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Editorials

Proliferative vitreoretinopathy

The term proliferative vitreoretinopathy (PVR) is the latest and most enduring of a series of terms used since the early 1960s to describe the proliferation and migration of cells to form fibrocellular membranes on and around the retina. The clinical picture of fibrous contraction, leading to inoperable retinal detachment, was initially thought to be a process originating within the vitreous, the contracted gel leading to retinal shortening and irreversible fibrotic contraction, hence the term massive vitreous retraction (MVR). Both Taylor-Smith[1] and Cibis,[2] however, recognised and reported the significance of epiretinal membranes in the development of complicated retinal detachments.

With the introduction of closed intraocular microsurgery by Machemer,[3] direct access to the preretinal and subretinal spaces enabled him and others to confirm that PVR was in fact a process of periretinal cellular proliferation, the more clinically significant and damaging element of which was epiretinal. The term massive periretinal proliferation (MPP) was therefore coined by Machemer,[4] but subsequently changed to PVR, at the behest of the Retina Society.[5]

Proliferative vitreoretinopathy describes a fibrocellular cascade, in which both glial and retinal pigment epithelial cells participate[6-12] and, encouraged to proliferate, migrate, and undergo metaplasia by fibronectin, growth factors, and other stimulants,[13-22] form contractile membranes on the surface of the retina and beneath it. Contrary to previous thinking, the role of the vitreous gel in the development of PVR is comparatively small. Posterior vitreous detachment generally initiates the chain of events leading to PVR, by creating dehiscences in the internal limiting lamina and/or full thickness retinal breaks, but cells released into the vitreous gel proliferate only locally, do not form membranes, and do not cause contraction of the gel. Proliferation of cells forming contractile membranes on the posterior surface of the detached gel and at the vitreous base, nevertheless, contributes to the forces acting on the anterior retina (anterior PVR).

The simplest membranes are those that derive from glial cells and commonly develop in the absence of full thickness retinal breaks. They sometimes result in areas of localised retinal shortening, as in macular pucker, but are often found in the eyes of asymptomatic individuals, in response to small dehiscences in the internal limiting lamina.[23 24] Such membranes have only limited contractile properties and rarely lead to extensive retinal detachment.

In more complex membranes, usually resulting from the release of cells into the retrohyaloid space (through full thickness retinal breaks following posterior vitreous detachment), RPE cells together with glial cells proliferate, migrate, and form strongly contractile fibrocellular sheets.[4 6-11] These commonly lead to gross retinal shortening and may distort, enlarge, and hold open retinal breaks, leading to persistent, recurrent, and/or progressive retinal detachment. Proliferation of similar cells in the subretinal space, however, uncommonly gives rise to cohesive membrane formation and adhesion to the undersurface of the retina is usually sparse and weak, so that gross retinal shortening is uncommon.[25-27]

The paper by Mietz and Heimann, on page 874 of this issue of *BJO*, indicates that the time course during which the process of fibrocellular proliferation, migration, and contraction occurs, is remarkably consistent, adding weight to the view that the cascade of events leading up to development of clinical PVR is a consistent one and, hence, that its interruption by therapeutic agents at one or more points in the chain, may be feasible.

Treatment of PVR can be preventive or curative. Prevention is better than cure and, as Scott[28] and others have suggested, the most promising solution to the prevention of PVR lies in the success of primary retinal reattachment surgery. Nevertheless, PVR can, and often does, supervene even after initially appropriate and successful surgery for retinal detachment, or even before any attempt at repair has been made. Work has been undertaken in the past 15 years by Binder, Blumenkranz, Tano, Wiedemann and others,[29-41] to test a wide variety of agents, targeted at various points along the PVR cascade, most of them more or less successful in the laboratory, but with only limited success in the clinical arena. Why this should be so is a matter for conjecture, but it is probably because the timing of delivery in the animal model is very different from that which presents as an opportunity in the clinical context. This is what makes the paper by Mietz and Heimann so interesting and apposite. The tight time course of PVR development should allow us to target treatment at a specific stage, identifiable by the time at which each part of the process occurs, not only in primary cases, but in recurrences.

Prevention of PVR, rather than its cure, is particularly urgent at the present time because surgical treatment of complex retinal detachments is costly, in terms of a skilled workforce and expensive equipment, while the quality of visual outcomes, even in successful cases, is open to question. Although recent studies by some workers have indicated that patients with retinal detachments

complicated by PVR in one eye, but with a healthy fellow eye, are mostly pleased to have undergone surgery to the affected eye (even when the results seem to be of very limited value in visual terms),[42 43] work by Andenmatten and Gonvers[44] suggests that surgery for PVR in the eye of a patient with a healthy fellow eye, is helpful only if binocular single vision can be restored and this was found to be possible in less than one third of cases.

The use of a 'cocktail' of agents aimed at arresting the progress of PVR at an early stage in its development, each targeted at a specific point in the fibrocellular cascade, could be more effective than any single agent alone. A multicentre, randomised, clinical trial of just such a 'cocktail' of agents is about to be undertaken in the UK. The ultimate goal of the study is to find an agent or combination of agents which can be given safely to all patients who develop retinal breaks with posterior vitreous detachment, whether they require surgical intervention or just retinopexy. Such a compound, given locally, systemically, or both, would ideally prevent the migration and proliferation of cells which form membranes, without hindering the reparative processes in the retina necessary to seal retinal breaks. The problems concerned with developing such an agent are, in some ways, common to those experienced in the fight against neoplastic disease, the treatment sometimes being worse than the cure.

Advances in pharmacology, and other therapeutic modalities, combined with improvements in methods of retinopexy engendered by advances in laser technology, are most likely to result in the development of new treatment methods which will rid us of the scourge of PVR.

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