Vitreous: the resplendent enigma

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Arguably the most enigmatic of ocular structures, vitreous has long been unappreciated with respect to its role in health and disease. The classic anatomists and histologists of the 18th (Demours, 1741; Zinn, 1755) and 19th (Sir William Bowman, 1848; Virchow, 1885) centuries considered vitreous a tissue. However, in 1930, Duke-Elder[1] pointed out that vitreous is not a tissue but a cell product. This is consistent with our current concept of vitreous as an extended extracellular matrix composed primarily of water (98%), collagen and hyaluronan. The exact cells and processes responsible for the synthesis of these macromolecules are, as yet, unidentified. Also lacking is a comprehensive understanding of the supramolecular organisation of vitreous, limiting the ability of investigators and clinicians to study vitreous experimentally and evaluate it clinically. Indeed, even the roles of vitreous in ocular physiology are not universally established. One probable function of vitreous, however, is the maintenance of transparency within the eye (fig 1). This minimises light scattering and allows the unhindered transmission of photons to the retina for photoreception. Towards this end, vitreous possesses biochemical properties that inhibit cell migration and proliferation.[2 3] While essential for vision, the invisibility of vitreous has obliged generations on both sides of the slit lamp and ophthalmoscope to merely look through vitreous, unable to adequately look at it.

The absence of effective diagnostic techniques with which to evaluate vitreous, both scientifically and clinically, has also hindered our ability to elucidate the role of vitreous in retinal pathology. For example, in the "Argument" of his 1930 BJO monograph on vitreous,[1] Duke-Elder emphasised that "Inasmuch as the vitreous body is not a tissue but a cell product, its reaction to metabolic or toxic disturbances will be passive."

In particular, he proposed that it is passive gel liquefaction (and ensuing imbalances in "turgegescence" and "deturgescence") that detach the retina, even in the presence of a retinal break. Duke-Elder and his contemporaries failed to realise the paramount role of posterior vitreous detachment, a phenomenon that is not only acute, but unlikely passive. Recent advances in our knowledge of the molecular morphology of gel vitreous,[4 5] the ultrastructure of the vitreoretinal interface[6] and ageing changes in both[7 8] have improved our understanding of the role of posterior vitreous detachment in retinal disorders.

Posterior vitreous detachment (PVD) is the most common acute event to occur in the human eye during the course of life. PVD is characterised by gel liquefaction (synchisis) and vitreoretinal dehiscence with collapse (syneresis) of the posterior vitreous away from the retina. PVD is considered by most to be an abnormal event. It is plausible, however, that much like the phenomenon of apoptosis, PVD is a beneficent part of Nature's "plan." It is known, for example, that in diseases such as diabetic retinopathy[9] and age-related macular degeneration,[10] complete PVD protects against more advanced stages of disease. Is it conceivable, therefore, that Nature has developed a way to mitigate the risk of advancing disease by salubriously separating vitreous away from retina. Indeed, since PVD occurs without untoward sequelae in the overwhelming majority of individuals, it would appear that PVD is providential. In a minority of cases, however, liquefaction occurs without sufficient dehiscence at the vitreoretinal interface to allow for clean separation of the posterior vitreous cortex from the retina. This is known as "Anomalous PVD."[11] The sequelae of Anomalous PVD (fig 2) vary depending upon where the gel is most liquefied and where the posterior vitreous cortex is most firmly adherent to the retina. Also relevant is whether the posterior vitreous cortex that remains adherent to the retina is of full thickness or partial thickness. The latter is a consequence of a splitting in the posterior vitreous cortex, known as vitreoschisis.[12] Recent studies have further suggested that it may also matter whether the split occurs anterior or posterior to the level of the hyalocytes, the resident mononuclear phagocytes of the posterior vitreous cortex.[13]

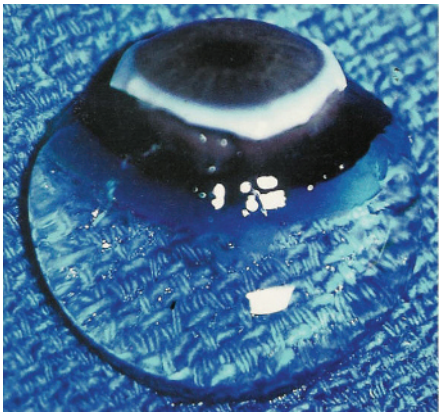

Figure 1 Human vitreous. The sclera, choroid and retina were dissected off the vitreous body, which remains attached to the anterior segment. Although placed on a surgical towel and exposed to room air, the shape of the vitreous body is spherical, and the gel is intact. The exquisite transparency of the vitreous body is evident. Specimen courtesy of the New England Eye Bank.

The advent of new non-invasive imaging of the vitreoretinal interface has provided useful information regarding the fine structure of the posterior vitreous cortex in humans. As demonstrated in fig 3, there is a lamellar organisation of the collagen fibrils in the posterior vitreous of humans, confirming studies in monkeys.[13 14] The lamellar structure within the posterior vitreous cortex constitutes a series of potential cleavage planes, making splits during anomalous PVD possible. Histopathological studies[15] at Moorfield's have shown that vitreoschisis is present in 80% of eyes with proliferative diabetic retinopathy. Clinical investigations[13] have detected vitreoschisis in half of eyes with macular holes and macular pucker. When vitreoschisis occurs, the outermost layer(s) of the posterior vitreous cortex remain(s) attached to the retina. Indeed, studies[16] have shown that splitting of the posterior vitreous cortex can occur during vitreous surgery in 80% of eyes with macular pucker. It is likely that this phenomenon is at least partly if not wholly responsible for the recurrences observed following surgery for macular pucker.[17]

In this issue, Kifuku and colleagues ***(see page 1016)*** present their experience with 46 eyes undergoing surgery for so-called idiopathic epiretinal (this author prefers the term "premacular") membranes and no other confounding conditions like diabetic retinopathy, uveitis or trauma.[18] Preoperatively, nearly all (96.7%) had

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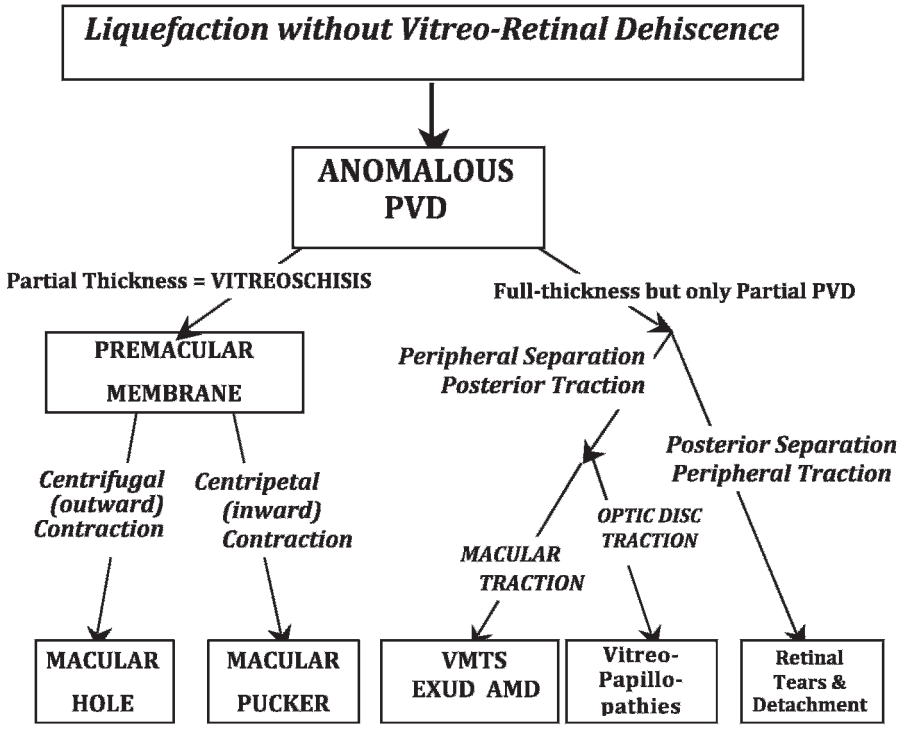

Figure 2 Anomalous posterior vitreous detachment (PVD). Schematic diagram of the various possible consequences of anomalous PVD. EXUD AMD, exudative age-related macular degeneration; VMTS, vitreomacular traction syndrome.

PVD, consistent with the findings of previous studies[19–23] and with the concepts of anomalous PVD[11] and vitreoschisis.[12] After vitrectomy and membrane removal with intraocular forceps, the investigators stained the posterior pole with Brilliant Blue G to identify remnant tissue. Based on positive staining, they claimed to find "residual ILM" in 23/46 (50%) eyes. It is important to note that the uptake of this dye is not definitive evidence that the remnant tissue was indeed the internal limiting lamina of the retina. Ten specimens were examined by flat-mount immunohistochemistry, which demonstrated that many cells, both immunopositive and immunonegative for glial fibrillar acid protein (GFAP), remained on this residual tissue. The true nature of this tissue cannot be ascertained by this histological approach, since a flat mount technique was employed with stains designed for cells, not tissue. Furthermore, if this tissue were indeed the ILM, why were so many cells present? These considerations all suggest, therefore, that this tissue is, at least in part, more likely the outer wall of a vitreoschisis cavity, with the GFAP-negative cells most likely representing hyalocytes and the GFAP positive cells of astrocytic origin.

The nature of the cells involved in macular pucker is controversial. Studies[19–23] have shown that nearly all eyes with macular pucker have a PVD; hence, it was believed that this caused breaks in the retina through which cells migrated and proliferated.[23] However, histological examinations in a very large postmortem study failed to show breaks in the retina of any macular pucker eyes.[24] The concept of anomalous PVD with vitreoschisis proposes that during anomalous separation of vitreous from retina, there is a split within the posterior vitreous cortex anterior to the hyalocytes, leaving these cells embedded in the outer layer of the vitreoschisis cavity that is still attached to the macula.[11–13] As was first hypothesised in 1989,[25] hyalocytes have the capacity to stimulate cell migration, proliferation and membrane contraction, and could thus cause macular pucker. Scientific investigations have now provided evidence in support of this postulate.

Kohno and collaborators ***(see page 1020)*** studied 10 surgically excised premacular membranes from humans with macular pucker, and in separate experiments explored the effects of Transforming Growth Factor (TGF)-beta2 stimulation in an established in vitro wound-healing assay to compare the contractile properties of hyalocytes with those of human astrocytes.[26] Human vitreous removed at surgery for macular pucker was also tested for its ability to stimulate hyalocytes to induce gel contraction. The results showed that the predominant cells in the contracted portion of premacular membranes from macular pucker eyes are most likely hyalocytes. In vitro, hyalocytes were shown to induce considerable gel contraction, while astrocytes had no such effects. Vitreous samples from human eyes with macular pucker also stimulated gel contraction, an effect that was inhibited by anti-TGF-beta2-neutralising antibody. This and the other findings suggest that hyalocytes are pivotal in macular pucker pathogenesis and that

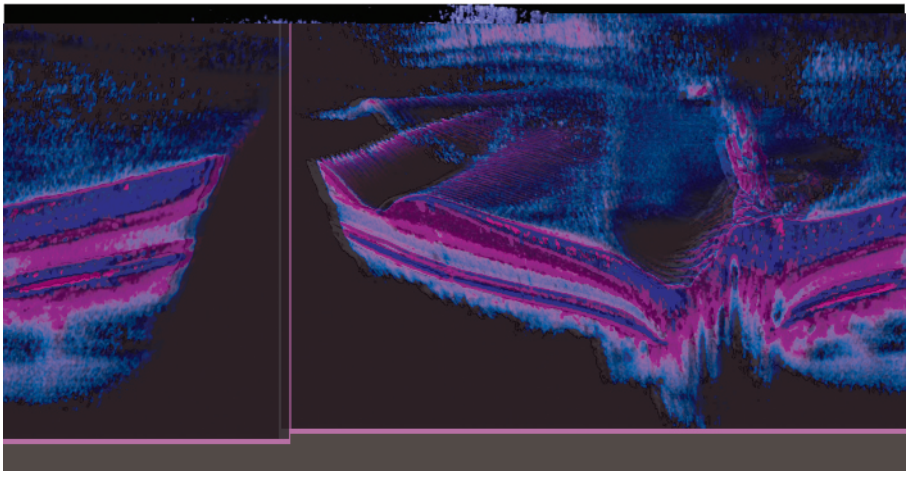

Figure 3 Lamellar structure of human posterior vitreous cortex. Three-dimensional optical coherence tomography imaging of the human postrior vitreous using the Spectralis (Heidelberg Engineering) with cinema 4DXL postprocessing. The left side of the image clearly demonstrates at least three layers in the posterior vitreous cortex. Courtesy of C Glittenberg and S Binder, Vienna, Austria.

TGF-beta 2 plays an important role in modulating the contractile phenomena. The authors suggest that further research will likely lead to pharmacotherapy that will modulate the behaviour of these critical cells. An alternative approach would be to induce total PVD prophylactically via pharmacologic vitreolysis,[27–29] before the onset of anomalous PVD and its untoward sequelae.

All these recent advances belie the fact that not long ago, vitreous was a much maligned structure. The homogeneity of vitreous and lack of structures such as blood vessels and cells led anatomists to regard vitreous as "despicable," physiologists to consider it "negligible," and clinicians to see vitreous as "annoying."[30] Our new understanding of vitreous and our ability to manage its contribution to blindness will surely lead us to appreciate the resplendency of this enigma, for as put by Redslob,

> Qu'y a-t-il de plus lumineux qu'un corps vitré
> Fraîchement décortiqué et exposé au soleil?
> [What could be more resplendent than a vitreus corpum
> Freshly excised and exposed to the sun?]
> E Redslob, Strasbourg, le 5 Janvier, 1932

Competing interests: None.

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