CORRESPONDENCE

Fundal white dots: observations from a murine model of congenital ocular toxoplasmosis

EDITOR,—In the *BJO* Ben Ezra and Forrester have reviewed extensively current knowledge concerning the phenomenon of multiple evanescent white dot syndrome (MEWDS), a specific clinical entity which is characterised by the presence of evanescent or permanent, small, discrete subretinal lesions, which occur in the absence of vitreous inflammation.[1]

Multiple pale lesions[2 3] (Fig 1) can be observed in the outer retina of a small proportion of mice with experimentally induced congenital ocular toxoplasmosis.[4] These focal lesions, which closely resemble MEWDS in humans, were clearly seen in the peripheral retina using indirect microscopy, and imparted an orange hue to the underlying choroid. The lesions were observed in the eyes of approximately 16% of congenitally infected mice and occurred either unilaterally or bilaterally. They were only observed from 3 weeks postpartum.

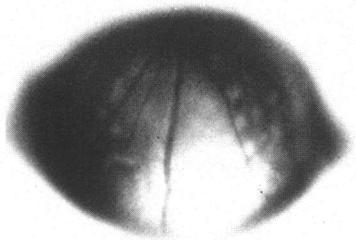

Figure 1 Peripheral fundus showing a number of foci of retinal disturbance.

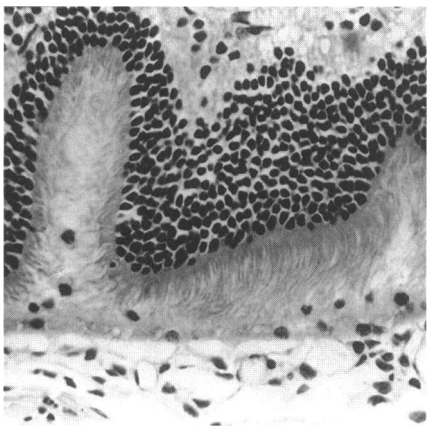

Figure 2 Inflammatory cells among the photoreceptor outer segments are associated with disruption to the architecture of the outer nuclear layer giving it an undulating appearance.

Histopathological examination of these refractive disturbances[3 5] within the otherwise transparent murine retina revealed that they consisted of focal elevations of the photoreceptor layer (Fig 2). Clusters of inflammatory cells in the form of lymphocytes and macrophages were a consistent feature and were located between the photoreceptor and pigment epithelial layers of the disorganised retina. Immunocytochemical labelling consistently failed to reveal *Toxoplasma* antigen within or in apposition to these lesions.[6]

Three dimensional reconstructions (Fig 3) of these lesions using serial sections of resin embedded tissue and standard SAS GRAPH routines, revealed that they were consistently dome-shaped, and did not result from artefactual folds in the tissue consequent upon processing or cutting of the tissue.

It is our contention that the focal cellular infiltrates are likely to impair the intrinsic processing mechanisms for removal of photoreceptor elements with the result that focal elevations of the photoreceptors appear in the retina; these are then perceived clinically, under direct illumination, as small discrete deep retinal lesions. They were evanescent in some eyes in which progression to atrophy of the photoreceptor layer had taken place in association with retinal vasculitis. This led us to hypothesise that there may be an autoimmune component associated with the pathogenesis of the ocular toxoplasmosis in the mouse model.[7]

Ben Ezra and Forrester suggest that extravasated foci of leucocytes will render the white dot lesions pale relative to the surrounding unaffected tissue when the fundus is illuminated with white light. Based on our own observations with the mouse model of ocular toxoplasmosis, we would concur with this notion. We contend further, however, that an additional contributor to the clinically observed white dot syndrome may be architectural modification to the overlying deep retina into dome-shaped configurations. This would result in refractive anomalies as well as reflectance of some of the incident light impinging on the retina. Such optical effects would also impart to the lesions a paler coloration relative to the surrounding non-affected areas.

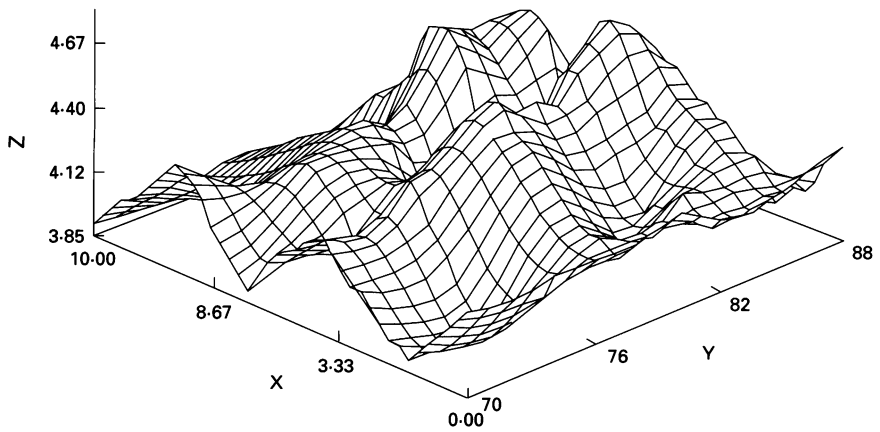

Figure 3 Three dimensional image demonstrates dome-shaped appearance of the lesions.

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1 Ben Ezra D, Forrester JV. Fundal white dots: the spectrum of a similar pathological process. *Br J Ophthalmol* 1995; **79:** 856–60.
2 Dutton GN, Hay J, Hair DM, Kerrigan P. Photography of the retina in mice congenitally infected with *Toxoplasma gondii*. *Ann Trop Med Parasitol* 1984; **78:** 435–7.
3 Dutton GN, Hay J, Hair DM, Ralston J. Clinicopathological features of a congenital murine model of ocular toxoplasmosis. *Graefes Arch Clin Exp Ophthalmol* 1986; **224:** 256–64.
4 Hay J, Hutchison WM, Lee WR, Siim JC. Cataract in mice congenitally infected with *Toxoplasma gondii*. *Ann Trop Med Parasitol* 1981; **75:** 455–7.
5 Dutton GN, McMenamin PG, Hay J, Cameron S. The ultrastructural pathology of congenital murine toxoplasmic retinochoroiditis. Part II: The morphology of the inflammatory changes. *Exp Eye Res* 1986; **43:** 545–60.
6 Hay J, Dutton GN, Ralston J. Congenital toxoplasmic retinochoroiditis in the mouse – the use of the peroxidase anti-peroxidase method to demonstrate *Toxoplasma* antigen. *Trans Roy Soc Trop Med Hyg* 1985; **79:** 106–9.
7 Lee WR, Hay J, Hutchison WM, Dutton GN, Siim JC. A murine model of congenital toxoplasmic retinochoroiditis. *Acta Ophthalmol* 1983; **61:** 818–30.

Reply

EDITOR,—Hay and Dutton refer to 'multiple pale lesions' in the model of congenital ocular toxoplasmosis in mice and believe that they are similar to the 'white dots' observed in humans in the various conditions we reviewed. We believe that they are confusing atrophic retinal patches and/or diffractive aberrations in the mouse model of congenital ocular toxoplasmosis with the evanescent (choroidal – retinal pigment epithelium) white dots we have described in our paper. We, therefore, would not concur with their assumption that the patches they observe are comparable with the white dots observed in humans.

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Natural outcomes of stage 1, 2, 3, and 4 idiopathic macular holes

EDITOR,—In order to evaluate the results of surgical intervention in the treatment of macular holes it is essential that we understand the natural history and visual prognosis of all four stages of macular holes. The paper by Hikichi *et al* in the *BJO*[1] was heralded in the accompanying editorial as providing just such an insight into the natural history of idiopathic macular holes. However, I would like to highlight some striking similarities between their data on stage 2 macular holes presented in this study and those reported by the same authors in an article entitled 'The natural history of stage 2 macular holes', published in the *American Journal of Ophthalmology*[2] (Table 1).

The authors may suggest that publication of such similar data is justified as this study is the first to document the natural history of all four stages of macular holes in a single article. However, the data on stage 3 and 4 holes do little more than echo the authors' findings in

Table 1

Data	*AJO May 1995*	*BJO June 1995*
Period of study	1982–94	1989–94
Patient numbers	48	25
MH ↑ in size ≥20%	41 (85%)	21 (84%)
MH no change in size	7 (15%)	4 (16%)
Visual acuity ↓ ≥2 lines	34 (71%)	17 (68%)
Posterior vitreous separation	14 (29%)	7 (30%)

MH=macular hole.

Table 2

Data	*AJO 1993*	*BJO June 1995*
Period of study	1979–92	1989–94
Stage 3 MH		
Patient numbers	83	58
MH ↑ in size ≥20%	44 (55%)	32 (55%)
Stage 4 MH		
Patient numbers	29	31
MH ↑ in size ≥20%	4 (14%)	5 (16%)

their 1993 *American Journal of Ophthalmology* article entitled 'Effect of the vitreous on the prognosis of full thickness idiopathic macular holes'[3] (Table 2).

If the data on stage 2 holes in these studies have been derived from the same cohort of patients I would suggest to the authors that this duplication may detract from the scientific merit of the individual articles.

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1 Hikichi T, Yoshida A, Akiba J, Trempe CL. Natural outcomes of stage 1, 2, 3, and 4 idiopathic macular holes. *Br J Ophthalmol* 1995; **79:** 517–20.
2 Hikichi T, Yoshida A, Akiba J, Konno S, Trempe CL. Prognosis of stage 2 macular holes. *Am J Ophthalmol* 1995; **119:** 571–5.
3 Hikichi T, Akiba J, Trempe CL. Effect of the vitreous on the prognosis of full thickness idiopathic macular holes. *Am J Ophthalmol* 1993; **116:** 273–8.

Reply

EDITOR,—We thank Dr Ferris for his interest in our recently published articles,[1–3] and we appreciate his comments. In 1992, when we began to study the natural history of idiopathic macular holes, only patients with stages 3 and 4 macular holes underwent vitreous surgery.[4] In 1994, the results of vitrectomy to treat stage 2 macular holes were reported, which resulted in more favourable visual outcomes than those achieved with stage 3 and 4 holes.[5] Patients with all stages of full thickness holes – that is, 2, 3, and 4, now undergo surgical management. The efficacy of the surgery has been documented in numerous articles; however, most of them have provided a compilation of data on all stages rather than by individual stage,[6] even though the natural outcomes of the macular holes vary by stage. Because macular holes currently are receiving much attention and many new findings have been reported, the background of our studies also has changed, and thus each series[1–3] has a different background, aims, and conclusion. Although there is some patient overlap in our studies, we believe that the individual articles have scientific merit and contribute significantly to the body of knowledge about management of idiopathic macular holes.

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1 Hikichi T, Akiba J, Trempe CL. Effect of the vitreous on the prognosis of full-thickness idiopathic macular hole. *Am J Ophthalmol* 1993; **116:** 273–8.
2 Hikichi T, Yoshida A, Akiba J, Konno S, Trempe CL. Prognosis of stage 2 macular holes. *Am J Ophthalmol* 1995; **119:** 571–3.
3 Hikichi T, Yoshida A, Akiba J, Trempe CL. Natural outcomes of stages 1, 2, 3, and 4 idiopathic macular holes. *Br J Ophthalmol* 1995; **79:** 517–20.
4 Kelly NE, Wendel RT. Vitreous surgery for idiopathic macular holes. Results of a pilot study. *Arch Ophthalmol* 1991; **109:** 654–9.
5 Ruby AJ, Williams DF, Grand MG, Thomas MA, Meredith TA, Boniuk I, *et al.* Pars plana vitrectomy for treatment of stage 2 macular holes. *Arch Ophthalmol* 1994; **112:** 359–64.
6 Ryan EA, Lee S, Chern S. Use of intravitreal autologous blood to identify posterior cortical vitreous in macular hole surgery. *Arch Ophthalmol* 1995; **113:** 822–3.

NOTICES

Royal Society of Medicine, Section of Ophthalmology

The following meetings (beginning at 5 pm) are open to RSM members and their guests only.

TOXOPLASMOSIS, 8 February 1996
Epidemiology of toxoplasmosis; Representing people affected by toxoplasmosis; The diagnosis of ocular toxoplasmosis; Clinical aspects of toxoplasmosis.

LANG LECTURE, 14 March 1996
New perspective; corneal grafting Professor David Easty.

NEW HORIZONS IN THERAPEUTICS, 9 May 1996
The identification of human tumour antigens: a strategy for developing tumour vaccines; New developments in the management of CMV retinitis; The development of ophthalmic drugs; The challenge of gene therapy in the context of eye diseases.

Further details: Alyson Taylor, Sections Officer, Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. (Tel: 0171 290 2985; fax: 0171 290 2989.)

REGISTRARS' MEETING, 13 June 1996, 2 pm
For registrars to present research work and case reports. Papers to be considered for publication. Abstracts should be submitted (max 200 words) for the attention of P Murray, The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Closing date for entries is 12 April 1996.

Intraocular Implant Society, India

The Intraocular Implant Society, India (formerly the Indian Intraocular Implant Society) will hold the VI International Congress of Intraocular Implant Society, India at Chandigarh, India on 1–2 February 1996. Further details: Dr Amod Gupta, Organising Secretary, Department of Ophthalmology, Postgraduate Institute of Medical Education and Research, Chandigarh – 160 012, India.

Office of Continuing Medical Education

The 18th Annual Wilmer Institute's Current Concepts in Ophthalmology will be held on 11–16 February 1996 at the Hyatt Regency Cerromar Beach Hotel, Dorado, Puerto Rico.

The 13th Annual Wilmer Institute's Current Concepts in Ophthalmology will be held on 10–15 March 1996 at the Manor Vail Lodge, Vail, Colorado, USA. Further details: Conference Coordinator, Office of Continuing Medical Education, Johns Hopkins Medical Institutions, Turner 20, 720 Rutland Avenue, Baltimore, MD 21205–2195, USA. (Tel: (410) 955–2959; Fax: (410) 955–0807.)

First European Forum on Quality Improvement in Health Care

The first European forum on quality in health care will be held on 7–9 March 1996 at the QEII Conference Centre, London. Further details: Clare Moloney, BMA Conference Unit, BMA House, Tavistock Square, London WC1H 9JP. (Tel: 0171–383 6663; Fax: 0171–383 6478.)

XIth Symposium of the International Society for Genetic Eye Disease and VIIIth Symposium of the Retinoblastoma Society

The XIth Symposium of the International Society for Genetic Eye Disease and VIIIth Symposium of the Retinoblastoma Society will be held on 10–14 March 1996 at the Wrest Point Convention Centre, Hobart, Tasmania, Australia. Further details: ISGED Secretariat, PO Box 309, Rosny Park, Tas 7018, Australia. (Fax: +61 02 34 44 64.)

Paediatric Week – Alder Hey Education Centre

A national study day on screening for visual defects in children – present evidence and future prospects, will be held at the Royal Liverpool Children's NHS Trust Alder Hey on Wednesday 13 March 1996. Further details: Education Centre, Royal Liverpool Children's NHS Trust Alder Hey, Eaton Road, Liverpool L12 2AP. (Tel: 0151 252 5218; Fax: 0151 252 5103.)

XI Tübingen Detachment Course: Retinal and Vitreous Surgery

The XI Tübingen Detachment course on retinal and vitreous surgery will be held on 11–12 April 1996 at Kupferbau, Gmelinstrasse 8, 72076 Tübingen, Germany. Further details: Office Professor Dr I Kreissig, Univ-Augenklinik, Schleichstrasse 12, 72076 Tübingen, Germany. (Tel: 07071 294758; Fax: 07071 293746.)