Vitreoretinal juncture; epiretinal membranes and vitreous

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This report reviews current knowledge of the ultrastructural features of the vitreoretinal juncture in its normal state, in eyes with posterior vitreous detachment (PVD), and in eyes with epiretinal membranes (ERM's) and then presents new concepts concerning the interrelationship of ERM's and the vitreous. Results show no vitreous residues on retinal surface following uncomplicated rhegmatogenous (senescent) PVD. In eyes that develop ERM's before vitreous detachment, however, a layer of vitreous may be entrapped beneath the ERM and on adjacent membrane-free retina when PVD occurs. ERM's may be a cause as well as an effect of PVD.

Key words: Vitreoretinal juncture, epiretinal membrane, posterior vitreous detachment, rhegmatogenous, senescent, surface wrinkling retinopathy.

Nonvascular proliferative lesions of the vitreoretinal juncture are an interesting and important class of lesions which not only cause mild visual disability but also have a potential for catastrophic destruction of vision. Those in the posterior fundus are manifest in enucleated eyes as epiretinal membranes (ERM's), with or without wrinkling of the retinal surface. Their major—and usually only—cellular constituents are glia, which are derivatives of accessory glial cells that normally reside in the superficial retina and migrate through breaks in the retinal surface. The question of the interrelationship of these lesions and the vitreous, especially to posterior vitreous detachment (PVD), is not settled. Studies of simple ERM's have shown vitreous variably associated with the membranes. Bellhorn and colleagues also identified vitreous in variable amounts within the ERM of a lesion they studied with electron microscopy, but they did not comment further regarding its significance. On the other hand, at least one investigator feels that vitreous is not only present but is pathologically altered and is a fundamental cause of physical distortion of the retinal surface. In discussing this class of lesion, others have implicated changes in the vitreous, along with proliferation of hyalocytes or fibroblasts within the vitreous cortex. Laqua and Machemer, in their studies of experimental retinal detachment in the owl monkey, concluded that a collagenous component

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Fig. 1. Vitreoretinal juncture in posterior fundus, before (A) and after (B) posterior vitreous detachment. A, Fibrils of vitreous cortex form lamellae approximately horizontal to retinal surface. Inner aspect of inner limiting lamina contains electron-dense line (arrows). B, After posterior vitreous detachment, vitreous residues and line at surface of inner limiting lamina are lacking.

found in epiretinal as well as retroretinal membranes was more likely newly formed collagen and not native vitreous. These conflicting observations and interpretations clearly indicate the need for a better understanding of the role of the vitreous in both the formation of ERM's and the complications following their development. This report will review the ultrastructural features of the vitreoretinal juncture in its normal state, in eyes with PVD, and in eyes with ERM's and then discuss the interrelationship of ERM's and the vitreous.

The material for this study consisted of human eyes that were surgically enucleated for a variety of ocular as well as extraocular lesions. Specimens were processed for electron microscopic study according to our standard methods, with care taken to select tissue that was sufficiently separated from any intraocular lesion to permit adequate interpretation.

Normal vitreoretinal juncture

At the normal vitreoretinal juncture the vitreous fibrils insert into and blend with the fibrillary material of the inner limiting lamina (ILL), which in the posterior fundus is very thick. The depth of vitreous penetration is suggested by a thin electron-dense line at the surface of the ILL (Fig. 1). This line also may indicate the presence of a biologic "glue" cementing the vitreous to the retina. Whatever the nature
Fig. 2. Simple epiretinal membrane. Compact layer of glial cells, many fully differentiated as fibrous astrocytes, forms membrane (ERM) on surface of inner limiting lamina (ILL). Surface of ERM is focally villous and shows occasional junctional complexes.

of the vitreolaminar attachments, the bond is normally strong and resistant to substantial tractional forces in life and in enucleated eyes when examined by suspension. Although there has been speculation that vitreolaminar attachments weaken with age, no morphologic evidence to support this has been published.

Posterior vitreous detachment
Studies in this laboratory have emphasized that processing specimens for light or electron microscopic study commonly leads to artefactual derangement of vitreolaminar attachments. Thus, for proper interpretation of vitreoretinal relations, ultrastructural studies should be preceded by and supplemented with bi microscopic examination in the clinic or with macroscopic study in the enucleated specimen. Ultrastructurally, uncomplicated (senescent) PVD occurs at the anatomical vitreoretinal juncture. Those specimens with recent detachment may show a few residual fragments of vitreous, but these and the linear density at the surface of the lamina soon disappear, leaving a smooth surface without vitreous residues (Fig. 1). These observations in enucleated eyes complement those derived from clinical studies by Linder and by Eisner, which have shown a prefoveal hole in the detached posterior hyaloid in rhegmatogenous (senescent) PVD. Thus, as presently conceived, rhegmatogenous PVD is initiated by exaggerated degeneration of the premacular vitreous cortex, which finally breaks and permits either the central pool of liquefied vitreous or the herniating "formed" vitreous to dissect into the potential retrohyaloid space. Thereafter, vitreolaminar attachments rapidly rupture throughout the retrobasal fundus. The cause of exaggerated degeneration of the premacular vitreous cortex with age is not presently known, but it may be caused by visible light focused in this region by the ocular dioptric system.

Epiretinal membranes
In a previous study of the ultrastructural features of simple ERM's (asymptomatic and macroscopically subtle lesions of posterior fundus), I found that vitreous was
Fig. 3. Epiretinal membrane adjacent to region with surface wrinkling. Compact layer of vitreous fibrils (arrow) is interposed between inner limiting lamina and epiretinal membrane, whose glial cells show a few dense bodies, scattered glycogen granules, dilated cisternae of granular endoplasmic reticulum, and a delicate basal lamina next to the layer of entrapped vitreous.

Fig. 4. Epiretinal membrane adjacent to retinal surface wrinkle. Segment of long-spacing collagen is embedded in compact layer of vitreous fibrils beneath epiretinal membrane. Inset, Detail of ball-shaped fibrous long-spacing collagen** (macroperiod 1,200 Angstrom units).

Inconstantly present and rarely intermingled with the glial cells of the membranes (Fig. 2). However, studies of more complex processes (such as surface wrinkling retinopathy, where in addition to an ERM, there is distortion of the retinal surface) often show condensed collagenous fibrils indistinguishable from native vitreous interposed between the ILL and the ERM (Fig. 3). The presence of vitreous in this location was noted also by Bellhorn and associates. A few of these lesions also
contain occasional pieces of fibrous long-spacing collagen embedded in the native vitreous, an observation originally mentioned by Rentsch (Fig. 4). In some lesions, in which PVD has occurred, a thin layer of vitreous extends from under the ERM onto the adjacent membrane-free retinal surface (Fig. 5). Rarely, a thin layer of vitreous fibrils also may be found on the inner aspect of an ERM.

**Interrelationship of epiretinal membranes and vitreous**

The presence of vitreous beneath some ERM's and the absence in others can be explained best by considering the temporal relationship of ERM formation and PVD. Thus, when an ERM forms before vitreous detachment, the glial cells grow into the vitreous cortex, and as the membrane extends over the surrounding retina, a layer of vitreous becomes entrapped against the ILL of the retina. On the other hand, if a membrane forms after vitreous detachment, no vitreous is available to become associated with the membrane.

Despite the intimate relationship that sometimes develops between the vitreous and ERM's, vitreoretinal tractional lesions mediated by ERM's are rare. Apparently
Fig. 6. Surface break and epiretinal membrane; vitreoretinal juncture over arteriole in posterior fundus. Anomalously thin inner limiting lamina is missing at surface break (arrow), and a glial cell process extends from superficial retina through break into epiretinal membrane. Although fine structure of glial process (including cytoplasmic density) suggests origin from Mueller cell, this process arose from accessory glial cell in subjacent nerve fiber layer. Residues of cortical vitreous are present under membrane.

Fig. 7. Simple epiretinal membrane with hemidesmosomes. Compact membrane largely contains fibrous astrocytes, one (immediately adjacent to inner limiting lamina) showing attachment plaques (arrows). Inset, Detail of hemidesmosomes: focal densities in cytoplasm beneath cell membrane, delicate fibrils traversing space outside cell membrane, and thin basal lamina adjacent to inner limiting lamina of retina.

When rheumatogenous vitreous detachment occurs, the vitreous cortex splits as the detaching vitreous reaches the surface membrane, leaving behind the layer of vitreous entrapped beneath the membrane and perhaps a thin layer on the surface of the immediately adjacent membrane-free retina. Thus, although the detaching
vitreous may be temporarily or briefly arrested upon reaching an ERM, significant vitreoretinal adhesions and traction (as occur frequently at sites of extraretinal neovascularization) only rarely develop, and membranes are seldom avulsed. This is somewhat surprising since morphologically identifiable attachments between ERM’s and the retina are inconstant or subtle. One obvious method whereby ERM’s become attached to the underlying retina is by means of surface breaks, through which glial cell processes extend from the retina into the overlying membrane (Fig. 6). Despite extensive sampling in regions with membranes, however, surface breaks are rare in our material, and most are found over superficial retinal vessels. Another method, hemidesmosomes in glial cells lying adjacent to the limiting lamina, was initially reported by Bellhorn and associates, but these specialized structures are found only in foci where vitreous is lacking and are rare in lesions studied in our laboratory (Fig. 7). Since the entrapped layer of vitreous usually is still attached to the ILL, this also may contribute to the adherence of the membrane to the retina. Despite the rarity and inconstancy of these biomechanical membranoretinal attachments, they are apparently stronger than those between the vitreous and the epiretinal membrane, since tractional lesions or avulsion of membranes seldom are found.

Several studies have shown a high incidence of PVD in eyes with ERM’s and with surface wrinkling retinopathy. Most investigators have interpreted this as an indication that vitreous detachment is a direct or an indirect cause of ERM formation (by rupturing the retinal surface). Since ERM’s occur frequently in the macula (where posterior vitreous begins) one cannot be certain that vitreous detachment is not an effect of ERM’s (by disturbing vitreolaminar attachments).

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REFERENCES