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Experimental Ocular Toxoplasmosis in Naive and Primed Rabbits

Key Words
Experimental ocular toxoplasmosis
Rabbit model
Disease reactivation
Survival
Retinal detachment

Abstract

Purpose: Investigations of the course of ocular toxoplasmosis and the influence of a host's immunological status in an animal model would contribute to our understanding of the pathophysiology underlying this condition. In the current study, these aspects are addressed using naive and primed rabbits infected transvitreally with the non-cyst-forming BK strain of *Toxoplasma gondii.* **Materials and Methods:** Of 45 latex agglutination test-negative rabbits, 27 were infected subcutaneously with 5,000 *Toxoplasma* tachyzoites, and the ensuing infection treated by systemic administration of clindamycin for 20 days. Four of these rabbits died from generalized infection. The remaining 23 primed rabbits were then inoculated periretinally with a further 5,000 *Toxoplasma* tachyzoites, administered via the transvitreal route; the 18 naive rabbits were treated likewise. **Results:** All 18 naive and 21 of the 23 primed rabbits developed toxoplasmic retinochoroiditis. As regarded progression of the disease, dissemination of the condition ($p = 0.0001$), degree of vitreal infiltration ($p = 0.0001$) and incidence of retinal detachment ($p < 0.05$) were all more pronounced in the naive group. Despite treatment, 4 of the 18 (22%) naive rabbits died from generalized infection, as did 4 of the 27 (15%) subcutaneously infected ones (prior to periretinal infection). In the primed (secondarily infected) animal group, only moderate signs of systemic infection were manifested, and there were no fatalities. **Conclusion:** The high incidence (>90%) of retinochoroiditis achieved even in primed animals, by introducing *Toxoplasma* tachyzoites via the transvitreal route, may reflect the maintenance of an intact uveovascular barrier during the early stages of the disease. The pattern of infection, in being restricted primarily to the retina, mimics the situation evinced in humans. Regarding propagation of the disease, the condition manifested in naive rabbits resembles that occurring in immunodeficient patients, whereas that evoked in primed animals corresponds to recurrence of infection in immunocompetent patients.

Introduction

In 1946, Johnson [1] introduced a neutralizing antibody test to assist in the diagnosis of 'human toxoplasmic choroiditis'. The importance of this condition in the etiology of chorioretinal disease was, however, not fully appreciated until 1952, when Wilder [2] demonstrated histologically that in many of such manifestations, the causative agent was *Toxoplasma gondii* and not, as previously supposed, the lues or tuberculosis bacterium. Since this time, toxoplasmic

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retinochoroiditis has received increasing attention, and numerous reports have described a variety of clinical manifestations of this condition [3]. Attempts to lay down criteria for an unequivocal laboratory confirmation of the clinical diagnosis have been even more concerted [4–6], but unrewarded. Unfortunately, data revised, from the analysis of paired serum and aqueous humor samples do not always tally with clinical activity [5], and this may reflect our poor understanding of the distinct pathophysiology and immunological dynamics involved in this condition. In an endeavor to investigate diagnostic as well as therapeutic aspects of ocular toxoplasmosis, this disease has been induced experimentally in several animal models [7], but an appropriate simulation of the human situation has not been achieved.

In this study, we describe the clinical manifestations and course of experimental ocular toxoplasmosis in naive and primed rabbits infected periretinally via the transvitreal route, using a modification of the technique described by Culbertson et al. [8]. This mode of injection may have advantages over the commonly applied suprachoroidal one, and these are discussed in the light of our own findings and those of other authors.

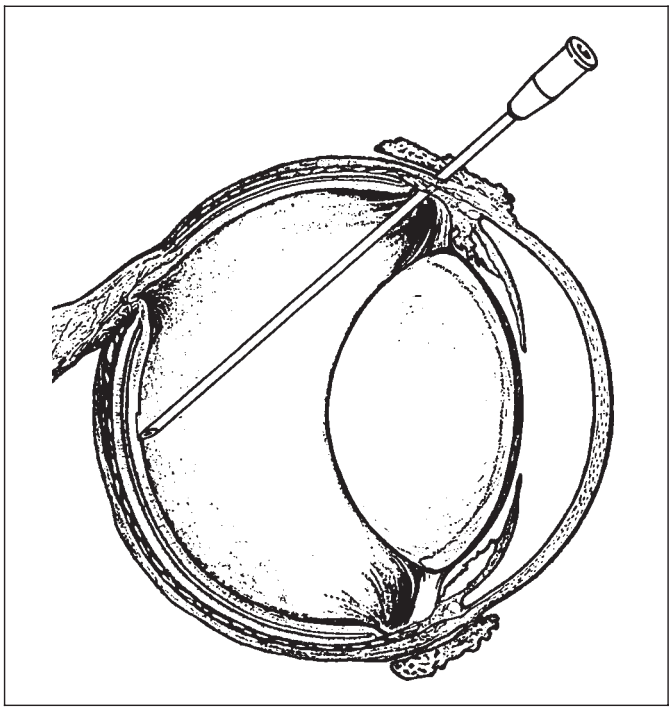


Fig. 1. Transvitreal route for inoculating *Toxoplasma* tachyzoites periretinally into the rabbit eye under indirect ophthalmoscopic control. Entry is effected via the pars plana, at the site of insertion of the superior rectus muscle (4–5 mm behind the limbus).

Materials and Methods

The BK strain of *T. gondii* is a non-cyst-forming clinical isolate, which shares many antigenic properties and symptomatic features [9, 10] with the RH strain [11]. The parasite was grown in Vero cell cultures using Eagle's minimal essential medium supplemented with 10% fetal calf serum, 0.1 mg/ml gentamycin and 25 μg/ml amphothericin B, and in a humified atmosphere containing 5% CO_2 at 36°C.

Prior to infection, the cell culture supernatant was withdrawn and cell debris allowed to sediment for 6–8 h. The resulting supernatant was aspirated and the tachyzoites sedimented by centrifugation at 1,700 *g* for 15 min; they were then resuspended in phosphate-buffered saline (pH 7.4) to a final concentration of 100 tachyzoites/μl. Parasite motility was assessed by phase-contrast microscopy (Leitz Wetzlar, Germany). Tachyzoites obtained between passages 7 and 15 were used as a source for infection experiments; their viability was verified by inoculation of an aliquot in HEp-2 cell cultures after each rabbit infection experiment.

Forty-five brown Burgundy rabbits of either sex, 4–5 months of age, and with body weights between 2.5 and 3.5 kg, were included in this study after approval by the National Health Authorities and the Local Veterinary Ethical Committee. All animals tested negative for the presence of serum anti-*Toxoplasma* antibodies. Twenty-seven rabbits (primed animal group) were injected subcutaneously with 5,000 tachyzoites in 50 μl of phosphate-buffered saline (pH 7.4), and the ensuing systemic infection treated between days 8 and 28 by intramuscular administration of clindamycin (25 mg/kg body weight/day); of these, 4 died from generalized infection. After recovery, the remaining 23 rabbits were observed at fixed time intervals for a further 2 months. The development of humoral immunity was assessed by periodic analysis of serum and aqueous humor samples. The remaining 18 rabbits (naive animal group) remained untreated throughout the entire 3 month period.

Each eye of the 41 rabbits (23 primed; 18 naive) then underwent fundoscopic examination to check for the absence of preexisting retinal scars. For this purpose, animals were maintained under general anesthesia (ketamine: 15 mg/kg body weight; xylazoline: 10 mg/kg body weight). Mydriasis was induced using 0.5% tropicamide eye drops. Gentamycin was administered (0.3% drops into the conjunctival sac and a single intramuscular injection of 4 mg/kg body weight) immediately prior to transvitreal inoculation as a prophylactic measure against bacterial endophthalmitis.

Transvitreal infection of the left eye of each rabbit was achieved under indirect ophthalmoscopic control using a 24-gauge needle, which was introduced 4 mm behind the limbus and then forwarded across the vitreous until contact with the retina was realized (fig. 1). An inoculum of 5,000 *Toxoplasma* tachyzoites contained within 50 μl of phosphate-buffered saline (pH 7.4) was discharged from a tuberculin syringe periretinally, near the retinal wing at the posterior pole. The postoperative treatment protocol included daily administration of 1% atropine eye drops between days 0 and 28 and intramuscular injection of clindamycin (25 mg/kg body weight) between days 8 and 28. The course of infection was assessed on a daily basis up to 5 days; thereafter on days 10, 15, 21, 28, 42 and 60. A scoring system was devised to grade the severity of ocular infection (table 1). Statistical analyses were performed using the χ^2 test for proportions and the Student's t test for quantitative (score) data.

Results

Local Disease Profile

Seven days after transvitreal inoculation of *Toxoplasma* tachyzoites, a retinochoroiditis had developed in each of the 18 naive (100%) and in 21 of the 23 (91%) primed rabbits ($p = 0.3085$). The infection was further characterized by dissemination of retinochoroiditis, vitreal infiltration and retinal detachment, all of which were more pronounced in the naive animal group (table 2).

Naive rabbits developed disseminating retinitis, with secondary involvement of the choroid, this condition having been elicited presumably by multiplication and subsequent periretinal spread of parasites beyond the inoculation site (fig. 2a). In primed rabbits, the retinochoroiditis remained discrete (multiplication damped by prior immunization) and was restricted to several satellite foci located in the vicinity of the inoculation site.

In naive rabbits, vitreal infiltration progressed from a moderate effusion on day 5 to a dense exudation, including fibrin, cells and a Tyndall effect, between days 5 and 20, which hampered fundoscopy. By day 42, these symptoms had cleared up almost completely, but the resumption of purposeful fundoscopic examination then revealed that epiretinal membranes had formed during the interim period. These were, however, restricted to the region around the inoculation site (fig. 2b) and did not progress. Vitreal infiltration was accompanied by marked elevation of anterior chamber cell count and protein content, but fibrin exudation into this region remained moderate and was restricted to the period between days 5 and 20. In primed rabbits, vitreal and anterior chamber infiltration with cells, protein and fibrin was observed between days 10 and 20, but the effusion was moderate and never dense enough to handicap fundoscopy (fig. 3).

Between days 6 and 15, 10 of 18 (56%) naive, and 3 of the 23 (13%) primed rabbits developed an exudative retinal detachment, and this was not always confined to the inoculation site ($p < 0.05$); the extent to which this condition progressed did not differ significantly between the two animal groups ($p = 0.087$).

Systemic Effects

At the peak of infection (days 6–12), the body temperature of naive rabbits was markedly elevated, and these animals stopped feeding from day 8 or 9 onwards for the following 8–10 days; 4 of the 18 periretinally infected (22%) and 4 of 27 (15%) subcutaneously infected rabbits died from generalized infection between days 9 and 16, despite systemic treatment ($p = 0.8113$). Primed animals manifested a moderate (if any) increase in body temperature and a slightly reduced food uptake for 8 days after the peak of infection, but there were no deaths in this group ($p = 0.0644$).

Ocular Complications

A small granuloma developed at the scleral site of injection in 1 naive rabbit. Also within this group, the lens of 1 animal was inadvertently contacted during transit of the inoculating needle, but a cataract did not ensue. In one of the primed animals, the development on day 1 of a retinal detachment involving the inoculation site was presumed to have been elicited by mechanical damage incurred during

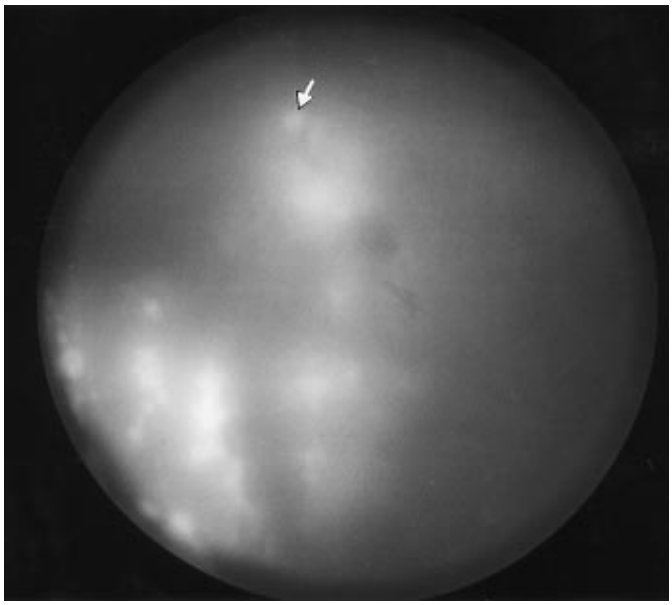
Table 1. Grading of retinochoroiditis

Parameter	Score	Definition
Dissemination of retinochoroiditis	0	no dissemination
	1	1 focus distinct from inoculation site
	2	2–5 satellite foci
	3	>5 satellite foci
	4	multiple confluencing foci, retinal necrosis
Vitreal infiltration	0	no infiltration
	1	moderate (focal) infiltration
	2	marked (diffuse) infiltration
	3	severe infiltration, view of fundus obscured
	4	infiltration thwarts fundus examination
Retinal detachment	0	no detachment
	1	detachment <2 papilla diameters in extent
	2	detachment involving up to 1 quarter of retina
	3	detachment involving <75% of retina
	4	total detachment (>75% of retinal surface involved)

Table 2. Course of experimental ocular toxoplasmosis in naive and primed rabbits

Parameter	Naive rabbits	Primed rabbits	p value
Development of retinitis or retinochoroiditis	18/18 (100%)	21/23 (91%)	0.3085
Dissemination of retinochoroiditis (score[1])	2.88±0.99	1.65±1.03	0.0001
Vitreal infiltration (score[1])	2.44±0.62	1.63±0.65	0.0001
Retinal detachment	10/18 (56%)	3/23 (13%)	0.0495
Retinal detachment (score[1])	1.50±1.62	0.65±1.47	0.087

[1] Mean ± SD.



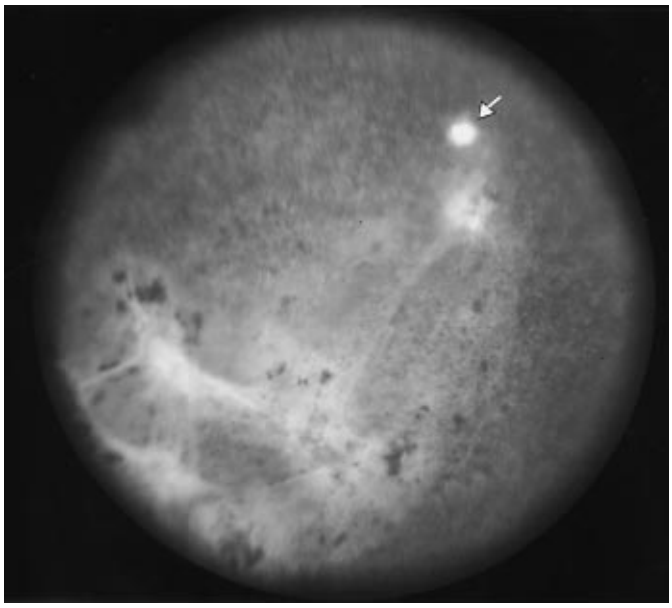


Fig. 2.a Disseminating retinitis, 5 days after transvitreal inoculation of *Toxoplasma* tachyzoites periretinally in a naive rabbit. Arrow denotes inoculation site. **b** Diffuse retinochoroidal scar involving a large area around the inoculation site, 42 days after transvitreal infection of a naive rabbit with *Toxoplasma* tachyzoites. Note the occurrence of marked membrane formation originating at the inoculation site (arrow).

injection rather than being a consequence of infection. No other ocular complications were observed except for an anticipated [12] circumscript bleeding from the retina at the inoculation site in 25% of the animals within each group. In no instance retinal perforation was induced.

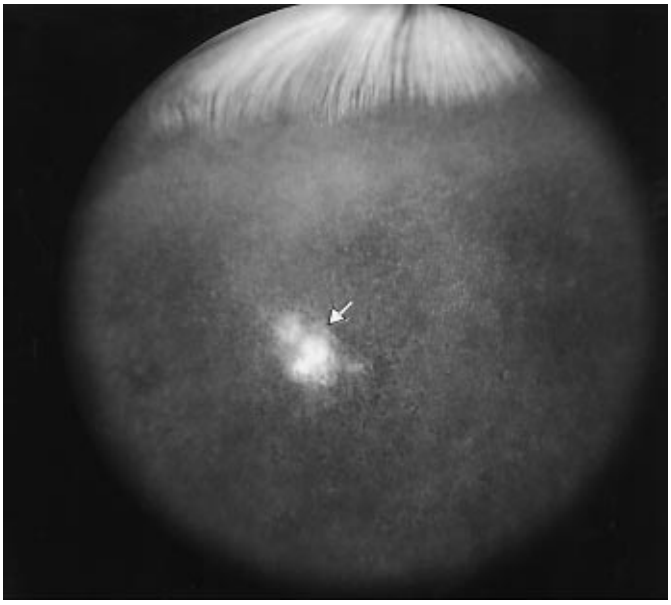


Fig. 3. Circumscript scar manifested after healing of *Toxoplasma* retinitis in a primed rabbit, 28 days after transvitreal inoculation of *Toxoplasma* tachyzoites. Arrow denotes inoculation site.

Discussion

In this report, we describe a higher morbidity in naive as compared to primed rabbits with ocular toxoplasmosis. We also observed that, after transvitreal inoculation of *Toxoplasma* tachyzoites, retinochoroiditis can be reproducibly induced even in primed rabbits with high dye test titers. This is most likely achieved by a prolonged maintenance of the uveovascular barrier after transvitreal as compared to suprachoroidal inoculation; this may also account for the high incidence of fatalities in naive rabbits.

Rabbits are known to have a genetically determined low resistance against infection by *Toxoplasma* [13–15], and this situation will, of course, be either tempered or exacerbated in accordance with the virulence and antigenicity of the parasite strain involved [16]. Prognosis may, moreover, be even poorer if intraocular propagation of the parasite is implicated. This may reflect deferred violation of the blood-retinal barrier, which will have the effect of delaying neutralization by the immune system. Such an explanation would account for the greater severity of systemic symptoms manifested in naive as compared to primed rabbits, a finding which has not previously been reported.

The immunoreactivity of animals with low and negative anti-*Toxoplasma* antibody titers does not differ [8, 17–19], but attempts to induce retinochoroiditis in primed nonhu-

man primates with high dye-test titers have failed, and this may reflect a situation in which the parasite has been neutralized before multiplication [18]. Consistent with this concept is the finding of Newman et al. [12] that systemic injection of *Toxoplasma* antigen in primed primates failed to induce a uveal reaction, whereas transvitreal inoculation elicited an inflammatory response characterized by vitritis, retinal vasculitis and edema.

Ocular toxoplasmosis was first induced experimentally by Hogan [20] in 1951, using naive rabbits and an intracarotid mode of injection of *Toxoplasma* tachyzoites. Two years later, Frenkel [21] demonstrated an ocular involvement in primed animals (hamsters), but only after chronic systemic infection with certain low-virulent strains of *T. gondii*, and in 1954, Jacobs et al. [22] and Beverley et al. [23] independently described the induction of ocular toxoplasmosis by local injection of the parasites into the anterior chamber of rabbits. Using this technique, Beverley et al. [23] observed iritis, the severity of which depended on the strain inoculated. Owing to the presence of fibrinous exudates, they were not able to perform fundoscopic examination, but histological analysis revealed choroidal infiltration and *Toxoplasma* cysts in all uveal tissues [24].

The potential of the transscleral route as a means of introducing various fluids into the suprachoroidal space had been investigated 7 years earlier by Vogel [25]. Although access to this region was achieved reproducibly, injection was associated with the not inconsiderable risk of producing retinal defects, as found by Nozik and O'Connor [26], who subsequently adopted this technique for eliciting toxoplasmic chorioretinitis in rabbits; they described the development of chorioretinal lesions involving primarily the choroid. This finding is consistent with Vogel's [25] observation that antigens and bacteria injected into the suprachoroidal space tend to migrate to the choroidal vessel walls, where they cause a minor structural disturbance and transient hyperemia; such damage would clearly facilitate an early systemic dissemination of *Toxoplasma* tachyzoites. Hence, the disease profile manifested after suprachoroidal inoculation involves an initial local infection followed by a very early systemic one, and, as such, the situation is not immunologically comparable to that evinced in humans [19]. Its value as a model for imitating and of deriving useful information pertaining to the clinical situation is therefore limited. As mentioned above, failure to induce ocular toxoplasmosis in systemically primed nonhuman primates with a high dye-test titer may be attributed to neutralization of parasites before amplification [18]. A comparable situation may be envisaged when the suprachoroidal route of infection is adopted [27], and may similarly account for the failure to induce ocular toxoplasmosis in primed rabbits reported by several groups [19, 26, 28]. The detection of circulating antigen both prior to and shortly after the development of ocular lesions (when manifested) in rabbits supports this contention [29]. Hogan et al. [30] were the first to explore the possibility of inducing ocular toxoplasmosis by injecting parasites intravitreally into guinea pigs, and Kaufman [31] later adopted this model to study therapeutic modalities. He observed vasculitis with fibrinous exudation into the anterior chamber and vitreous, diffuse retinal infiltration, and disorganization of the retina and choroid.

Culbertson et al. [8] employed the transvitreal route for inducing ocular toxoplasmosis in monkeys, and found the technique to be a suitable one for studying this disease, violation of the vitreal cavity being, in their opinion, the principal drawback. The blood-retinal barrier may, however, be better maintained using this rather than the suprachoroidal approach, at least during the initial phase of the infection. This will hinder the development and modification of immunity [19], i.e., as set against a background of the selectively impaired, but incompletely understood, delayed-type hypersensitivity response pertaining in isolated ocular diseases [32], by which means the human condition will be more closely approximated. That transvitreal inoculation does not cause an immediate compromise of the uveovascular barrier is indicated by the successful induction of ocular toxoplasmosis even in primed rabbits, and also by the occurrence of fatalities solely in the naive animal group, when breakdown is ultimately induced at the peak of infection.

Recurrent ocular toxoplasmosis is, according to old and current opinions, a consequence of tissue cyst rupture with an ensuing liberation of parasites [33]. However, since the injection of 500 parasites does not elicit ocular toxoplasmosis in primed animals [8, 18, 34], and the introduction of 5,000 tachyzoites induces only a moderate and focal retinochoroiditis with no signs of systemic involvement, rupture of a cyst would have to liberate at least 5,000 virulent parasites at once for this to be the sole reactivation mechanism, and this is extremely unlikely.

Hence, our findings furnish evidence that other, probably immunologic, factors are involved. This has, indeed, been suggested, although not proven, by other groups [34, 35].

Clearly, the rabbit model of experimental ocular toxoplasmosis does not closely resemble the human situation in every pertinent detail, there being important immunological as well as anatomical differences between the respective eyes. Indeed, it is in relation to the latter that the principal constraint for adapting the transvitreal technique to the rabbit model lies, namely, in the risk of traumatizing the large

lens. Albeit so, when entry is effected at the site of insertion of the superior rectus muscle, i.e. 4–5 mm posterior to the limbus, this potential hazard is minimized and, in our hands, lens damage was incurred in a single instance only. Inadvertent damage to the retina, with resulting detachment, was also observed but once. Hence, despite its limitations, adaptation of the pars plana route of inoculating *Toxoplasma* tachyzoites offers a further approximation to the clinical and morphological changes manifested in human ocular toxoplasmosis and may, at least partially, obviate the need for experiments with nonhuman primates.

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References

1 Johnson LV: Use of neutralizing antibody test in the diagnosis of human toxoplasmic choroiditis. Arch Ophthalmol 1946;36:677–684.
2 Wilder HC: Toxoplasma chorioretinitis in adults. Arch Ophthalmol 1952;48:127–136.
3 Tabbara KF: Toxoplasmosis; in Duane (ed): Ocular Diseases. Churchill Lipinscott Inc., 1990, vol 4, chapt 46, pp 1–23.
4 Desmonts G: Definite diagnosis of ocular toxoplasmosis. Arch Ophthalmol 1966;76:839–851.
5 Kijlstra A, Luyendijk L, Baarsma GS, Rothova A, Schweitzer CM, Timmermann Z, et al: Aqueous humor analysis as a diagnostic tool in toxoplasma uveitis. Int Ophthalmol 1989;13: 383–386.
6 Rothova A: Ocular involvement in toxoplasmosis. Br J Ophthalmol 1993;77:371–377.
7 Darcy F, Zenner L: Experimental models of toxoplasmosis. Res Immunol 1993;144:16–23.
8 Culbertson WW, Tabbara KF, O'Connor GR: Experimental ocular toxoplasmosis in primates. Arch Ophthalmol 1982;100:321–323.
9 Winser J, Verlinde JD, van Thiel PH, Davel J, van der Elst P: Isolation of Toxoplasma from cerebrospinal fluid of a living child in Holland. Proc Soc Exp Biol Med 1948;67:292–294.
10 Gross U, Roos T, Appoldt D, Heesemann J: Improved serological diagnosis of *Toxoplasma gondii* infection by detection of immunoglobulin A (IgA) and IgM antibodies against p-30 by using the immunoblot technique. J Clin Microbiol 1992;30:1436–1441.
11 Sabin AB: Toxoplasmic encephalitis in children. JAMA 1941;116:801–807.
12 Newman PE, Ghosheh R, Tabbara KF, O'Connor GR, Stern W: The role of hypersensitivity reactions to Toxoplasma antigens in experimental ocular toxoplasmosis in nonhuman primates. Am J Ophthalmol 1982;94:159–164.
13 Jacobs L: Propagation, morphology, and biology of Toxoplasma. Ann NY Acad Sci 1956;64: 154–179.
14 Olisa EG, Herson J, Headings VE, Poindexter HA: *Toxoplasma gondii:* Survival time and variability in mouse host strains. Exp Parasitol 1977;41:307–313.
15 Fuji H, Kamiyama T, Hagiwara T: Species and strain differences in sensitivity to Toxoplasma infection among laboratory rodents. Jpn J Med Sci Biol 1983;36:343–346.
16 Eyles DE, Coleman N: Relationship between size of inoculum to time of death in mice infected with *Toxoplasma gondii.* J Parasitol 1956;42: 272–275.
17 Huldt G: Experimental toxoplasmosis: Effect of inoculation of Toxoplasma in seropositive rabbits. Acta Pathol Microbiol Scand 1966;68: 592–604.
18 Webb RM, Tabbara KF, O'Connor GR: Retinal vasculitis in ocular toxoplasmosis in nonhuman primates. Retina 1984;4:182–188.
19 Friedrich R, Müller WA: Der Einfluss einer subretinalen Injektion von *Toxoplasma gondii* auf den Serumantikörperspiegel in einem Kaninchenmodell der Augentoxoplasmose. Angew Parasitol 1989;30:15–17.
20 Hogan MJ: Ocular Toxoplasmosis. New York, Columbia University Press, 1951. Cited from Frenkel JK: Ocular lesions in hamsters with chronic Toxoplasma and Besnoitia infection. Am J Ophthalmol 1955;39:203–225.
21 Frenkel JK: Host, strain and treatment variation as factors in the pathogenesis of toxoplasmosis. Am J Trop Med Hyg 1953;2:390–415.
22 Jacobs L, Hart WM, Ryan RW, Cook MK: The production of experimental ocular toxoplasmosis in rabbits. Acta VII Conc Ophthalmol 1946–1953, 1954. Cited from Jacobs L, Melton ML, Kaufman HE: Treatment of Experimental Ocular Toxoplasmosis. Arch Ophthalmol 1964;71: 145–152.
23 Beverley JK, Beattie CP, Fry BA: Experimental toxoplasmosis of the uveal tract. Br J Ophthalmol 1954;38:489–496.
24 Beverley JK: Experimental ocular toxoplasmosis. Surv Ophthalmol 1961;6:897–905.
25 Vogel AW: Experimental fundal lesions: A method and observations. Arch Ophthalmol 1954;51:535–548.
26 Nozik RA, O'Connor GR: Experimental ocular toxoplasmic retinochoroiditis. Arch Ophthalmol 1968;79:485–489.
27 Wilson CB, Remington JS: Activity of human blood leucocytes against *Toxoplasma gondii.* J Infect Dis 1979;140:890–895.
28 Friedrich R, Simon HU, Müller WA, Sych FJ: Ocular toxoplasmosis: The role of cellular immune defense in the development of recurrences. Ger J Ophthalmol 1992;1:54–57.
29 Rollins DF, Tabbara KF, O'Connor GR, Araujo FG, Remington SG: Detection of toxoplasmal antigen and antibody in ocular fluids in experimental ocular toxoplasmosis. Arch Ophthalmol 1983;101:455–457.
30 Hogan MJ, Zweigart PA, Lewis A: Persistance of *Toxoplasma gondii* in ocular tissues. Am J Ophthalmol 1956;42:84–89.
31 Kaufman HE: The effect of corticosteroids on experimental ocular toxoplasmosis. Am J Ophthalmol 1960;50:919–925.
32 Streilein JW: Immune regulation and the eye: A dangerous compromise. FASEB J 1987;1:199–208.
33 Frenkel JK, Jacobs L: Ocular toxoplasmosis: Pathogenesis, diagnosis, and treatment. Arch Ophthalmol 1958;59:260–279.
34 Nozik RA, O'Connor GR: Studies on experimental ocular toxoplasmosis in the rabbit. III. Recurrent inflammation stimulated by systemic administration of antilymphocyte serum and normal horse serum. Arch Ophthalmol 1971; 85:718–722.
35 Holland GN, O'Connor GR, Diaz RF, Minasi P, Wara WM: Ocular toxoplasmosis in immunosuppressed nonhuman primates. Invest Ophthalmol Vis Sci 1988;29:835–842.