

Glaucoma

Is extreme surgery so extreme?

D Wong

The jury is out

At first sight, using retinectomy for treating glaucoma seemed extreme, even when most of the eyes treated were legally blind. More than 20 years ago, Robert Machemer described performing retinotomy to relieve traction in two patients with retinal detachment complicated by proliferative vitreoretinopathy (PVR).¹ At the time retinotomy was considered extreme and surgically the last resort. Several years elapsed before small case series began to appear in literature.²⁻⁵ By the time that the Silicone Oil Studies Report 5 was published in 1993, retinotomy was firmly established.⁶ The surprise was not only that gas and oil were equally effective, but that nearly one third of all patients in the study were treated with relieving retinotomy. One side effect of retinotomy was, of course, hypotony.⁷

The clearance of radioactive water from the vitreous in rabbit eyes was studied by Moseley *et al* in the early 1980s.⁸ Foulds and Damato made the observation that the retinal pigment epithelium was not necessary for retinal reattachment and that the bulk flow of water was sufficient to keep the retina apposed.⁹ It was Kirchoff, however, who went on to identify the neurosensory retina as the main barrier to water outflow in 1993.¹⁰ With the courage of his conviction, he went on to publish the use of retinotomy and retinectomy to lower intraocular pressure on the first nine patients in 1994.¹¹ The latest report in this month's issue of the *BJO* (p 1094) by Jousseaume *et al* demonstrated the safety and efficacy with a 5 year follow up.

Modifying wound healing has made important contributions to the success of glaucoma drainage surgery.¹² Despite the use of antimetabolites, there are a number of patients with so called intractable glaucoma refractory to conventional surgical treatment. The retina, of

course, does not heal in so far as defects do not close.¹¹ Theoretically, retinectomy should provide a predictable outflow. None the less, the results show hypotony in some patients but, more importantly, there was a significant complication rate in terms of retinal detachment and PVR. While the theory may be sound and the treatment valid, ultimately retinectomy is complex surgery only achievable in relatively few hands. Cyclodiode treatment is readily available, easy to apply and perhaps associated with less frightening complications.¹³

Retinectomy is complex surgery only achievable in relatively few hands

In the 1980s, there was a high prevalence of glaucoma among patients with retinal detachment and PVR treated with repeated vitrectomies and silicone oil.¹⁴ Since then, the number of glaucoma cases has fallen dramatically partly as a result of the use of high viscosity purified silicone oil,¹⁵ but partly also because of the increasing use of retinotomy and retinectomy. The recently finished British prospective trial of 5-FU and heparin for PVR showed that 53% of patients were treated with retinotomy and retinectomy (Charteris DG, The use of 5-FU and low molecular heparin as adjuvant to surgery for proliferative vitreoretinopathy: a prospective randomised control trial, 2003, in preparation). For patients with PVR at least, cutting the retina is more commonplace than extreme, often first line treatment rather than last resort. In that sense, we may all be using retinectomy for glaucoma. There is no doubt cutting the retina lowers the intraocular pressure. However, the jury is out on whether, in

the long run, retinectomy is more controllable or "titratable" than cycloablation.

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Stem cell research

Therapy may yet stem from cells in the retina

R R Ali, J C Sowden

The eye is outstandingly well suited for the development of new treatments

The paucity of effective treatments for inherited retinal disease and age related macular degeneration (AMD) underlines the need for the development of novel therapeutic approaches such as gene therapy. Luckily, the eye is outstandingly well suited for the development of new treatments. Non-invasive procedures for the determination of ocular structure and function in both the clinic and laboratory are better developed than for any other organ. Ease of access to the eye enables manipulation at all levels from subcellular to whole organ; the understanding of the eye, from developmental biology to biochemistry, is highly advanced and there are many established animal models of retinal disease. This has enabled rapid progress in the development of gene therapy approaches for retinal disease compared with that for other forms of neurological disorders. While there has been tremendous progress over the past 10 years with the development of gene therapy strategies, this approach will not be effective once degeneration has occurred and some form of cell transplantation may be required to enable the replacement of lost photoreceptor cells. The first trials of cell replacement have been performed using mature photoreceptors or their late progenitors as donor cells for transplantation into dystrophic mouse retinas. They have been shown to partially engraft and to survive for long periods in the host retina, but they fail to integrate efficiently within the host tissue.¹ Alternative cell sources such as neural progenitor/stem cells have therefore been investigated.

Stem cells are the multipotent, self renewing cells that sit at the top of the lineage hierarchy.² An archetypal stem cell is represented by the embryonic stem (ES) cell. ES cells are routinely derived from mouse blastocysts and, when introduced into host blastocysts, contribute to all adult tissues. Furthermore, ES cells can be induced to differentiate in vitro towards many cell lineages, including beating heart muscle cells, blood cells, neurons, glial cells, and adipocytes.³ Over the past few years,

stem cells have also been isolated from adult tissues such as skin, blood, and only recently from liver and brain. In particular, adult neural stem (ANS) cells can be stably cultured in vitro and can be induced to differentiate into oligodendrocytes, astrocytes, and neurons.⁴ It has also been suggested that ANS cells have a very broad plasticity, and are capable of undergoing transdifferentiation to give rise to mature blood and muscle cells both in vitro and in vivo⁵ and this has prompted investigations into determining whether they might be used to replace missing photoreceptor cells.

The identification of human retinal stem cells is an important landmark that might ultimately lead to new treatments for retinal disease

A number of studies have examined the behaviour of brain derived neural progenitor cells transplanted into the mouse neural retina and assessed their potential for mediating retinal reconstruction.⁶⁻⁹ Survival and integration of such cells when transplanted into the retina has been observed. The greatest morphological integration and differentiation is observed after transplantation into younger eyes,¹⁰ but the failure to fully differentiate into retinal cells suggests either that appropriate cues are absent or that they already have some level of terminal commitment that precludes using them to replace lost photoreceptors. While it is well established that adult amphibians and fish and embryonic chicks regenerate their neural retina following loss of neurons, the mammalian eye is not known to regenerate. However, contrary to previous assumptions, in 2000, work in two laboratories demonstrated that the adult mouse retina contains progenitor cells in the ciliary margin that have stem cell-like properties with the capacity to give rise to new photoreceptors, bipolar neurons, and Muller glia in vitro.^{11 12} Perhaps these so called "retinal stem cells" when transplanted will have greater potential than brain derived neuronal progenitors to reconstitute a damaged retina.

In this issue of the *BJO*, Mayer *et al* (p 1154) report the existence of nestin positive cells in adult human retina. Nestin immunoreactivity is a key indicator that these cells are neuronal progenitors. Although further studies, involving in vitro culture and differentiation of these cells, are required to determine whether they do indeed have stem cell-like properties, the data presented here would suggest that these cells may be retinal stem cells. Their location is consistent with the location of retinal stem cells in the mouse retina. More remarkable is the identification of nestin positive cells in epiretinal membranes from patients with proliferative vitreoretinopathy (PVR) with the implication that this newly identified cell type might be contributing to the disease. In order to proliferate and differentiate stem cells in vitro it is necessary to supplement the culture medium with growth factors. An intriguing possibility is that in patients with PVR just such a milieu may promote retinal stem cell proliferation, if not differentiation. The identification of human retinal stem cells is an important landmark that might ultimately lead to new treatments for retinal disease. It is obvious that an enormous amount of work will be required before therapies based on stem cell transplantation are tested in the clinic. Nevertheless, the groundwork required for such trials is now being established and as the first gene therapy trials for eye disease are being initiated 10 years after the first ocular gene transfer experiments in mice, we anticipate that progress in this field will be as rapid and exciting.

The key challenge is now to provide appropriate developmental cues to induce re-enactment of photoreceptor development in the mature retina by determining the local cues and transcription factors required for in vivo expansion, integration, and differentiation of retinal stem cells in order to repair a degenerating retina. A number of growth factors have been identified that are capable of promoting progenitor proliferation and differentiation, along with the expression of some of the critical genes controlling cell commitment and differentiation during retinal development.^{13 14} Stimulation of these pathways is likely to be the key to activating retinal repair from transplanted retinal progenitors.

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