THE DOYNE MEMORIAL LECTURE, always the main event of the Oxford Ophthalmological Congress (OOC), this year was given by Elizabeth Engle, Professor of Neurology and Ophthalmology at Harvard Medical School. She is, said Master Professor Tony Moore (Moorfields Eye Hospital, London), a clinician-scientist par excellence. He told us he had witnessed Professor Engle running on a treadmill while simultaneously working at her computer – something, he confessed, he could not hope to emulate.

For those older members of the audience, whose last formal genetics lecture may have predated Dolly the sheep, Professor Engle’s talk – on the congenital cranial dysinnervation disorders (CCDD) – provided a crash course on the state of the art. She treated delegates to a dizzying ride through the multifaceted genetics of these disorders, liberally lacing her talk with colourful cartoons, magnetic resonance images and, in genetic mouse knockout models, beautiful fluorescence micrographs of the effects of the various mutations on neural development.

Her research interest began when she encountered, as a young doctor, a toddler born with a complex eye movement disorder, a paralytic form of strabismus, which segregated in his family as a dominant trait. Many CCDD can be linked to developmental abnormalities in the abducens and/or the oculomotor nerves, due to mutations in proteins critical to axon growth or guidance. While her findings as yet have no therapeutic implications, Professor Engle conceded, her research is dissecting out pathways that can begin to inform human disease and normal developmental processes. She said she would ‘love to hear from anyone who would like to share families… or would like us to do a genetic analysis on any of their patients.’

THE MASTER’S SYMPOSIUM

Another major OOC highlight was Monday morning’s Master’s Symposium on ‘Current and new approaches to treatment of retinovascular disease.’ Dr Marcus Fruttiger (Institute of Ophthalmology, London) explained how normal growth of retinal blood vessels depends on correct levels of vascular endothelial growth factor (VEGF). Research in animal models has demonstrated that hypoxia drives oxygen-induced retinopathy. VEGF is induced under hypoxic conditions but very high oxygen levels actually suppress VEGF production, leading to obliteration of adjacent vessels. Restoring oxygen tension to normal results in tortuous neovascularisation. High VEGF levels have the same effect. VEGF blockers, conversely, lead to healthy vessel regeneration.

The link between VEGF and the retinopathy of prematurity (ROP) was explored by Professor Birgit Lorenz (Department of Ophthalmology, University Hospital, Giessen). She explained there is a ‘big debate’ about the use of VEGF blockers in ROP. Bevacizumab may be effective initially but can be associated with later recurrence. There are also concerns about blockage of a growth factor needed for development of the lung, brain and retina. Moreover, measuring VEGF levels is problematic: serum levels show a considerable variation, may not reflect the total amount in the blood (thrombocytes also contain VEGF) and provide no indication of levels in the eye. Bevacizumab remains off-label for ROP and laser therapy is still the first-line approach, she said.
Treat the macula as well as the tumour

In his discussion of ‘Oncology and the peripheral retinal vasculature’, Professor Heinrich Heimann (Royal Liverpool University Hospital) emphasised the need to treat the macula as well as the peripheral vascular tumour. ‘You should always perform OCT of the macula because at the end of the day ...it is the macular disease you are treating, not so much the tumour in the periphery. You can get rid of the tumour... [But] from the word go we also treat the macular disease.’ He warned against using cryotherapy for vasoproliferative tumours or retinal angiomas because of the risk of an uncontrolled exudative reaction.

Retinal vein occlusion was next on the morning’s programme. Dexamethasone implants, ranibizumab and aflibercept are all EMA-licensed for the treatment of macular oedema due to non-ischaemic central retinal vein occlusion (CRVO), said Mr Phil Hykin (Moorfields Eye Hospital, London). No treatment has been shown to improve visual acuity outcomes in patients with ischaemic CRVO, although early indirect panretinal photocoagulation and bevacizumab are the preferred therapies. For patients with macular oedema due to non-ischaemic branch retinal vein occlusion (BRVO), the recommendation is early laser therapy followed by either dexamethasone implants or ranibizumab. The latter are also suitable for ischaemic BRVO.

Despite the emphasis on diabetic retinopathy screening in the UK, people are still going blind from this disease, said Professor Simon Harding (University of Liverpool). This is due to a combination of late presentation, the increasing prevalence of diabetes and the fragmentation of services. He said he agrees with Margaret Hodge, Chair of the Public Accounts Committee, that the standard of diabetes care has deteriorated in the last 5 years. Despite this pessimistic introduction, Professor Harding had some good news: the use of anti-VEGF agents to treat diabetic macular oedema has been a ‘game changer’, while fenofibrate has shown promise in the treatment of diabetic retinopathy.

Macular telangiectasia — MacTel, for short — remains something of a mystery, explained Ms Cathy Egan (Moorfields Eye Hospital, London). Loss of central vision is inevitable but its timing is unpredictable. Anti-VEGF agents work well in the neovascular, but not the non-neovascular stage. The current MacTel research project owes its existence to an Australian patient, a captain of industry who raised the funds to support it. The aim is to study over 200 patients and to discover an effective treatment within five years — a ‘very ambitious’ goal, Ms Egan acknowledged. Professor Moore asked about the relationship between Type 2 diabetes and MacTel; did patients whose diabetes is diagnosed later develop MacTel, or is MacTel a signal for the later development of diabetes? Ms Egan replied that her group is now designing a study to see if patients with Type 2 diabetes are more likely to develop MacTel or if MacTel is a specific manifestation of diabetes.

‘Terrifying’ surgery

The last speaker before lunch was Professor José García-Arumi (Institute of Ocular Microsurgery, Valle Hebrón University Hospital, Barcelona) who gave an impressive account of vitreo-retinal surgery. His talk kept his audience on the edge of their seats, especially while watching a video showing the removal of an embolus from a retinal arteriole; this won him an extra round of applause. Professor Moore described such surgery as ‘nerve-wracking’ and asked how surgeons he had trained to do these procedures. Professor García-Arumi admitted he did not train other surgeons as this surgery ‘is not easy.’ Perhaps a more apt adjective — heard in the lunch queue — was ‘terrifying’ but then, as this delegate also noted, ‘the patients have nothing to lose.’
The lecture on military injuries particularly enthralled this civilian audience. Lt-Col Nick Glover (Birmingham Royal Centre for Defence Medicine) reviewed the changing incidence and type of wartime injuries, from the Napoleonic War to the Gulf and Afghanistan wars. The increase in eye injuries as a proportion of the total number increased between World War I (4%) and the Gulf and Afghanistan wars (16%). This reflects improved survival rates in modern warfare. Ballistic eye protection can reduce the eye injury rate to less than 1%. Transport from the site of injury to Lt-Col Glover’s unit is usually achieved within 24 hours. Surgical time is limited, however, as the patient usually has other injuries. The ophthalmological surgeon must work at the same time as the other trauma surgeons and use portable ophthalmological equipment.

Asked during the discussion about his approach to open eye injuries, Lt-Col Glover explained he prefers to operate as soon as possible. Although surgeons at Camp Bastion do not usually undertake primary repair, the patient generally arrives in Birmingham within 36 hours of the injury. Another delegate asked whether American surgeons have a different approach. Lt-Col Glover said that, unlike UK surgeons, those from the US once had been ‘quite keen’ on primary enucleation. Now, however, the two nationalities have a ‘very similar pathway.’ He admitted that some of his training has been ‘picked up along the way’ but that it is important not to become overstretched and to know when to hand over to the specialists.
Another enthralling symposium was on ‘Ocular regeneration: facts and some fiction.’ Chair Mr Gerry Fahy (Galway University Hospital) noted this was an area of work that has been receiving a considerable amount of attention recently. The symposium opened with a review of the biology, therapeutics and future prospects for mesenchymal stem cells (MSC), presented by Professor Frank Barry (Regenerative Medicine Institute, National Centre for Biomedical Engineering Science and the National University of Ireland, Galway). Such pluripotent stem cells present multiple opportunities for ophthalmology. MSC have been shown to prevent rejection of allogeneic corneal transplants and to be neuroprotective in a rat glaucoma model. MSC are unlikely to have the potential to treat neural disorders, however. Neural stem cells, restricted progenitor stem cells and differentiated cells (motor and other neurons, retinal pigmented epithelium, astrocytes, oligodendrocytes, Schwann cells) are likely to be more useful for neurological applications, by virtue of the mediators they secrete.

In his second presentation of the Congress, Professor Harminder Dua reviewed the history and development of ocular surface regeneration. The limbal epithelium, he explained, appears to be a stem-cell repository so limbal transplantation can be effective. Success rates are highest (100% in Professor Dua’s experience) with autologous transplantation, which is possible only in patients with unilateral stem cell deficiency. Transplants from living-related or cadaveric donors are less successful: 9/10 eyes (89%) and 2/6 eyes (33%), respectively, in the same series. Quality of life is more important than visual acuity. Bowman’s zone is a barrier to the anterior migration of keratocytes – a problem that can be overcome by the use of an amniotic membrane patch and/or graft. Research continues into techniques of ex-vivo expansion and the use of regenerating agents. Professor Dua concluded his talk by looking into the future possibility of using both corneal epithelium (expanded ex-vivo on suitable substrates) and MSC in ocular surface regeneration. He explained that the limbus plays a minimal role in normal corneal epithelial homeostasis. The central epithelium can behave like the limbus in terms of proliferative potential, as indicated by good results in a few patients who have received corneal stromal transplants without any limbal tissue. Corneal stromal stem cells share many of the characteristics of MSC and, under appropriate conditions, can differentiate into corneal epithelial cells, he said.

Ophthalmologists planning to use allogeneic stem cell therapy need to be aware of the many regulatory requirements, as outlined by Mr Stephen Tuft (Moorfields Eye Hospital London, and Medical Advisor, Moorfields Lions Eye Bank and Cells for Sight Therapy Unit). Eye and tissue banks are subject to the Human Tissues Act, which covers consent, a serology screen for infectious diseases, issue procurement and the design of purpose-built, validated, facilities that can cost £800,000 to construct and are expensive to maintain. Raw materials need a certificate of suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) and must undergo a risk assessment. To satisfy regulatory authorities of their safety, induced pluripotent stem cells and embryonic stem cells are subject to new procedures – to haplotype them, to trace their ultimate anatomical destination and to determine their tumorigenic potential. Serious breaches of the law could result in prosecution and even imprisonment. At the very least, inexperience will delay progress through the regulatory process. However, during discussion, Mr Tuft explained that the Medicines and Healthcare Products Regulatory Agency (MRHA), the competent authority in the UK, provides good advice and will willingly explain its concerns.
Retinal regeneration, the subject of the talk by Professor Robert MacLaren (University of Oxford) is becoming a possibility. Transplantation of photoreceptors has been successful in a mouse model of retinitis pigmentosa. This research is described below. Other work focuses on using induced pluripotent stem cells to produce differentiated photoreceptor precursor cells. In parallel with this work, the Oxford team is collaborating with Professor Eberhard Zrenner (University Eye Hospital Tübingen and Retina Implant AG) in a trial of the electronic retina. First results are highly promising, showing restoration of light sensitivity to the eyes of patients who have been blind for many years. However, the technique ‘has a long way to go,’ Professor MacLaren cautioned.

The optic nerve does not regenerate, explained Professor Keith Martin (University of Cambridge). Central nervous system (CNS) neurons can regenerate but the CNS environment is inhibitory because uncontrolled proliferation would lead to unwanted plasticity. However, blocking these inhibitory factors or stimulating the retinal ganglion cell (RGC) can facilitate regeneration. In the rat, optic nerve crush produces inflammation which can stimulate RGC axon regeneration. Raised intraocular pressure (IOP) also increases RGC axon regeneration after optic nerve crush, a surprising finding, Professor MacLaren acknowledged. This regeneration is mediated by activated RGC which produce the soluble growth factors apolipoprotein E and osteonectin, and the antioxidants peroxiredoxin and superoxidedismutase. Full-length axon regeneration has been achieved in the adult mouse optic nerve with partial recovery of simple visual behaviours. This suggests that axon guidance signals persist in the adult brain, although for how long is unknown.

Also unclear is whether these signals remain in glaucoma, and how much regeneration would be needed for functional recovery. There is a need for stem cell therapy for optic nerve disease because many patients have lost vision before diagnosis and lose more despite treatment, Professor MacLaren continued. MSC are neuroprotective in a rat glaucoma model, reducing cell loss from 40% to 10%. Moreover, the purified proteins the cells secrete are neuroprotective in explant culture while platelet-derived growth factor (PDGF) receptor activation occurs in RGC following MSC transplantation. PDGF has been shown to be powerfully neuroprotective in experimental glaucoma with a single intravitreal injection reducing RGC loss from 30% to 5%. Encapsulated human retinal pigment epithelium cells modified to secrete ciliary neurotrophic factor (CNTF), one of the factors identified in the MSC secretome, are in clinical trials for both retinitis pigmentosa and the dry form of age-related macular degeneration (AMD). There is also the exciting prospect of using an ink-jet printer to print adult RGC and glia, an idea that grew from a conversation with an engineer colleague ‘over a couple of beers’ at a barbeque, Professor MacLaren explained.
EFFECTS OF AGING

The OOC’s last session was entitled ‘Normal for 90?’ and examined various ophthalmological features of the aging process. Professor Peter Shah (University Hospitals, Birmingham) warned of the impending ‘big bow wave’ of glaucoma due to the aging population.

The trabecular meshwork, lens and zonule all change with age. The lamina cribrosa loses tissue elasticity, resulting in an increase, at the same IOP, in biomechanical stiffness and in stress and strain. OCT reveals aging is also associated with retinal nerve fibre layer (RNFL) thinning at a rate of 0.5μ/year. In addition, the extremely elderly are risk the adverse events of long-term use of the drugs used to treat glaucoma: ocular surface disease and prostaglandin-associated periorbitopathy. This raises the question of whether laser surgery should be carried out earlier than currently. Primary selective laser trabeculoplasty might be the way forward, Professor Shah suggested.

The aging population also will lead to a virtual doubling in the prevalence of AMD in the next 25-50 years, said Professor John Marshall (Moorfields Eye Hospital, London). The aging retina contains high levels of reactive oxygen species. Movement of nutrients and water decreases, and waste products accumulate, as transport across the retinal pigment epithelium and Bruch’s membrane becomes less efficient. Waste disposal is the driver of retinal aging and eventually these transport systems will ‘crash’, Professor Marshall said. This crash – the transition from aging to age-related disease – occurs earlier in people with defective genes coding for structural or functional alterations in the RPE, Bruch’s membrane or extra-ocular immune-inflammatory processes. Gene therapy to correct these defects remains a distant prospect. In the meantime, Professor Marshall’s group has been working on rejuvenating Bruch’s membrane using a nanosecond laser pulse. He thinks this technique holds ‘tremendous promise for the future.’

Little is known about age-related changes in the visual cortex in humans although, in monkeys, there is little evidence of anatomical or histological changes, explained Dr Martyn Bracewell (University of Bangor). However, human V1 layer 4C cells show more numerous dendrites in young, than older, adults. The signal also loses specificity, with an increase in mean firing rate (especially for non-optimal stimuli) and in signal variability. Orientation tuning becomes less efficient with age. Age-related changes in acuity, contrast sensitivity, binocular summation and motion perception may be relatively small. However, performance in useful field of view tasks – foveal letter identification and peripheral localisation – declines with age, especially in divided attention tasks, suggesting less efficient suppression of unwanted stimuli. Dr Bracewell discussed how visual problems may be the presenting symptoms in Alzheimer’s disease, posterior cortical atrophy, Parkinson’s disease and Creutzfeldt-Jakob disease, and hence useful in diagnosing these disorders.

Saccade measurement for pre-prodromal diagnosis of Alzheimer’s, Parkinson’s and Huntingdon’s

Professor Christopher Kennard (University of Oxford) ended the symposium with his presentation on ‘Aging eye movements – healthy aging or neurodegeneration?’ He explained that both the latency and peak velocity of saccadic eye movements change with age and that normal elderly subjects are less able to voluntarily suppress pro-saccade responses in anti-saccade tasks. This is consistent with other studies suggesting that decreased inhibitory modulation of cognitive and perceptual processes is central to the psychology of normal human aging. Saccade measurements can act as biomarkers to identify early onset of disease pathology and to monitor disease progression and the effect of treatment. Antisaccade errors are a biomarker for early Alzheimer’s disease. There is also evidence of significant saccade errors in early Parkinson’s disease. Individuals who have tested positive for the CAG repeat expansion in the huntingtin gene but who are currently asymptomatic for Huntingdon’s disease show an increased antisaccade error rate up to 10 years before the onset of clinical disease. This finding could help determine the best time to start using the neuroprotective drugs that are likely to become available in the next few years, Professor Kennard suggested.
CASE PRESENTATIONS

The meeting ended with case presentations. Mr Omar Durrani (Birmingham and Midland Eye Centre) presented the challenging case of a patient with a recurrent sticky eye following a right tarsal strip. He eventually identified the cause: the lower lid tightening procedure had allowed the right eyelid to override the lower lid, with the lower lashes scratching the eye and introducing repeated infections. His main message was that surgery can disturb the local anatomical balance. Mr Mandeep Sagoo (Institute of Ophthalmology and Moorfields Eye Hospital, London) described a rare case of unilateral uveal melanocytic proliferation in an infant with a history of congenital unilateral uveal melanoma. Dr Gordon Plant (Moorfields Eye Hospital, London) talked about two patients in whom coeliac disease was associated with occipital lobe calcification. The main visual symptom in both patients was progressive difficulty reading. Further testing using the cortical vision screening test (CORVIST) and the visual object and space perception battery (VOSP) revealed other deficits, the pattern of which differed between the two patients. The last case, presented by Mr Mike Burdon (University Hospitals, Birmingham), was that of a 33-year-old Caucasian woman with a three-week history of ‘foggy vision’ in the right eye. She had a previous diagnosis of Charcot-Marie-Tooth (CMT) disease. On examination, she had a right relative afferent pupillary defect and slight temporal pallor of both discs. Cranial nerves III-XII appeared normal but visual fields were somewhat abnormal particularly on the right side. Primary optic atrophy was once thought rarely to occur in CMT, although is now known consistently to be associated with CMT Type 6, said Mr Burdon. But an MRI revealed this patient had an additional diagnosis – a meningioma, which was removed. However, his exploration into the further, more esoteric, reaches of CMT were not in vain as three weeks later he was referred a patient with CMT Type 6 and visual loss who had already had a scan. ‘I was at able to at least tell him what he had.’

AWARDS

Of the 80 posters on display during the Congress, 20 were picked for the rapid fire presentation session, on the second morning. Dr Mandeep Singh - Nuffield Laboratory of Ophthalmology, University of Oxford and Oxford Eye Hospital NIHR Biomedical Research Centre won the Founder’s Cup for his poster on ‘Reversal of end-stage vision loss by photoreceptor transplantation.’ As his model for human retinitis pigmentosa, Dr Singh used rd1 mice with total loss of photoreceptors from the retinal outer nuclear layer. He assessed the success of the transplantation of photoreceptor precursors by examining cortical blood flow and testing the animals’ aversion to light and comparing these parameters with those of both wild-type and sham-operated mice. Dr Gregory Fincham (University of Cambridge) won the Ian Fraser Cup for his ‘Prevention of retinal detachment in Stickler syndrome: safety and efficacy of prophylaxis cryotherapy.’ Dr Fincham reported that his prophylactic cryotherapy protocol, when used on both eyes, reduced the risk of retinal detachment to 8% compared with 54% in control patients. For patients receiving unilateral prophylaxis following fellow eye retinal detachment, the risk of detachment was reduced to 12% from 80% in the control group.

Next year’s OOC

Master Tony Moore closed the meeting by inviting delegates to return to next year’s OOC when the Doyne Memorial Lecturer will be Professor Russell Foster (University of Oxford) and Professor Andrew Dick (University of Bristol) will be ‘wearing the Master’s jewellery.’

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The Doyne Memorial Lecturer
Professor R Foster, Oxford

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