Potential diagnostic dilemmas using the multifocal electroretinogram in intermittent exotropia

Multifocal electroretinography (mfERG) is a valuable technique in assessing macular function in retinal disease objectively as it provides spatial information. Altered responses give an estimate of the extent of central retinal dysfunction. Fixation is known to be an important technical factor in mfERG recording. We present findings in a patient with asymptomatic intermittent exotropia that reinforce the importance of adequate consideration of potential fixation errors.

Case report

The patient was a 52 year old man with maternally inherited diabetes and deafness (MIDD) consequent upon a mitochondrial DNA nucleotide A3243G point mutation, and examined as part of a series of patients with MIDD. Visual acuity was 20/20 (ETDRS chart) bilaterally. Fundi showed symmetrical bilateral irregular patches of retinal pigment epithelium atrophy at the posterior poles. The foveas were normal.

Macular function was assessed initially by mfERG recorded binocularly with a stimulus size of 61 hexagons using the RETIscan System (Roland Consult, Wiesbaden, Germany). The patient fixated on the centre of a large diagonal cross, centred over the central hexagon, at a viewing distance of 33 cm. Pupils were dilated. Refractive errors were corrected with −6.25 dioptre (D) right eye and −6.25 spherical dioptres combined with −0.75 cylindrical dioptres at 5° left eye. Additional +3D were given for a viewing distance of 33 cm. Each recording session consisted of eight trials over about 20 minutes.

Upon binocular recording, changes reflecting the retinal dystrophy were visible in the right eye trace array outside the central hexagon. The normal foveal response was consistent both with normal foveal function and central fixation throughout testing (fig 1A). Amplitude reduction was observed in many left eye traces with an additional "off centre" peak also visible in three dimensional plot (fig 1B). These findings are not suggestive of MIDD. The mfERG was repeated monocularly. The left eye findings now showed a normal central response and alterations in parafoveal function consistent with MIDD (fig 1A, B).

Subsequent orthoptic examination revealed a near type intermittent exotropia with poor motor fusion and additional microtropia. The latent deviation of the left eye was 2 prism dioptres base-in at 33 cm. A small vertical height component was demonstrated on the Hess chart. Stereopsis was subnormal.

Comment

Patients with intermittent exotropia can be completely controlled having binocular vision or may have a manifest exotropia. Under binocular mfERG stimulation, the left eye presumably fixated in exotropia at times of fusional decompensation, and the stimulus pattern shifted by the extent of the squint deviation. At times of positive binocular vision the fixation was located almost centrally. The fixation was slightly shifted because of the microtropia (fig 1B) which was not detected by direct observation. Examiners should always be aware that not only retinal disease can affect the mfERG. Asymptomatic strabismus is a reason for fixation instability and represents a potential dilemma in the interpretation of binocular mfERGs. Even with direct observation a small intermittent strabismus may not be detected. This could result in a broadened central peak rather than the double peak seen in our patient and thus be mistaken for macular dysfunction. This would be potentially disastrous in a patient with optic nerve disease where the mfERG should be normal.

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doi: 10.1136/bjo.2003.040584
Accepted for publication 31 January 2004

Figure 1 (A) Three dimensional plot (left) and trace arrays (right) of the right eye recorded binocularly. See text for details. (B) Left eye under binocular recording. On the three dimensional plot (left) the left peak is consistent with fixation in exotropia. At times of positive binocular vision the fixation is almost centrally located (right peak). Trace array changes are seen in most hexagons (right).
Furosemide is a potent diuretic which is an
anthranilic acid derivative. Chemically, it is
4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. Furosemide is indicated for the treatment
of oedema associated with congestive heart
failure, cirrhosis of the liver, and renal
disease, including the nephrotic syndrome.

Here I report a case of a diabetic patient,
with nephrotic syndrome, who experienced
marked improvement in diabetic macular oedema after systemic treatment with fur-
osemide.

Case report
A 41 year old woman with type II insulin
dependent diabetes mellitus was referred for
decline in vision over the past 2 months. Besides the diabetes, her past medical history was positive for irregular
menstrual cycle and gastroparesis. The
patient had also noticed a gain in weight of
about 30 lb (13.5 kg) over the same period of
time, from 154 lb (69.3 kg). Three weeks later her vision had improved to 20/80 in both eyes. On fundus examination there was marked improvement
in the macular oedema in both eyes. OCT
examination confirmed the partial resolution
of the macular oedema. The central retinal thickness measured by OCT was 250 μm in the right eye and 218 μm in the left eye (fig 2C, D).

Comment
Diabetic macular oedema is characterised by
hyperpermeability of retinal blood vessels and
subsequent formation of hard exudates and
macular oedema, the degree of which can be estimated by measurement of retinal thickness. The severity and progression of diabetic macular oedema has been associated with the presence of nephrotic syndrome and to the degree of proteinuria.

Partial resolution of diabetic
macular oedema after systemic
treatment with furosemide

Furosemide is a potent diuretic which is an
anthranilic acid derivative. Chemically, it is

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Figure 2. (A) Monocular mfERG recording of the right eye. (B) Monocular mfERG recording of the left eye. Changes reflecting MIDD are visible outside the central hexagon.

We thank Roland Consult for mfERG facilities.

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Supported by the European Commission NoQLK6-CT2000-51262 (Marie Curie Individual Fellowship) and by the Faun-Foundation to CB.

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study Knudsen et al demonstrated the presence of an association between retinal thickness as evaluated OCT, and glomerular leakage as evaluated by urinary albumin excretion rate in type II diabetic patients with diabetic macular oedema.

Nephrotic syndrome is characterised by massive proteinuria, which leads to hypoproteinaemia/hypoalbuminaemia, hyperlipidaemia with elevated cholesterol triglycerides and other lipids, and oedema. The oedema results not only from the hypo-osmolar state caused by the loss of plasma proteins, but also from abnormal salt and water retention.

Furosemide is used in the treatment of fluid overload experienced by patients with nephrotic syndrome because it is a potent and rapid acting diuretic. It has been demonstrated that furosemide inhibits primarily the absorption of sodium and chloride not only in the proximal and distal tubules but also in the loop of Henle.

I reported what is, to my knowledge, the first case of marked improvement of diabetic macular oedema after systemic treatment with furosemide documented by OCT examination. I think that the fluid overload secondary to the nephrotic syndrome was the main cause of the worsening of the macular oedema in this patient, and that the intensive treatment with furosemide was responsible for reducing the amount of fluid overload and resolving the macular oedema.

The exact mechanism of the action of furosemide in resolving the macular oedema is unknown. Tsuibo et al demonstrated that furosemide inhibits fluid absorption across retinal pigment epithelium (RPE) in an experimental model of retinal detachment in monkeys. According to their study furosemide could worsen the presence of a neurosensory macular detachment especially in a patient where the subneurosensory retina fluid collection is secondary to a defect in RPE pump. However, the FA study of this patient at presentation demonstrated multiple retinal microaneurysms at the posterior pole of both eyes and diffuse intraretinal microvascular leakage of dye in the late phase of the study. The FA study was consistent with the appearance of diffuse diabetic macular oedema. In such cases the intraretinal and subneurosensory retina leakage of dye is secondary to a microvascular retinal defect and not to a failure in the RPE pump. I think that restoration of more normal oniotic pressure within the retinal vasculature was the underlying reason for the response to the drug of the diabetic macular oedema.

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doi: 10.1136/bjo.2004.042580
Accepted for publication 17 March 2004

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Our patient had a vision loss to 20/200 associated with the onset of right sided facial numbness 10 months after low dose (40 Gy) gamma knife radiosurgery for TN. Although high dose radiosurgery (90 Gy) is a known risk factor for complications with gamma knife radiosurgery, the low dose our patient received has not been associated with such complications. Patients undergoing gamma knife radiosurgery for TN should be warned of this potential complication and should be evaluated preoperatively and postoperatively by an ophthalmologist.

...declined. During the next 6 weeks, the corneal surface improved, and at last follow up the patient’s vision was 20/60.

**Comment**

Gamma knife radiosurgery is an effective treatment for TN with few complications. Pollock et al noted an increased incidence of “trigeminal dysesthesia” and “corneal numbness” after high doses (90 Gy) of gamma knife irradiation. In an animal model, a 100 Gy dose caused nerve necrosis. Matsuda et al identified a “dry eye complication” of epithelial keratopathy after gamma knife radiosurgery for TN. Despite these documented ocular side effects, no cases of vision loss have been reported.

Neurotrophic keratopathy has been recognised in patients with herpes simplex, herpes zoster, and after laser in situ keratomileusis (LASIK) surgery. Mild neurotrophic keratopathy may be manifested as a punctate epithelial keratopathy. In severe cases, corneal decompensation can lead to severe vision loss.

...combined use of aspirin and clopidogrel for 1 week in patients on COM. Clopidogrel taken alone causes less gastrointestinal haemorrhage than aspirin, but has an otherwise similar risk profile to aspirin.

Post-marketing surveillance of clopidogrel has recorded “conjunctival, ocular, and retinal haemorrhage.” Further information regarding these events, and whether they occurred during oculary surgery, was not available at the time of writing (November, 2004). A detailed Medline literature search has produced no relevant ophthalmic case experience.

The CURE study found higher “major and minor” bleeding rates in patients taking COM compared with aspirin alone, but showed no increase in life threatening or intracranial haemorrhage, and does not record ocular haemorrhage. Of note is the significant increase in major bleeding events recorded in COM patients undergoing coronary artery bypass graft surgery where the clopidogrel was stopped less than 5 days before the procedure.

A February 2004 telephonic survey of nursing staff running cataract pre-assessment clinics at 15 ophthalmic units across the United Kingdom indicated variable approaches to such agents. Individual consultants at three units stopped clopidogrel preoperatively. Twelve units continued clopidogrel; none had specific policy for patients on aspirin and clopidogrel. The related and relevant issue of anaesthetists’ approach to regional ocular anaesthesia in patients on such treatment was not addressed.

Translating the CURE study results into a “number needed to treat,” approximately 47 patients with acute coronary syndrome would require treatment for 9 months with aspirin and clopidogrel to prevent one cardiovascular death, non-fatal myocardial infarction, or stroke. Stopping clopidogrel for a short period is therefore unlikely to make a material difference to the vascular event risk for an individual.

In summary, there is an increased risk of systemic bleeding associated with COM compared to aspirin alone. The degree of perioperative bleeding risk with elective eye surgery is still undefined. Our departmental policy has been changed to stopping clopidogrel for 1 week in patients on combination treatment given for cataract surgery, and to use a similar approach to that normally
employed for patients taking aspirin in those on clopidogrel alone. Other departments’ experience with this increasingly used antiplatelet agent would be valued.

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doi: 10.1136/bjo.2004.045997
Accepted for publication 11 March 2004

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The role of corticosteroids in fungal keratitis: a different view
Fungal infections of the cornea continue to be an important cause of ocular morbidity. This report describes a situation which occurs in clinical practice in patients with misdiagnosed fungal ulcers who are treated with a combination of topical steroids and antibiotics drops. A common strategy when these patients are finally diagnosed with fungal keratitis is to switch to antifungal agents and discontinue the corticosteroids. We have recently seen two patients with fungal keratitis who demonstrated severe inflammation and corneal necrosis after the abrupt discontinuation of corticosteroids.

Case 1
A 32 year old woman with a corneal transplant in her right eye was referred for evaluation of an unresponsive corneal ulcer in her transplant. The patient had been treated with a combination of moxifloxacin 0.5% drops hourly and prednisolone 1% drops four times per day. On initial examination there was a central stromal infiltrate with an overlying epithelial defect. The infiltrate had feathery edges reminiscent of fungal infection. The cultures had been taken up to this point. After cultures were taken the therapeutic regimen was switched to cefazolin 50 mg/ml and gentamicin 15 mg/ml while we discontinued the corticosteroids drops. The clinical picture remained relatively unchanged during the next 48 hours. The preliminary culture results revealed fungal yeasts. We then started amphotericin 0.15% drops and fluconazole by mouth but the infection worsened over the next 2 days leading to descemetocele formation and perforation; the patient underwent an emergency keratoplasty.

Case 2
A 13 year old girl who was a soft contact lens wearer was referred for evaluation of a corneal ulcer. The patient had been treated for 2 weeks with cefazolin 50 mg/ml and tobramycin 0.3% on an hourly basis, prednisolone 1% five times per day, and ketocnazole 400 mg by mouth. On initial examination there was a diffuse central stromal infiltrate with the presence of an endothelial plaque and hypopyon. We performed confocal microscopy which showed hyphae characteristic of a fungal infection. After cultures were taken we continued the corticosteroids drops. The clinical picture worsened and the ulcerative process continued the next 48 hours. The preliminary culture results revealed fungal yeasts. We then started modified the therapeutic regimen to fluconazole by mouth, natamycin 5 drops, cefazolin 50 mg/ml, while we discontinued the steroid drops. The patient showed signs of worsening during the next 2 days; the cornea perforated and an emergency keratoplasty was performed.

Comment
The analysis of the previous cases suggests that in patients with fungal keratitis who previously received topical corticosteroids, the abrupt cessation of these agents is likely to lead to an acute rebound inflammatory reaction and even perforation. The proper use of corticosteroids in the treatment of fungal corneal infections continues to be debated among experts. The controversy arises because there are two goals in the treatment of corneal infection that are inherently incompatible: (a) to rid the affected tissue of the replicating microorganisms causing the infection, and (b) to limit the degree of structural damage caused by the infectious process.

We recommend a gradual tapering of the corticosteroids in these cases which allows for the antifungal agents to act, and the host immune mechanisms to take control of the inflammatory response. However, clinical application in patients should be determined individually in all cases.

Authors’ qualifications and the BJO
It is not often that journal policy is dictated by input from the readership. A notable exception to this probably occurred in the ANZ Journal of Surgery in 2002, following a letter to the editor in 2001 addressing authors’ qualifications. In it we pointed out that journal aspirations to international recognition and increased circulation may be enhanced by having the authors’ qualifications consistently published. We indicated that the qualifications of one’s international colleagues, including departmental heads where one may have trained overseas, can be recognised. The educational progress of one’s colleagues—for instance, a clinician’s higher qualifications (for example, PhD) may be determined. We pointed out that the reader can determine whether the author is in effect a qualified ophthalmologist, a resident, or still a medical student. In some parts of the world, the rivalry between optometrists and ophthalmologists may be highlighted by one group publishing in the other’s journal. Thus, qualifications may be used to discriminate between the two groups. Where the qualification discriminates between physicians and surgeons, this too can be recognised. In these days of enhanced medical forensic confrontations, a medical practitioner’s viewpoint can be differentiated from that of a lawyer. Finally, we pointed out that if author qualifications are designated, the reader may be quite sure that the article was not written by the medical records librarian, let alone the hospital trolley boy in a moment of inspiration.

We have observed that in recent issues of the BJO, there appears to be an inconsistent approach to appending qualifications. Only the corresponding author is likely to be given a qualification; the first author usually goes without. For example in volume 88 number 5 (May 2004), in the perspective, only the corresponding author, Azuara-Blanco writing on cannabinoids and glaucoma received a qualification. In the extended reports, only Miyamoto on oil droplets in rabbits, Shaarawy on day one intraocular pressure, Orgul on blood flow in glaucoma, and Probst on fibronectin in diabetics received recognition of qualifications that the authors of all the other extended reports missed out. In other words, in this issue of the journal, only one third of the corresponding authors, let alone the co-authors of extended reports were given qualifications. No one in the letters section was designated with a qualification. None of the three editorial writers received a qualification. We are left wondering as to whether Professor König, writing on the cost effectiveness of treatment for amblyopia, was a paediatric ophthalmologist branching out into community medicine, a medical politician, a health economist, a statistician, or a psychotherapist having a different weekend. Whatever he is, he reached a reassuring conclusion in his article, that amblyopia therapy “is likely to be very cost effective.” We also do not know whether Schwab, writing about the preoperative course in “Halcyon days,” with the university affiliation of UC Davis, was an artist, the university photographer, an ornithologist, an anthropologist, or a Greek mythen, having written an article on postoperative leak in trabeculectomy. Henderson can be recognised as a surgeon by the British appellative “Mr.” We thus presume he has an FRCS or an FRCOphth, but we don’t really know.

Our point is made. As we demonstrated in our original article,¹ 89.5% of the 19 journals regularly read by us use author qualifications.

PostScript
Mohs surgery: efficient and effective

We read with interest the report of Hsuan et al.1 The authors present a case series of 55 patients with basal cell carcinoma on the eyelids. There are no details regarding the size or histological subtypes of basal cell carcinoma in the results and therefore it is difficult to assess the applicability of the results to other groups of patients who may have more or less severe basal cell carcinoma. The authors make several generalisations regarding Mohs surgery that we believe are unsubstantiated and we wish to take the opportunity to clarify a few points.

The essence of Mohs micrographic surgery is 100% histological frozen section margin control. There is no other technique that enables 100% margin examination, including the authors’ bread loaf section technique. Mohs micrographic surgery has 99% 5 year cure rates for basal cell carcinoma because of the thorough margin examination. In distinction, standard bread loaf section technique examines approximately 0.1% of the surgical margin, with an increased potential to miss infiltrative tumour extensions. Because the bread loaf technique is least likely to accurately detect a positive margin, many surgeons employ a tangential peripheral section analysis as a means of obtaining more thorough examination of the margin. Mohs micrographic surgery has another advantage, which is true tissue spacing. The margin of normal skin removed during Mohs micrographic surgery may be as little as 0.5 mm. When operating on the eyelid, I have been the difference between sacrifice and preservation of a critical structure (that is, punctum). The authors sacrificed 2 mm on both sides of the skin cancer, which in some cases may have resulted in up to 3 mm of unnecessary skin removal. This could result in more complicated reconstruction for patients.

The authors state that their patients were happy to have multiple operative sessions. For patients undergoing Mohs micrographic surgery, complete tumour removal is accomplished in one session, with reconstruction performed on the same day as tumour extirpation. The inconvenience to patients associated with staged re-excision after 48 hours of histological examination and then a final stage reconstruction 48 hours after the last histological sample is taken should not be underestimated. Patients in general are pleased with their care based primarily with their interaction with the physicians. However it is our doubt that any patient would choose three surgical interventions over 5 days rather than one surgical intervention with 100% margin control in 1 day.

The authors state that Mohs surgery is “too expensive.” This statement is unsubstantiated. In a cost analysis by Cook and Zitelli,2 Mohs surgery was found to be similar in cost to excisional surgery and less expensive than frozen section analysis. With three potential operative encounters, the cost of staged excision of basal cell carcinoma in the United States would exceed that for Mohs micrographic surgery with reconstruction on the same day. It is also important to note that the pathological charges are included in the Mohs surgery fee, as the Mohs surgeon functions as both the surgeon and pathologist. Therefore, pathology charges generated for multiple staged re-excisions must be included in any calculation of cost associated with staged excision.

The authors characterised Mohs surgery as “laborious.” I would argue that one doctor performing a very efficient tissue sparing operation all in a matter of 2–4 hours, a typical duration for Mohs surgery and reconstruction, with the pathology included within that time frame and fee, is both cost efficient and labour efficient. Mohs surgery has been especially designed for accuracy, tissue sparing, convenience, cost efficiency, and labour efficiency.

Mohs surgeons are expert in the complete removal of complex skin cancers, particularly on the central facial area. Mohs surgeons work closely with our colleagues in oculoplastic surgery in the United States to coordinate expert reconstruction of the resultant defects. In places where Mohs surgery is less available, close communication between the surgeon and pathologist, and tangential vertical margin processing may offer a reasonable therapeutic option, although one that is more inconvenient, costly, and laborious for patients and physicians alike.

References

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doi: 10.1136/bjo.2004.042838
Accepted 22 January 2004

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LASIK in children?

O’Keefe and Nolan report on LASIK surgery in five children with unilateral high myopia who were presumed to have amblyopia.3 One subject had bilateral high myopia.
Optic nerve hypoplasia is associated with high myopia. In addition, anisometropic myopia is a common sequela of retinopathy of prematurity. Thinning of the sclera with posterior staphyloma formation has long been known to be associated with high myopia. Best corrected visual acuity in these patients is often limited by associated retinal and periventricular pathology. None of the treated eyes obtained acuity better than 6/15. This limited outcome following refractive surgery may be because optical enlargement of the retinal image rather than enhanced neurosensory function.

In the three children who were less than 3 years old improved literacy, familiarity with the test procedure, and the Hawthorn effect were certainly important factors in their assumed improvement. The absolute lack of progress in one child was a probable manifestation of pre-existing retinal pathology rather than non-compliance with patching."

The authors advocate increased use of LASIK to thin the corneas of highly myopic children who already have profound reductions in scleral thickness. "From a clinical viewpoint, optic nerve hypoplasia should be carefully looked for in all patients with unilateral bilateral high myopia and visual loss." It may well be more appropriate to improve the quality of retinal and optic nerve evaluations before performing irreversible surgical procedures with unknown long term consequences for these abnormal eyes.

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doi: 10.1136/bjo.2004.042853
Accepted for publication 22 January 2004

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In the letter titled Prospective case control study on genetic association of apolipoprotein e2 with intraocular pressure (Br J Ophthalmol 2004;88:581–582) the authors were listed incorrectly. The correct listing is as follows: A Jünemann, S Bleich, U Reulbach, K Henkel, N Wakili, G Beck, B Rautenstrauss, C Mardin, G O H Naumann, A Reis, J Kornhuber. The journal apologises for this error.

4th International Congress on Autoimmunity
The 4th International Congress on Autoimmunity will take place 3–7 November 2004 in Budapest, Hungary. The deadline for the receipt of abstracts is 20 June 2004. Further details: Kennes International Global Congress Organisers and Association Management Services, 17 Rue du Cendrier, PO Box 1726, CH-1211 Geneva 1, Switzerland (tel: +41 22 908 0488; fax: +41 22 732 2850; email: autoimm04@kennes.com; website: www.kennes.com/autoimm04).

XVI International Congress for Eye Research

Ophthalmic Anesthesia Society
The 18th Annual Meeting of the Ophthalmic Anesthesia Society will be held on 1 – 3 October 2004 in Chicago, USA. For further details: Ophthalmic Anesthesia Society (OAS), 793-A Foothill Blvd, PMB #119, San Luis Obispo, CA 93405 USA (tel: 001 805 534 0300; fax: 001 805 534 9030; email: info@eyeanesthesia.org; website: www.eyeanesthesia.org).

Glaucoma Society Silver Jubilee Meeting
2004
The Silver Jubilee Meeting and Dinner for the Glaucoma Society will be held on 3 December 2004 at the Royal College of Physicians in Regents Park, London. The meeting will take place between 8.30am and 5pm and the dinner will be held between 6.30pm and 10pm. For further information, please contact: Janet Flowers, Administrator, 29 Quarry Hill, Grays, Essex, RM17 5BT (tel: 01375 383172; e-mail: glauco@uakeire.freeserve.co.uk).

Amsterdam Retina Debate
The Amsterdam Retina Debate will be held on 10 December 2004 at the Academic Medical Centre, Amsterdam, The Netherlands. For further information, please contact: Nicolas van der Tulp Institute; tel: +31 20 566 8585; fax: +31 20 696 3228; email: retinadebate@amc.uva.nl

Prestigious Helen Keller Foundation prize awarded to one of London’s most eminent ophthalmologists
Professor Alan Bird, Institute of Ophthalmology, University College London and Consultant Ophthalmologist at Moorfields Eye Hospital NHS Trust, has been awarded one of ophthalmology’s most prestigious prizes, the Helen Keller Prize for Vision Research. The prize was created in 1994 by the Helen Keller Foundation for Research and Education, based in the USA, and honours the scientists and researchers working in the field of blindness and visual loss. Professor Bird is one of the world’s leading experts on age related macular degeneration (AMD), inherited macular degeneration and Retinitis Pigmentosa (RP), and has led research into the identification of the genes which cause retinal degeneration. As well as his scientific research, Professor Bird also continues to treat patients at regular clinics at Moorfields Eye Hospital. Further information on Moorfields is available at: www.moorfields.nhs.uk. Further information about the Helen Keller Foundation is available at www.helenkellerfoundation.org. Further information on the Institute of Ophthalmology is available at www.ucl.ac.uk/oo.

Sophie sees sight saving projects in Tanzania with VISION 2020
HRI The Countess of Wessex has recently returned from a trip to Tanzania in her role as Patron of VISION 2020: The Right to Sight. Throughout the trip The Countess met with representatives of and visited projects supported by VISION 2020 Partners, including Sight Savers International (SSI), Christian Blind Mission (CBM), International Eye Foundation, International Trachoma Initiative (ITI), Helen Keller International (HKI), International Centre for Eye Education (ICEE), the SEVA Foundation and the Kilimanjaro Centre for Community Ophthalmology (KCCO). VISION 2020: The Right to Sight is a global initiative of the International Agency for the Prevention of Blindness (IAPB) and the World Health Organization (WHO), with a coalition of international Non-Governmental organisations. VISION 2020 aims to eliminate unnecessary blindness in order to give all people, particularly the millions of needlessly blind, The Right to Sight. For further information, please visit www.v2020.org.
Mohs surgery: efficient and effective

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Br J Ophthalmol 2004 88: 1228
doi: 10.1136/bjo.2004.047068