Another Anglo-American editorship

Creig Hoyt, Andrew Dick

In December 1999, as the new millennium neared, Richard Smith, former editor of the *BMJ*, and Alex Williamson, Publishing Director of BMJ Journals, offered one of us (CH) the opportunity to assume the position of editor of this journal. The sage counsel of the retiring editor, John Forrester, was sought. On his advice, Andrew Dick was named UK editor, to run with a non-UK editor. Despite all the changes John Forrester had already brought to the journal, this was a conceptual prospect for the BJO to advance the BMJ publishing group's mission of global dissemination of medical and scientific knowledge. The two of us agreed that each of us would assume an equal voice in the journal's design, policies and long-term goals. Our Anglo-American alliance has endured with a minimum of disagreement about our visions for the journal. It was our aim to build on the previous successes of John Forrester and his editorial group. That seemed a daunting task; how to continually strive to publish expeditiously and in a reader-friendly form, excellence in both

clinical and laboratory based ophthalmology. We suspect readers of and contributors to the journal may have varying opinions of how successful we have been.

Now that our term as editors is ending there are several people we wish to thank for their assistance. We have been fortunate to have an active, international editorial board whose multiple perspectives have been invaluable. Scott Rostler and Anne Williams have been active partners in the daily activities of the San Francisco and Bristol offices. They have excelled in their positions as editorial assistants. We are deeply indebted to them both. In the BMJ publishing offices in London we have been assisted by numerous people with a myriad of skills. These include Andrea Horgan, Claire Folkes, Rachel Christopher, Gavin Stewart, Louise Camp, Leanne Tite, Liz Standing, Craig Raybold, Dominic Mitchell and Carol Torselli. A special thanks goes to Glen Hughes, a superb technical editor and a mentor to us both in the first months of our learning the ropes of journal layout and design. Bob

Bhisitkul has been a creative and skilled web editor who, we are pleased to say, will remain with the new editorial team. Finally, we struggle to find the appropriate words to describe the contributions of our polymath cover editor, Ivan Schwab. He has produced 87 unique, eye-catching covers that have become the trademark of our editorship. His essays in describing these photographic masterpieces have been erudite, engaging and always witty. We are aware of more than one journal subscriber who insists it is only the covers of the journal that are to be saved. We hope some of the other journal's content has approached the noteworthiness of Ivan's contributions. Finally, we wish to thank all our readers and authors for their support. We are well aware that the dramatic increase in the number of manuscript submissions over the past few years has resulted in a significant decrease in our acceptance rate. This has undoubtedly disappointed numerous would be contributors to the journal.

The next issue of the journal will be edited by a new Anglo-American team, Professors Harinder Dua and Arun Singh. They will undoubtedly bring new ideas and energy to the journal. We look forward to watching the journal evolve under their leadership. We wish them well and will provide them support in every way possible.

Br J Ophthalmol 2007;**91**:1099

Triamcinolone acetonide injections

Effects of triamcinolone acetonide injections with and without preservative

Jost B Jonas

Using triamcinolone acetonide without preservative may improve safety

Though the vitreous body was long considered to be "untouchable", it was Robert Machemer who taught the ophthalmic community how to surgically interact with the vitreous and how to perform direct surgery on the retina. Robert Machemer, along with others like Gholam Peyman, also proposed using the vitreous cavity as a reservoir for drugs to directly treat intraocular diseases.^{1,2} Robert Machemer and colleagues thought

in particular on the use of intravitreal triamcinolone acetonide for therapy of proliferative vitreoretinopathy.^{1,3} As a result of Machemer's suggestion, intravitreal triamcinolone has been used to treat a considerable number of intraocular proliferative, oedematous and neovascular diseases such as proliferative diabetic retinopathy,⁴ diffuse diabetic macular oedema,⁵⁻⁸ branch and central retinal vein occlusions,⁹⁻¹¹ neovascular glaucoma,¹²

exudative age-related macular degeneration,¹³⁻¹⁹ presumed ocular histoplasmosis syndrome, chronic pre-phthical ocular hypotony, chronic uveitis,¹⁹ persistent pseudophakic cystoid macular oedema, sympathetic ophthalmia, radiation-induced macular oedema, immunological corneal graft reaction, perifoveal telangiectasia, ischaemic ophthalmopathy, extensive exudative retinal detachment, and other disorders such as cystoid macular oedema due to retinitis pigmentosa, endocrine orbitopathy, Vogt-Koyanagi-Harada syndrome, among others.^{20,21} Intravitreal triamcinolone has also been applied in combination with intraocular surgery to visualise the vitreous.²⁰ This list of indications for intravitreal triamcinolone has recently been markedly changed by the clinical introduction of intravitreal anti-vascular endothelial growth factor (VEGF) drugs such as bevacizumab and ranibizumab which, for the time being, have replaced intravitreal triamcinolone for many indications. The future may show, however,

whether these anti-VEGF drugs may be combined with intravitreal triamcinolone.

The reasons for using a steroid to treat intraocular oedematous and proliferative diseases have been that the abnormal proliferation of intraocular cells is often accompanied and stimulated by intraocular inflammation which may be suppressed by steroids; that triamcinolone has shown some anti-angiogenic effect in experimental studies;²³ and that besides the intraocular proliferation of cells, defects in the blood–retina barrier due to capillary leakage with accumulation of fluid in the intraretinal and subretinal space of the macula are other major causes for impaired vision. The reason for injecting the steroid into the eye has been that corticosteroids applied topically as drops, given systemically or injected into the subconjunctival or sub-Tenon space, usually do not reach a sufficiently high intraocular concentration to achieve a therapeutic level, or the systemic side effects are too pronounced for a prolonged treatment. The reason for using triamcinolone acetonide was that soluble substances injected into the eye usually leave the globe within hours to a few days.²¹ In an attempt to achieve long-lasting concentrations of a drug, the drug may have to be used in a crystalline form or packed into a slow-release device.

Comparing the various diseases with respect to effect and side effects of the treatment, the best response in terms of gain in visual acuity has been achieved for intraretinal oedematous diseases such as diffuse diabetic macular oedema, branch retinal vein occlusion, central retinal vein occlusion and pseudophakic cystoid macular oedema. In eyes with various types of non-infectious uveitis, including acute or chronic sympathetic ophthalmia and Behçet's disease, visual acuity increased and degree of intraocular inflammation decreased. Some studies have suggested that intravitreal triamcinolone may be useful as angiostatic therapy in eyes with iris neovascularisation and proliferative ischaemic retinopathies. Intravitreal triamcinolone may possibly be helpful as adjunct therapy for exudative age-related macular degeneration, particularly in combination with photodynamic therapy. In eyes with chronic, therapy-resistant, ocular hypotony, intravitreal triamcinolone can induce an increase in intraocular pressure and may stabilise the eye.

The complications of intravitreal triamcinolone therapy include secondary ocular hypertension in about 40% of the eyes injected; medically uncontrollable high intraocular pressure leading to antiglaucomatous surgery in about 1–2% of the eyes; posterior subcapsular cataract and

nuclear cataract leading to cataract surgery in about 15 to 20% of eyes in older patients within one year after injection; postoperative infectious endophthalmitis with a rate of about 1:1000; non-infectious endophthalmitis and pseudo-endophthalmitis with triamcinolone acetonide crystals appearing in the anterior chamber. Intravitreal triamcinolone injection can be combined with other intraocular surgeries including cataract surgery, particularly in eyes with iris neovascularisation. Cataract surgery performed some months after the injection does not show a markedly elevated complication rate. The injection may be repeated if vision decreases again. In non-vitreotomised eyes, the duration of the effect and side effects of a single intravitreal injection of triamcinolone is about 6 to 9 months for a dosage of about 20 mg, and it is about 2–4 months for a dosage of 4 mg.²¹

Despite more than approximately a million applications of intravitreal triamcinolone acetonide worldwide, it has remained unclear so far whether it is necessary to remove the solvent agent from the commercial preparation of triamcinolone acetonide prior to the intravitreal injection.^{24–32} In this issue (see page 1122), Maia and colleagues examined the frequency of non-infectious endophthalmitis after 646 intravitreal injections of triamcinolone, with 577 injections of a preservative-free formulation of triamcinolone and 69 injections of a triamcinolone preparation (Kenalog) including the solvent agent. The solvent agent consists of 0.99% benzyl alcohol, 0.75% carboxymethylcellulose and 0.04% polysorbate 80. A non-infectious endophthalmitis developed in 12 (1.9%) eyes, with a significantly ($p = 0.005$) higher frequency of non-infectious endophthalmitis in the group with preservative than in the preservative-free study group. Particularly in view of the widespread off-label use of intravitreal triamcinolone, the data suggest that safety may be improved if a preservative-free preparation of triamcinolone acetonide is used for intravitreal.

Br J Ophthalmol 2007;**91**:1099–1101.
doi: 10.1136/bjo.2007.117432

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Competing interests: None.

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Which colour suits the vitreoretinal surgeon?

Which colour suits the vitreoretinal surgeon?

Nanny Collaer, Peter Stalmans

Finding the true colour

Vitreoretinal surgery underwent major innovative changes over the past few years in the treatment of traction maculopathies, such as macular puckers and macular holes. The complete removal of epiretinal tissue from the posterior pole is a prerequisite for maximal functional recovery after surgery.^{1–4} However, the peeling of an optically semitransparent layer of tissue, which is only a few micrometers thick, such as epiretinal membrane (ERM) and internal limiting membrane (ILM), remains a surgical challenging manoeuvre, even for the more experienced vitreoretinal surgeons. In view of this, the introduction of vital stains allowed precise preoperative identification and delineation of ERM and ILM, enabling surgeons to perform peeling procedures with improved safety and ease. The concept of chromovitrectomy was born and staining tissues during vitreoretinal surgery became a popular procedure.

Since a number of years, three dyes are commonly used in current ophthalmic surgery: indocyanine green (ICG) and infracyanine green, exhibiting an affinity for the acellular ILM;⁵ and trypan blue, merely staining cellular structures such as epiretinal membranes but also, to a lesser degree, the ILM.^{6–8} ICG was the first dye to be introduced as a macular stain.⁸ Known for its use in choroidal angiography, it has become widely adopted for enhanced visualisation of ILM during macular hole surgery.^{5, 8–11} However, there is growing evidence of ICG-related toxicity when applied intraocularly, causing retinal damage by phototoxicity¹² and the osmolarity¹³ of ICG. Both in vitro^{12–17} and

in vivo experiments^{18, 19} have shown possible toxic effects. The initial enthusiasm was replaced by a bittersweet taste and the issue on ICG toxicity remains the subject of heavy debate (Annual Meeting of the American Academy of Ophthalmology, 2006).

Owing to the potential retinal pigment epithelial toxicity associated with the use of hypo-osmotic ICG solution, infracyanine green was advocated as an alternative vital stain^{20, 21}—less likely to induce osmolarity related toxic effects on the retinal pigment epithelial cells because of its iso-osmotic solvent.¹³ ICG contains iodine to enhance its solubility in pure water. Infracyanine green does not contain iodine, precipitates in water and must be dissolved in glucose 5%. However, experimental studies suggested possible toxic effects for the use of infracyanine green too.^{16, 22, 23}

Consequently, trypan blue arose as the second generation of ophthalmic dyes. Trypan blue was first used to facilitate anterior segment surgery in staining the anterior lens capsule to facilitate circular curvilinear capsulorhexis in patients with mature cataracts,²⁴ and in evaluating the corneal endothelium of donor tissue prior to penetrating keratoplasty through identification of devitalised endothelial cells.²⁵ Its safety was demonstrated in rabbit studies²⁶ and because of its affinity to ERM, and to a lesser extent to ILM, it soon became a commonly used dye, making it useful for both macular hole and macular pucker surgery.^{6, 7, 21, 27–32} However, there are conflicting reports about the safety of trypan blue. No adverse clinical events have been

reported, but there is an ongoing debate about the toxicity in cell culture models with several authors reporting on toxicity^{23, 33–36} and others reporting on safety.^{16, 37–42}

It appears that the above-mentioned vital stains were introduced as dyes in chromovitrectomy because clinicians were familiar with the use of this readily available dye in other fields. ICG had a history as a diagnostic tool for choroidal angiography and trypan blue had proven to be useful in anterior segment surgery. Under those particular applications, ICG and trypan blue had not shown any adverse effects; however, extensive experimental studies on the safety for their particular use as macular stains had not been undertaken prior to their introduction as an intraocular dye for vitreoretinal procedures.

Because of the limitations of ICG and trypan blue, with possible toxic effects that cannot be excluded, alternative dyes are anticipated. Novel vital stains with a broad safety margin and superior membrane staining potential are being investigated. A systematic step-by-step approach to evaluate new potential intraocular dyes has been proposed, with preliminary ex vivo safety testing prior to animal and then human studies.^{43, 44}

Here we want to refer to the work in this issue of *BJO* by Haritoglou *et al* (*see page 1125*).⁴⁵

In earlier work they demonstrated in an ex vivo experimental setting the biocompatibility of certain dyes in different cell culture models, one of the dyes being bromophenol blue that showed no relevant toxicity in vitro.⁴³ Two in vivo experiments became the next step in their systematic approach. Bromophenol blue revealed satisfactory staining characteristics during short-term investigations in porcine eyes⁴⁶ and did not produce a histologically detectable toxic effect on the retina in an in vivo rat model.⁴⁷ In view of these findings, both ex vivo and in vivo, which demonstrated excellent staining characteristics and biocompatibility for bromophenol blue, Haritoglou *et al* now present the first series of patients in whom the application of bromophenol blue as a macular stain was used in the