PERSPECTIVE

Toxoplasma gondii and ocular toxoplasmosis: pathogenesis

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The protozoan *Toxoplasma gondii* is an obligate intracellular parasite that can infect any warm blooded animal,[1] as well as reptiles and fish,[2-4] and shows a high incidence in humans, with approximately 500 million people throughout the world having antibodies to *T gondii*.[5] The organism is ubiquitous in nature and produces one of the most common infections of humans.[4] It is the most common cause of retinochoroiditis worldwide in humans,[6] with figures ranging from 28% to 55% of all cases of posterior uveitis.[7-9] Even though the causative organism was described at the beginning of the century,[10 11] the life cycle was only understood in 1970,[12] and most of the aspects related to the interactions between the parasite and the host are still unknown. The formation of tissue cysts after an acute infection, which shows a predilection for some organs, is still poorly understood. The mechanism for the recurrences of the infection, with its most devastating consequences in the eye and the brain, has not been elucidated. Loss of visual acuity occurs as a direct consequence of lesions affecting the macula or optic nerve, or secondary to massive vitreous involvement, and also as the result of vascular changes in the retina or subretinal space. This paper tries to summarise the knowledge related to the pathogenesis of ocular toxoplasmosis, including aspects related to its transmission, clinical manifestations, and some studies on animal models that may allow a better understanding of this disease.

Life cycle

The Felidae are the definitive hosts for *T gondii* [1 13] and after primary infection millions of resistant oocysts are shed in the faeces in a single day.[1 4] Oocysts are shed in the faeces for periods varying from 7 to 20 days with peak production between days 5 and 8.[4] Infected cats rarely show signs of illness, and after repeated infections there is usually minimal or no oocyst shedding although some animals can shed oocysts intermittently.[14] The oocysts are initially unsporulated and thus not immediately infective. After 1 to 4 days at room temperature they become infective, and may remain so for more than 1 year in warm, moist soil.[15-17] Oocysts do not sporulate below 4 °C or above 37 °C.[18] When fully sporulated oocysts are ingested by intermediate hosts they give rise to the extracellular forms or tachyzoites.[4] The tachyzoites are crescent shaped, and they have pellicle (outer covering), polar ring, conoid, rhoptries, micronemes, mitochondria, subpellicular microtubules, endoplasmic reticulum, Golgi apparatus, ribosomes, rough endoplasmic reticulum, micropore and a well defined nucleus.[19] In intermediate hosts only the asexual phase develops, with tachyzoites responsible for the acute form of the disease and bradyzoites for the chronic infection, inside cysts. Penetration of host cells occurs very rapidly (15–30 seconds),[20] primarily by active invasion[20-22] with only a few, probably non-viable organisms, entering by phagocytosis, the mechanism previously proposed by others as the main method of penetration[23] (Figs 1 and 2).

The significance of different strains of *T gondii* and their interaction with the host in the pathogenesis of systemic or ocular disease is not entirely clear, but some recent findings have shed some light on this issue. The fact that subsequent passage of the same *Toxoplasma* strain results in progressive increase of virulence, suggests that the host–parasite interaction plays a role in the degree of pathogenicity.[24] This issue is confused by the fact that virulent strains seem to become attenuated so as to survive and complete their life cycle.[25] This attenuation would be related to an innate cystogenic capacity of the parasite or to host induced mechanisms.[25] Recent studies looking at DNA polymorphism among *T gondii* strains have detected significant genetic heterogeneity differentiating virulent and non-virulent strains in mice.[26 27] A study in mice has shown that genetic factors of the host are important for the immune response against *T gondii*, which is ultimately responsible for the course and outcome of the infection.[28]

Host cell invasion and cyst formation

In active invasion two organelles play an important role—the conoid and the rhoptries. The conoid, located at the anterior end of the organism, moves by extension, retraction, and rotation,[29 30] and probably plays a mechanical role in invasion.[31] The rhoptries are elongated, fusiform organelles, located in the anterior half of the *Toxoplasma*, extending from the region of the nucleus through the conoid to the anterior plasmalemma. They show significant changes at the moment of cellular invasion. They shorten considerably, lose some of their dense content, and within seconds are found as small ovoid saccules at the anterior tip of the parasites. This occurs as the macrophage plasmalemma is disrupted and clusters of small vesicles are found in the host cell cytoplasm around the advancing tip of the parasite.[32 33] It is believed that the rhoptries contain enzymes that aid in the penetration of the host cell.[34-37] In 1986 Schwartzman produced monoclonal antibodies to *Toxoplasma* and selected four that produced fluorescence at the anterior pole of the parasites.[38] The antibodies were localised in rod-shaped bodies by immunofluorescence. The localisation by transmission electron microscopy was less convincing, but showed staining of dense bodies consistent with oblique sections of rhoptries although elongated rod-shaped organelles were not demonstrated. He obtained further information about the antibodies in assays of penetration enhancing factor obtained from conditioned culture medium. The antibodies that were earlier localised to the rhoptries reduced penetration enhancement by conditioned medium thus suggesting that the penetration enhancing factor is localised in the rhoptries. Later, a family of antigens that react with the same monoclonal antibody, therefore presumably sharing one common epitope, was characterised.[37] Using these monoclonal antibodies and immunocytochemistry they showed, by electron microscopy, that these antigens are localised in the *Toxoplasma* rhoptries of tachyzoites, bradyzoites, and sporozoites.

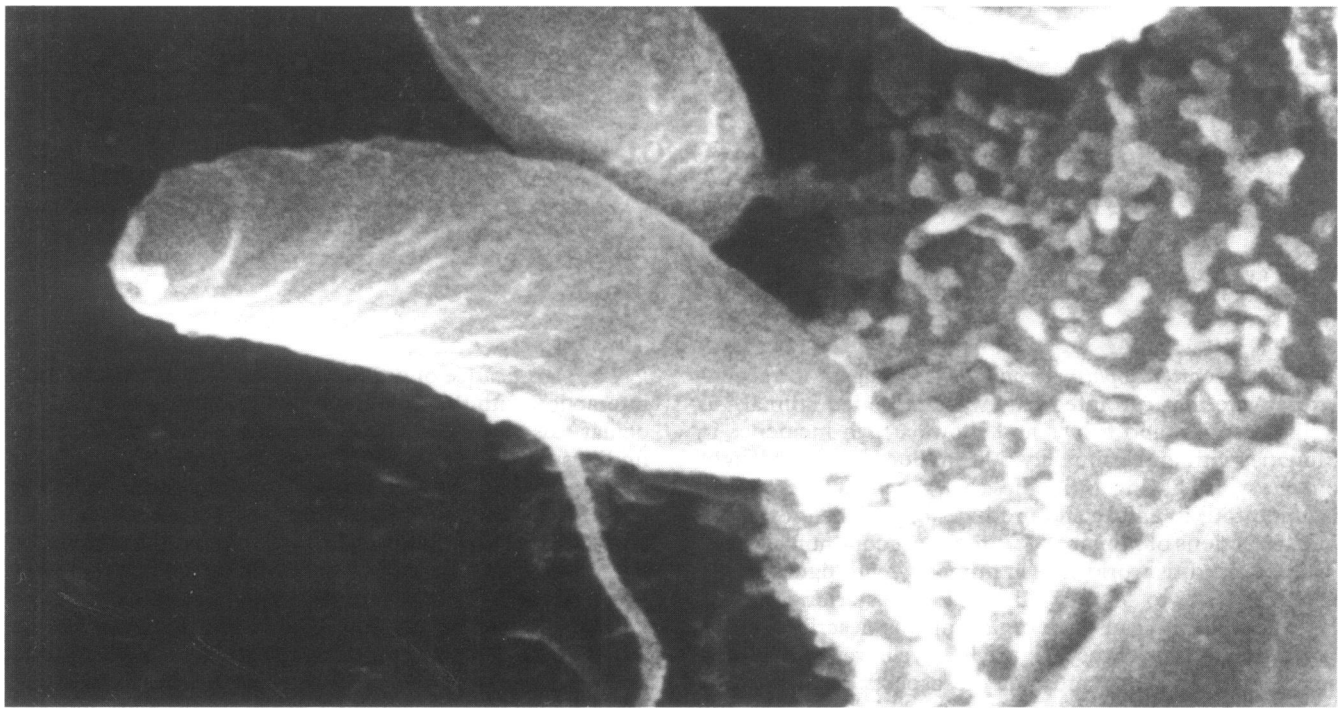

Figure 1 Scanning electron micrograph of Toxoplasma invading a heat inactivated macrophage. Note the spiral ridges indicating torsion of the parasite body. × 32 000. (From Chiappino ML et al, J Protozool 1984;31:288–92. Reproduced with permission of Society of Protozoologists.)

For a short time after invasion the parasites are partially free in the cytoplasm, but after approximately 15 minutes all of the parasites are located inside a parasitophorous vacuole that has a hybrid membrane composed of both host cell elements and of a membranous components originated from the rhoptries.[33]

Sibley *et al*[39] studied the parasitophorous vacuole of *Toxoplasma* and interpreted their results to indicate that proteins from the surface of *Toxoplasma* modified the membrane of the parasitophorous vacuole. Later it was shown that, in fact, an antigen localised within the anterior part of the parasite appeared in the host cell around the advancing tips of invading organisms and shortly thereafter appeared throughout the parasitophorous vacuole membrane.[36] They concluded that the antigen is secreted by *Toxoplasma* during invasion and becomes associated with the vacuole membrane shortly thereafter, thus confirming the findings of Nichols *et al*.[33]

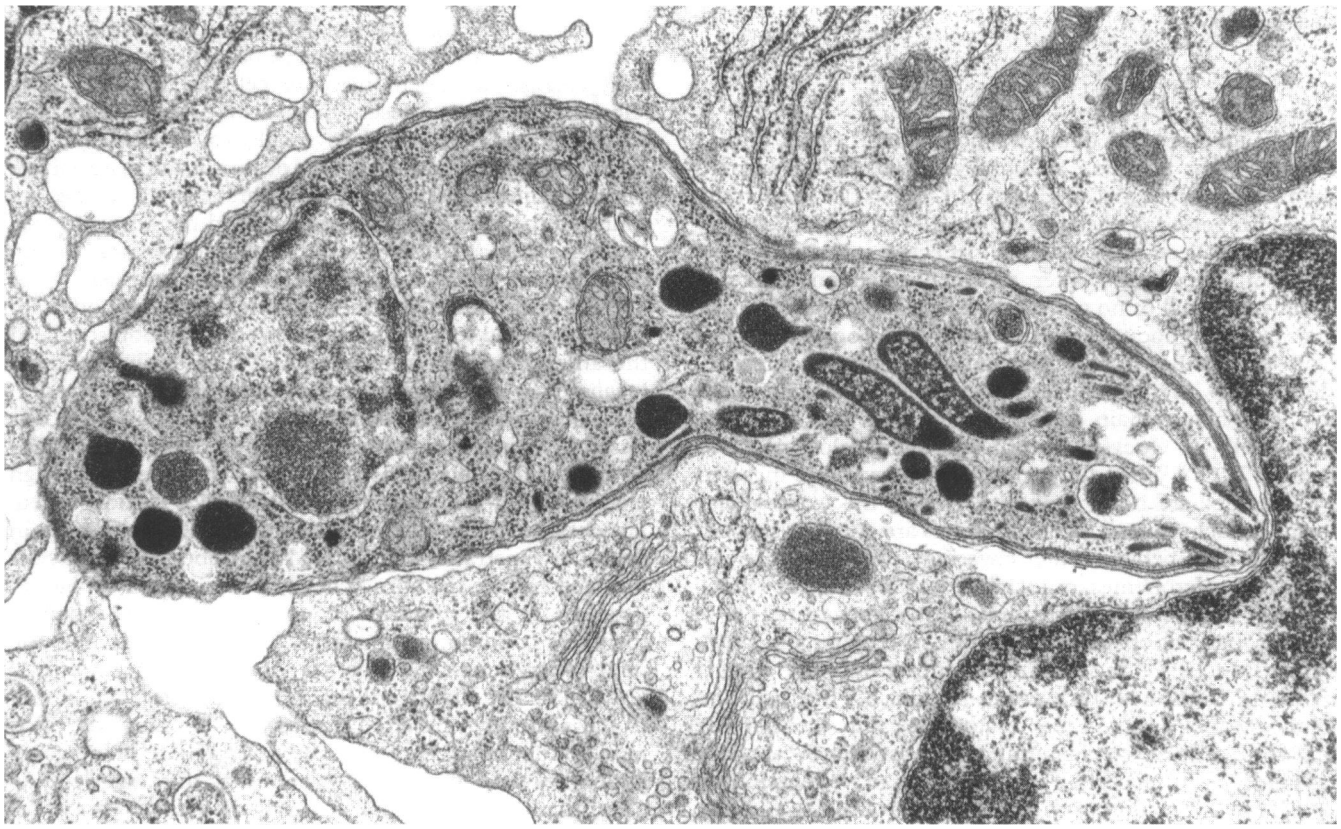

Figure 2 Toxoplasma parasite invading a peritoneal macrophage in vivo. Note the disruption and vesiculation of the host cell plasma membrane. × 33 600. (From Nichols and O'Connor, Lab Invest 1981;44:324–35. Reproduced with permission of the International Academy of Pathology.)

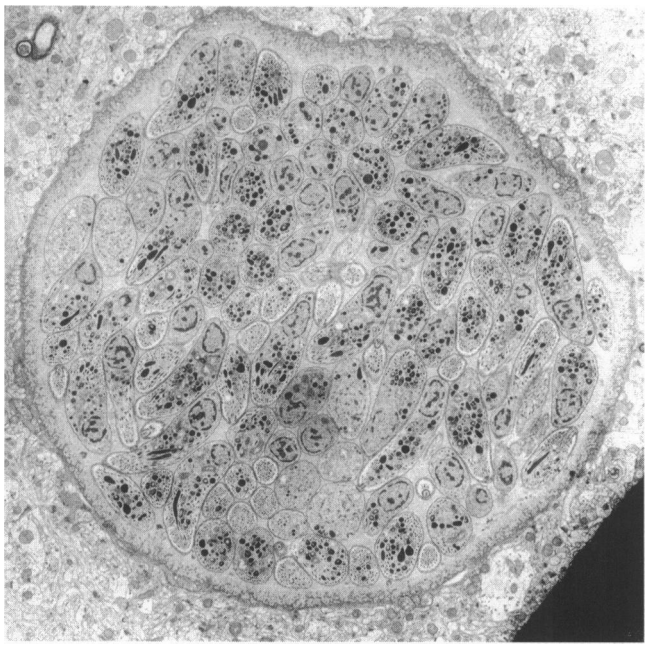

Figure 3 Cyst from the brain of a mouse inoculated with strain ME 49 Toxoplasma. × 3500. (From Pavesio et al, Parasitol Res 1992;78:1–9. Reproduced with permission of Springer-Verlag Press.)

Using an indirect immunocytochemical technique, Ferguson[40] also observed that *T gondii* antigens were present in the cyst wall and the ground substance of the cyst.

This mechanism of active invasion plays an important role in the survival of the *Toxoplasma* inside macrophages. By invading phagocytes, *Toxoplasma* organisms escape the lethal effects of the oxidative metabolites of the respiratory burst generated during phagocytosis.[41] The secretory product of the rhoptries also contributes to parasite survival. By altering the membrane of the parasitophorous vacuole, as pointed out above, the secretory product prevents lysosomal fusion.[42] The parasites, having safely arrived within the cell by evading the respiratory burst, are in a site protected from antimicrobial agents such as lysozyme, cationic proteins, lactoferrin, and the lowered pH that accompanies lysosomal fusion. In this environment the parasites are free to grow and replicate until immunity is established and maintained.[33]

The tissue cyst formed during this process is the 'resting' stage of the parasite (Fig 3). *T gondii* cysts are usually subspherical or conform to the shape of the host cell. The cyst wall is elastic, argyrophilic, and encloses up to several hundred crescent-shaped bradyzoites. The cyst wall is intimately associated with the host cell endoplasmic reticulum and mitochondria, and it is ultimately lined by granular material which also fills the space between bradyzoites.[1]

Transmission

Transmission of *Toxoplasma* to humans may occur by direct contact with contaminated soil, as in the case of workers in flower gardens or children playing in sandboxes, by the ingestion of food containing the tissue cysts, or vertically through the placenta.

The cysts are not invariably destroyed by freezing,[1 43] but can be eliminated by cooking meat to 70 °C (temperature at the centre of the roast).[1] Most studies indicate that beef is less frequently contaminated than pork or lamb.[1 44–47] The walls of cysts in infected meat are probably digested by peptic and tryptic digestive juice in the gastrointestinal tract, liberating free forms that are resistant up to 3 hours to these digestive secretions.[4 48]

ACQUIRED TRANSMISSION

Acquired transmission is probably the most common form of infection and causes a wide spectrum of presentations, varying from the most frequent subclinical lymphadenopathy[43 49–52] to fulminating pneumonitis and encephalitis, which is probably related to the virulence of different strains and to the immunological competence of the host.[43]

Other forms of transmission include blood transfusion from asymptomatic people with parasitaemia,[53 54] organ transplantation,[55] laboratory accident[53] and ingestion of raw cows' milk.[56] The penetration of tachyzoites via the conjunctiva has been described in an animal model using the guinea pig conjunctiva as the experimental mucosal tissue.[57] In this experiment the authors found that the parasites invaded both epithelial and goblet cells within 15 seconds and replicated within 4 hours; serological tests indicated that the infected animals responded to this route of inoculation with high antibody titres of 1:2000 to 1:64 000.

CONGENITAL

Transmission can also be congenital which is believed to result from acute but often subclinical maternal infection acquired during pregnancy.[58 59] The optimal conditions for transmission are the initial parasitaemia that occurs before development of cellular immunity in the mother and a well developed placental blood flow at the end of pregnancy.[4] Congenital disease may have several different manifestations including abortion, stillbirth, liveborn offspring with severe multiple organ involvement,[51] or offspring that are asymptomatic at birth but with neurological and ocular sequelae later in life,[51 60–62] depending on the time of infection during pregnancy.[59] The more severe sequelae are related to infection acquired from the second to the sixth month of pregnancy; transmissions in the third trimester are more frequent, but usually associated with subclinical disease.[59] It is important to note that infection acquired during pregnancy does not necessarily result in congenital infection. Some studies report incidences of 33%[61] and 44%[63] of fetal infections in these cases. According to Beverley[64] the strain of the parasite may be of importance when considering the possibility of transplacental transmission.

Congenital toxoplasmosis has never been convincingly demonstrated in consecutive surviving siblings,[65] except in twins,[66] and in these cases the severity of the disease may be greater in one infant.[67 68] In subsequent pregnancies following the birth of a child with congenital disease, the maternal humoral antibodies will protect subsequent fetuses from infection.[65 68 69] Reports demonstrating the presence of *Toxoplasma* in abortion materials from the same mother on more than one occasion,[70] could be explained, according to some authors,[71–73] by a chronic *Toxoplasma* infestation of the uterine wall. Perkins[65] has not found a typical congenital case of toxoplasmosis in surviving siblings, although he believes that abortions and stillbirth may result from this type of chronic uterine infestation.

Ocular toxoplasmosis has been considered by many authors as primarily a result of congenital infection.[65 74 75] Even in the cases where no previous scar is visible in the retina of an adult, they consider that the inflammation may result from rupture of cysts present in the nerve fibre layer of the retina since birth. The arguments in favour of a congenital origin were based on the fact that few cases of retinochoroiditis have been found in association with active, acquired systemic disease.[74] However, authors have reported cases of retinochoroiditis in patients with acute acquired toxoplasmosis, confirmed by high titres of IgM detected by indirect immunofluorescence.[75–78] In a recent report, eight patients with unilateral focal retinochoroiditis had positive IgM antibodies against *T gondii* and seven of

them had concurrent high IgG levels.[79] According to these reports, retinochoroiditis can occur with acquired toxoplasmosis, although it is rare, and is most commonly seen in cases of toxoplasmic encephalitis.[65] The importance of acquired *Toxoplasma* infection in the pathogenesis of ocular disease was demonstrated by a study which described families, with no twins, in which three to six siblings had documented retinochoroiditis; many of these patients had IgM serum antibodies suggesting a recently acquired infection.[79]

Chronicity and recurrences

After an active infection the disease enters a chronic stage when tissue cysts are formed mainly in the brain, skeletal muscles, heart, and eyes.[1 43] In these tissues, cysts will form as early as 8 days after infection[43] and they eventually may contain hundreds or thousands of organisms that show slow metabolic activity and are known as bradyzoites. The cysts have been described as intracellular by some authors, being very well tolerated by tissues, with usually few or even no inflammatory cells around them.[40 80] This protection against the host's immune mechanisms may be explained by the fact that no extracellular *Toxoplasma* antigens could be demonstrated by indirect immunocytochemistry.[40]

The signal for the formation of cysts is not clear but many studies have demonstrated that the beginning of the host's immune response may be an important factor.[6 81 82] However, the formation of cysts as early as 7 to 8 days in acute infections of animals[83] and the formation of cysts in tissue cultures in the absence of an immune reaction[84 85] do not support this theory. The fact that only a few tissues are involved in the chronic stage and that cysts start forming while active proliferation is still occurring might suggest that a major role is played by the type of host cell involved.[81 86] Cysts may persist throughout life without evoking host tissue response[1 4 40 87] or may suffer intermittent rupture and then cause recurrences of the infection.[86 87]

The sporadic attacks of retinochoroiditis may be associated with rupture of tissue cysts,[88 89] although the breakdown of cysts has never been observed in human retinas.[6] A hypersensitivity reaction to *Toxoplasma* antigens released from cysts was proposed by Frenkel,[90] in his hamster studies, as another possible explanation, based on the observation that recurrent lesions are generally self limited and short lived. Such a response was considered more consistent with hypersensitivity reactions than with invasion of retinal cells. A study of experimental ocular toxoplasmosis in primates demonstrated that the injection of dead organisms directly inside the eye did not produce substantial retinal necrosis, indicating that the constituents of the *Toxoplasma* organism alone can not produce the same results as active retinal infections by live organisms.[9] These authors feel that both acute and recurrent types of necrotising retinochoroiditis are due to the multiplication of *Toxoplasma* parasites in the retina.

Another theory related to the recurrence of the ocular disease was promulgated by other authors,[91] who proposed that the mechanism is related to the development of hypersensitivity to retinal autoantigens. They suggest that patients become sensitised to autoantigens released from the rods' outer segments, since peripheral lymphocytes from patients with recurrent ocular toxoplasmosis respond to retinal S-antigen, a soluble autoantigen of the rod outer segment.

The study by Frenkel and Escajadillo[89] in monkeys reports that more than half of the glial nodules in the brain of infected animals are of toxoplasmic origin, supporting the concept of cyst rupture against hypersensitivity, since hypersensitivity would not induce this type of inflammatory reaction. At this moment there is no definitive conclusion about the origin of recurrences, and it is even possible that the inflammation is due to a combination of all the mechanisms mentioned above.

The mechanism by which tissue cysts break down is still poorly understood. In 1958, Beverley[92] proposed that the increase in number of bradyzoites within the cyst after prolonged duration of the infection causes the cysts eventually to burst. Some authors have shown that cysts increase in size from 11 days to 6 months after inoculation,[82 93] which is associated with the proliferation of the organisms, but not thereafter. Although the majority of cysts contained tightly packed organisms, approximately 40% of older cysts (6–22 months) contained loosely arranged bradyzoites embedded in electronlucent ground substance.[93] In a study of the differentiation of *T gondii* bradyzoites, many cysts containing a mixture of intact and degenerating parasites were described.[94] Some cysts contained primarily mature bradyzoites and others displayed predominantly degenerated bradyzoites, suggesting a longer period of development, and also progressive changes inside the cysts. This fact explains the finding by Ferguson and Hutchison[93] of fewer organisms inside older cysts and raises the issue of the possible role of lytic enzymes, released from degenerating organisms, in the internal weakening of the cyst wall and cyst rupture. These results contradict the possibility of a mechanical explosion of the cysts. The possible role of endogenous enzymes, as a product of the inflammatory process, has been raised by Frenkel and Escajadillo[89] based on the fact that pepsin and trypsin can digest the cyst wall.

Ocular disease

The classic clinical presentation of an active lesion is that of a fresh, white, elevated focus of necrotising retinochoroiditis near an old pigmented scar (satellite lesion) (Fig 4). This lesion can vary greatly in size, is usually oval or circular, and more frequently located posterior to the equator. The central, bilateral lesions, especially the macular ones, are more common in the congenital form, while the acquired form tends to be unilateral, discrete, and solitary.[95] Hogan[96] found that 30% of the congenital lesions were unilateral, which makes bilaterality not an essential element in the diagnosis of these lesions.[73] The preference for the posterior pole, and more specifically for the macula in younger patients, is not clearly understood, but some authors have proposed that it is related to the fact that the organisms gain access to the eye via the optic nerve[97] or posterior ciliary arteries.[98] The lesion classically begins in the superficial layers of the retina, but with progression of

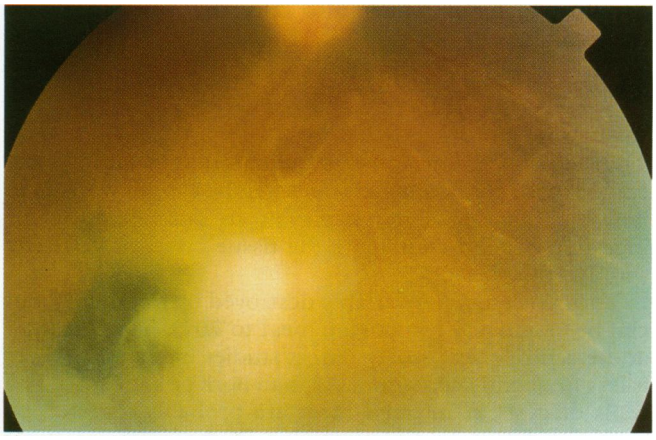

Figure 4 Reactivation of toxoplasmic retinitis adjacent to pigmented scar. Retinal oedema can be seen around main focus of activity, with vitritis and vacuolar sheathing.

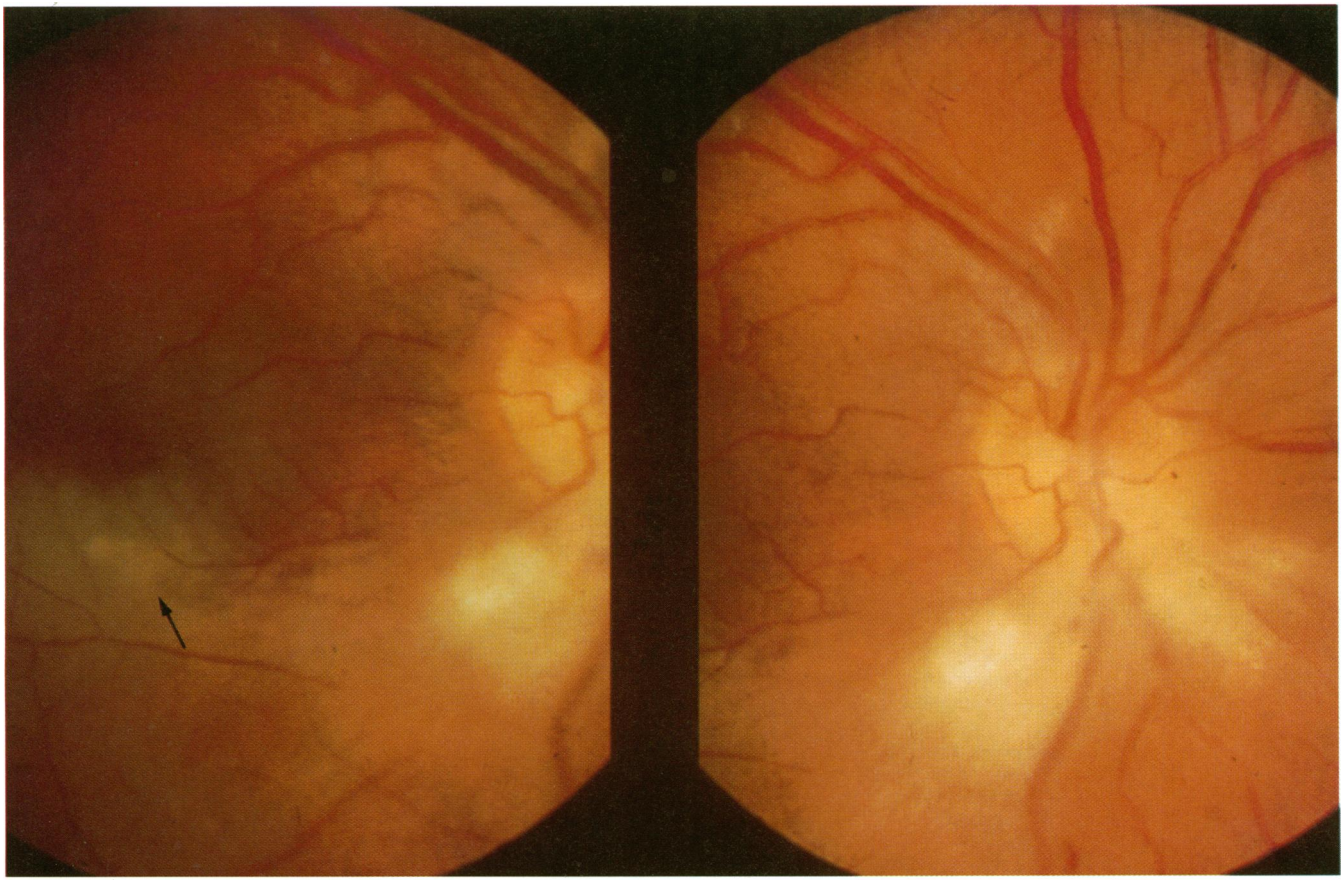

Figure 5 Area of active retinitis superior and adjacent to left optic disc. Note area of retinal swelling in the superior aspect of macular area (arrow). (Reproduced by courtesy of Professor A C Bird.)

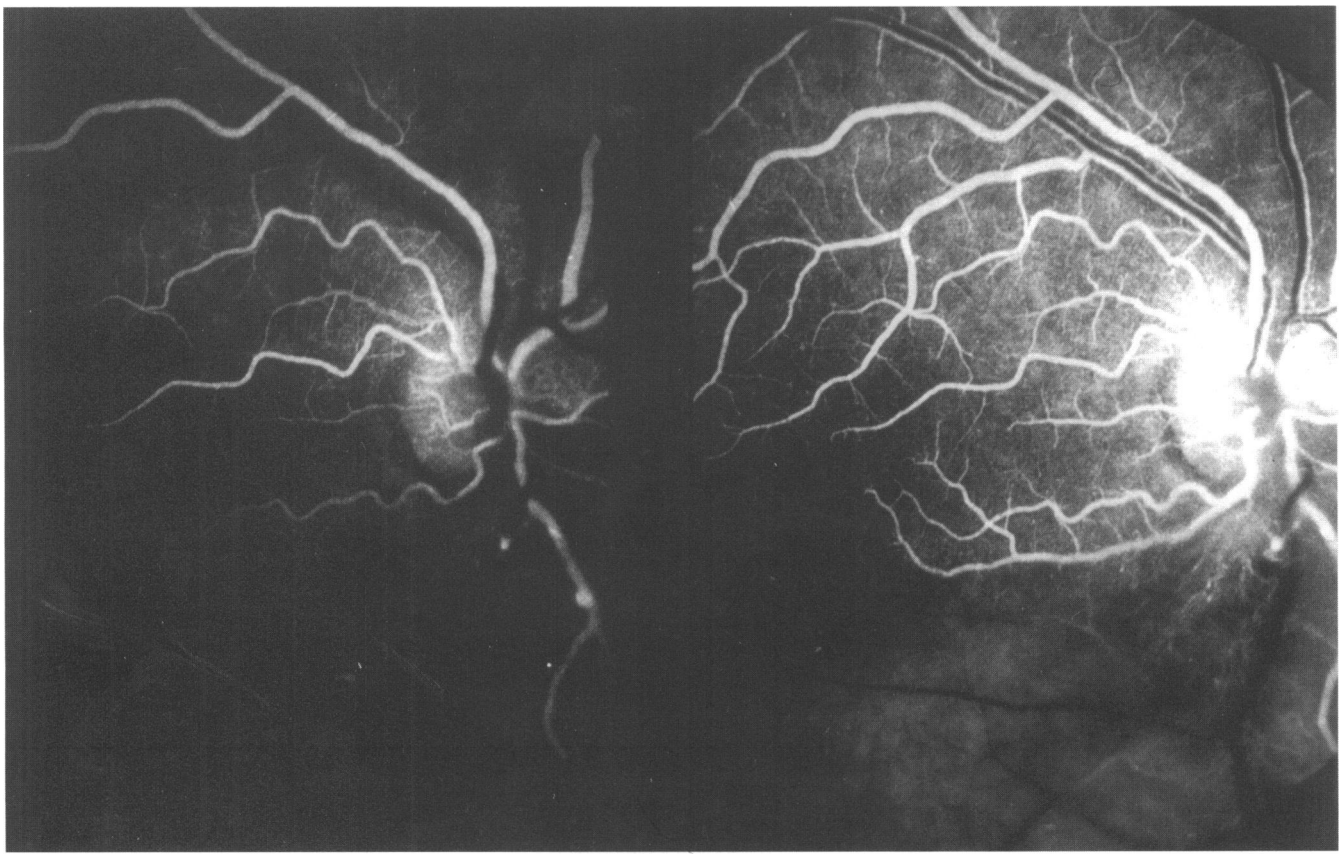

Figure 6 Fluorescein angiography of retina in Figure 7 showing arterial vascular occlusion with ischaemic area extending to the macula. (Reproduced by courtesy of Professor A C Bird.)

Figure 7 Fundus photograph showing area of serous elevation of the retina (arrow) adjacent to a chorioretinal scar. (Reproduced by courtesy of Professor A C Bird.)

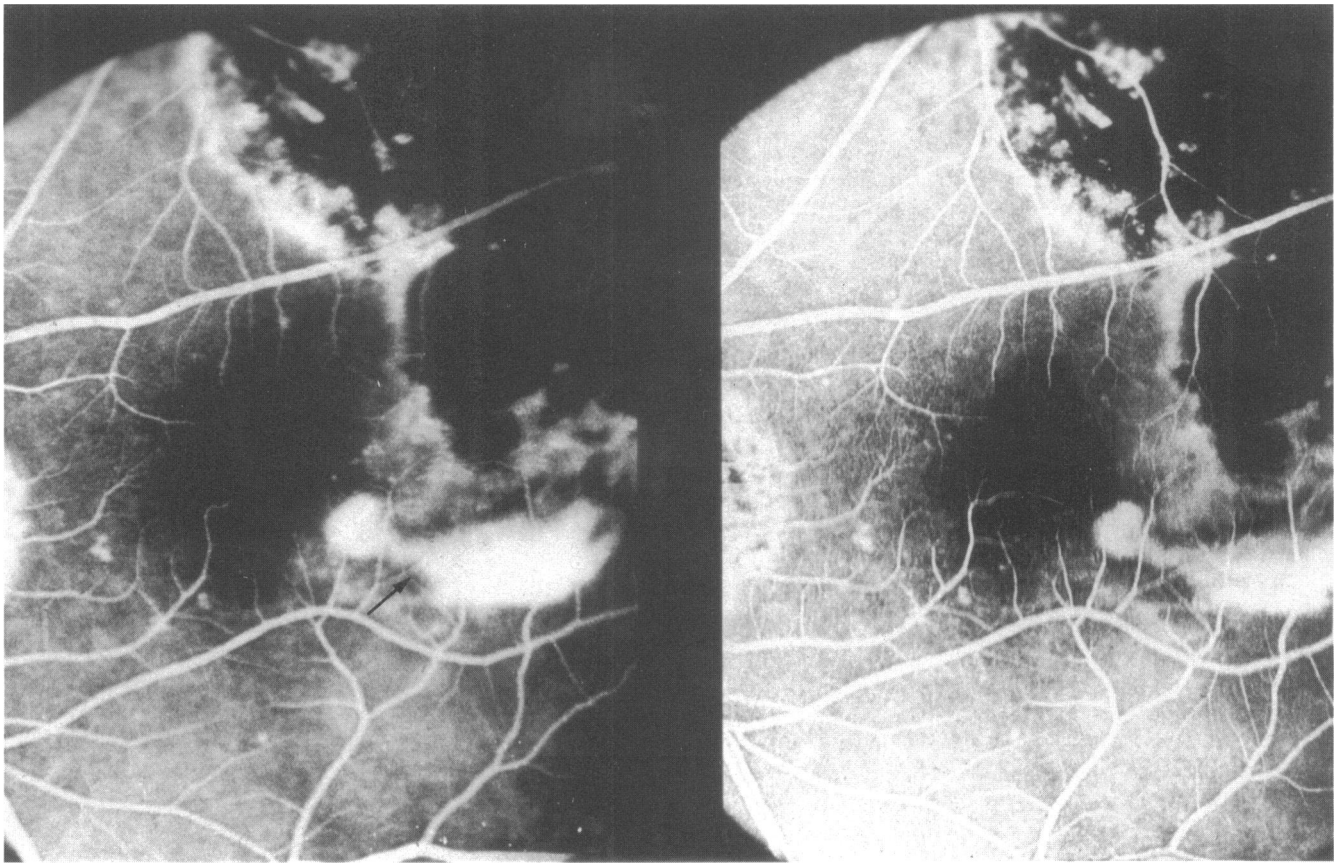

Figure 8 Fluorescein angiography of retina in Figure 5 showing the lacy pattern of choroidal neovascularisation (arrow). (Reproduced by courtesy of Professor A C Bird.)

the inflammation, the deeper retinal layers, as well as the choroid and sclera can become involved. There is much exudation of cells into the vitreous, particularly overlying the active lesions. When the retina can barely be seen because of vitreous inflammation, an active retinitis can still be glimpsed as a 'headlight in the fog'.[99] Friedmann and Knox,[100] and more recently others,[101 102] have described another subset of clinical presentations, characterised by grey-white fine punctate lesions of the deep retina, with initially little or no overlying vitreal activity. O'Connor[103] observed some patients with lesions initially behaving like those, but that gradually changed to classic lesions. A different clinical presentation has been reported by Silveira *et al*,[104] who described cases of unilateral pseudoretinitis pigmentosa in eyes with classic toxoplasmosis.

The anterior segment of the eye can also become involved with a non-granulomatous or granulomatous type of uveitis. This is assumed to be a hypersensitivity phenomenon,[105] since actual infection of the anterior segment by *T gondii* has never been demonstrated in an immunocompetent host.[43] This reaction may be accompanied by high rises in intraocular pressure and by cataract.[106] Rehder *et al* [107] reported the finding of a *Toxoplasma* cyst in a biopsy obtained from the iris of a patient with AIDS.

Direct optic nerve involvement by *Toxoplasma* organisms was first described by Zimmerman,[108] and cases reported as Jensen's juxtapapillary retinochoroiditis, initially specifically associated with tuberculosis, might in fact be due to toxoplasmosis.[43 99] A picture of toxoplasmosis neuroretinitis has been described in five patients who developed a sudden decrease in visual acuity with optic nerve oedema, vitreous inflammation, and macular star formation.[109] These patients had positive serology for toxoplasmosis and the features that differentiate this presentation from idiopathic neuroretinitis were the permanent loss of vision in one patient and the presence of recurrent episodes in two patients. Peripheral lesions, probably due to toxoplasmosis have also been described,[110 111] including a wide, ring-like lesion near the extreme periphery resembling the snow banking seen in pars planitis.[112] According to Tessler[14] the incidence of peripheral lesions is higher than the reported rates, which is probably due to its clinical unimportance. Some authors[113 114] have described the association of chorioretinal scars typical of toxoplasmosis in cases of Fuchs' heterochromic cyclitis, but the causal relation of the two is still not clear. A recent study comparing the presence of toxoplasmic scars and non-toxoplasmic scars with Fuchs' cyclitis has shown no statistical association of toxoplasmic scars and this condition.[115]

Although scleral involvement in toxoplasmosis had already been mentioned by others[99 116 117] it has recently been emphasised to be a more common occurrence than previously thought.[118] Retinal vascular involvement may occur as diffuse or segmental perivascular sheathing, involving the vessels in the vicinity of, as well as remote to, a focus of active retinitis.[119] According to O'Connor[103 105] the perivasculitis is secondary to a reaction between local antigens and circulating antibody, and the beads seen along the vessels represent cuffs of mononuclear cells (Fig 4). The Kyrieleis arterialitis, seen as focal periarterial exudates or plaques, are not associated with vascular leakage or obstruction, and their pathogenesis is unknown.[120 121] Branch artery obstruction, although infrequent, has been described when a vessel passes through an acute toxoplasmic lesion[120 122 123] (Figs 5 and 6). Choroidal neovascularisation can also be seen[124 125] with the new vessels located either directly at the border of the scar (Figs 7 and 8) or at a distance with feeder vessels arising from the scar.[112]

The main reason for decreased vision in these patients is the direct involvement of the macula by the inflammation.[112] Vision may be decreased by vitreous opacification alone, but macular oedema is often observed in the acute or subacute phase of inflammation,[103] and can occur even when the focus of retinitis is located far from it, in a phenomenon similar to that seen in pars planitis.[112] In cases of continuing inflammatory disease, the vitreous may contract and lead to posterior vitreous and even retinal detachment. In cases of posterior hyaloid detachment, precipitates of inflammatory cells, equivalent to keratic precipitates in the anterior segment of the eye, are seen on the posterior face of the vitreous. Healing time for the active lesion varies from several weeks to several months, with an average of 4.2 months.[43 110]

Immunocompromised hosts

Immunocompromised hosts, as a result of immunosuppressive therapy, malignancies, or AIDS, are at high risk for serious disseminated toxoplasmosis. In these individuals recurrent toxoplasmosis represents the most common cause of central nervous system (CNS) mass lesions,[126] and along with cryptococcal meningitis, it is the most common form of non-viral opportunistic infection of the CNS.[127–131] The risk of an AIDS patient with positive *Toxoplasma* serological tests developing CNS infection has been estimated at 6–12%.[127] Although not as frequently reported as CNS involvement, recurrent retinochoroiditis is found in patients with AIDS.[132–134] It has been hypothesised that only 1–3% of ocular infections in patients with AIDS are due to *T gondii*.[135] In one report ocular toxoplasmosis was the first opportunistic infection in 13 HIV positive patients and preceded serological diagnosis of HIV infection in five.[136] There may be several clinical manifestations, including single discrete lesions in one or both eyes, multifocal discrete lesions, or diffuse areas of retinal necrosis.[134] A pattern of bilateral miliary retinitis, initially diagnosed as fungal retinitis, has been described in a 28-year-old AIDS patient.[137] One report describes a unilateral case of diffuse necrotising retinochoroiditis resembling acute retinal necrosis[133] in an AIDS patient. In a recent report two cases of toxoplasmosis in AIDS patients were initially misdiagnosed as panophthalmitis because of the severe intraocular reaction, with the definitive diagnosis being established only by light and electron microscopy.[138] Such a severe form of presentation has been previously reported, most often in association with iatrogenic immunosuppression and lymphoreticular malignant neoplasms.[139–141] The clinical findings in these patients suggest that the ocular lesions result from acquired disease.[134 142] In AIDS and other immunodeficiency states, the lesions frequently begin adjacent to a retinal blood vessel, suggesting haematogenic dissemination.[143] The possibility of extension from the brain via the optic nerve has also been considered in some cases.[134] The proliferation of *Toxoplasma* organisms in tissues other than the retina is another important observation in AIDS patients.[107 143]

Histopathological study from two patients has shown extensive retinal necrosis, little inflammation, and the presence of organisms in the retinal pigment epithelium, choroid, and the retina.[134] This suggests that differently from the competent host, where the inflammatory response plays a major role in the destructive process, in the immunosuppressed host the destruction is caused by proliferating organisms. This is the reason why steroids have no role in the management of these patients, and anti-*Toxoplasma* drugs are effective and needed chronically.

Only a better understanding of the causative organism, especially of its complex cystic form, will improve our comprehension of the pathogenesis of toxoplasmosis. The finding, in the cyst, of degenerating bradyzoites alongside viable looking organisms is probably indicative of the fact

that cysts have a lifespan and that cysts are constantly breaking down. The quick action of the host immunity, immediately after cyst rupture, would control the spread of organisms and determine the absence of clinical manifestations. On the other hand, an ineffective immune response would allow spread of tachyzoites and invasion of enough neighbouring cells to cause clinical infection. The old concept of recurrences in the presence of debilitating disease could be explained by this mechanism. In situations of immunodeficiency, as discussed above, there would be continuous proliferation of organisms and widespread disease. The contraindication for the use of periocular steroids, and oral steroids without antiparasitic cover, is probably based on this concept.

A model of reactivation of toxoplasmosis in the hamster has just been developed (unpublished data), and will allow evaluation of the histopathology in this situation. It will also give us the opportunity to test different forms of therapy in the immunocompromised state, when the infection shows its most devastating effects.

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