retinal disease is relatively avascular. It is not reasonable to expect that Daraprim and the sulfonamides will penetrate such a mass. Attacking the question from another point of view, individuals with chronic progressive disease may be compromised hosts whose cell-mediated defense systems are inadequate despite the appearance of enormous numbers of mononuclear cells in their lesions. It may be that their macrophages are unable to kill the parasites. Virulence of the infecting organism may also play a role, some strains being much more difficult to cope with than others.

The average retinal lesion retains its inflammatory activity for a period ranging from two weeks to two months, as nearly as we can judge by ophthalmoscopic observation. If such lesions are at the periphery of the fundus, we prefer to treat them by observation alone or by placebo therapy. These lesions usually cause no permanent embarrassment of vision. Our only concern is that they might turn into the chronic progressive form of the disease. For this reason frequent observation is necessary. Although Frenkel[24] has suggested that all active lesions attributable to toxoplasmosis should be treated with pyrimethamine and sulfonamides, we do not feel that we can make this recommendation to every patient. Certain patients, having endured the severe nausea, the expense, and the inconvenience of one course of therapy will refuse additional treatment. These patients, of course, serve as controls.

Some would argue that recurrent lesions are merely the result of hypersensitivity. They state that short-lived inflammations stem from reactions to nonliving antigens released from cysts. From my own experimental work in the rabbit,[4] I am led to doubt that cell-free solutions of antigen injected into the retina can ever cause necrotizing retinochoroiditis, although such antigens can certainly cause other forms of inflammation in the eye. I feel that the vast majority of focal retinic lesions are caused by multiplying *Toxoplasma*, and that immunologic responses of the host—a combination of cell-mediated and antibody responses—bring the lesions to the point of healing. While this issue still needs to be

resolved, the patient with a vision-threatening lesion of the retina or optic nerve deserves every form of treatment that has a chance of preserving visually important structures.

Vision-threatening lesions are defined as those which occupy the macula, the papillomacular bundle, or the optic nerve. A fourth category consists of those large, elevated lesions of the periphery which, because of extensive involvement of the vitreous, engender retinal detachment because of massive contracture of vitreous strands. In lesions that are a threat to vision we prefer to use a combination of corticosteroids and antimicrobials. Oral corticosteroids in doses of 80 to 120 mg. of prednisone per day are administered, along with pyrimethamine and sulfonamides as outlined above. In those patients who have a history of intractable vomiting or serious hematopoietic depression from Daraprim, we sometimes use sulfonamides as the sole antimicrobial drugs, or we substitute Aureomycin (2.0 gm. initially, followed by 250 mg. four times a day) as an alternative. Under no circumstances do we administer corticosteroids alone, despite Acers'[25] defense of such therapy.

What was once only a theoretical objection to the use of corticosteroids in ocular toxoplasmosis has now become a practical reality. This has been highlighted by the use of repository forms of corticosteroid such as subconjunctival injections of Depo-Medrol, Depo-Kenalog, or similar preparations. These injections are often used by ophthalmologists to arrest acute inflammatory processes in the eye, because sustained high levels of corticosteroids can be delivered to the lesion without the side-effects that are usually caused by steroids given systemically in high doses. Injections are sometimes given into the retrobulbar space in order to make the most direct approach to macular or paramacular lesions.

Within the past two years Dr. Robert Nozik and I have seen seven patients with presumptive ocular toxoplasmosis whose condition deteriorated as the result of repeated injections of depot corticosteroids without antimicrobal coverage. No such case has yet been observed among persons treated with both antimicrobial agents and corticosteroids. The results of these studies will be published separately, for we believe that it is important to alert the ophthalmologic community to the dangers of using corticosteroids alone in suspected ocular toxoplasmosis, as Dr. Remington and I tried to point out in 1964.[26]

Corticosteroids seem to act like a two-edged sword. On the one hand they help to quell the acute inflammation that threatens to eradicate

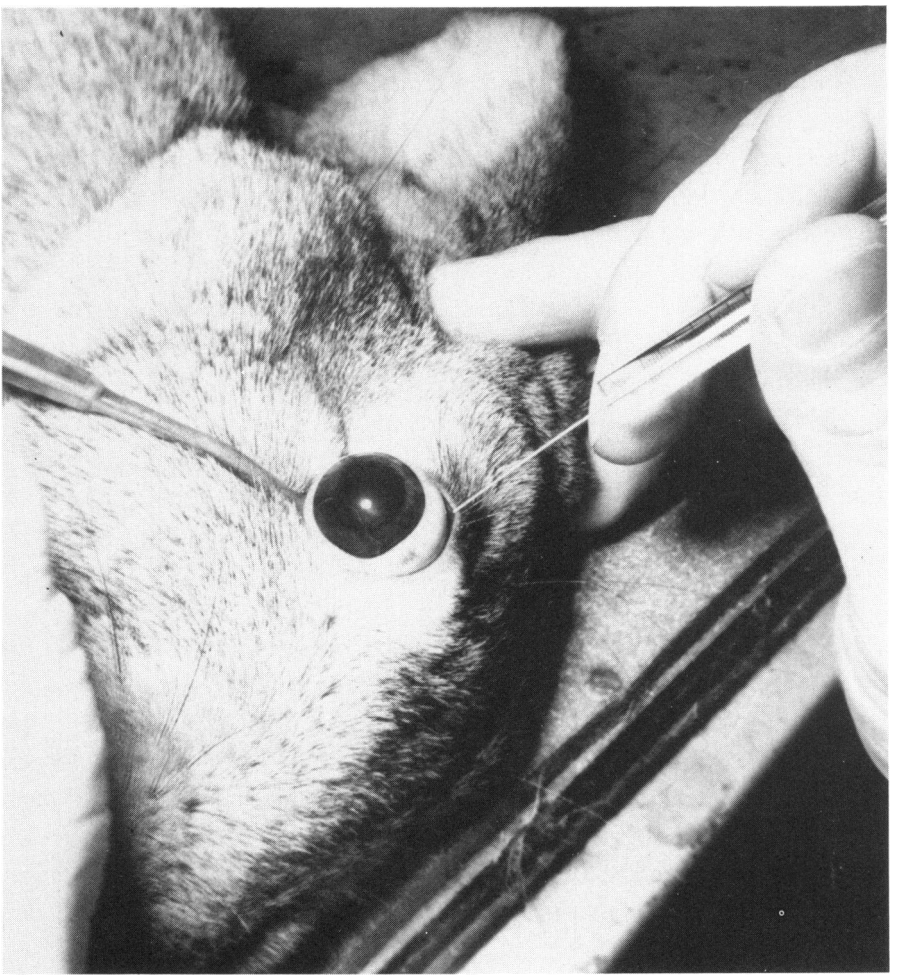

Fig. 3. Injection of a small inoculum of living *Toxoplasma gondii* into the posterior pole of the rabbit eye.

visually important structures such as the macula; on the other hand, they limit or nullify certain cell-mediated defense reactions that seem to be essential for holding the proliferative form of *Toxoplasma* at bay. In the treatment of lesions which are a threat to vision the only reasonable compromise at present seems to be that of administering both antimicrobial agents and corticosteroids.

New antimicrobial drugs are constantly being evaluated for their

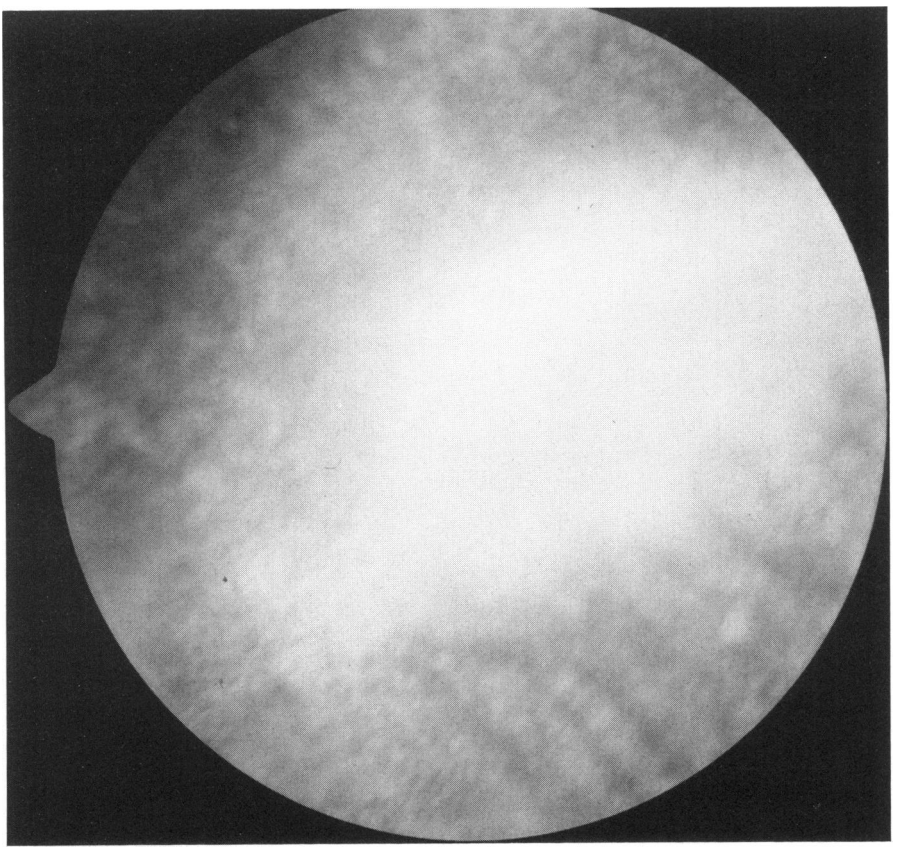

Fig. 4. Acute toxoplasmic retinochoroiditis in the rabbit fundus six days after inoculation of *Toxoplasma*. Compare with lesions depicted in Figure 2.

effect on toxoplasmic lesions. Clindamycin, recently found by McMaster et al.[27] to have considerable efficacy in the treatment of acutely-infected mice, appears to hold great promise for the treatment of experimental ocular lesions. Retrobulbar injection of the soluble form of the drug that is commercially prepared for intramuscular use is tolerated well by the rabbit. Using an animal model for ocular toxoplasmosis that Dr. Robert Nozik and I described in 1968,[28] Dr. Khalid Tabbara, Dr. Nozik, and I have attempted to judge the effect of this drug on posterior lesions (Figures 3-6). In preliminary work on experimental retinochoroiditis in the rabbit we have found that a single retrobulbar injection of 150 mg. of clindamycin, performed on the day that the retinochoroiditic

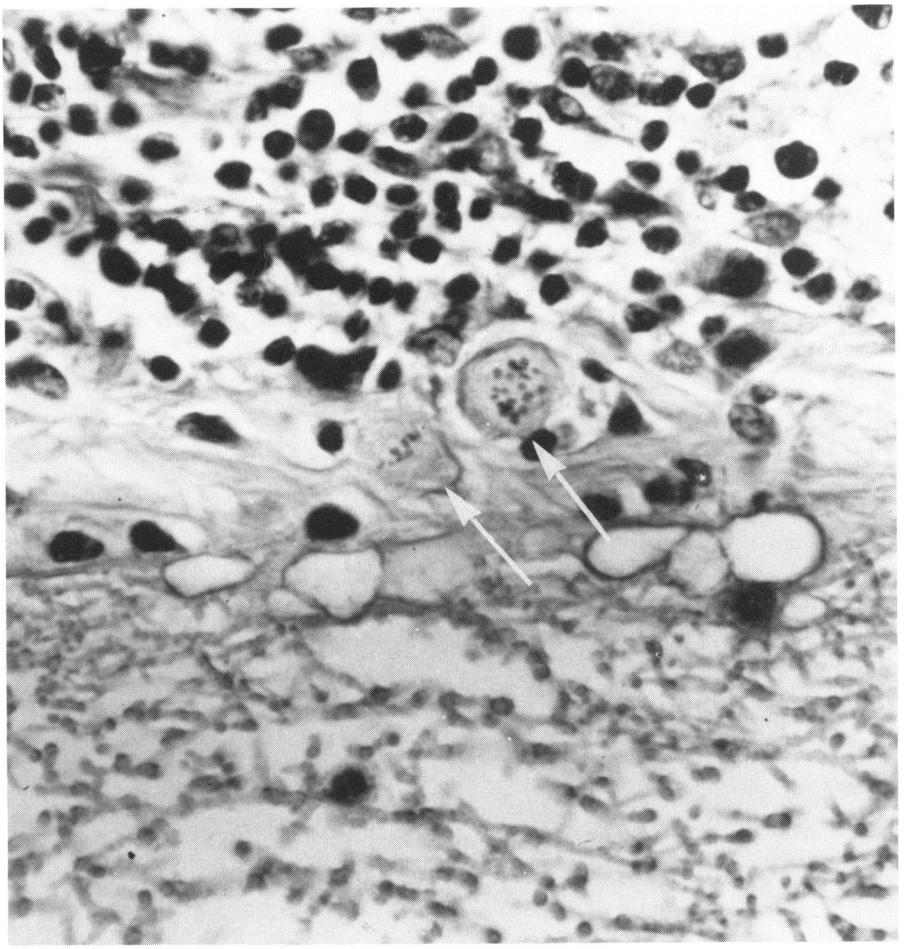

Fig. 5. Formation of *Toxoplasma* cysts in the subsiding retinochoroiditic lesion, 26 days after inoculation of the Beverley strain of *T. gondii* into a rabbit's eye. Arrows denote cysts. H & E (230 ×). Reproduced by permission from O'Connor, G. R. and Nozik, R.: Experimental toxoplasmic retinochoroiditis. *Arch. Ophthal. 79*:487, 1968.

lesion first becomes visible, and followed by intramuscular injections of 50 mg. per kg. of body weight twice a day for eight days, brings about the healing of the lesion in three to four days and sterilizes the eye. No organisms could be recovered from the eyes of seven rabbits treated by this method and sacrificed two days after the cessation of treatment, whereas organisms were recovered from all seven control rabbits that were treated with similarly timed injections of normal

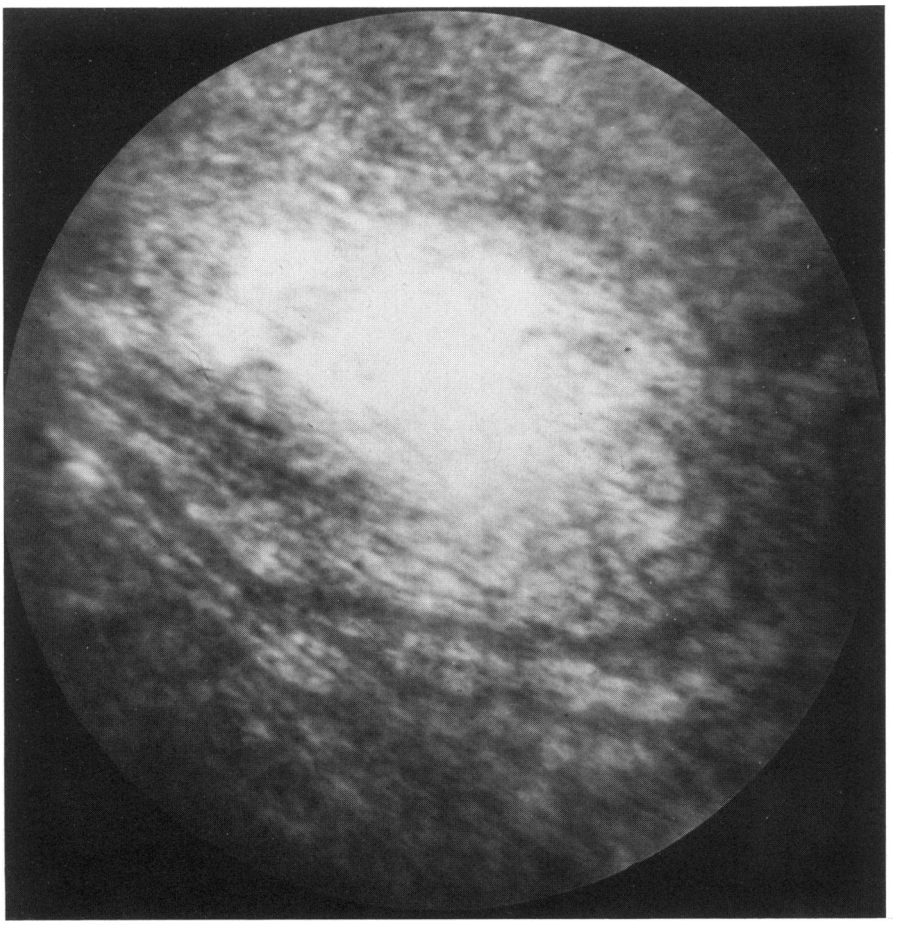

Fig. 6. Healed retinochoroiditis in the rabbit eye. Fundus photograph taken three months after inoculation of living *Toxoplasma.*

saline. Thus far, this drug seems to hold no more promise for eradicating viable organisms within cysts than any other drug that has been tested. However, a full-scale investigation of its use against the proliferative form of the organism seems justified.

Many physical modalities have been used in the treatment of retinal lesions; some have yielded promising results. Spalter et al.[29] reported success in the treatment of recurrent toxoplasmic retinochoroiditis with laser photocoagulation. The rationale for this form of therapy is that most of the cysts are located in areas contiguous to old lesions. Photo-

coagulation of an area surrounding an old lesion might destroy cysts in that region and prevent recurrences. Such treatment of a lesion whose borders have approached closer and closer to the macula with each succeeding recurrence has potential merit. Spalter and others may have preserved useful vision in some patients with frequent recurrences who were otherwise condemned to blindness, but the study is difficult to control.

Cryotherapy, as described by Dobbie,[30] has a similar rationale and may be easier for the eye to tolerate. If rapid freezing to −70°C. destroys the organism, as documented by Work[31] and others, this form of treatment may be extremely useful. The problem with Dobbie's work, as with Spalter's, is that one can never predict the exact location of cysts; it seems unreasonable to destroy large areas of retina in the blind hope of eradicating organisms.

I am not optimistic about the therapeutic efficacy of either of these physical modalities or of the large number of antimicrobial drugs that are, or will be, available. *Toxoplasma*, like most intracellular parasites, will ultimately have to be brought under control by the cell-mediated defense system of the host. The role of the sensitized lymphocyte has been correctly emphasized by Frenkel,[32] and the role of activated macrophages has been brought to light by Remington and his group.[33] A role for antibody, working in concert with complement, has recently been discovered by Shimada and myself.[34] If there were some safe way to activate or augment the cell-mediated defense systems of the body without provoking the excessive secretion of lymphocytotoxins or of macrophagic enzymes that might, in turn, destroy the cellular architecture of visually important structures, this would represent an ideal form of treatment. In our laboratory we have recently performed a series of experiments with BCG (bacillus of Calmette-Guérin) in an attempt to augment macrophagic activity in rabbits that had been subjected to the induction of toxoplasmic ocular lesions. I can report preliminary success with both intravenously and locally injected BCG. Toxoplasmic lesions of the retina are prevented or greatly limited by these forms of treatment, and thus far no deleterious effects have been produced. If, as Frenkel[24] suggests, the retina and central nervous system somehow represent inadequately defended tissues, against which the ravages of *Toxoplasma* can easily prevail, active steps must be taken to increase the efficiency of the immunologic defense systems in these

and other areas. Immunologic manipulation in the treatment of toxoplasmosis may achieve the same beneficial results in this disease that it has attained in malignant melanoma. At the very least, it is worthwhile to explore this avenue of approach fully in our never-ending search for the cure of toxoplasmosis.

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