

Shaken not Stirred

On numerous occasions in modern history, the world has been the beneficiary of significant contributions from Great Britain in fields such as literature, music, and science. Ushered in by Sir William Bowman and catapulted by the great works of Sir Stewart Duke-Elder, modern British ophthalmology has similarly made many great advances in the diagnosis, treatment, and prevention of ophthalmic disorders. With this issue of *Ophthalmology*, the world is witness to another in this series of achievements. Where others have previously failed in attempts to prevent the development of proliferative vitreoretinopathy (PVR), a group of surgeons in England have succeeded by using a "cocktail" of agents for combination drug therapy during vitreous surgery for retinal detachment.

PVR is the leading cause of failed retinal detachment surgery.¹ This predominantly iatrogenic disease is characterized by the development of cellular membranes at the vitreoretinal interface, vitreous base, and, less commonly, in the subretinal space. The membranes are composed of retinal pigment epithelial cells, glial cells (primarily Müller cells and astrocytes), fibroblasts, and inflammatory cells (mostly macrophages and lymphocytes).² Contraction of these membranes induces recurrent retinal detachment by counteracting the therapeutic effects of scleral buckling and retinopexy. Best characterized as the end result of anomalous wound healing,³ PVR is the consequence of several predisposing factors that lead to the two main pathogenic processes of this disorder: the dispersion of retinal pigment epithelial cells and release of chemoattractant serum components into vitreous.⁴ The presence of large retinal breaks and the use of excessive cryopexy are the major risk factors for retinal pigment epithelial cell dispersion.⁴ As is the case for extensive retinal detachment and choroidal detachment, cryopexy also induces breakdown of the blood-ocular barrier,⁵ introducing serum components into vitreous. Of course, vitreous hemorrhage represents the extreme case of blood-ocular barrier breakdown and, additionally, introduces cellular immunomodulators such as T and B lymphocytes, which are important in normal wound healing and have also been implicated in the pathogenesis of PVR.⁶ Of recent interest in this regard is the hyalocyte, resident macrophage in the posterior vitreous cortex.^{7,8} Among the first cells to be exposed to the noxious stimuli attendant to retinal detachment and its surgical repair, hyalocytes are capable of eliciting the type of immune response that characterizes PVR.⁷ Because these cells are entwined within the dense collagen matrix of the posterior vitreous cortex, hyalocytes, along with the other cells in these membranes, could readily mediate traction to the retina in PVR.⁸ Furthermore, as the extracellular matrix on which constituent cells in PVR membranes migrate and proliferate, the posterior vitreous cortex can greatly influence the development and course of PVR.⁹

To date, attempts to treat PVR have succeeded only in the surgical arena, where vitreous microsurgery has increased the reattachment rate for PVR. In the 1970s and early 1980s the reported surgical success rates were no better than 40%, with reattachment in less than 20% of severe cases.¹⁰ At the close of the 20th century, advances in surgical technique and instrumentation increased the reattachment rates to 70% for grade C3 PVR but were still less than 60% for grade D3 PVR.¹¹ Until now, pharmacologic approaches to treat this disease have failed.^{12,13} However, the study performed by Asaria and colleagues in London and Liverpool, England, and published in this issue of *Ophthalmology* (pages 1179–1183) showed statistically and clinically significant efficacy using 5-fluorouracil, the same agent as that used in the previous attempts that failed, but this time in combination with low molecular weight heparin. Vitrectomy was performed in 174 cases of primary rhegmatogenous retinal detachment with half of the cases receiving the "British PVR cocktail" as part of the solution infused during surgery, whereas half

received a placebo infusion solution. Combination therapy with 5-fluorouracil and heparin decreased the incidence of postoperative PVR by more than 50% ($P = 0.02$). As a secondary result, final visual acuity was substantially better in the group that did not develop PVR ($P < 0.001$).

The principal reason for the success of this is the fact that each of the two major components in the pathogenesis of PVR are treated by the "British PVR cocktail": the antimitogenic properties of 5-fluorouracil prevent the proliferation of cells within vitreous, whereas heparin reduces the effects of inflammation by binding postoperative fibrin and growth factors. Furthermore, because the cells responding to the chemoattractant and mitogenic stimuli of inflammation do so within the extracellular matrix of the vitreoretinal interface,^{9,14} heparin can have additional beneficial effects by interacting with extracellular matrix components at this interface, likely rendering the scaffold less suitable for cell migration and proliferation. Moreover, this study randomly assigned only patients determined to be at risk for PVR on the basis of selected clinical criteria previously found to have high discriminant power (Kon et al. *Br J Ophthalmol*, in press). A companion article in this issue of *Ophthalmology* (pages 1184–1186) describes the results of a prospective study of 212 patients that were classified as low or high risk for PVR on the basis of this discriminant analysis. The incidence of PVR was 9.2% in the "low-risk" group vs. 28% in the "high-risk" group ($P < 0.001$). The use of this approach to increase the prevalence of PVR in the combination drug therapy study increased the "signal-to-noise" ratio in this population, amplifying the beneficial effects of preventive therapy to a statistically and clinically significant level.

As a result of these two landmark studies, ophthalmologists throughout the world can now identify which of their patients are at risk of developing PVR and serve them the concoction of 5-fluorouracil and heparin as effective prophylaxis. Thus, from the folks who brought us "tonic" for malaria, we now have the "HEPURA" cocktail for PVR.

References

1. Ryan SJ. Traction retinal detachment. XLIX Edward Jackson Memorial Lecture. *Am J Ophthalmol* 1993;15:1–20.
2. Charteris DG. Proliferative vitreoretinopathy: pathobiology, surgical management, and adjunctive treatment. *Br J Ophthalmol* 1995;79:953–60.
3. Weller M, Wiedemann P, Heimann K. Proliferative vitreoretinopathy—is it anything more than wound healing at the wrong place? *Int Ophthalmol* 1990;14:105–17.
4. Nagasaki H, Shinagawa K, Mochizuki M. Risk factors for Proliferative vitreoretinopathy. *Prog Retin Eye Res* 1998;17:77–98.
5. Campochiaro PA, Jerdan JA, Glaser BM. Serum contains chemoattractants for human retinal pigment epithelial cells. *Arch Ophthalmol* 1984;102:1830–3.
6. Charteris DG, Hiscott P, Grierson I, Lightman SL. Proliferative vitreoretinopathy. Lymphocytes in epiretinal membranes. *Ophthalmology* 1992;99:1364–7.
7. Sebag J. The vitreous. In Hart WM Jr, ed. *Adler's Physiology of the Eye: Clinical Application*, 9th ed. St. Louis: Mosby, 1992;268–347.
8. Sebag J. Vitreous pathobiology: In: *Duane's Clinical Ophthalmology*. Tasman W, Jaeger EA, eds. Philadelphia: JB Lippincott Co, 1992; vol. 3, chap 39.
9. Hiscott P, Sheridan C, Magee RM, Grierson I. Matrix and the retinal pigment epithelium in proliferative retinal disease. *Prog Retin Eye Res* 1999;18:167–190.
10. Michels RG, Wilkinson CP, Rice TA. *Retinal Detachment*. St. Louis: Mosby, 1990;680–705.
11. Pastor JC. Proliferative vitreoretinopathy: an overview. 1998; *Surv Ophthalmol* 43:3–18.
12. Blumenkranz M, Hernandez E, Ophir A, Norton EW. 5-fluorouracil: new applications in complicated retinal detachment for an established antimetabolite. *Ophthalmology* 1984;91:122–30.
13. Blankenship GW. Evaluation of a single injection of 5-fluorouracil in vitrectomy cases. *Graefes Arch Clin Exp Ophthalmol* 1989;27:565–68.
14. Sebag J, Hageman GS. Interfaces. *Eur J Ophthalmol* 2000;10:1–3.

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