BjO

British Journal of Ophthalmology

Editorials

Care to share?

It is reassuring to learn that the Bristol shared care glaucoma study, reported in the May issue of the *BJO*,[1] confirms that the clinical outcome for patients followed up by community optometrists is similar to that for those who remained in the conventional hospital eye clinic. That should not surprise us because we know from many years of experience sharing patient care with optometrists, orthoptists, and nurse specialists, that our colleagues in these professions can be relied on to work with precision and integrity. The General Medical Council distinguishes delegation from referral.[2] Shared care schemes[3] are examples of delegation where the medical practitioner, in this case the ophthalmologist, remains responsible for the overall management of the patient and has a duty to ensure that the optometrist is suitably trained and qualified for the task. The separate process of referral to an optometrist will also be appropriate for some patients in whom a possible but low risk of glaucoma has been identified. They are referred to the community optometrist for the usual regular eye examination with the request that they be sent back to the ophthalmologist if the findings indicate an increasing risk. Here, it is the optometrist who assumes professional responsibility. Therefore when setting up shared care schemes it is necessary to avoid overloading the system with patients who should be referred (discharged) to the optometrist. Even when patients are properly included in shared care schemes they should be reviewed periodically and discharged to the care of an optometrist if, after a period of supervision, the risk of glaucoma is judged to be reduced.

The Bristol study uses a commendably simple test of field of vision which is rapid and reliable, without the spurious hyperaccuracy of more complex testing stratagems. This is one example of the strict discipline of the study and it minimises inaccuracies which might be caused by the use of different field testing equipment or programmes. In other ways the problems of communication and standardisation have been closely controlled, but this may not always be possible and could affect reliability when shared care is developed elsewhere. It is surprising to note that 55% of the community patients were sent back to hospital at least once in the relatively short (for glaucoma) follow up period of 2 years. This seems a high figure for such a carefully specified scheme and it may limit the efficiency and viability of the system.

The great source of disappointment in the experience of the Bristol group is that the cost analysis shows the community based scheme to be so much more expensive than the hospital clinic that it is likely to overwhelm the balancing advantage of improved geographic access. If lack of hospital capacity is a problem then expanding that capacity would be more cost effective and, in any case, the stable glaucoma patients are likely to require follow up visits at infrequent intervals of between 6 months and 1 year. It is therefore likely that the cost will be the critical factor in deciding whether shared care for glaucoma in the community will be worthwhile. Calculating the true cost will be complex and must assess five elements: the cost of each examination in terms of staff, equipment, and administrative overheads; the cost of timely communication between the professionals who share the care; the cost of additional examinations which take place because there has been uncertainty about the significance of a result—uncertainty may be more likely to occur if a practitioner sees few patients and consequently has less extensive experience; the opportunity costs of losing the ability to deploy professional skills elsewhere; and the cost of unnecessary examination of patients whose risk of sight threatening disease is so low that they should be discharged. If sufficient care is taken to supervise the shared care schemes in the community, there is no doubt they can be safe and effective but it is likely that they will not represent the most efficient use of resources, except in areas where travel to the hospital clinic is especially difficult.

J L JAY

Tennent Institute of Ophthalmology, Gartnavel General Hospital, Glasgow G12 0YN

1 Gray SF, Spry PGD, Brookes ST, *et al*. The Bristol shared care glaucoma study: outcome at follow up at 2 years. *Br J Ophthalmol* 2000;**84**:456–63.
2 General Medical Council. *Good medical practice*. London: GMC, 1998.
3 The Royal College of Ophthalmologists, The Royal College of General Practitioners, and The College of Optometrists. *Shared care*. London: RCOphth, 1996.

Selective ganglion cell death in glaucoma

The primate visual system is designed to provide maximum performance under a variety of conditions. Much of the enhanced sensitivity of the rod system comes from post-receptor neuronal organisation that pools impulses from thousands of receptors. In the retinal periphery multiple rods converge onto a single ganglion cell resulting in poor acuity but high sensitivity. At the fovea a one to one relation between cone and ganglion cell produces fine discrimination, colour perception and, by fusing the images of both eyes, binocular vision.

The "receptive field" for an individual ganglion cell is determined by the spatial arrangement of the connecting receptor fibres. These are designed to enhance perception of the stimulus and is achieved by an antagonistic arrangement of a concentric centre surround response where the surround is opposite in polarity to the centre.[1]

Ganglion cells have been subdivided according to their temporal response properties. Primate ganglion cells have been divided into *tonic* and *phasic* types.[2] Phasic cells respond transiently to changes in stimulus, while tonic ones provide a more sustained response. Phasic ganglion cells have both rod and cone input, make up about 10% of the total, and have large overlapping receptive fields. They subserve motion and contrast function and project via large diameter fibres to the magnocellular layers of the lateral geniculate body.[3]

Tonic ganglion cells by contrast are small, with small receptive fields and slower conducting axons. They comprise 80% of all ganglion cells with maximum representation for the foveal cones. They subserve colour and discriminatory function and project to the parvocellular layers of the lateral geniculate body.[3] The axon size would appear to differ according to the cone wavelength perceived, with short wavelength cones having the largest diameter fibres.[4] These cells connecting to the magnocellular and parvocellular layers of the lateral geniculate body are also known as parasol cells (feeding to the magno system, and therefore "M" cells) and midget cells (feeding to the parvo system, "P" cells).

The idea of separate visual function based on different receptors and different post-receptor organisation has led to the concept of "parallel visual processing". This concept has proved useful for identifying different aspects of visual loss in ocular disease.

The search for specific tests which made use of this psychophysical separation was greatly stimulated by the discovery that glaucoma was associated with selective ganglion cell death. Histological examination of eye with "early glaucoma" revealed that substantial numbers of ganglion cells were lost before defects appeared with white on white perimetry.[5] In the experimental monkey model large ganglion cells were found to be more vulnerable, although the magnitude of this selective loss varied.[6] Human necropsy material showed relatively greater loss of magnocellular cells in glaucoma.[7] These pieces of evidence pointing to selective cell death have led to the development of tests of large fibre ganglion cells including contrast sensitivity,[8] motion detection,[9] and, perhaps, frequency doubling.[10]

Recently, the theory that selective cell death first affects large fibre ganglion cells has been questioned. Sample and associates reported on the results of testing glaucoma patients with short wavelength perimetry and motion automated perimetry, and found that both tests successfully diagnosed glaucomatous damage.[11] They suggested that in glaucoma the damage that occurs may affect either the magnocellular or parvocellular system, or that there may be individual differences between eyes that decide which system is damaged first. The numeric difference between the two types of ganglion cells could mean a disproportionate effect on visual function if equal numbers of M and P cells were lost in disease. Willis and Anderson noted that the age related rate of decline was faster in the glaucomatous eye than the normal eye.[12] Morgan has suggested that the appearance of differential cell death could be an artefact due to postmortem shrinkage producing the impression of large cell loss.[13]

In the March issue of the *BJO*, Morgan and coworkers contributed further to this debate.[14] They induced ocular hypertension in six primate eyes and then examined the retinal ganglion cell populations after retrograde labelling with horseradish peroxidase. They did not find a significant reduction in the proportion of parasol to midget cells. They did find an overall reduction in mean size for both the surviving M and P cells suggesting cell compromise before cell death. They pointed out that the use of a tracer to study the ganglion cell changes induced by ocular hypertension was not subject to the potential for artefact inherent in the methodology of earlier studies. They noted that another similar primate study[15] also found a reduction in cell size before cell loss (although the exact significance of this finding was open to interpretation).

Where does this debate leave the clinician who is looking to detect early glaucomatous visual loss? Selective cell death may still occur in early glaucoma, although alternative explanations are possible. However, this doubt as to mechanism does not remove the validity of selective psychophysical testing. Whether the tests target the magno or the parvo system they are still likely to provide earlier diagnosis than white on white perimetry and as such should continue to be introduced into clinical practice.

Morgan and co-workers are to be thanked for reminding us that in biological systems all is rarely black and white, and that even certainties in medicine are worth re-examination. Their work has caused us to rethink the process by which ganglion cells are damaged in hypertensive eyes. In addition, by identifying premortem changes in the ganglion cell size that suggested compromise, they may have also provided a marker for worthwhile studies on neuroprotection in the future.

Note added at proof stage: Kerrigan-Baumrind et al (*Invest Ophthalmol Vis Sci* 2000;**41**:741–8) looked at the ganglion cell loss for the entire retina in 17 eyes of 13 people with well documented glaucoma. They looked for retinal ganglion cell loss associated with visual field defects. They also found evidence to corroborate their previous findings that ganglion cells with larger axons preferentially die in glaucoma.

R A HITCHINGS

Moorfields Eye Hospital, London EC1V 2PD
roger.hitchings@virgin.net

1 Hubel D, Wiesel T. Receptive fields of optic nerve fibres in the spider monkey. *J Physiol* 1960;**154**:568–72.
2 Gouras P. Identification of cone mechanisms in monkey ganglion cells. *J Physiol* 1968;**199**:533–6.
3 Kaplan E, Shapley RM. The primate retina consists of two types of ganglion cells with high and low contrast sensitivity. *Proc Natl Acad Sci USA* 1986;**83**:2755–67.
4 DeMonasterio F. Asymmetry of on- and off-pathways of blue sensitivity cones of the retina of macaques. *Brain Res* 1979;**166**:39–46.

5 Quigley HA, Dunkelberger GR, Green WR. Chronic human glaucoma causing selectively greater loss of large optic nerve fibers. *Ophthalmology* 1988;**95**:357–63.
6 Glovinsky Y, Quigley HA, Dunkelberger GR. Retinal ganglion cell loss is size dependent in experimental glaucoma. *Invest Ophthalmol Vis Sci* 1991;**32**:484–91.
7 Chaturvedi N, Hedley-Whyte E, Dreyer B. Lateral geniculate nucleus in glaucoma. *Am J Ophthalmol* 1993;**116**:182–8.
8 Arden GB, Gucugoglu AG. Grating test of contrast sensitivity in patients with retrobulbar neuritis. *Arch Ophthalmol* 1978;**96**:1262–9.
9 Fitzke FW. Clinical psychophysics. *Eye* 1988;**2(Suppl)**:S233–41
10 Chauhan BC, Johnson CA. Test-retest variability of frequency-doubling perimetry and conventional perimetry in glaucomapatients and normal subjects. *Invest Ophthalmol Vis Sci* 1999;**40**:648–56.

11 Sample PA, Bosworth CF, Weinreb RN. Short-wavelength automated perimetry and motion automated perimetry in patients with glaucoma. *Arch Ophthalmol* 1997;**115**:1129.
12 Willis DA, Anderson DR. Effects of glaucoma and aging on photopic and scotopic motion perception. *Invest Ophthalmol Vis Sci* 2000;**41**:325–35.
13 Morgan JE. Selective cell death in glaucoma: does it really occur? *Br J Ophthalmol* 1994;**78**:875–9.
14 Morgan JE, Uchida H, Caprioli J. Retinal ganglion cell death in experimental glaucoma. *Br J Ophthalmol* 2000;**84**:303–10.
15 Weber A, Kaufman P, Hubbard WC. Morphology of single retinal ganglion cells in the glaucomatous primate retina. *Invest Ophthalmol Vis Sci* 1998;**39**:2304–20.

What is Sorsby's fundus dystrophy?

The past decade has seen a resurgence of interest in the molecular defects underlying macular dystrophies. Firstly, this is because these diseases are important causes of incurable blindness and, secondly, the molecular defects highlighted by these studies may be relevant to the much commoner disease, age related macular degeneration (AMD). In this issue, Assink *et al* (p 682) have undertaken a molecular genetic study of one of these macular dystrophies: Sorsby's fundus dystrophy (SFD), an important addition to the literature, which also raises new questions.

The scientific literature describes SFD as a fully penetrant, autosomal dominant, retinal disease first described by Sorsby in 1949.[1] Clinically, early, mid-peripheral, drusen[2] and colour vision deficits are found.[3] Some patients complain of night blindness.[4] Most commonly, the presenting symptom is sudden acuity loss, manifest in the third to fourth decades of life, due to untreatable submacular neovascularisation.[5] Histologically, there is accumulation of a confluent lipid containing material 30 µm thick at the level of Bruch's membrane.

Parametric linkage analysis originally localised the SFD gene to chromosome 22q13-qter[6] between marker loci *D22S273* and *D22S281*. Subsequently, five different missense mutations[7] and a splice site mutation[7] have been identified in *TIMP3* (tissue inhibitor of metalloproteinases 3). In the British Isles, to date, all SFD families carry the same *Ser181Cys TIMP3* mutation and it has been suggested that this all relates to one single founder.[8] *TIMP3* encodes a retinal pigment epithelium expressed member of a group of zinc binding endopeptidases involved in retinal extracellular matrix remodelling, particularly in Bruch's membrane.[9]

Assink *et al* describe a large family with autosomal dominant maculopathy, the earliest features being drusen and "pisciform" lesions in the fourth decade of life. These are later complicated by disciform lesions that progress to chorioretinal atrophy. A key question is, does this truly represent the SFD phenotype? Pisciform lesions are not a feature normally associated with Sorsby's fundus dystrophy. Also, delayed choroidal filling on fluorescein angio-

graphy is thought to be a cardinal SFD finding but is not seen in this study family.[2] Other maculopathies are known to lead to drusen and subretinal neovascularisation in this age group. For instance, the study family may represent an example of dominant drusen? Or, alternatively, does the study describe a new phenotype? Is it important that a family diagnosed as expressing SFD has exactly the symptoms and signs itemised in the literature or is it sufficient that they express the cardinal features as suggested in this study? Should SFD be confined to haemorrhagic maculopathies with proved TIMP3 mutation?

Have Assink *et al* truly excluded an association between *TIMP3* and the phenotype expressed in their study? To completely exclude *TIMP3* not only must coding sequence be screened but also the promoter and enhancer sequences that control *TIMP3* expression. The authors have almost but not entirely done this. Most pertinent here are the enhancer sequences which can be found quite distant from the relevant gene. These sequences could conceivably lie within the *D2S275* and *D2S274* linked region and be composed of an as yet unknown sequence; mutation therefore becoming impossible to exclude.

Sorsby's fundus dystrophy, both clinically and histopathologically, shares some similarities with AMD. It is appropriate, therefore, that *TIMP3* coding sequence be screened in cohorts expressing this much more frequent cause of blindness in the developed world. No *TIMP3* mutation, however, has yet been associated with AMD. Genes associated with other macular dystrophies have also undergone mutation screen in AMD (Table 1). No positive association has yet been identified except initially in the case of *ABCA4*.[10] Recent work, however, has cast doubt on a link between *ABCA4* mutation and AMD. The initial, positive, association has not been reproduced in other studies and *ABCA4* has proved to be such a polymorphic gene that large numbers of base changes in unaffected control groups have cast doubt on the significance of *ABCA4* base changes in AMD patients. Despite this, screening genes causing rare macular dystrophies for mutation in AMD is still a valid undertaking. Mutation of the glucagon gene in rare families expressing early onset,

Table 1 *Molecular genetic loci and genes associated with macular dystrophies*

Phenotype	Inheritance	Genomic locus	Gene	Mutation in AMD
Stargardt's disease	AR	1p21-p22	ABC4R	No
Dominant drusen	AD	2p16	*EFEMP1*	No
Pattern dystrophy	AD	6p21.2-cen (+other loci?)	*Peripherin/RDS*	No
"Macular" dystrophy	AD	6p21.2-cen (+ other loci?)	*Peripherin/RDS*	No
Adult vitelliform macular dystrophy	AD	6p21.2-cen (+ other loci?)	*Peripherin/RDS*	No
Stargardt-like fundus dystrophy	AD	6q11-q15, 13q34	—	—
Best's disease	AD	11q13	*Bestrophin*	No
Sorsby's fundus dystrophy	AD	22q12.1-q13.2	TIMP3	No
X linked retinoschisis	XL	Xp22.2	*XLRS1*	—

AR = autosomal recessive, AD = autosomal dominant, XL = X linked.

autosomal dominant, diabetes mellitus leads to a significant association between this gene and diabetes mellitus as more commonly seen as a polygenic complex trait.[11]

Regardless of whether the study family truly has SFD or whether the work will prove helpful in identifying AMD genes, the work presented by Assink *et al* is an important contribution to the ocular genetics literature. Retinal dystrophies are proving to be among the most genetically heterogeneous conditions known, with dozens of genes now associated with inherited disease of the retina and with more to come. This is beginning to stimulate interest in unravelling of the molecular steps involved in these diseases. It is possible that as we more fully understand the complexity of the molecular consequences of mutation, new ideas will emerge of how to modify progression of disease in a way that may prove more practical than "conventional" gene therapy protocols that treat the primary gene deficit.

KEVIN GREGORY-EVANS

Western Eye Hospital, Imperial College School of Medicine,
London NW1 5YE
k.gregory-evans@ic.ac.uk

1 Sorsby A, Mason MEJ. A fundus dystrophy with unusual features. *Br J Ophthalmol* 1949;**33**:67–97.
2 Polkinghorne PJ, Capon MRC, Berninger T, *et al*. Sorsby's fundus dystrophy: a clinical study. *Ophthalmology* 1989;**96**:1763–8.
3 Kalmus H, Seedburgh D. Probable common origin of a hereditary fundus dystrophy (Sorsby's familial pseudoinflammatory macular dystrophy) in an English and Australian family. *J Med Genet* 1976;**13**:271–6.
4 Jacobson SG, Cideciyan AV, Regunath G, *et al*. Night blindness in Sorsby's fundus dystrophy reversed by vitamin A. *Nat Genet* 1995;**11**:27–32.
5 Holz FG, Haimovici R, Wagner DG, *et al*. Recurrent choroidal neovascularization after laser photocoagulation in Sorsby's fundus dystrophy. *Retina* 1994;**14**:329–34.
6 Weber BHF, Vogt G, Woltz W, *et al*. Sorsby's fundus dystrophy is genetically linked to chromosome 22q13-qter. *Nat Genet* 1994;**7**:153–61.
7 Tabata Y, Isashiki Y, Kamimura K, *et al*. A novel splice site mutation in the tissue inhibitor of the metalloprotease-3 gene in Sorsby's fundus dystrophy with unusual clinical features. *Hum Genet* 1998;**103**:179–82.
8 Wijesuriya S, Evans K, Jay MR, *et al*. Sorsby's fundus dystrophy in the British Isles: demonstration of a striking founder effect by microsatellite generated haplotypes. *Genome Res* 1996;**6**:92–101.
9 Chong NHV, Alexander RA, Gin T, *et al*. TIMP-3, collagen and elastin immunohistochemistry and histopathology of Sorsby's fundus dystrophy. *Invest Ophthalmol Vis Sci* 2000;**41**:898–902.
10 Stone EM, Webster AR, Vandenburgh K, *et al*. Allelic variation in ABCR associated with Stargardt disease but not age-related macular degeneration. *Nat Genet* 1998;**20**:328–9.
11 Hager J, Hansen L, Vaiisse C, *et al*. A missense mutation in the glucagon receptor gene is associated with non-insulin dependent diabetes mellitus. *Nat Genet* 1995;**9**:299–304.

Cover illustration: Spots before your eyes

The polyphemus moth (*Antheraea polyphemus*) is a large North American moth with a wing span of 100–130 mm. This member of the Saturniidae family in the Lepidoptera order is generally cinnamon coloured with a large eye spot on each wing and subtle pink borders on its inside wings. Although it is the only species of *Antheraea* to occur in North America, it is relatively common and widespread. The eye spots, best seen when the wings are fully spread, are protective and presumably resemble an owl's eyes. These ocellated wings are thought to be an evolutionary protection against predation. Several North American owls, including the great horned owl, long eared owl, and screech owl have yellow eyes with black pupils which closely resemble the eye spots on the lower wings of *Antheraea polyphemus*. When disturbed, the moth will open its wings showing these eye spots as a defence mechanism. This will give an appearance of a rather large animal peering directly at the predator.

Another closely related Saturniidae moth, *Hyalophora cecropia*, is the principal species being investigated for a class of compounds known as cecropins. These short chain peptides, which appear to be highly conserved over many divergent animal species, are generally known to be in the group of defence peptides that include the defensins in mammals and magainins in frogs. These lytic peptides are induced by microbial agents and are capable of membrane perturbation, resulting in bacterial cell lysis. These short chain peptides appear when the moth overwinters as a cocoon and must protect itself using only a humoral system of defence. The cecropins are the "gorillamycin" of the animal world. They are effective agents against almost all bacteria, enveloped viruses, many fungi, and perhaps even certain protozoa. These compounds offer great hope and promise as a powerful agent fashioned by evolution against almost any microbial agent. Interestingly enough, the only bacterium known to be resistant to the cecropins is *Bacillus thuringiensis*. Empirically, this bacterium has been used as a pesticide without completely understanding why it is useful. Since it is resistant to the humoral defence of many insects, one of its mechanisms of attack on these insects is almost certainly the ability to remain indifferent to their defence systems.