Communications

Ocular toxoplasmosis

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A large amount of research has been done on toxoplasmosis in the last 30 years, and the world-wide incidence of the infection, and its clinical manifestations, are recognized and documented in an extensive literature. New discoveries concerning the life-cycle of the organism (Frenkel, 1970; Hutchison, Dunachie, Siim, and Work, 1970) promise to solve many of the problems of the transmission of infection and will give added stimulus to epidemiological studies. In the field of ophthalmology the importance of toxoplasmosis is now established, but some problems still remain.

The ocular lesions in infants with congenital toxoplasmosis are well recognized as pathogenic, but whether similar chorioretinal lesions in adults, although now acknowledged to be due to toxoplasmosis, result from recurrences of congenital infection or follow a postnatally acquired infection is still controversial. Other types of uveitis have been attributed to toxoplasmosis, and if this is correct it is important to recognize such cases. The present study attempts to clarify these problems by a review of the relevant literature supported by clinical studies in patients with uveitis. A further problem which will be discussed is whether congenital toxoplasmosis results from a chronic maternal infection or from one acquired during pregnancy: although this is not strictly an ophthalmological problem, ophthalmologists are often asked to advise on the prognosis for future pregnancies.

Review of the literature

No attempt is made here to provide a comprehensive general review of the literature on toxoplasmosis, but a list of recent reviews is given in the Bibliography. Attention here will be concentrated on the incidence of ocular complications in acquired systemic infections with clinical manifestations, the evidence for acquired infection in cases of uveitis, and the type of maternal infection causing toxoplasmosis.

Incidence of ocular complications in recently acquired toxoplasmosis

In reviewing the literature on this subject, an immediate problem is that of deciding on the criteria which should be accepted as evidence of infection. Most authors have relied on one or a combination of three methods: the detection of high levels of antibody, particularly the demonstration of rising titres; the observation of organisms in biopsy specimens or tissue fluids; and the demonstration of infection in animals after the inoculation of tissue extracts.

The demonstration in biopsy or post mortem specimens of organisms morphologically resembling Toxoplasma is not entirely reliable, as nuclear fragments (Duke-Elder, Ashton, and Brihaye-van Geertruyden, 1953) and even pine pollen (Langer, 1966) can cause confusion. Even if the organism

Received for publication March 21, 1972
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can be identified unequivocally, this is not definite evidence of a recently acquired infection. It is interesting to note that, in the original series described by Wilder (1952), cerebral calcification was found in three of six patients X-rayed, indicating that the infection was almost certainly congenital in origin. If the organism can be found in the ocular tissues of the adult as a result of congenital infection there seems no reason why they should not also be found in other tissues (brain, lymph nodes, muscles, etc.) after congenital infection. Organisms have been found in patients with circulating antibodies absent or at very low levels (Hogan, Kimura, and O'Connor, 1964; Francescochetti and Engelbrecht, 1964; Tanaka, Takada, Sakamoto, Takasu, Sano, and Uemichi, 1965), which again suggests very long-standing or congenital infection.

LABORATORY INFECTION

A number of accidental laboratory infections have been reported, and as these are usually well documented it is worth considering them in some detail. In 21 cases* no ocular disease was reported except for conjunctival hyperaemia in one (Ström, 1951). Conjunctivitis accompanied the infection in two cases (Ström, 1951; Straub, 1962). Matsubayashi, Kioke, Uyemura, Soh, and Hamano (1961) and Mikuni (1968) each reported the infection of a pathologist during an autopsy: both patients developed an exudative retinitis and organisms were recovered from the subretinal fluid. In neither were the ocular lesions typical of the focal chorioretinitis seen in congenital infection.

In summary, therefore, uveitis occurred in only two of 26 laboratory infections, and in neither case were the lesions similar to those seen in the congenital disease. The infection of six volunteers (Fair and Walls, 1962) did not result in any ocular signs or symptoms.

ACQUIRED TOXOPLASMOSIS WITHOUT OCULAR DISEASE

In reviewing the literature I have found accounts of over 1,600 cases of acquired toxoplasmosis reported over the last 10 years in which the clinical diagnosis was supported by serological, and in some cases histological, evidence.† This does not include cases in which the clinical signs were confined to the eyes; these will be discussed later.

It is clear from this review that the commonest clinical manifestation of acquired toxoplasmosis is a lymphadenopathy, often with fever, and sometimes a skin rash, hepatosplenomegaly, or involvement of other systems. Such cases account for 89.2 per cent. of those reviewed (Table I). Cases in which the signs and symptoms were mainly confined to the central nervous system accounted for 4.3 per cent., myocarditis and pericarditis 1.4 per cent., and pulmonary disease 0.8 per cent. The remaining 4.2 per cent. consisted of a variety of conditions including hepatitis, polymyositis, psychiatric disorders, skin lesions, etc. The evidence for the diagnosis of toxoplasmosis was often less convincing in this miscellaneous group of cases.

It is possible that ocular lesions were not recognized in some of these cases, but many authors described others in their series with ocular signs (see below) and it is unlikely that many with active uveitis would have been overlooked.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Systemic toxoplasmosis without ocular complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>1,461</td>
</tr>
<tr>
<td>CNS disease</td>
<td>71</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>23</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>13</td>
</tr>
<tr>
<td>Miscellaneous conditions</td>
<td>69</td>
</tr>
<tr>
<td>Total</td>
<td>1,637</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table II</th>
<th>Ocular manifestations in acquired toxoplasmosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of lesion</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Focal chorioretinitis</td>
<td>44</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2</td>
</tr>
<tr>
<td>Papillitis and optic atrophy</td>
<td>8</td>
</tr>
<tr>
<td>Pan-uveitis</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
</tr>
</tbody>
</table>


†A list of the references to cases without ocular signs included in this part of the review can be obtained from the author.
ACQUIRED TOXOPLASMOSIS WITH SYSTEMIC AND OCULAR SIGNS

These cases were described as having systemic conditions compatible with a diagnosis of acquired toxoplasmosis and also ocular manifestations during the course of the disease.* The type and percentage incidence of ocular disease are shown in Table II.

The cases of focal chorioretinitis occurred with the types of systemic disease shown in Table III. As might be expected, the cases of papillitis and optic atrophy were all associated with disease of the central nervous system. A pan-uveitis occurred in five cases of lymphadenopathy and three cases with CNS signs. The group with miscellaneous ocular conditions comprised three cases with exudative retinal lesions (one with haemorrhage and one resembling Coats's disease), one with uveitis (unspecified), two with extraocular muscle palsies (associated with encephalitis), and one with macular oedema (associated with hepatitis).

A uveitis confined to the anterior segment seems to be extremely rare in association with acquired toxoplasmosis. Pillat and Thalhammer (1957) have described a 12-year-old boy who presented with a severe bilateral granulomatous iridocyclitis with cervical adenopathy, myositis, and hepatomegaly, whose dye test rose from 1:64 to 1:16,384 during the course of the disease. One eye became blind and painful and organisms were isolated after the enucleation. The fact that the eye was so severely damaged suggests that this was a pan-uveitis rather than a pure iridocyclitis.

<table>
<thead>
<tr>
<th>Type of systemic disease</th>
<th>No. of cases</th>
<th>No. of cases with chorioretinitis</th>
<th>No.</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenopathy</td>
<td>1,479</td>
<td>18</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>CNS disease</td>
<td>81</td>
<td>13</td>
<td>16.1</td>
<td></td>
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<tr>
<td>Myocarditis</td>
<td>25</td>
<td>2</td>
<td>8.0</td>
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<td>Pulmonary disease</td>
<td>15</td>
<td>2</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>69</td>
<td>9</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,669</td>
<td>44</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>

The figures in Table IV show the frequency of all ocular complications in the different types of acquired systemic toxoplasmosis. These figures show that the highest incidence of ocular complications occurs when the central nervous system is affected, and that the lowest incidence is associated with lymphadenopathy. Whether this is due to the fact that the retina is more likely to be affected with disease of the central nervous system, or whether it is only a reflection of a more severe infection, is difficult to decide. Possibly both factors are involved.

It is interesting to note that the commonest clinical manifestation of systemic toxoplasmosis—lymphadenopathy—is accompanied by such a low incidence of ocular complications. This suggests that such complications would be even less common in subclinical cases of acquired toxoplasmosis.

Doubtful cases of systemic toxoplasmosis with ocular signs

In addition to the cases described in the previous section, there are a number of reports in the literature of ocular lesions reputed to be associated with acquired toxoplasmosis in which the diagnosis is in doubt, either because the possibility of a congenital infection cannot be excluded, or because the diagnostic criteria are not convincing. A brief description of some of these cases follows.

Brennan, Brown, Warren, and Vranian (1949) described a 30-year-old man with bilateral iritis, a duodenal ulcer, and a nodular skin rash who also had a healed area of choroiditis in the left eye. Inoculations from blood and CSF were negative, as was a skin biopsy. The main diagnostic criterion was a positive complement-fixation test in a titre of 1:128.

*The papers reviewed are marked with an asterisk in the list of References.
Frugoni (1951) described a patient with meningeal signs who developed bilateral exudative retinal detachments going on to blindness with optic atrophy and pigmentary degeneration of the retina. The diagnosis of toxoplasmosis was made on the positive dye test in a titre of 1:128.

Wollheim (1952) reviewed fourteen cases with positive dye tests in titres of 1:36 to 1:144, including one with choroiditis.

Seitelberger and Spiel (1953) described two brothers aged 6 and 7 years with encephalitis. What were thought to be toxoplastic organisms were found at autopsy in the brain of one child, but no serological tests were carried out. The dye test was negative in the second child.

Rieger (1955) described three patients with extraocular muscle paresis and a positive dye test (1:64 in two and 1:1,024 in the third), and with optic neuritis and a dye test positive at 1:256.

Paulley, Green, Jones, and Kane (1954) described a patient with myocarditis who developed papillitis and a hemiplegia. The dye test was positive at 1:64.

Koeze and Klingon (1964) described a 67-year-old patient with anaemia and signs of chronic disease of the central nervous system who had flame-shaped haemorrhages in the fundi. Toxoplasma granulomas were found post mortem but the retinal haemorrhages could have resulted from the anaemia.

Lalisse, Mises, and Durand (1964) described five patients aged 3 to 10 years with positive serology who had abnormal EEGs. One child had had a recent chorioretinitis but there was no convincing evidence of recent systemic infection.

As Straub has pointed out, it is well recognized that congenital ocular lesions can become reactivated in childhood or adult life, and there is no reason why toxoplastic lesions of congenital origin in other tissues should not similarly recur. Lavat (1962), for example, quoted a case in which congenital ocular lesions were observed at 2 months and an encephalitis developed at 8 years, and a rather similar case was reported by Saraux, Seringe, Bach, and Le Besnerais (1962).

Martinelli and Rossi (1964) described abnormal EEG findings in fourteen cases, in eight of which there was a chorioretinitis with a positive dye test. The other patients had optic atrophy, extraocular muscle pareses, dystrophia adiposogenitale, and spastic tetraplegia. The dye test titres were less then 1:500 in all but two cases and it is not certain that the condition described resulted from acquired infection.

Harris (1967) reported a 2-year-old child with stomatitis and adenopathy and a healed chorioretinal lesion in one eye. The dye test was positive at 1:512, but this could have been a recurrence of congenital infection.

Manissadjian, D'Oliveira Penna, Costa Vaz, Ramos, Borges, and Schwartsman (1967) reported 26 children to have acquired toxoplasmosis. Six of them showed ocular lesions: nystagmus in two (associated with bilateral optic atrophy, with chorioretinitis in one and chorioretinal scars in the other); bilateral optic atrophy and chorioretinal scars in two further cases; macular pallor in one, and bilateral chorioretinal lesions in another. All had high dye test titres and all except one had hepatomegaly or signs of pulmonary disease. The two with nystagmus probably had defective vision from an early age, but it is possible that the condition was acquired in the other four cases.

Macchi (1968) described a 12-year-old child with an enlarged heart who had been found to have chorioretinal scars at the age of 6 and so had most probably had a congenital infection.

Ohkawa, Yonekura, and Ito (1969) described a 38-year-old woman with hemiparaesthesiae, fits, and dysphagia, who was found to have bilateral small cystic lesions in the fundi. Toxoplasma organisms were isolated from a mouse inoculated with CSF but were not isolated from further passages. The dye test was positive at 1:256. The fundus lesions in this case were unlike any previously described as resulting from toxoplastic infection.

SUMMARY OF THE OCULAR COMPLICATIONS OF ACQUIRED SYSTEMIC TOXOPLASMOSIS

Uveitis has been described in 52 out of 1,669 cases of acquired toxoplasmosis (3.1 per cent.), but the highest incidence of uveitis is associated with the relatively rare cases of toxoplastic encephalitis. Papillitis and optic atrophy may also occur in these cases. The uveitis is usually a focal chorioretinitis, but some cases of pan-uveitis or exudative retinitis have been described.

OCULAR DISEASE AS THE ONLY MANIFESTATION OF ACQUIRED TOXOPLASMOSIS

This is a particularly difficult group to assess; even if the diagnosis of toxoplastic uveitis is well substantiated, it is difficult to prove that the condition results from an acquired infection. The isolation of the organism from the eye of an adult does not exclude congenital infection: for example, the
Ocular toxoplasmosis

Patient described by Duke-Elder and others (1953), a man aged 40, had a history of defective vision since childhood and the infection was probably congenital. Even the apparent absence of a previous chorioretinal scar does not entirely exclude congenital infection, as toxoplasmic pseudocysts have been seen in the retina with little evidence of tissue reaction and would not be recognized clinically.

In some of the cases reported by Wilder (1952), in which the organism was demonstrated in histological sections, the history suggests long-standing disease which could have resulted from congenital infection, and in the 21 cases re-examined by Jacobs, Cook, and Wilder (1954a), the dye titres were low except for one of 1:2,048.

Other cases of apparently acquired ocular toxoplasmosis in which the organism was recovered from the eye were described by Straub (1949), Habegger (1954), Jacobs, Fair, and Bickerton (1954), Pillat and Thalhammer (1957), Jacobs (1960), Conrads (1961), and Frenkel (1962). High dye test titres supported a diagnosis of acquired infection in the cases described by Habegger (1954), Jacobs and others (1954b), Conrads (1961), and Frenkel (1962). The diagnosis of toxoplasmosis is well substantiated in these cases and an acquired infection would seem to be responsible.

Many papers have now been published in which a toxoplasmic aetiology for cases of chorioretinitis in children and adults has been well supported by statistical data based on the results of serological tests. Most authors have stated that the condition may result from infection acquired after birth or may be a recurrence of congenital infection, but few have ventured to give definite figures for the two types. When figures are quoted they range from a very low incidence of congenital disease to a very high incidence. Chodos and Habegger-Chodos (1963), for example, considered two of 100 cases to be congenital; Friedmann and Knox (1969) considered 61 of 63 cases to have a congenital origin. I have always felt that acquired infection was a rare cause of toxoplasmic chorioretinitis and that almost all cases seen in the United Kingdom are recurrences of congenital infection (Perkins, 1961).

In the case reports (Table V, overleaf), the diagnosis of acquired ocular toxoplasmosis was suggested by the results of serological investigations and sometimes by the response to antitoxoplasmatic treatment in patients presenting with a chorioretinitis or pan-uveitis. It is possible that a number of these, particularly the young patients, had recurrences of congenital infection. Others more likely to have had congenital rather than acquired infection have been described by Franke and Horst (1951), Jacobs and others (1954b), Hewson (1961), Boericke (1962), Genz (1963), Stankovic and Milojkovic (1963), Engelbrecht and Franceschetti (1963), Franceschetti and Engelbrecht (1964), and Jones, Kean, and Kimball (1969).

Table V shows that not all cases attributed to acquired toxoplasmosis presented with a focal chorioretinitis. Remky (1962), Bencini and Frezzotti (1964) both described cases of central serous retinopathy, and the latter authors also included cases of geographic chorioiditis and exudative macular lesions without inflammatory signs. I believe we should be cautious in accepting a diagnosis of toxoplasmosis in such cases. These conditions do not occur without any evidence of toxoplasmosis and have not been described in association with systemic toxoplasmosis, with the possible exception of the account given by Binkhorst (1948) of a woman with a haemorrhagic macular lesion. François (1963, p. 405) found a negative dye test in three out of six cases of central serous retinopathy, and in only one of the others was the dye test sufficiently high (1:512) to suggest recent infection.

Frezzotti, Berengo, Guerra, and Cavallini (1965) described a case of Coats's disease in which organisms were recovered from the enucleated eye. The patient had had defective vision since the age of 4 years and examination at age 11 showed old scars. The exudative lesion which developed later was described as typical of Coats's disease, but no abnormalities of the retinal vessels were described clinically or histologically.

The condition described by Bencini and Frezzotti (1964) as geographic choroiditis will be discussed in relation to a personal series of cases. Some authors have suggested that Eales's disease may be toxoplasmic in origin, but in a series of 31 cases (Perkins, 1961) I could find little evidence to support this suggestion. The retinal vessels may certainly be affected during the course of a toxoplasmic chorioretinitis but the clinical picture is quite distinct from that of Eales's disease.
## Table V  Cases of ocular disease attributed to acquired toxoplasmosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>No. of cases</th>
<th>Age (yrs)</th>
<th>Eye signs</th>
<th>Dye test titre (maximum)</th>
<th>Other evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnusson</td>
<td>1951</td>
<td>1</td>
<td>56</td>
<td>Unilateral choroiditis</td>
<td>1:2,000</td>
<td></td>
</tr>
<tr>
<td>Habegger</td>
<td>1953</td>
<td>1</td>
<td>60</td>
<td>Bilateral severe posterior uveitis</td>
<td>1:1,024</td>
<td></td>
</tr>
<tr>
<td>Koke</td>
<td>1953</td>
<td>1</td>
<td>25</td>
<td>Macular choroiditis during pregnancy</td>
<td></td>
<td>Infant with congenital toxoplasmos born 2 months later; mother’s dye test 1:256 7 years later</td>
</tr>
<tr>
<td>Hudson</td>
<td>1954</td>
<td>1</td>
<td>35</td>
<td>Unilateral choroiditis</td>
<td>1:800</td>
<td></td>
</tr>
<tr>
<td>Hogan</td>
<td>1958a, b</td>
<td>3</td>
<td>53</td>
<td>Pan-uveitis</td>
<td>1:1,024</td>
<td>Doubtful response to Daraprim</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>Chorioretinitis</td>
<td>1:1,024</td>
<td>Good response to Daraprim</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48</td>
<td>Chorioretinitis</td>
<td>1:1,024</td>
<td>Good response to Daraprim</td>
</tr>
<tr>
<td>Cassady</td>
<td>1960</td>
<td>2</td>
<td>70</td>
<td>Acute iritis</td>
<td>1:32,768</td>
<td>Positive CFT with significant rise in titre</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>38</td>
<td>Retinitis</td>
<td>1:8,192</td>
<td>CFT 1:320</td>
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<tr>
<td>Garin</td>
<td>1960</td>
<td>2</td>
<td>?</td>
<td>Bilateral pan-uveitis</td>
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<tr>
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<td>Impetigo of lids</td>
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<td></td>
<td></td>
<td>Unilateral choroiditis</td>
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</tr>
<tr>
<td>Martenet and</td>
<td>1961</td>
<td>1</td>
<td>16</td>
<td>Macular choroiditis</td>
<td>1:4,000</td>
<td>Eye enucleated; organism isolated</td>
</tr>
<tr>
<td>Pestalozzi</td>
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<td></td>
<td></td>
<td>Generalized uveitis with peripheral choriorretinitis</td>
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<tr>
<td>Frenkel</td>
<td>1962</td>
<td>1</td>
<td>60</td>
<td>Central serous retinopathy</td>
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<td></td>
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<td></td>
<td></td>
<td>Central retinitis</td>
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<td>Paracentral retinitis</td>
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<td>Recurrent retinitis</td>
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<tr>
<td>Remky</td>
<td>1962</td>
<td>8</td>
<td>14-55</td>
<td>Chorioretinitis</td>
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<td>Cyclitis with vitreous opacities</td>
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<td></td>
<td>Vitreous bands</td>
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<tr>
<td>François</td>
<td>1963</td>
<td>6</td>
<td>12-61</td>
<td>Chorioretinitis</td>
<td>1:1,024</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td>1:1,096</td>
<td>Diagnosis based on serological results and aqueous antibody quotient</td>
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<td></td>
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<td>1</td>
<td></td>
<td>1:1,024</td>
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<tr>
<td>Nutt and Beverley</td>
<td>1963</td>
<td>2</td>
<td></td>
<td>Chorioretinitis</td>
<td>1:2,500</td>
<td>High dye test titre</td>
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<td></td>
<td></td>
<td>Granulomatous anterior uveitis and interstitial keratitis</td>
<td></td>
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</tr>
<tr>
<td>Benzini and</td>
<td>1964</td>
<td>14</td>
<td></td>
<td>Exudative retinitis (Coats’s disease)</td>
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<tr>
<td>Frezzotti</td>
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<td></td>
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<td>Pseudo-degenerative lesions</td>
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<td></td>
<td></td>
<td></td>
<td>Other</td>
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<td></td>
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<tr>
<td>Ffrench</td>
<td>1965</td>
<td>1</td>
<td>40</td>
<td>Previous attack age 19</td>
<td>1:256</td>
<td>Probably congenital</td>
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<tr>
<td>Pasmanik</td>
<td>1966</td>
<td>8</td>
<td></td>
<td>Pan-uveitis</td>
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<td></td>
<td></td>
<td></td>
<td>4</td>
<td>Irido-cyclitis</td>
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<td>12</td>
<td>Chorioretinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spaulding and</td>
<td>1967</td>
<td>1</td>
<td>64</td>
<td>Chorioretinitis one eye; anterior uveitis and secondary glaucoma in other</td>
<td>1:2,000</td>
<td></td>
</tr>
<tr>
<td>Font</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friedmann and</td>
<td>1969</td>
<td>2</td>
<td></td>
<td>Chorioretinitis with no old scars</td>
<td></td>
<td>No detailed serological results</td>
</tr>
<tr>
<td>Knox</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In summary, we may conclude that there is some evidence that a chorioretinitis, and more rarely a pan-uveitis, may be the only manifestation of acquired toxoplasmosis. When the high incidence of subclinical acquired infections in many countries is taken into account, it is clear that ocular complications are extremely rare.
Ocular toxoplasmosis

TOXOPLASMOSIS IN PREGNANCY

This subject has been well reviewed by Kouba (1970), and there are two approaches to the problem of whether congenital toxoplasmosis is a result of acute infection in the mother. The first is primarily statistical and consists of comparing the incidence of abortion, stillbirth, and congenital defect in women with and without evidence of chronic toxoplastic infection. The second approach, and that with the most practical application, is concerned with the outcome of subsequent pregnancies in women who have given birth to a child with congenital toxoplasmosis.

The interpretation of the statistical studies is often difficult because the incidence of positive dye tests rises with age; mothers with positive dye tests are likely to be older than those with negative test, and therefore more liable to develop complications during pregnancy and to have children with congenital defects. When the groups are carefully matched for age (Thalhammer, 1965), the results suggest that abortion is not more frequent in association with a positive dye test.

The organism has been isolated from the uterus and products of conception (Langer, 1963) in 23 out of seventy women whose pregnancy terminated in abortion or stillbirth. Remington, Newell, and Cavanaugh (1964) found toxoplastic cysts in the uterus, and Werner, Schmidtke, and Thomascheck (1963) considered that there was a definite relationship between chronic toxoplastic endometritis and complications of pregnancy. Eckerling, Neri, and Eylan (1968) showed a high incidence of abortion, premature delivery, stillbirth, mental retardation, and neonatal death in a series of women with positive dye tests who were subsequently treated with pyrimethamine and Lederlyn before pregnancy and with tetracycline during pregnancy. Of the 42 pregnancies occurring after treatment, 41 ended in the delivery of normal healthy children. However, no evidence is given that the children affected in the pregnancies before treatment were infected with toxoplasmosis.

From the above accounts and others reviewed by Kouba (1970), it seems likely that chronic toxoplasmosis may sometimes be responsible for abortion, but the figures of Desmonts, Couvreur, and Ben Rachid (1965), Offret and Campinchi (1967), and Kimball, Kean, and Fuchs (1971) strongly suggest that congenital toxoplasmosis in full-term infants occurs only when the mother is infected during pregnancy.

It is possible that separate mechanisms are responsible for recurrent abortion on the one hand and congenital toxoplasmosis on the other. Chronic endometritis due to toxoplasmosis could interfere with implantation, resulting in abortion without the entry of organisms into the bloodstream of the foetus. When the mother is infected during pregnancy, toxoplasma organisms can reach the foetus via the maternal circulation before antibodies can be formed by the mother.

An epidemiological study on a South Pacific island (Darrell, Pieper, Kurland, and Jacobs, 1964) is of some interest in that a very high incidence of toxoplastic infection was found (90 per cent. of the population over the age of 20 had dye test titres of 1:16 or more) and yet no cases of congenital toxoplasmosis were found. Presumably the mothers had all been infected in childhood and the maternal antibodies protected their children from acquiring the disease in utero.

Prospective studies on women who have given birth to a child with congenital toxoplasmosis have received little attention. Feldman (1963) wrote that he had never seen more than one child affected except in twins; and Eichenwald (quoted by Maumenee, 1962, p. 872) followed up over 600 mothers who had given birth to an affected child, and in no case was a subsequent child affected. In view of the negative results in such a large series the few reports of congenital toxoplasmosis in siblings must be reviewed critically.

Campbell and Clifton (1950) reported four members of a family who were thought to have congenital toxoplasmosis, but the clinical findings as described in these cases are so different from those normally associated with congenital toxoplasmosis that strong evidence for this diagnosis would be required. The four patients all had a congenital papular rash and saddle noses; two had hydrocephalus and nerve deafness. Ocular signs were present in three of them: one had microcornea and macular and peripheral chorioretinitis, and two others had optic atrophy and slight peripheral pepper-and-salt fundus changes. The dye test results in these three cases were 1:32, 1:128, and 1:32 respectively. One child without ocular signs had negative toxoplasmosis tests on three occasions. An hereditary condition seems a much more likely diagnosis than toxoplasmosis in these cases.

Campbell (1953) also described a family in which the birth of a child with typical congenital toxoplasmosis had been preceded by that of a child who had died at birth with jaundice. There is no evidence that toxoplasmosis was responsible for this death.
Crothers (1943) reported two cases of siblings thought to have toxoplasmosis. In the first, one boy in a family had convulsions, choroiditis, and cerebral calcification, and a younger brother had choroiditis, hemiplegia, mental retardation, and cerebral calcification. Serological tests for toxoplasmosis were said to be positive. In another family, two children had convulsions, choroiditis, and cerebral calcification: the mother and a sister also had cerebral calcification. This would imply that the mother had congenital toxoplasmosis and transmitted the infection to the children. The details of the serological tests are not sufficient for their significance to be assessed.

Langer (1963) reported the isolation of toxoplasma organisms from a stillbirth and again from an abortion 5 months later. He also reported the case of a mother who had had three abortions followed by a premature infant which died and in whom organisms were isolated. There is no direct evidence however that the previous abortions were caused by toxoplasmosis.

Remington and others (1964) reported one case of spontaneous abortion in which mouse inoculation from uterine scrapings was positive for toxoplasmosis. The mother's dye test was positive at a titre of 1:256 on two separate occasions, suggesting chronic infection. In a further case an abortion at 5 weeks when the dye test in the mother was positive at 1:512 was followed by a further abortion with isolation of Toxoplasma one year later. The dye test titre was the same and the previous positive test excluded infection of the mother during the second pregnancy.

Coppola and Tondi (1965) described three children in the same family who had signs of the Laurence-Moon-Biedl syndrome with positive dye tests of 1:250, 1:50 and 1:500 respectively. There is, however, no evidence that this syndrome is caused by toxoplasmosis.

Giulla, Zanibelli, and Privitera (1964) described a family in which a child aged 3 years had motor disturbances, cerebral calcification, and a dye test positive to 1:1,000; a brother aged 18 months had a superior oblique paresis and a dye test positive to 1:250; a sister aged 13 years showed mental retardation, a choriod-retinal scar, and a dye test positive to 1:10; and another sister aged 14 years had cerebral calcification but a negative dye test. A diagnosis of toxoplasmosis is possible in the three siblings with positive dye tests but other causes cannot be excluded.

Rieger (1966) reported six families in which two or more siblings were thought to have toxoplasmosis on the basis of positive dye tests. The ocular findings included congenital defects, such as microphthalmos and coloboma of the iris, but no typical chorioretinal lesions. The diagnosis of toxoplasmosis was made on the basis of positive dye tests, but in only two cases was the titre above 1:64. In one case, a second sibling, toxoplasma organisms were seen histologically. Unless further confirmation can be obtained that toxoplasmosis is responsible for these congenital anomalies, I feel that the results should be accepted with reservations.

Garcia (1968) reported the case of a woman who had a febrile illness at the fifth month of pregnancy and whose child was born at the seventh month by Caesarean section. The child died after 24 hours and toxoplasma organisms were seen in the foetal tissues and placenta. Toxoplasma skin tests in the mother were negative. A subsequent pregnancy ended in abortion at 5 months and pseudocysts were seen in the adrenals and in the placenta; 15 months later the mother’s dye test was positive 1:64, and a year after it was positive 1:1,024.

Khanna, Singh, Chowdhyry, and Om Prakash (1969) described an 11-month-old infant in whom the haemagglutination test was positive 1:256 and who showed retinal oedema. Parasites were isolated by mouse inoculation from the CSF. This child was the sixth and only surviving child, all the previous children having died of CNS disease before the age of 6 years. The diagnosis of toxoplasmosis was presumptive only, as far as the earlier children were concerned.

Miller, Aronson, and Remington (1969) reported an infant who died at birth and from whom toxoplasma organisms were recovered. The mother’s dye test rose from 1:4,096 to 1:32,768 after 14 months, strongly suggesting a recently acquired infection. A second child was born with jaundice but no other evidence of congenital toxoplasmosis.

My personal impression of these reports is that they provide some evidence that abortion and stillbirth can be caused by maternal toxoplasmosis, but that no cases of typical congenital toxoplasmosis in surviving siblings have been proved to occur. If this view is correct, and it is strongly supported by some of the statistical studies, congenital toxoplasmosis results from acute infection of the mother during pregnancy and is extremely unlikely to result from chronic infection.

The salient points of this review of the literature can be summarized as follows:

(1) A uveitis complicating laboratory infection with toxoplasmosis has been reported in two out of 26 cases.

(2) Lymphadenopathy is the commonest clinical manifestation of acquired toxoplasmosis, occurring in 89 per cent. of cases.
(3) Uveitis occurs in 1·5 per cent. of cases of toxoplasmic lymphadenopathy, and in 19 per cent. of the rarer cases in which the central nervous system is involved. Papillitis and optic atrophy also occur in the latter cases.

(4) There is some evidence that a chorioretinitis, and more rarely a pan-uveitis, may be the only manifestation of acquired toxoplasmosis.

(5) Congenital toxoplasmosis only occurs when the mother is infected during that pregnancy.

**Clinical studies**

Over 3,700 patients have now been seen in the Uveitis Clinic at the Institute of Ophthalmology and Moorfields Eye Hospital. Detailed statistical studies of the first 1,718, with particular reference to toxoplasmosis, were published in 1961 (Perkins, 1961). It was concluded from these studies and from the cases seen subsequently that toxoplasmosis was responsible only for cases of focal chorioretinitis and that the infection was nearly always congenital. A search through the last 2,800 case histories has now been made for evidence of uveitis of any type associated with acquired toxoplasmosis.

From the well-documented cases of uveitis associated with acquired systemic infection, it is apparent that the uveitis occurs during the active phase of the disease and when the dye test is positive in a high titre—usually over 1:1,000. I have therefore reviewed all cases of uveitis with a dye test titre of 1:500 or more.

**Review of cases with dye test titre $\geq 1:500$**

Of the 1,898 patients in whom tests were done, there were 25 with a dye test titre of 1:500 or more; the distribution of these titres is shown in Table VI. The country of origin of these patients is particularly interesting, as nearly half came from outside the United Kingdom (Table VII). This confirms our previous finding (Chesterton and Perkins, 1967) that the incidence of toxoplasmosis is high in immigrants from West Africa and the West Indies and that these patients tend to have higher dye test titres than those found in the indigenous population.

### Table VI Distribution of high dye test titres (total number tested 1,898)

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Titre</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1:512</td>
</tr>
<tr>
<td>1</td>
<td>1:660</td>
</tr>
<tr>
<td>1</td>
<td>1:760</td>
</tr>
<tr>
<td>2</td>
<td>1:880</td>
</tr>
<tr>
<td>8</td>
<td>1:1,024</td>
</tr>
<tr>
<td>2</td>
<td>1:1,500</td>
</tr>
<tr>
<td>5</td>
<td>1:2,000</td>
</tr>
<tr>
<td>1</td>
<td>1:4,000</td>
</tr>
</tbody>
</table>

### Table VII Country of origin of patients with dye test titres $\geq 1:500$

<table>
<thead>
<tr>
<th>Country</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>13</td>
</tr>
<tr>
<td>West Africa</td>
<td>4</td>
</tr>
<tr>
<td>West Indies</td>
<td>3</td>
</tr>
<tr>
<td>India</td>
<td>2</td>
</tr>
<tr>
<td>Malaysia</td>
<td>1</td>
</tr>
<tr>
<td>Egypt</td>
<td>1</td>
</tr>
<tr>
<td>Eire</td>
<td>1</td>
</tr>
</tbody>
</table>

**Clinical evidence of systemic toxoplasmosis**

Only one patient in this series was known to have an acquired infection. She was a woman aged 22 years with a dye test titre of 1:4,000, who had had a cervical adenitis; lymph node biopsy was suggestive of toxoplasmosis. She was referred for ocular examination but no ocular lesions were found.
Two other patients gave a history of systemic disease which could possibly have been due to toxoplasmosis although there was no direct evidence for this apart from the positive serology. One was a man aged 51 (No. 3435, Table IX) with a dye test titre of 1:1,024, who had an anterior uveitis with oedema of the posterior pole but no focal lesions; 11 years previously he had developed diplopia due to an external rectus paresis; he also had cardiac enlargement and occlusive arterial disease in the right leg. The other patient was a woman aged 54 (No. 2161, Table IX) with a dye test titre of 1:800 who had a generalized uveitis with one area of focal choroiditis. She gave a history of anaemia, eczema, and chronic bronchitis with asthma.

Although the systemic symptoms in the two latter patients could conceivably have been due to toxoplasmosis, there is little to support such a diagnosis. The one with confirmed toxoplasmic adenitis (No. 3347, Table IX) had no ocular lesions.

The remaining 22 cases could be grouped into those with recurrences of a previous chorioretinitis, with or without other evidence suggesting that the disease was congenital in origin, and those with ocular lesions of apparently recent origin.

Recurrences of congenital toxoplasmosis

There were eleven cases in which the ocular lesions were typical of recurrences of a congenital infection, and of these four were known to have had poor vision since birth (Table VIII). Previous recurrences were recorded in two others, and all but one had chorioretinal scars. The exception, No. 3567, is particularly interesting as at the first examination a dense white area of activity was seen above the macular region of the right eye and no old scars were apparent. There were, however, typical areas of cerebral calcification, so that the ocular lesion was almost certainly the result of congenital infection.

Other cases with dye test titres of 1:500 or more

No clear pattern emerges from the small number of cases, details of which are given in Table IX (overleaf). In Nos. 1418 and 1769 the infection could have been congenital, and the only other case of typical focal chorioretinitis was No. 3557, in which the dye test titre of 1:2,000 was suggestive of recent infection. There was no other clinical evidence of toxoplasmosis, but the possibility remains that the small area of chorioretinitis was the only manifestation of systemic infection. In four cases (Nos. 2529, 3315, 3476, and 3497) the only evidence of toxoplasmosis was the positive dye test, and the association with the ocular lesions was most probably coincidental. The three cases of geographic choroiditis will be discussed below.

Conclusion

High dye test titres can be found in adults with recurrences of congenital infection, particularly in immigrants from West Africa and the West Indies. High dye test titres may occasionally be found in other types of uveitis, but the rarity of this finding suggests that in the absence of other evidence of a recent systemic infection this finding is purely coincidental.

Geographic choroiditis

This interesting condition has been described by a number of authors (Witmer, 1952; Maumenee, 1968; Gass, 1968; Schlaegel, 1969; Krill and Archer, 1971; Perkins and Dobree, 1972). Affected patients complain of the sudden onset of defective vision, and
Ocular toxoplasmosis

Table VIII Recurrences of congenital infection with high dye test titres

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yrs)</th>
<th>Country of origin</th>
<th>Dye test titre</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2246</td>
<td>2</td>
<td>UK</td>
<td>1:880</td>
<td>Microophthalmos L Chorioretinal scars R Cerebral calcification</td>
</tr>
<tr>
<td>2495</td>
<td>13</td>
<td>UK</td>
<td>1:760</td>
<td>Poor vision since birth Old scars L Severe generalized uveitis R Convergent squint</td>
</tr>
<tr>
<td>2678</td>
<td>26</td>
<td>Jamaica</td>
<td>1:2,048</td>
<td>Several old scars both eyes Recent activity R No systemic symptoms</td>
</tr>
<tr>
<td>2710</td>
<td>18</td>
<td>UK</td>
<td>1:1,024</td>
<td>Vision always poor Bilateral macular lesions</td>
</tr>
<tr>
<td>3108</td>
<td>28</td>
<td>English but born India</td>
<td>1:1,600</td>
<td>Divergent squint since birth Juxtapapillary scar with ectasia and high myopia</td>
</tr>
<tr>
<td>3432</td>
<td>20</td>
<td>UK</td>
<td>1:1,024</td>
<td>First known attack age 11 Macular scar with recurrence L</td>
</tr>
<tr>
<td>3448</td>
<td>36</td>
<td>Jamaica</td>
<td>1:512</td>
<td>Old scar R No active lesions</td>
</tr>
<tr>
<td>3482</td>
<td>31</td>
<td>Nigeria</td>
<td>1:1,024</td>
<td>Pan-uveitis R Old scars L</td>
</tr>
<tr>
<td>3503</td>
<td>27</td>
<td>Nigeria</td>
<td>1:1,024</td>
<td>Old scars both eyes Recurrence R</td>
</tr>
<tr>
<td>3533</td>
<td>34</td>
<td>UK</td>
<td>1:2,000</td>
<td>First known attack age 17 Old scars both eyes Recent recurrence L</td>
</tr>
<tr>
<td>3567</td>
<td>21</td>
<td>UK</td>
<td>1:512</td>
<td>Dense white active lesion above R macula Typical cerebral calcification</td>
</tr>
</tbody>
</table>

Fundus examination shows multiple focal lesions which often coalesce to form map-like areas mainly confined to the posterior pole. Fluorescein angiography has demonstrated that the lesions lie at the level of the pigment epithelium. The overlying retina may be oedematous but in most cases there is visual recovery, with only slight choroidal atrophy and pigment clumping.

Bencini and Frezzotti (1964) described nine cases of this condition, which they attributed to toxoplasmosis on the grounds of positive serology. We have seen ten cases in the Uveitis Clinic and three of them had dye test titres above 1:500. However, the other seven had negative dye tests, and none of those with positive tests had any systemic symptoms suggesting recent toxoplasmosis. These three came from overseas: one was Egyptian, one Nigerian, and one an Indian doctor who had worked in South America. It is probable, therefore, that the positive dye test was entirely incidental and not related to the ocular condition.

The aetiology of geographic choroiditis remains obscure. There has been some suggestion of an association with exposure to tuberculosis in the patients of Witmer (1952) and in those of Gass (1968). One of our patients had radiological evidence of a healed tuberculous lesion and the Mantoux test was positive in the four other cases in which it was
Table IX  Miscellaneous cases with high dye test titres

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yrs)</th>
<th>Country of origin</th>
<th>Dye test titre</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1418</td>
<td>34</td>
<td>UK</td>
<td>1:1,500</td>
<td>Generalized uveitis with total detachment and old chorioretinal scar</td>
</tr>
<tr>
<td>1769</td>
<td>30</td>
<td>West Indies</td>
<td>1:512</td>
<td>Generalized uveitis with large chorioretinal focus 5-year history</td>
</tr>
<tr>
<td>2161</td>
<td>54</td>
<td>UK</td>
<td>1:800</td>
<td>Generalized uveitis with chorioretinitis Also anaemia, eczema, bronchitis, and asthma</td>
</tr>
<tr>
<td>2529</td>
<td>44</td>
<td>UK</td>
<td>1:660</td>
<td>Bilateral chronic uveitis No fundus lesions</td>
</tr>
<tr>
<td>3315</td>
<td>60</td>
<td>UK</td>
<td>1:1,024</td>
<td>Recent visual failure Anterior uveitis Disciform lesion at right macula and early degenerative changes Macrocytic anaemia</td>
</tr>
<tr>
<td>3345</td>
<td>32</td>
<td>India</td>
<td>1:512</td>
<td>Geographic choroiditis R</td>
</tr>
<tr>
<td>3347</td>
<td>22</td>
<td>UK</td>
<td>1:4,000</td>
<td>Cervical adenitis Biopsy suggestive of toxoplasmosis No evidence of uveitis</td>
</tr>
<tr>
<td>3435</td>
<td>51</td>
<td>Eire</td>
<td>1:1,024</td>
<td>Anterior uveitis with slight oedema of disc and macula Previous history of diplopia Also cardiac enlargement and occlusive arterial disease of lower limbs</td>
</tr>
<tr>
<td>3476</td>
<td>35</td>
<td>UK</td>
<td>1:2,000</td>
<td>Heterochromic uveitis with 13-year history</td>
</tr>
<tr>
<td>3492</td>
<td>38</td>
<td>Egypt</td>
<td>1:512</td>
<td>Geographic choroiditis</td>
</tr>
<tr>
<td>3497</td>
<td>45</td>
<td>UK</td>
<td>1:1,024</td>
<td>R amblyopic Anterior uveitis L with retinal detachment History of pulmonary tuberculosis</td>
</tr>
<tr>
<td>3557</td>
<td>33</td>
<td>Malaysia</td>
<td>1:2,000</td>
<td>Recent small area of chorioretinitis No old scars seen</td>
</tr>
<tr>
<td>3708</td>
<td>32</td>
<td>West Africa</td>
<td>1:2,000</td>
<td>Geographic choroiditis</td>
</tr>
</tbody>
</table>

Erythema nodosum has been reported in association with geographic choroiditis by Van Buskirk, Lessell, and Friedman (1971). Whatever the aetiology may ultimately prove to be, the finding of a negative dye test in seven out of ten patients in our series and the absence of systemic symptoms in the remaining three excludes toxoplasmosis as a likely aetiology.

Discussion

From this review of the literature and the clinical data presented, it can be concluded that, although a high proportion of the population of most countries in the world becomes infected with toxoplasmosis, systemic clinical manifestations are rare, and even in these cases ocular involvement occurs in only 2 or 3 per cent. When the central nervous system is affected ocular lesions will be found in about one-quarter of the cases, but as central nervous involvement occurs in only about 4 per cent. of cases of acquired infection the number of cases of ocular disease resulting is extremely small.
If uveitis is such an uncommon complication of overt systemic infection with toxoplasmosis, it is likely to be even more uncommon in association with subclinical infection. Population surveys have always shown that the incidence of infection increases with age, and if toxoplasmic chorioretinitis resulted from chronic acquired infection, as many authors have suggested, the number of cases would rise with age. This is not so; toxoplasmic chorioretinitis occurs most frequently in the second and third decade of life and is rare after the age of 50 (Perkins, 1961; Hogan and others, 1964).

If the ocular lesions result from acquired infection, it would be expected that the patients would have higher levels of circulating antibody than asymptomatic members of the population. High dye test titres are, however, exceptional in toxoplasmic uveitis and even when found are not conclusive evidence of acquired infection, as some cases of undoubted congenital infection may have dye test titres of over 1:500 in adult life. Hogan and others (1964) considered that only forty of 240 cases of toxoplasmic uveitis were congenital in origin, and yet 201 of these cases had dye test titres of 1:256 or less. Three of the cases with high dye test titres had signs and symptoms of recent systemic infection which would account for the high titres.

In a personal series of 1,718 cases of uveitis, 188 were considered to be due to toxoplasmosis (Perkins, 1961) and in only one of these was there evidence of possible recent systemic infection. The possibility that the uveitis resulted from subclinical acquired infection could not be entirely excluded, but the presence of old scars in the fundus strongly suggested that almost all cases were recurrences of congenital infection. On the other hand it is not possible to exclude congenital infection in many of the cases described in the literature (see above) as resulting from acquired infection without systemic signs or symptoms.

I believe, therefore, that cases of focal chorioretinitis with positive serological evidence of toxoplasmosis should be considered to result from congenital infection unless there is a clear history of recent systemic signs and symptoms of toxoplasmosis. This view is supported by Schlaegel (1969), who stated that it was possible that all cases of toxoplasmic chorioretinitis were congenital in origin, and that when no previous scar was visible the inflammation arose from the rupture of cysts in the nerve-fibre layer of the retina which were not visible on ophthalmoscopic examination.

When ocular complications do occur in systemic toxoplasmosis, focal chorioretinitis is the typical manifestation, but extraocular muscle pareses, papillitis, and optic atrophy may accompany disease of the central nervous system. Apart from a few cases of pan-uveitis which have been described in association with systemic disease, there is no convincing evidence that anterior uveitis, retinal vasculitis, or geographic choroiditis are caused by toxoplasmosis.

Although it is possible that chronic uterine infection with toxoplasmosis is responsible for abortion and stillbirth, congenital toxoplasmosis has never been confirmed in siblings and results only from infection of the mother during pregnancy. It follows, therefore, that a woman with circulating antibodies to Toxoplasma will not have a child with congenital toxoplasmosis. There is, however, a serious risk to the child if the mother becomes infected during pregnancy.

**Summary**

From a review of the literature and from clinical data presented, the following conclusions were drawn:

(1) Subclinical infection with toxoplasmosis is very common throughout the world but
systemic clinical manifestations are rare and even in these cases ocular involvement occurs in only 2 to 3 per cent.

(2) Ocular complications of systemic infection are more likely to occur when the central nervous system is affected.

(3) Uveitis as the only sign of acquired toxoplasmosis is very rare.

(4) Almost all cases of toxoplasmic chorioretinitis seen in the United Kingdom are the result of congenital infection.

(5) There is no convincing evidence that anterior uveitis, retinal vasculitis, or geographic choroiditis are caused by toxoplasmosis.

(6) Chronic uterine infection may be responsible for abortion or stillbirth but congenital toxoplasmosis has never been confirmed in siblings and results only from infection of the mother during pregnancy.

(7) A woman with circulating antibodies to Toxoplasma will not have a child with congenital toxoplasmosis.

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