

Retinopathy of prematurity

## ROP and neurodevelopmental disabilities

G E Quinn

### The dilemma in premature babies

There are essentially three ways in which blindness from retinopathy of prematurity (ROP) can be prevented, including elimination of premature birth, changes in neonatal care, and improved detection and treatment of established sight threatening retinopathy. It is on the latter that the attention and efforts of the ophthalmic community have been focused, leaving the first two to the paediatricians, perinatologists, neonatologists, nurses, and others who care for these tiny babies. What Darlow *et al* have done in the paper in this issue of the *BJO* (p 1592) is direct our attention to the second possibility—that is, neonatal care may be able to be altered to decrease the incidence of potentially blinding disease.

Darlow *et al* document a remarkable variability in the prevalence of severe ROP among the nurseries in the neonatal intensive care units in the Australian and New Zealand Neonatal Network. Such variability is generally expected when morbidity or mortality results are compared across centres, even in an essentially population based study that this report represents (the four tertiary paediatric care referral centres are excluded from the analysis reported by Darlow *et al*). The variability in such reports can usually be explained by a combination of several factors, including case mix, assessment of the primary outcome measure, viability considerations by neonatologists at the various centres, and variations in clinical practice. For example, the percentage of high risk deliveries may differ dramatically among nurseries, leading to more at-risk infants in one nursery than another. Smaller nurseries may also have greater variation in the incidence of severe ROP because of sampling variability. In addition, standardisation of outcome measures in multicentre studies represents a huge challenge and can seriously impact the perceived prevalence of severe disease.

Thanks to a large enough sample and novel analytical techniques, Darlow *et al*

have been able to take into account many of the potential confounding variables using logistic regression models. They find that variability across nurseries in the rates of severe ROP requiring treatment is not explained by case mix, sampling, or outcome assessment, but rather is probably the result of clinical practice in the individual nurseries. In their analysis, they wisely chose to highlight the improvement in rates of serious ROP that could be reached if clinical practice was altered to achieve the “best practice” rates achieved in the top 20th percentile of the nurseries, rather than focusing on the “problem” nurseries. Using this systemwide approach to changes in clinical care would lower the rate of severe ROP to 5.9% in the top 20% of nurseries from the overall rate of 9.6%. They estimate that 79 cases of severe ROP would have been prevented.

A major problem that arises when practice patterns are changed is that interventions aimed at decreasing the rate of one serious problem may increase the rate of another, equally serious problem. A very clearcut example of this was provided in the 1950s when oxygen was found to be the root cause of blinding ROP and its delivery markedly restricted.<sup>1</sup> This led to an increase in mortality<sup>2</sup> and spastic diplegia among premature babies,<sup>3</sup> and it was estimated that 16 infants died from curtailed oxygenation for each case of blindness prevented.<sup>4</sup> This observation has particular clinical relevance when evaluating possible changes in clinical care of premature babies, a population that has had an increased survival rate as a result of advances in perinatal and neonatal medicine over the past 20 years in countries with high levels of human development<sup>5</sup>; it is also a population in which we have only an evolving understanding of the developmental disabilities that are detected later in life.<sup>6–8</sup> Since clinical care of the premature baby is directed broadly at prevention of illness, undernutrition,

and infection during a time of rapid brain growth and development, it is not hard to postulate that systemwide changes in practice may differentially impact on the occurrence of cerebral palsy, visual and hearing impairments, behavioural and social problems, and learning difficulties.<sup>9</sup> When considering changes in practice patterns, clearly the possible effect of any change must concentrate not only on survival, but also on lifelong disabilities that may occur in this vulnerable population.

Identifying and implementing practice pattern changes may decrease the prevalence of severe ROP and, with appropriate treatment, of blindness. However, most children being blinded from ROP do not live in countries with high levels of human development, but rather they are born in countries with middle levels of human development, where neonatal services are rapidly expanding and where limited resources may severely impact delivery of the highest levels of neonatal care.<sup>9</sup> Thus, the alterations in clinical practice that may arise from examining the “best practice” nurseries in Australia and New Zealand may have limited generalisability to the nurseries that care for the largest proportion of babies at risk of blindness because of severe ROP.

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Deep lamellar keratoplasty

# Overcoming the technical challenges of deep lamellar keratoplasty

M Yamada

With continued improvements in surgical technique it may become the procedure of choice

Lamellar keratoplasty was the first form of corneal transplantation attempted, with a history over a century, and has been regarded mainly as a therapeutic technique.<sup>1,2</sup> Lamellar grafting offers several advantages over penetrating keratoplasty, including the elimination of allograft rejection and the avoidance of intraocular complications. In addition, more donor cornea can be used in lamellar keratoplasty since the procedure does not require donor endothelium. This is particularly important in countries where donor corneas are scarce. However, the use of lamellar keratoplasty has been limited by difficulties such as irregularity and scarring of tissue interfaces, leading to poor visual outcomes compared with penetrating keratoplasty,<sup>1-3</sup> as well as technical difficulties and prolonged operating time. Penetrating keratoplasty has thus been the most common corneal transplantation procedure for visual restoration for many years. Although penetrating keratoplasty has been shown to be effective and safe for most anterior segment pathologies, there are persistent long term risks such as endothelial failure and immunological graft rejection.<sup>4</sup>

Deep lamellar keratoplasty (DLK) is a logical step in the surgical management of corneal stromal opacification in the setting of functional endothelium.<sup>1</sup> In DLK, pathological stroma is excised down to Descemet's membrane, and offers the promise of better visual outcomes compared with conventional lamellar grafting. Since this procedure was first reported by Arichila in 1985,<sup>5</sup> several large case series have described favourable visual results after DLK.<sup>3,6</sup> A report of 120 cases by Sugita and Kondo demonstrated that corrected visual acuity improved by 0.09 to 0.6 on average after DLK.<sup>6</sup> Anwar and Teichmann reported that 89% of 181 eyes treated by DLK achieved visual acuity of 20/40 or better.<sup>3</sup> More recently, Shimazaki and associates performed a randomised prospective trial of DLK versus penetrating keratoplasty,<sup>7</sup> showing that visual function after DLK, as

measured by corrected visual acuity, contrast visual acuity, the glare test, and corneal topography, was comparable to that achieved in penetrating keratoplasty. It should be noted that DLK was superior to penetrating keratoplasty in measures of operative morbidity such as continuous endothelial cell loss and intraocular complications.<sup>7,8</sup> These results suggest that DLK is a safe alternative to penetrating keratoplasty in eyes without endothelial abnormalities. These promising findings regarding DLK underscore the importance of overcoming technical challenges such as achieving thorough stromal tissue excision without perforation of Descemet's membrane.

**Deep lamellar keratoplasty is a logical step in the surgical management of corneal stromal opacification in the setting of functional endothelium**

Most corneal surgeons have confronted the technical challenge of deep lamellar dissection and the attendant risk of puncturing Descemet's membrane during DLK. To facilitate the dissection of stromal tissue while reducing the risk of perforation, Arichila<sup>5</sup> and Price<sup>9</sup> employed an air injection technique to separate tissue planes. Sugita and Kondo<sup>6</sup> and Amayem and Anwar<sup>10</sup> used hydrodelamination to separate the deep stromal fibres from Descemet's membrane. Manche and associates<sup>11</sup> used a hyaluronic acid for viscodelamination. These dissection based procedures appear to be useful both in the identification of stromal layers, and in the separation of stromal layers from Descemet's membrane. An alternative approach involves improving visualisation of the deep stromal layers during surgery. Balestrzzi *et al*<sup>12</sup> used trypan blue to stain and visualise the posterior stromal fibres. Moore and associates<sup>13</sup> attempted to use an ocular endoscope to visualise the posterior corneal surface. However, despite all these efforts, perforation of Descemet's

membrane remains common in DLK. Even experienced DLK surgeons have been reported to demonstrate a perforation rate of as high as 25%.<sup>2,6</sup> Sugita and Kondo<sup>6</sup> also reported that stromal tissue was incompletely removed in one third of cases. Thus, thoroughly baring Descemet's membrane without perforation has proved to be a difficult, time consuming, and elusive operative goal for most corneal surgeons.

When employing air, fluid, or viscoelastic injection to dissect Descemet's membrane from the stromal tissue planes, it is ideal to achieve complete separation of these tissue planes with a single injection. When this is achieved, as described by Anwar and Teichmann,<sup>3</sup> a large bubble is formed, indicating perfect separation of tissue planes. However, this result is not always achieved, in large part because the proper depth of dissection is difficult to estimate. Melles and associates<sup>14</sup> described a technique for the visualisation of the posterior corneal surface by filling the anterior chamber with air. Through a scleral incision, a deep stromal pocket was created across the cornea, using the mirror image of a 30 gauge needle as a reference for dissection depth. Senoo and associates, in this issue of the *BJO* (p 1597), describe another approach to determining the proper depth of dissection. A sclerocorneal flap, as is employed during trabeculectomy, is made, and direct microscopic visualisation is used to guide dissection of stromal tissues to the region directly overlying Descemet's membrane. The continued development of such techniques promises to make DLK easier, safer, and less time consuming.

Trends in keratoplasty have been changing over the past decade. Ocular surface reconstruction, consisting of limbal transplantation combined with amniotic membrane transplantation, has enabled us to improve the management of cicatrising diseases.<sup>15,16</sup> Posterior lamellar keratoplasty, also referred to as deep lamellar endothelial keratoplasty, was developed for patients with endothelial dysfunction.<sup>2,17</sup> These procedures are based on the concept that only the pathological part of the cornea, such as the epithelium or endothelium, should be replaced by donor tissue, leaving the healthy portion of the host cornea intact. DLK is consistent with this paradigm, and can be viewed as a procedure designed to remove pathological stroma from healthy corneas. With continued improvements in surgical technique, including the advance described by Senoo and associates in this issue, DLK may become the procedure of choice for keratoplasty in most eyes without endothelial abnormalities.

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Age related macular degeneration

# Mouse models may provide new insight into the relation between cholesterol and age related macular degeneration

J L Duncan

With the goal of preventing vision loss from this disease, it is important to identify modifiable risk factors that may be targets for intervention

Age related macular degeneration (AMD) is the leading cause of severe vision loss among the elderly in the United States, Europe, and Australia. However, the cause of this blinding disease remains a topic of active investigation. Most agree the pathogenesis of AMD is multifactorial and that it results from the interaction of genetic, environmental and ageing effects. Evidence from population based studies has supported a role for heredity in the pathogenesis of AMD. Recent studies have identified a polymorphism in the gene for complement factor H which may be present in up to half of all white AMD patients.<sup>1–4</sup> However, polymorphisms in this gene are also frequently found in Japanese<sup>5</sup> and Chinese<sup>6</sup> populations, where AMD infrequently causes vision loss. Clearly, development of AMD depends on the interaction of genetic background with other, presumably environmental, factors.

With the goal of preventing vision loss from this disease, it is important to

identify modifiable risk factors that may be targets for intervention. Some, but not all, epidemiological studies have identified an association between cardiovascular disease risk and AMD.<sup>7</sup> Cigarette smoking, a well recognised risk factor for cardiovascular disease, is the most consistently demonstrated modifiable risk factor contributing to AMD,<sup>8</sup> and its role in complement activation has been considered supportive evidence of the part played by complement factor H mutations.<sup>3</sup> Recent case-control<sup>9</sup> and prospective<sup>10</sup> studies have identified elevated C reactive protein, an inflammatory biomarker associated with cardiovascular disease, as a risk factor for AMD and AMD progression. Systemic hypertension has been associated with neovascular AMD<sup>11</sup> and a poorer response to laser therapy for choroidal neovascularisation (CNV) in patients with AMD.<sup>12</sup> Some studies have found an association between markers of systemic atherosclerosis and AMD,<sup>13–14</sup> but other large population based studies have found no consistent

association.<sup>11–15</sup> Increased dietary consumption of saturated fat,<sup>16–17</sup> monounsaturated and polyunsaturated fat and vegetable fat<sup>17</sup> and cholesterol<sup>16</sup> has been associated with early and late AMD in various studies. Some recent studies have identified an association between use of cholesterol lowering medications, such as statins, and reduced risk of early or late AMD,<sup>18–22</sup> while others have found no such association.<sup>23–25</sup> Although total serum cholesterol has been associated with neovascular AMD in a large case-control study,<sup>26</sup> many large population based studies have found no association.<sup>8–27</sup> Some studies have suggested an association between different lipoprotein polymorphisms and risk of AMD, including apoE,<sup>28–29</sup> apo B, and apo A1.<sup>30</sup> Certainly the relation between cardiovascular risk factors, lipid metabolism, and AMD remains confusing.

The findings described in LDL receptor deficient mice may provide insight into the mechanism of early AMD

Insight into the role lipid metabolism has in the development of early AMD has come from the study of preclinical models. Although no murine model exists that exactly replicates the phenotype seen in human AMD, studies have shown that C57Bl/6 mice fed a high fat diet and briefly exposed to blue-green light develop basal laminar deposits,<sup>31</sup> a histological feature of human eyes with AMD.<sup>32</sup> Mice with null mutations in apoE have shown basal linear deposits and thickened Bruch's membranes, similar to findings in human eyes with AMD.<sup>33–34</sup> However, neither of these models develops choroidal neovascularisation or geographic atrophy, the stages

of AMD associated with vision loss in patients, limiting our understanding of the mechanisms responsible for these sight threatening complications.

In this issue of the *BJO* (p 1627), Rudolf and colleagues present novel information about mice with a null mutation for the low density lipoprotein (LDL) receptor, which have been studied as a murine model of atherosclerosis. After receiving a high fat diet, LDL receptor deficient mice develop membrane bound translucent particles within a significantly thickened Bruch's membrane, while control mice with normal LDL receptors show no Bruch's membrane abnormalities. The membrane bound translucent particles observed in the LDL receptor deficient mice resemble vesicles observed in histological sections of basal linear deposits and large drusen, findings specific for early AMD.<sup>35</sup> Although plasma cholesterol is significantly elevated in LDL receptor deficient mice fed both normal and high fat diets, it is not clear from the present work that the changes in Bruch's membrane in LDL receptor deficient mice derive from plasma cholesterol rather than from an intraocular source.<sup>36</sup> Further ultrastructural analysis of the lipid composition of Bruch's membrane in LDL receptor deficient mice, using previously described methods to preserve neutral lipids,<sup>36</sup> may provide insight into whether these deposits result from elevated plasma lipid levels or an intraocular source. Such information may clarify the discrepancies noted between plasma lipid abnormalities and risk of AMD in epidemiological studies.

Of interest, the authors demonstrate immunohistochemical reactivity for vascular endothelial growth factor (VEGF) in the basal retinal pigment epithelial (RPE) cells, the outer plexiform layer, and the photoreceptor inner segments of LDL receptor deficient mice, which increased after the mice received a high fat diet. The authors state that no spontaneous CNV was observed in the mice studied despite high levels of VEGF expression. However, the mice in this study were investigated at 4 months of age. It will be interesting to observe LDL receptor deficient mice at senescent ages to determine if the changes described in Bruch's membrane progress with advanced age or are accompanied by the development of CNV or RPE atrophy. Other mutant mice with phenotypes similar to human AMD develop fundus and histological changes only after the age of 9 months, with geographic atrophy and CNV developing only after 16 months and 18 months of age, respectively.<sup>37</sup>

Even in the absence of correlates of late AMD, the findings described in LDL receptor deficient mice may provide insight into the mechanism of early AMD. The fact that the mice develop abnormally thickened Bruch's membranes, similar to early AMD, and demonstrate VEGF upregulation suggests that ischaemia or oxidative stress occurs even in early stages of AMD, perhaps as a result of compromised diffusion from the choriocapillaris to the outer retina. LDL receptor deficient mice will serve as a useful model of early AMD and may allow investigators to determine the part abnormalities of cholesterol metabolism may play in its pathogenesis. Whether or not deficiencies in the LDL receptor are associated with AMD in humans, the ocular phenotype of LDL receptor deficient mice described in the present work should encourage investigators to study murine models of atherosclerosis with careful attention to the eyes.

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## ROP and neurodevelopmental disabilities

G E Quinn

*Br J Ophthalmol* 2005 89: 1547  
doi: 10.1136/bjo.2005.077388

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