BJO

**British Journal of Ophthalmology**

## *Editorials*

# The continuing need to publish laboratory science in clinical journals

Over the past decade the *BJO* has continued to emphasise the importance of basic science findings, and thus generated a section dedicated to "Laboratory science" for this purpose—but why, and should we continue? There is always some deliberation when wearing a clinical hat. Questions arise such as is it science for science's sake? And although we learn, do we move on? We are very much in the era of evidence based medicine[1] and, as such, we are compelled to deliver an optimal service with maximal therapeutic benefit. Although this undoubtedly is what we should be doing and what the public expects (at least in the short term), there is an unarguable necessity to understand the underlying molecular and cellular biology and pathology to improve what are, mostly, unsatisfactory therapies. Indeed from what evidence and data do we generate such evidence based practices? The *BJO* has always made concerted efforts to deliver science to both their scientific peers and the clinical audience by, for example, endorsement of basic science by lead editorials. Such editorials were either to emphasise the importance of scientific knowledge to the clinician[2] or, for example, to highlight and discuss the merits of individual laboratory science manuscripts in that issue.[3 4] However, a BMA sponsored *BJO* readership survey showed that laboratory science is one of the least read sections of the journal.

Why should we continue? Firstly, as shown in the 1999 special issue dedicated to impact of new technologies in ophthalmology (*BJO* 1999;**83**:issue11 (Nov)), were the highlighted benefits of laboratory science in the advancement of diagnostic tools—for example, imaging, and therapies—for example, gene therapy. Indeed without such basic science investment none of the developments in that issue, some of which are now entering our clinical practice, would have been possible.[5] The *BJO* would fail in its remit to deliver such advances in ophthalmology if it did not publish relevant laboratory science. The future of medical research is dependent upon the translation of laboratory findings directly into patient management, and continuing to publish such work in the *BJO* will target an audience most interested in the future development of patient care. Secondly, we should all be encouraged in some capacity or other to directly or indirectly generate and support research developments. In the UK the Wellcome Trust[6] has recently documented its continued support of vision research. The Wellcome Trust summarised its review of the burden of human suffering associated with visual disease and disorders, both in the United Kingdom and worldwide. Acknowledging the considerable extent of visual handicap and the present economic cost of eye disorders, the Wellcome Trust continues to support vision research, not only via project grants but also by research training fellowships (£32m over past 10 years). With the support of such schemes, vision research has grown, although more slowly than other fields of biomedicine. Across the Atlantic, the Association for Research in Vision and Ophthalmology (ARVO) and the National Institutes of Health continue to actively promote vision research. Moreover, the ARVO annual meeting is a great testament to promoting research and, particularly, the interaction between basic scientists and clinicians. The future should be viewed with great optimism and excitement for such developments. By increased knowledge of underlying biological and pathological processes of visual disorders we will undoubtedly improve patient care further. Of course there are many journals available for publishing laboratory science. Basic and clinical scientists are arguably further conditioned by impact factors and, in the UK, by scoring well in the research assessment exercise. Everyone wishes to publish in the best quality journals but also needs to target the most appreciative audience. An international journal such as the *BJO* has published formative laboratory science articles with direct clinical relevance on such topics as diabetic retinopathy and growth factors, improved diagnostic molecular biological techniques, biology of trabecular meshwork, immunopathology of thyroid eye disease, and many papers on molecular and genetic ophthalmic research. We are now entering an exciting era of both functional genomic and proteomic research that will increase our understanding of both gene and protein changes during disease, and avenues may open to improve current and future therapies. These innovations have a major part to play in a spectrum of basic science studies, including degenerative disorders, glaucoma, cataract, and immunobiology of inflammation and infection. The information that will be gained is of interest to the clinician as well as to scientific peers.

Publishing in the *BJO* will help target appropriate audiences and help foster closer collaboration between clinicians and scientists. Continued reporting of laboratory science in the *BJO* means that the journal publishes a range of visual science from the laboratory to pilot clinical

studies that leads us to the evidence we require to embark on clinical trials and ultimately best evidence based service delivery.

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*UK editor*

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# From eye spots to eye shine

In the marginalia of Darwin's *On the Origin of Species*, the author's spouse wondered if, indeed, an eye could possibly "evolve" since it is so complex. Others, more recently, have asked the same question. Fortunately, similar doubt did not afflict Darwin. A review of the evolutionary evidence reveals ample evidence that eyes can and do evolve. For example, there are creatures that have multiple and very specific eyes, suggesting that eyes are not only rather easy to evolve, but, in some creatures, ocular evolution can be quite rapid.

The process of organism photoreception probably started shortly after life began on this planet, stimulated by the sun. Ocular evolution responded to the sun's energy by producing phototaxis leading to crude eye spots, then ascending to the complex and elegant ocular structure of certain birds having two foveae and asymmetric lenses for precise focusing. Fantastic adaptations, often beyond imagination, have occurred and are with us today, including irregularly shaped eyes and special photopigments to view ultraviolet, infrared, and bioluminescence. The extension of the interpretation of electromagnetic waves into realms we cannot understand must create a fantastic panoply of colours and stimulations. And, yet, as ophthalmologists, we rarely consider that any visual system is significantly better than or even that different from our own. This is folly for many species have evolved spectacular and stunning adaptations to the visual imperatives of their world.

The crepuscular aerial drama of a swallow on the wing hunting for a small erratic insect illustrates the profoundly complex visual processing necessary to provide identification, tracking, pursuit, and eventual capture in a dimly lit and almost clueless three dimensional environment. Yet, a swallow does this hundreds of times a day. Similarly, a bathypelagic piscine predator, living at a depth of 1500 metres, must face staggering problems merely identifying prey in a place where bioluminescence is the only source of light. If that is not interesting enough, consider this. A jumping spider must define an image, detect small movement, and successfully judge distance with very small eyes that approach the defraction limits of the multiple faceted ommatidia. Very small invertebrates run headlong into the dense wall of defractional limits like crash test dummies and must have relatively larger eyes proportional to body size, but still face serious morphological problems.

Certain owls are able to perceive small cryptically coloured rodents with as little illumination as 0.00000073 of a foot candle. Mesopelagic and bathypelagic fish have photon sensitivity several orders of magnitude better than our own. The aforementioned jumping spider has miniaturised its ommatidia so that it will carry four pairs of eyes and is a master at movement detection. Certain birds are capable of motion detection so slight that they are able to "see" the sun move across the sky.

The series of cover photographs for the *BJO*, beginning in July 2000, was the idea of the newly appointed editor, Creig Hoyt. He has asked us to provide covers representing comparative ophthalmology or optics, accompanied by a brief description of their natural histories. He wanted to illustrate these dramatic visual adaptations to our natural world. This idea represents a break from a tradition that is followed by most medical journals, which includes cover art, content description, or representative photography from an article within that particular issue of the journal. I applaud this new direction for it represents an intellectual side of our profession often neglected.

We will provide you with interesting images, their natural histories, and enough thought provoking questions to last a lifetime. Because many of the species and mechanisms we will discuss are only superficially understood, we will welcome corrections, suggestions, and especially questions from readers. We will occasionally feature the work of guest photographers or scientists who will help with the images and descriptions. We will investigate natural history, evolution, and any related visual aspects of the image presented. We may present answers to many, but certainly not all, of the questions posed by the reader. Understand that this series will not provide you with practical suggestions for patient care, but it may fire your imagination and may lead you to appreciate even more your education and training. You are reading this journal because of your interest in sight and if you have got this far into this editorial you are probably interested in something else—the natural history of vision. That topic is, indeed, worthy of your consideration for it will enrich your life beyond patient care. With your education you are in a unique position to understand the biology behind these images and to be beguiled by their implications. Our visual processes allow us to perceive this magnificent world of sight, but ours is not the only world. Vicarious understanding of the natural history of other visual mechanisms allows us to pull the curtain aside to see the excitement and drama on another stage ever present in other sighted worlds. It is our hope that it may lead you to a better understanding of your own visual world.

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**Cover illustration: The original slit beam**

The pupil of the Tokay gecko (*Gekko gekko*) creates an arresting image of this remarkable nocturnal reptile, but it is not the only interesting aspect and probably not the most profound.

At night, this noisy and aggressive gecko has a large, nearly round, pupil when fully dilated. But when these geckos must be active during the day (they are somewhat arrhythmic in that they may occasionally be diurnal), their pupils constrict to a vertical ellipse with four diamond-shaped pinholes decorating the vertical stenopeic slit. This bizarre pupil with its multiple pinholes probably serves a variety of functions, but the most important function likely is employment as a Scheiner's disc. Murphy and Howland in 1986 (*Vis Res* 1986;**26**:815–6) provided clear and convincing evidence that this principle allows the gecko to use these multiple pinholes as a focus indicator or range finder by forming four images of an object on the same point on the retina. If the object lies precisely within the plane of focus, with a relatively shallow depth of field around that plane, the image will be in focus. If the object is closer or more distant, the four images will not be in proper focus or coincident, and the gecko will know the distance for prey capture or predator avoidance. If the object were not in the plane of focus, however, each individual pinhole would also provide relative image clarity if the brain were capable of suppression of the multiple images produced by the other apertures.

With the pupil constricted, the vertical polycoria combined with the stenopeic slit would produce an image of considerable clarity without any dioptric mechanism or accommodative adjustment and would significantly limit the light flux to the retina. The stenopeic slit provides other potential advantages and is frequently found among nocturnal creatures especially if they are occasionally diurnal. A slit pupil will tend to improve focus in the direction perpendicular to the slit so a vertical pupil will provide the best view of the horizontal meridian relative to the animal's head (remember, a gecko's horizon may be different from yours since they are often found on vertical walls or ceilings). Many carnivorous predators, such as snakes and cats, have vertical pupils presumably to assist in the hunt on the horizontal plane. Prey species are almost exactly the opposite with horizontal slit pupils (such as herbivorous animals), presumably to create the same phenomena when the head is lowered to graze allowing for visualisation of a predator coming towards them in the horizontal meridian. The multiple apertures and the slit will provide a relatively larger visual field than would a circular pupil of equal surface area. The pupil dilates to nearly circular in nocturnal conditions, but there is a hexagonal characteristic even when fully dilated, and some observers believe the pupil may be under "voluntary" control.

The pupil is only part of this animal's interesting ocular adaptations. Since the species is primarily nocturnal, some investigators have considered that the retinal photoreceptors would be best described as being rods, although these cells may be phylogenetically unique. Ultrastructurally, the outer segments of the single photoreceptors are large and resemble cones. Interestingly, the retina probably contains two visual pigments that appear to be more like cone pigments, one with longer wavelength absorption characteristics. The gecko photoreceptors have an unusual spectral sensitivity curve similar to the human scotopic curve but with two maxima at 521 nm and a shorter wavelength maximum at 467 nm. The latter pigment is possibly responsible for the ultraviolet capabilities. (For reference, human rhodopsin peaks at about 500 nm.) These two pigments may be the residua or vestige of complete colour vision of a diurnal phylogenetic ancestor. Otherwise, it is more difficult to provide speculation on the duality of the photopigments in this nocturnal predator. One of the few species of animals with paired photoreceptors (whether described as rods or cones), these duplex photoreceptors are slender with pigment granules between them much like a myoid sheath that can be used to shield the cells from bright stimuli. Visual acuity measurements have not been attempted in this species, but the retina does have a slight foveal depression.

There is no lacrimal gland and no tears. Although this gecko has a special ocular surface, the animal will cleanse this ocular surface with an unusual habit of licking its eyes when necessary.

Geckos are worldwide in their distribution consisting mainly of tropical and subtropical species. The Tokay gecko on the cover is native to Indonesia, South East Asia, the Philippines, Sri Lanka, and India. Almost all geckos (save for a few such as *Phelsuma madagascariensis* of Madagascar, which eats fruit) are carnivorous and nocturnal. To hunt small active prey (insects) in the darkness requires not only good vision, but also the speed and agility to chase these prey and geckos have met this challenge. Perhaps the most profound aspect of their natural history relating to this agility was just recently discovered. In order to chase prey, often up a wall (even glass) or a ceiling, requires the ability to adhere to that surface. Recently reported in *Nature* (2000;**405**:681–5) Autumn *et al* found that some species of geckos have approximately half a million fine microscopic hairs, called setae, each of which splits into hundreds of ends like a brush on large footpads that assist in this adherence, which actually utilise submolecular attraction to molecular gaps in any surface including glass. These setae operate by van der Waals forces, creating dramatic powers of adherence. The geckos break this adherence by slightly bending their footpad to extract the hairs from their bond. This most remarkable climbing and adherence mechanism evolved by this awesome little predator may revolutionise the solution to other adherence problems such as walking on a surface in zero gravity. Pretty good for a gecko!—IVAN R SCHWAB, *UC Davis Department of Ophthalmology, Sacramento, California, USA (irschwab@ucdavis.edu)*

# Diabetes and primary open angle glaucoma

The potential association between diabetes and primary open angle glaucoma (POAG) has been studied by many groups, with most studies supporting a weak association between the two diseases. The present population based study by Ellis *et al*, published in this issue of the *BJO* (p 1218), has determined an *incidence* for newly diagnosed glaucoma and ocular hypertension among diabetics and non-diabetics. The authors make the distinction that previous studies assessed prevalence rather than incidence when determining an association. However, with diseases that have a low incidence, such as POAG, determination of prevalence may be preferable, in order to achieve an adequate number of affected patients and the necessary power to come to a more definitive conclusion. This is especially the case with POAG and diabetes, in which the association seems tenuous.

In their study, Ellis *et al* relied on the detection of new glaucoma prescriptions and glaucoma surgical procedures among their large study population of 6631 diabetics and 166 144 non-diabetics. Case notes of these patients were then reviewed for further categorisation (POAG, ocular hypertension, misclassification). This reliance on detection within the established medical community has the same disadvantage as many earlier studies—namely, the potential for detection bias since diabetics are more likely to receive eye examinations and be screened for glaucoma. However, in the Blue Mountains Eye Study[1] the entire study population underwent a detailed eye examination including automated perimetry, stereo optic disc photographs, and applanation tonometry to establish a diagnosis of glaucoma or ocular hypertension. (The need for very large numbers of patients in incidence rate studies would have precluded such detailed screening examinations.) The age-sex adjusted odds ratio (OR) for glaucoma in diabetics compared with those without diabetes was 2.12 (95% confidence intervals (CI) 1.18–3.79), and the authors concluded that there was a real association between glaucoma and diabetes. On the other hand, the Baltimore Eye Study,[2] which was conducted similarly to the Blue Mountains Eye Study, found an age-race adjusted odds ratio of 1.03 (95% CI 0.85–1.25). In the present study, the relative risk for POAG diagnosis was 1.57 (95% CI 0.99–2.48). The authors acknowledge that detection bias probably contributed to the observed increased risk among diabetics and conclude that an association is not supported.

Unfortunately the question of whether or not the diabetic condition is a significant risk factor for glaucoma development remains open and controversial. The authors make an earnest attempt to address this issue by determining the incidence of newly diagnosed glaucoma but arrive at a relative risk that is somewhat increased but not statistically significant. Most population based studies that have explored the possibility of an association have found similar results and harbour the same concern about detection bias as in this study.

Thus, conclusions that have been drawn are usually tentative and conflicting. In the final analysis, it is clear that the association between diabetes and POAG, if it exists, is not a strong one.

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