

## MAILBOX

## TTT and CNV

EDITOR,—The article by Newsom *et al*<sup>1</sup> on transpupillary thermotherapy (TTT) raises more questions than it is able to answer. Although TTT is definitely a method which seems to show a certain efficacy in occult choroidal neovascularisation (CNV) and thus warrants further investigation, we must take issue with the authors' conclusions concerning its use in classic CNV.

The authors state that 78% of the predominantly occult membranes and 75% of the predominantly classic membranes closed as a result of TTT. This seems hard to believe, in particular because only 24 of 44 patients had angiographic follow up, which is the criterion for determining CNV closure. Furthermore, how is the irradiance used to be understood? On the one hand, the authors state—without providing any evidence—that smaller lesions need a higher irradiance, but on the other hand larger lesions—which are presumably requiring only lower irradiance—received confluent treatment with several overlapping spots of TTT, which implies that the amount of irradiance necessary on a cumulative basis might be similar to the irradiance needed to treat smaller lesions!

The authors also state that TTT compared well with the results of the TAP study group for predominantly classic CNV.<sup>2</sup> They imply that the 75% of their cases which showed stabilised vision (nine eyes with a visual loss of less than 3 lines) can be compared with the TAP results at 1 year (246 eyes with a visual loss of less than 3 lines). Firstly, the TAP study was a masked and placebo controlled multicentre study performed on 609 patients which, without doubt, has a much higher statistical value than the present study with 12 predominantly classic membranes.

Secondly, Newsom *et al* cannot compare their visual results adequately as the TAP study used a standardised testing procedure employing Early Treatment for Diabetic Retinopathy charts as well as masked and certified vision examiners in comparison to the Snellen values mentioned in the above study, which were obtained by unmasked, and therefore biased, examiners. Furthermore, on closer examination of the results, not one of the 12 patients showed any improvement for visual acuity at 12 months after TTT; in comparison, in the TAP study 5.7% of all verteporfin treated patients showed an improvement of more than 15 letters (approximately 3 lines) at the 12 months visit.

While we recognise the potential of the TTT method, we would like to warn against extrapolating the data of this study in a relatively small patient cohort to make conclusions on the efficacy in treating classic CNV.

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1 Newsom RSB, McAlister JC, Saeed M, *et al*. Transpupillary thermotherapy (TTT) for the treatment of choroidal neovascularisation. *Br J Ophthalmol* 2001;85:173–8.

2 Treatment of age-related macular degeneration with photodynamic therapy (TAP) study group. Photodynamic therapy of subfoveal choroidal

neovascularization in age-related macular degeneration with verteporfin. One-year results of 2 randomized clinical trials—TAP report 1. *Arch Ophthalmol* 1999;117:1329–45.

## Further pathophysiological insights into age related macular degeneration

EDITOR,—We read with great interest the excellent editorial by Ciulla,<sup>1</sup> which describes pathophysiological paradigms for age related macular degeneration (ARMD) and the development of choroidal neovascular membranes (CNVM). We were particularly pleased to note that Ciulla considered that “whatever the initial stimulus for CNVM formation, it is clear that angiogenic growth factors are ultimately involved.” Furthermore, he observed that primary vascular changes in the choroid may also be responsible.

In light of these observations, we had hypothesised a relation between abnormal vascularisation (angiogenesis), haemorrhological factors, and endothelial dysfunction in patients with ARMD. We felt that abnormalities in the systemic and choroidal vasculature, may relate to the release of angiogenic factors and subsequent proliferation of choriocapillaris through a defect in Bruch's membrane in susceptible individuals. To investigate this hypothesis further, we recently reported a cross sectional study<sup>2</sup> of patients presenting with ARMD and measured plasma levels of VEGF (an index of angiogenesis), haemorrhological factors (fibrinogen, plasma viscosity), and von Willebrand factor (an index of endothelial damage/dysfunction) from these patients. Median plasma VEGF (225 v 195 pg/ml,  $p = 0.019$ ) and mean von Willebrand factor (124 v 99 IU/dl,  $p = 0.0004$ ) levels were higher in ARMD patients compared with healthy controls. Mean plasma fibrinogen and plasma viscosity levels were also higher in the patients (both  $p < 0.0001$ ). Our observations would therefore suggest further pathophysiological insights into ARMD, with an association between this disorder and markers of angiogenesis (VEGF), haemorrhological factors, haemostasis, endothelial damage/dysfunction.

Rather than the existence of individual pathogenic processes,<sup>1</sup> perhaps a close interaction between abnormal angiogenesis and the components of Virchow's triad for thrombogenesis may contribute to the pathogenesis of ARMD and the development of CNVM. Indeed, the availability of a blood marker for ARMD could have potential value, as measurement of such a marker can be a non-invasive way of perhaps predicting individuals at high risk of developing ARMD. We have recently applied such a concept (that is, a blood marker to monitor the progression of eye disease) in a study of plasma VEGF in diabetic proliferative retinopathy, where the high plasma levels were normalised at the 4 month follow up, after treatment with panretinal laser photocoagulation.<sup>3</sup>

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- 1 Ciulla TA. Evolving pathophysiological paradigms for age related macular degeneration. *Br J Ophthalmol* 2001;85:510–12.
- 2 Lip PL, Blann AD, Hope-Ross MW, *et al*. Age-related macular degeneration is associated with increased vascular endothelial growth factor, hemorrheology and endothelial dysfunction. *Ophthalmology* 2001;108:705–10.
- 3 Lip PL, Belgore F, Blann AD, *et al*. Plasma VEGF and soluble VEGF receptor Flt-1 in proliferative retinopathy: relationship to endothelial dysfunction and laser treatment. *Invest Ophthalmol Vis Sci* 2000;41:2115–19.

## A new colour vision arrangement test to detect functional changes in diabetic macular oedema

EDITOR,—We refer to the interesting article by Maar *et al* published in the *BJO*. The authors should be congratulated for presenting a new method of screening for diabetic macular oedema. However, the paper contains some statistical errors, and we believe the results can be interpreted in other ways.

Firstly, there are some internal inconsistencies with some of the results reported in the paper. Specificity of the Mollon T test (score >1) for detecting clinically significant macular oedema (CSMO) was reported as 88.9% and specificity was reported as 99.3%. These values could not possibly be obtained with the subject numbers specified, and we believe they have been erroneously published.

From other data provided by Maar *et al* we are able to reconstruct values for these statistics. The mean Mollon T score and SD for non-CSMO patients implies 28 non-CSMO patients passed the test (true negatives) and one failed (false positive). The number of eye with CSMO was 10 and there were 29 eyes without CSMO. Table 1 can be constructed.

Table 1

	No CSMO	CSMO	Total
Test negative	28	2	30
Test positive	1	8	9
Total	29	10	39

It is apparent from this table that the sensitivity of the test is 8/10 or 80.0% and not 88.9% and the specificity of the test is 28/29 or 96.6% and not 99.3% as quoted in the paper.

These values are of course only estimates of the true specificity and sensitivity and are based on fairly small numbers of subjects. It is good practice to report such figures accompanied by the 95% confidence intervals of these proportions.<sup>2</sup> For the purpose of assessing the practical value of a screening tool the lower limit or 5% confidence limit of the proportion is of clinical interest because it reflects the sensitivity and specificity of this test in the “worst” scenario. Various methods could be used to calculate or approximate such an interval. For example, using the Wilson's score method incorporating continuity correction,<sup>3</sup> the 95% CI of the sensitivity is 44.2%–99.1% and the specificity is 80.4%–99.8%. The clinician will be quick to notice the wide confidence interval for the sensitivity. This is an inherent problem in such studies, where the absolute number of cases of CSMO is relatively small. Thus it is possible that the Mollon test is only a mediocre indicator of the presence of CSMO and the high sensitivity was obtained by chance.

The authors have mentioned that “the Mollon-Reffin test was a better predictor than the other tests because it had a lower false

positive rate (1 – specificity)” in the legend to the Figure 3 of their paper.<sup>1</sup> Perhaps it would be better (but not mandatory) to present the area under the receiver operator curves (ROC). This will state the probability of correctly identifying a randomly selected participant as a case or non-case and is therefore a measure of overall test validity. This will also offer an objective way of comparing different ROCs. We also note that the shape of the ROC for the DD-15 test was unusual (some sensitivity values were associated with two different specificity values). It is difficult to conceive of a data set that could generate a non-monotonic ROC curve and some comment on its unusual shape might have been useful.

Previous presentations: Nil.  
Commercial interests: Nil.

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- 1 Maar N, Tittl M, Stur M, *et al.* A new colour vision arrangement test to detect functional changes in diabetic macular oedema. *Br J Ophthalmol* 2001;85:47–51.
- 2 Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 1998;17:857–72.
- 3 Blyth CR, Still HA. Binomial confidence intervals. *J Am Statist Assoc* 1983;78:108–16.

## BOOK REVIEWS

**The Eye Book. Eyes and Eye Problems Explained.** By Ian Grierson. £12.95; pp 218. Liverpool: Liverpool University Press, 2000. ISBN 0-85323-755-7.

The cover of *The Eye Book* states that it is written for anyone needing to wear glasses and for healthcare professionals looking for an overview of eye health. As a non-ophthalmic clinician working in an eye hospital I hoped this short book would give me greater knowledge to do my job and, more importantly, to impress my colleagues without too much effort on my part. *The Eye Book* is an eclectic mix of information with topics covered ranging from detailed anatomy and physiology to facts about famous people and their sight problems.

The book starts with a clear and comprehensive introduction to the structure and function of the eye and the mechanism of vision. Although medical terms are included, Grierson uses simple language and he usefully illustrates some of harder to understand concepts with everyday comparisons. Eye care through the ages is summarised and the role of modern ophthalmologists and associated healthcare professionals described. Grierson includes an interesting short debate regarding the extension of healthcare professional roles in ophthalmology, although this is unfortunately slightly dated considering the recent rapid rise in nurse and optometrist led services.

Surprisingly, only a small part of the book is given over to common eye diseases and treatments. Again Grierson gives a clear and easily

comprehensible account; however, it is disappointing that practical advice on coping with low or reduced vision is not included as it could be assumed that many people buying this book would be looking for this type of information. Instead a considerable portion of the book is taken up with accounts of famous people and their eye problems. Although very interesting to read, the usefulness of its inclusion is debatable, especially when considering the likely audience. The book concludes on a slightly political note with a discussion of world blindness and the issue of training overseas ophthalmologists in the United Kingdom where they may not receive an experience appropriate to their local population. A brief overview of future developments in eye care is outlined and an extensive glossary, further reading list, and addresses of useful agencies complete the volume.

I found the book an interesting and enjoyable read. It will probably appeal more to healthcare professionals interested in a career in ophthalmology than members of the general public who may require more practical information on eye conditions. I am still waiting for my colleagues to comment on the sudden improvement in my ophthalmic knowledge; however, I was able to correctly answer that Nelson was blind in his right eye at the hospital quiz night!

HELEN JULIAN

**Fundamentals of Clinical Ophthalmology: Scleritis.** By Peter McCluskey. (Series editor: Susan Lightman.) £40; pp 130. London: BMJ Books, 2001. ISBN 072791586X.

Scleritis is part of a book series *Fundamentals of Clinical Ophthalmology* to update general ophthalmologists in specific areas and also, most probably, for ophthalmologists in training. Each book has been edited by a specialist, in this case Peter McCluskey in Australia, with expertise in each chapter from individual authors.

Overall, I think the book is good and achieves its aim if directed to the ophthalmic trainee as an introduction to scleritis and its differential diagnosis. However, as a result, a frequent collating problem of multiauthor books, it does not read fluently and is sometimes frustrating. This, however, should not discourage any trainee reading this book. It takes the reader logically through the anatomy and biochemistry of the sclera, highlighting reasonably up to date knowledge on cellular components and extracellular matrix and their steady state in relation to matrix metalloprotease and corresponding tissue inhibitors. If we were then to read chapter 3, which is the pathology of scleritis, it would have been more rewarding to have some link between the basic cell biology and the pathology. That is the relation of the inflammatory response to the breakdown of the steady state and the extracellular matrix. As it stands both chapters are excellent in their own right, but do fail to be linked.

The rest of the book is clinical with good figure representation of both anterior segment and posterior segment disease. The reading is easy and encourages constant thinking of the differential diagnosis.

There are also chapters on the investigation and management of scleritis. Again these chapters might have been more informative if they were linked to the overall cell biology, biochemistry, and pathology so as to educate

us in why we may be undertaking such investigations. There is a lack of explanation as to the serology assays performed to look for anti-nuclear antibodies or ANCA and its specific antigenic components. I think this slightly disjointed approach may still leave the ophthalmic trainee confused despite the information being present. The section on treatment is well presented and highlights the requirement for pretreatment assessment, prevention of side effects, and overall management of patients on immunosuppression.

Overall, the book is an enjoyable read and certainly useful for the trainee. For a small book it would have benefited from greater editorial licence to merge the information in all the chapters more coherently.

ANDREW DICK

**Electrophysiologic Testing in Disorders of the Retina, Optic Nerve, and Visual Pathway.** 2nd ed. By Gerald A Fishman, David G Birch, Graham E Holder, Mitchell G Brigell. Pp 308; \$95. San Francisco: American Academy of Ophthalmology, 2001. ISBN 1-56055-198-4.

This is a concise, well written reference for students, residents, and clinicians interested in gaining a better understanding of electrophysiological tests of the visual system.

The book is divided into five chapters, each devoted to one of the following electrophysiological tests: the electroretinogram (ERG), the electro-oculogram (EOG), the focal and multifocal ERG, the pattern electroretinogram (PERG), and the visual evoked potential (VEP). Each chapter begins with a description of the physiology underlying each test and the specific techniques used to record responses. The chapters then include examples of the results commonly seen in different hereditary and acquired disorders, with accompanying fundus photographs in many cases. The book also explains the molecular basis of diseases which have been genetically characterised.

The authors have made significant improvements to the second edition of this book. The first edition included only a page each on focal and pattern ERG. In response to the development of the multifocal ERG, the current edition devotes an entire chapter to both the focal and multifocal ERG. The multifocal ERG holds promise in early diagnosis of many diseases, including glaucoma, and both of these techniques will probably become increasingly important in future investigations of macular disorders. The section on pattern ERG has been greatly expanded and includes a lucid description of clinical applications for which the PERG is useful. In addition, the description of the PERG is integrated with the section on VEP, explaining how these tests can best be used to differentiate between macular and optic nerve dysfunction. The authors have included numerous clinical photographs and examples, making the text particularly relevant and easy to comprehend.

This textbook successfully meets the authors' stated objectives to "provide a background on the physiologic principles that underpin the measurement of various electrophysiologic components, describe the clinical phenotypes of various disorders . . . for which electrophysiologic investigations are of potential value, discuss the various electrophysiologic findings . . . anticipated in different disorders . . . (and to) clarify how the enlightened use of various procedures can be of value in the diagnosis and monitoring of patients with hereditary or acquired disorders of the retina,

optic nerve, and visual pathway." It is a valuable reference for anyone interested in obtaining a clear understanding of the objective measurement of visual function in a variety of diverse clinical disorders.

JACQUES L DUNCAN

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## NOTICES

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### Affordable eye care

The latest issue of *Community Eye Health* (37) discusses affordable eye care. For further information please contact *Community Eye Health*, International Centre for Eye Health, Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL. (Tel: (+44) (0) 20-7608 6909/6910/6923; fax: (+44) (0) 7250 3207; email: [eyesource@ucl.ac.uk](mailto:eyesource@ucl.ac.uk)) Annual subscription £25. Free to workers in developing countries.

### International Centre for Eye Health

The International Centre for Eye Health has published a new edition of the *Standard List of Medicines, Equipment, Instruments and Optical Supplies* (2001) for eye care services in developing countries. It is compiled by the Task Force of the International Agency for the Prevention of Blindness. Further details: Sue Stevens, International Centre for Eye Health, 11-43 Bath Street, London EC1V 9EL, UK (Tel: (+44) (0) 20-7608 6910; email: [eyesource@ucl.ac.uk](mailto:eyesource@ucl.ac.uk)).

### Second Sight

Second Sight, a UK based charity whose aims are to eliminate the backlog of cataract blind in India by the year 2020 and to establish strong links between Indian and British ophthalmologists, will be sending volunteer surgeons to India early in 2001. Details can be found at the charity website at [www.secondsight.org.uk](http://www.secondsight.org.uk) or by contacting Dr Lucy Mathen (email address [lucymathen@yahoo.com](mailto:lucymathen@yahoo.com)).

### American Institute of Ultrasound in Medicine—Millennium Ultrasound Course Series

A course entitled "Obstetrical and Gynecological Ultrasound" will be held in New York

City, NY, on 24-26 August 2001. Further details: Stacey Bessling, Public Relations Coordinator, AIUM, 14750 Sweitzer Lane, Suite 100, Laurel, MD 20707-5906, USA (tel: 301-498-4100; email: [sbessling@aium.org](mailto:sbessling@aium.org)).

### 14th World Congress of the International Society for Laser Surgery and Medicine

The 14th World Congress of the International Society for Laser Surgery and Medicine is to be held on the 27-30 August 2001 at Sri Ramachandra Medical College and University Hospital, Chennai, India. The American Society of Lasers in Medicine and Surgery has indicated that it will designate the 14th World Congress of ISLSM as its society's co-sponsoring meeting. A pre-conference course and separate sessions in ophthalmology will be held as a part of this international meeting. Further details: Dr B Krishna Rau, President, 14th World Congress of the International Society for Laser Surgery and Medicine, Department of Surgery, D2 Ward, Sri Ramachandra Medical College and Research Institute, Porur, Chennai - 600 116, India (tel: 91-44-4765856, 4768027-28, 8527776, 8594804; fax: 91-44-8594578, 4767008; email: [krishnar@giasmd01.vsnl.net.in](mailto:krishnar@giasmd01.vsnl.net.in) and website: [www.medindia.net/islsm2001](http://www.medindia.net/islsm2001)).

### 31st Cambridge Ophthalmological Symposium

The 31st Cambridge Ophthalmological Symposium will be held 3-5 September 2001 at St John's College Cambridge. The subject is Retinal Detachment. Further details: COS Secretariat, Cambridge Conferences, The Lawn, 33 Church Street, Great Shelford, Cambridge CB2 5EL, UK (tel: 01223 847464; fax: 01223 847465; email: [b.ashworth@easynet.co.uk](mailto:b.ashworth@easynet.co.uk)).

### 1st Asia Pacific Forum on Quality Improvement in Health Care

The 1st Asia Pacific Forum on Quality Improvement in Health Care will be held from 19-21 September 2001 in Sydney, Australia. Presented by the BMJ Publishing Group (London, UK) and Institute for Healthcare Improvement (Boston, USA), with the support of the Commonwealth Department of Health and Aged Care (Australia), Safety and Quality Council (Australia), NSW Health

(Australia) and Ministry of Health (New Zealand). Further details: [quality@bma.org.uk](mailto:quality@bma.org.uk); fax +44 (0) 7383 6869.

### 41st St Andrew's Day Festival Symposium on Therapeutics

The 41st St Andrew's Day Festival Symposium on Therapeutics will be held on 6-7 December 2001 at the Royal College of Physicians of Edinburgh. Further details: Ms Eileen Strawn, Symposium Co-ordinator (tel: 0131 225 7324; fax: 0131 220 4393; email: [e.strawn@rcpe.ac.uk](mailto:e.strawn@rcpe.ac.uk); website: [www.rcpe.ac.uk](http://www.rcpe.ac.uk)).

### 4th International Conference on the Adjuvant Therapy of Malignant Melanoma

The 4th International Conference on the adjuvant therapy of malignant melanoma will be held at The Royal College of Physicians, London on 15-16 March 2002. Further details: Conference Secretariat, CCI Ltd, 2 Palmerston Court, Palmerston Way, London SW8 4AJ, UK (tel: + 44 (0) 20 7720 0600; fax: + 44 (0) 20 7720 7177; email: [melanoma@onfcomm.co.uk](mailto:melanoma@onfcomm.co.uk); website: [www.confcomm.co.uk/Melanoma](http://www.confcomm.co.uk/Melanoma)).

### XXIXth International Congress of Ophthalmology

The XXIXth International Congress of Ophthalmology will be held on 21-25 April 2002 in Sydney, Australia. Further details: Congress Secretariat, C/- ICMS Australia Pty Ltd, GPO Box 2609, Sydney, NSW 2001, Australia (tel: +61 2 9241 1478; fax: +61 2 9251 3552; email: [ophthal@icmsaust.com.au](mailto:ophthal@icmsaust.com.au); website: [www.ophthalmology.aust.com](http://www.ophthalmology.aust.com)).

### International Society for Behçet's Disease

The International Society for Behçet's Disease was inaugurated at the 9th International Congress on Behçet's Disease. Professor Shigeaki Ohno represents the ophthalmology division (Department of Ophthalmology and Visual Sciences, Hokkaido University Graduate School of Medicine, Sapporo, Japan: tel: +81-11-716-1161 (ext 5944); fax +81-11-736-0952; email: [sohno@med.hokudai.ac.jp](mailto:sohno@med.hokudai.ac.jp)). The 10th International Congress on Behçet's Disease will be held in Berlin 27-29 June 2002. Further details: Professor Ch Zouboulis (email: [zoubbere@zedat.fu-berlin.de](mailto:zoubbere@zedat.fu-berlin.de)).



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