Use of polymerase chain reaction in detection of Mycobacterium tuberculosis complex DNA from vitreous sample of Eales' disease

EDITOR,—Eales' disease, first described by Henry Eales in 1880 is a primary retinal perivasculitis that predominantly affects the peripheral retina of young and otherwise healthy adults in the age group 15–40 years. Of the several aetiologies proposed, most are favoured to tuberculoprotein.1 Since polymerase chain reaction (PCR) using primers for the insertion repetitive DNA sequence specific for Mycobacterium tuberculosis complex DNA in clinical specimens,2 we applied it on vitreous fluid samples obtained from clinically diagnosed patients with Eales' disease and controls (undergoing vitreous surgery for proliferative diabetic retinopathy and proliferative vitreoretinopathy).

Uncontaminated vitreous fluid from 12 cases of Eales' disease and 45 non-Eales' disease control patients collected at the beginning of vitrectomy were subjected to PCR using IS6110 primers for the presence of M tuberculosis complex DNA.3 PCR was found to be specific and sensitive enough to detect 2.5 pg of M tuberculosis complex DNA. Five (41.6%) among 12 vitreous fluid samples from Eales' disease (Fig 1) and only one (2.2%) out of 45 vitreous fluid samples from the control group were positive by PCR and this difference was statistically significant (Pearson-χ² < 0.001). Vitreous fluid from both groups of patients did not reveal the presence of acid fast bacilli by direct smear and culture by standard conventional techniques.

The presence of M tuberculosis complex DNA in a statistically significant number of vitreous fluid samples of Eales' disease patients compared with the control group leads us to hypothesise the presence of sequestrated mycobacterium in the eyes of Eales' disease patients and a probable role of this bacterium in the pathogenesis of this enigmatic clinical condition.

Vertical cup/disc ratio in relation to optic disc size

EDITOR,—In a recent paper,3 the vertical cup/disc ratio (CDR) in relation to optic disc size was evaluated as a tool in the identification of optic discs with glaucomatous optic neuropathy. Two methods of using the vertical CDR were assessed, one method independent of disc size and the other dependent on disc size.

With the disc size independent method, for a group of patients with primary open angle glaucoma (POAG) and a control group, the authors calculated the vertical CDR and, based on a histogram plot of the control group, concluded that the vertical CDR is not normally distributed. An empirical cut off for the upper limit of normal was taken as the 97.5% percentile. When this test criterion (vertical CDR = 0.682) was applied to the two groups, this method yielded a sensitivity of 56.6% and specificity of 97.7% for the identification of glaucomatous optic discs. The conclusion that the vertical CDR is not normally distributed is not disputed (Chernoff-Lehmann test,4 p<0.10). However, the optimal vertical CDR may be selected rationally (rather than arbitrarily) by plotting sensitivity (S) against specificity (1−P) to produce a receiver operator characteristics (ROC) curve (Fig 1A). The optimal test criterion is the point on the ROC curve furthest from the line of zero discrimination; from the authors' data, the optimal test criterion is a vertical CDR cut off of 0.587 (sensitivity 86.6%, specificity 87.5%). Having rationally selected the optimal test criterion, its value as a clinical aid is best assessed by the predictive power of a positive test (rather than by isolated sensitivity and specificity values). This predictive power (V+) is the proportion of true positives (by reference test) to total positives (true positives + false positives) and is a function not only of sensitivity and specificity but also of prevalence. V+ may be calculated from: V+ = 1/(S)*(1−P) + (P), where N = sensitivity, S = specificity, and P = prevalence.

The prevalence of glaucoma varies according to the population studied and the criteria used as the reference test, but is generally considered to be approximately 2% in adults older than 40 years. We calculated the prevalence of 86.6% and a specificity of 87.5%, for an optimal vertical CDR cut off of 0.587, the predictive power of a positive test is 12.4%. This indicates that 87.6% of positives would be false. The prevalence of glaucoma in any population is indeterminate.
method is reminiscent of the concept of the “rim index” (observed neuroretinal rim area/expected neuroretinal rim area) first described in 1991 by Montgomery.

In general, the arbitrary selection of test criteria yield better predictive values but poorer sensitivity and specificity. Optimal selection of test criteria using ROC curves improves sensitivity but reduces predictive power. We therefore consider it important to appreciate that, in screening for a low prevalence disease with important health implications such as glaucoma, test criteria must be optimised to maintain a high sensitivity and steps taken to cater for a false positive rate of at least 80% which is inevitable in these circumstances.

Table 1 Case detection per 1000 population using cut off values given by Garway-Heath et al.

<table>
<thead>
<tr>
<th>Disc size</th>
<th>True positives</th>
<th>False positives</th>
<th>False negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent</td>
<td>11.3</td>
<td>22.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Dependent</td>
<td>12.5</td>
<td>10.8</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Table 2 Case detection per 1000 population using cut off values given by Barr and Nolan.

<table>
<thead>
<tr>
<th>Disc size</th>
<th>True positives</th>
<th>False positives</th>
<th>False negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent</td>
<td>17.3</td>
<td>122.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Dependent</td>
<td>18.0</td>
<td>75.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Reply

Editor,—We thank Barr and Nolan for their observations. We agree that the ROC curve is indeed a useful way of presenting such data, allowing a ready comprehension of the relation between sensitivity and specificity over a range of possible cut off values. In our paper, the arbitrary selection of test criteria was made to optimise sensitivity and maintain a false positive rate of at least 80% which is inevitable in these circumstances.

Application of the latter cut off values would result in a huge burden of false positive referrals to the hospital eye service, to be added to the false positive referrals that result from the application of the other tests (tonometry and visual field testing).

The true false negative rate using the cut off values we propose is much lower than suggested in Table 1. Our data set comprised glaucoma patients with minimal visual field loss (average MD = −3.44). In reality, there will be a greater range of glaucoma severity in the undiagnosed population,

In a population with a 2% glaucoma prevalence, application of Barr and Nolan’s cut off values would yield the number of cases (per 1000 population) given in Table 2. For the disc size dependent method, there are 9.3 referrals per 1000, 19.3% of whom have glaucoma.

Application of the latter cut off values would result in a huge burden of false positive referrals to the hospital eye service, to be added to the false positive referrals that result from the application of the other tests (tonometry and visual field testing).

The true false negative rate using the cut off values we propose is much lower than suggested in Table 1. Our data set comprised glaucoma patients with minimal visual field loss (average MD = −3.44). In reality, there will be a greater range of glaucoma severity in the undiagnosed population, making the test more sensitive. In addition, the results of disc biometry (of which estimation of the CDR is only a part) have to be taken together with the results of other tests. If it is assumed that half all individuals with glaucoma have raised IOP, then up to half the false negatives are likely to be referred for further assessment on that basis. Visual field testing would further reduce the false negative rate.

A more sophisticated application of the data is possible, with cut off values tailored according to the relative prevalence of glaucoma in subsets of the population. For instance, it is well established that the prevalence of glaucoma rises with the height of intraocular pressure (IOP). It would be possible to apply a cut off with high sensitivity to individuals with raised IOP and a cut off with high specificity to individuals with normal IOP. In this way, the overall pick up of cases can be maximised and the false positive rate kept to a minimum. A false positive rate of 80% is, therefore, by no means inevitable. However, making the method unnecessarily complicated would deter its use.

The method described in our paper was advocated as a simple adjunct to qualitative disc assessment. The great majority of cases not picked up by the CDR method (at our selected cut off) had focal changes in the neuroretinal rim, which can be detected by a careful qualitative examination. Over 90% of the more difficult cases to detect clinically, those with diffuse rim loss, were picked up by the method.

In summary, our selected cut off values were far from arbitrary, allowing CDR estimation to be integrated rationally with other aspects of the clinical examination, without resulting in unmanageable numbers of false positive glaucoma referrals.

D F GARWAY-HEATH
R A HITCHINGS
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City Road, London, EC1R 2PD

Editor,—We refer to a recent publication of Poole, discussing the incidence of conjunctival squamous carcinoma in Tanzania, notably in HIV affected patients. We have extensively studied a similar condition (bovine ocular squamous carcinoma) with a comparable genesis in veterinary cases, in the Harare area (Zimbabwe). We treated such cases with intravenous IL-2 injections of a recombinant form of interleukin-2 (Chiron) over 10 days. A large number of remissions and in 67% of the cases even complete cures (20 month observation period) were obtained. In fact, even tumours of 6 cm in diameter may regress completely with this therapeutic regimen. This form of treatment is cheap, non-toxic, effective, and feasible even in basic situations. It might be worth considering such treatment in human patients, obviously with the appropriate pre-requisites.

JAN-WILLEM KOTEN
WILLEM DEN OTTER
Department of Cell Biology and Histology, Utrecht University, Utrecht, Netherlands

Correspondence to: Willem Den Otter, Department of Cell Biology and Histology, Utrecht University, PO Box 80 176, 3508 TD, Utrecht, Netherlands.


Reply

Editor,—I thank Koten and Den Otter for their interest in my paper. Their experience with intranasal interleukin-2 in the treatment of bovine ocular squamous carcinoma makes very interesting reading. Regional low dose administration of interleukin-2 appears to be safe and is already used in other specialties: systemic toxicity is reduced and a high local concentration is achieved, and most adverse reactions are self limiting and can be managed on an outpatient basis. An appropriate clinical trial would be valuable if their good results in the bovine condition could be replicated in the human one.
It would be hard to justify experimental treatment in an advanced condition where local excision or enucleation might be life saving. A careful trial in the treatment of early conjunctival tumours, however, with vigilant follow up (sometimes difficult in an African setting), might be worthwhile. Another applicability of their useful work, when attempting to preserve an otherwise normal eye, might be to inject interleukin-2 at the excision margins after tumour resection, to prevent recurrence.

To be of use in Africa any treatment needs to be cost effective. One vial of recombinant interleukin-2 contains 18 million units and costs £140. If this could be used for several patients the cost might not be prohibitive. To put this cost in perspective, many patients I saw in Tanzania could not afford the £15 for cataract surgery.

THE DRUGS REVIEW

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This text is written by optometrists and its main strengths are as a practical guide to vision assessment and refraction in infants and young children. It is a comprehensive review of the up to date literature on visual development and assessment in the child. A chapter on normal child development emphasises that vision develops a parallel with motor, sensory, social, and language skills. Practical tips to help gain the child’s and parents’ confidence and cooperation in examination and assessment abound. (We must always ask and explain the toddler’s role in the examination if we are to expect cooperation and a meaningful result.)

There are a few omissions and inaccuracies in the medical section. A succinct review of congenital and childhood cataract management fails to mention examination of the red reflex with the direct ophthalmoscope for cataract as part of the routine neonatal examination of all newborns. Many paediatric ophthalmologists now utilise intraocular lens implants in the routine surgical management of childhood cataract, particularly after 1–2 years of age.

This book will be invaluable as a guide to vision assessment in childhood for optometrists, orthoptists, paediatricians, and ophthalmologists. The ophthalmologist will also find it an up to date source of the currently available knowledge on the development of vision in the infant and young child.

W H CHURCH


Ophthalmology is by definition a visual subject and this is evidenced by the fact that some of the best selling books in ophthalmology are books bought by someone who always preferred to read comics at school rather than books I therefore looked forward to reading through this new atlas of glaucoma. The two editors have assembled a well known list of contributors to write chapters in this atlas under three broad headings: the basics of glaucoma, clinical entities, and treatment. A range of topics is covered from aqueous humour dynamics and ocular blood flow, through to various aspects of treatment.

As one would expect from an atlas there are many large, high quality colour illustrations. However, the format does vary and inevitably some chapters have rather more text than one would expect for a colour atlas. I very much enjoyed some of the colour drawings, and I felt the illustrations for the subject of aqueous humour dynamics help to bring a normally dry subject to life. The colour illustrations are surprisingly effective in helping to explain some of the subjects such as tonography. I also liked the chapter on angle closure glaucoma with accompanying high frequency ultrasound photographs to back up the anatomical concepts. The chapter by Fellman on gonioscopy was also particularly good because of the accompanying line drawings and the pictures of dynamic gonioscopy, viewing the same drainage angles with different examination techniques. Finally, it was nice to browse through the rest of the book looking at the illustrations and accompanying text, as there were some very good illustrations that I had not previously seen in other books or publications.

The book does suffer slightly from the fact that it has multiple authors, are therefore formatting of the chapters is rather variable, which the authors acknowledge in the foreword. Some of the chapters have, for an atlas, rather too much text and too few pictures. In the chapter on filtration surgery, all of the illustrations are in black and white, which rather lets the book down, compared with the excellent colour illustrations in the rest of the book. There are two irritating features like incomplete references and mislabelled illustrations. However, these are minor details and should be easily remedied in the next edition.

In conclusion, this is a book I would certainly recommend to trainees in ophthalmology and those with an interest in glaucoma because of some of the excellent illustrations, which are a good aid to learning.

P T KHAW


This textbook is intended to provide the ophthalmologist with an up to date source of information on medical and surgical vitreoretinal disease. The book follows many others in being subdivided into basic sciences covering embryology, anatomy, and physiology followed by a further section on techniques of fundus examination, angiography, ultrasonography and electrophysiology. Finally, and fortunately, the most extensive section is clinical.

The editors have to be congratulated in ensuring that a multiauthor textbook manages to be consistent in its style. The quality of the illustrations is extremely high with many large, high quality colour photographs which add, rather than detract, from the text. An innovation in this textbook is the use of highlighted paragraphs which the authors call “pearls” or “controversial points”. Some readers might find these somewhat distracting but the reviewer found them to be very useful. Obviously a book running to 690 pages cannot claim to be fully comprehensive but there were very few obvious omissions and there are useful references at the end of each chapter. A very useful appendix is included which summarises the major multicentre trials as they pertain to vitreoretinal disease. This section would be extremely helpful for juniors in training and those practising ophthalmologists who perhaps have not read the trials in detail.

Inevitably there are minor quibbles in such a book; for example, the management of retinal detachment fails to mention the D-Ace procedure, a fault found in many American textbooks. It is also a pity that the proof reading was not entirely up to scratch—for example, page 190 the final paragraph ends in mid sentence.

Overall, however, this textbook is a valuable addition to the ophthalmic literature and the presentation is certainly different enough to make an essential purchase for all departmental libraries and, if the pricing is correct, I am sure many ophthalmologists will buy a personal copy.

P S BAINES

BOOK REVIEWS


Fear of eye disease is a major anxiety of individuals with diabetes. Monitoring the eyes of these individuals is a major anxiety of those charged with managing their diabetes. The situation is complicated by the fact that advanced diabetic retinopathy may have no effect on current visual function, but denied timely treatment it is likely to progress to irreversible visual loss. The need for efficient and reliable eye screening is therefore very considerable, as also is the need for the diabetic individual to participate in his own care and management.

This attractive and refreshingly unpretentious little volume embraces these central issues relating to the monitoring and treatment of diabetic eye disease in a concise “Introduction and Aims” chapter. It proceeds to summarise the classification and natural history of diabetic retinopathy followed by a description of ocular examination and a discussion of options for methodology and organisation of screening. The next two sections consider the indications for referral from the primary screener to the specialist ophthalmologist, and the management of diabetic retinopathy. Then, true to the pragmatic theme of the book, it concludes with a very useful chapter on management of visual loss, followed by an annotated picture
The latest issue of *Ageing and the eye* well spent. for those wishing to increase their understand-
services is contemporaneous with heightened
book at a time when the development of a
produce this thoughtful and informative
particular disappointment to those who do
look at. The quality of reproduction of some
of) illustrations makes the book attractive to
points or summarising information is also very
refer to. The liberal use of panels listing key
examination.
which may be encountered on funduscopic
gallery of non-diabetic eye abnormalities
perspective; epidemiology; delivery of eye
papers on ageing and the eye from a global
29) discusses ageing and the eye. Included are

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**NOTICES**

**Ageing and the eye**
The latest issue of *Community Eye Health* (no 29) discusses ageing and the eye. Included are papers on ageing and the eye from a global perspective; epidemiology; delivery of eye care to the elderly; and age related macular disease. 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) 171 608 6900/6910/6923; fax: (+44) 171 250 3207; email: eyeresource@ucl.ac.uk) Annual subscription £25. Free to workers in developing countries.

**Residents’ Foreign Exchange Programme**
Any resident interested in spending a period of up to one month in departments of ophthalmology in the Netherlands, Finland, Ireland, Germany, Denmark, France, Austria, or Portugal should apply to: Mr Robert Acheson, Secretary of the Foreign Exchange Committee, European Board of Ophthalmology, Institute of Ophthalmology, University College Dublin, 60 Eccles Street, Dublin 7, Ireland.

4th Meeting of the European Neuro-Ophthalmology Society
The 4th meeting of the European Neuro-Ophthalmology Society will be held on 29 August–2 September 1999 in Jerusalem, Israel. Further details: Secretariat, 4th Meeting of the European Neuro-Ophthalmology Society, PO Box 50006, Tel Aviv, 61500, Israel (tel: 972-3-514000; fax: 972-3-515764/972-3-5140077; email: Eunos99@kenes.com).

**International Agency for the Prevention of Blindness**
The sixth general assembly of the International Agency for the Prevention of Blindness will be held on 5–6 September 1999 at the Conference Centre, Beijing Friendship Hotel, Beijing, People’s Republic of China. The theme is ”The right to sight”. Further details: IAPB Secretariat, LV Prasad Eye Institute, LV Prasad Marg, Banjara Hills, Hyderabad 500 034, India (tel: 091-40-215389; fax: 091-40-248271; email: IAPB@lvpeye.stph.net).

**Ophthalmological Clinic, University of Creteil**
An international symposium on the macula will be held on 1–2 October 1999 at the Ophthalmological Clinic, University of Creteil. Further details: Professor G Soubrane, Chef de Service, Clinique Ophtalmologique Universitaire de Creteil, Centre Hospitalier Intercommunal, 40 Avenue de Verdun, 94010 Creteil, France (fax: 01 45 17 52 27).

**Jules François Prize**
The 2000 Jules François Prize of $100 000 for scientific research in ophthalmology will be awarded to a young scientist who has made an important contribution to ophthalmology. All topics in the field of fundamental and/or clinical research in ophthalmology will be considered. The application should be sent jointly with a curriculum vitae, the list of all publications, and three copies of the candidate’s 10 most relevant publications to Jules François Foundation Secretary, Professor Dr M Hanssens, Dienst Oogheelkunde, de Pintelaan 185, B-9000 Gent, Belgium. Deadline for applications 31 December 1999.

**Joachim Kuhlmann Fellowship for Ophthalmologists 2000**
The Joachim Kuhlmann AIDS Foundation, Essen, Germany, is sponsoring two fellowships per year for ophthalmologists at a well known institute, who want to train in CMV retinitis and other HIV related ophthalmologi-
cal diseases. The fellowships are valued at $US6000 each. deadlines for applications are 31 January and 31 July. Detailed applications, including CV and publication list, should be sent to the Joachim Kuhlmann AIDS Foundation, Bismarckstrasse 55, 45128 Essen, Germany (tel: 0201 87910-99; email: jk-stiftung@t-online.de).

XXXIV Nordic Congress of Ophthalmology
The XXXIV Nordic Congress of Ophthalmology will be held in Reykjavik, Iceland, 18–21 June 2000. This meeting celebrates the 100 year anniversary of the Nordic Ophthalmology Conference. Further details: Iceland Incentives Inc, Hamraborg 1–3, Is-Kopavogur, Iceland (tel: +354 554 1400; fax: +354 554 1472; email: incentiv@itn.is).

5th International Viteoretinal Meeting–IV 2000
The 5th International Viteoretinal Meeting–IV 2000 will be held in Parma, Italy, on 26–27 May 2000. The main topics will include “Hypoton and glaucoma in vitreoretinal surgery”, “Internal limiting membrane surgery”, “Macula oedema”, “Open globe injuries”, and “New pigment epithelium”. Further details: C Cantu, MA De Giovanni, or S Tedesco, Scientific Secretariat, Institute of Ophthalmology, University of Parma, Via Gramsci 14, 43100 Parma, Italy (tel: ++39 0521 239106; fax: ++39 0521 292358; email: nuzzi@ipruniv.cce.unipr.it).

DB-2000, International Forum on Diabetic Retinopathy
The International Forum on Diabetic Retinopathy will take place on 7–9 September 2000 at the Palazzo Reale, Naples, Italy. Further details: Francesco Bandello, Congress Secretary, Ophthalmological Clinic, University of Creteil, France (tel: 091 40 248271; email: infr@ucl.ac.uk). Further details: Professor G Soubrane, Chef de Service, Clinique Ophtalmologique Universitaire de Creteil, Centre Hospitalier Intercommunal, 40 Avenue de Verdun, 94010 Creteil, France (fax: 01 45 17 52 27).

12th Afro-Asian Congress of Ophthalmology
The 12th Afro-Asian Congress of Ophthalmology (Official Congress for the Afro-Asian Council of Ophthalmology) will be held on 11–15 November 2000 in Guangzhou (Canton), China. The theme is “Advances of ophthalmology and the 21st century”. Further details: Professor Lezheng Wu, Zhongshan Eye Center, SUMS, New Building, Room 919, 54 Xianlie Nan Road, Guangzhou 510060, PR China (tel: +86-20-8760 2402; fax: +86-20-8777 3570; email: lwuicv@gszsums.edu.cn).