Vitreous Aging and Posterior Vitreous Detachment

II.C.

Kevin Tozer, Mark W. Johnson, and J. Sebag

Outline

Keywords
Posterior vitreous detachment • Vitreoretinal interface • Liquefaction • Synchysis • Syneresis • Vitreous aging • Hyaluronan • Collagen • Myopia

Key Concepts

1. Posterior vitreous detachment is not an acute process, but is instead a series of aging changes in the vitreous body that take place over many years.
2. Changes to both hyaluronan and type IX collagen have been implicated as the cause of vitreous liquefaction. The mechanisms underlying dehiscence at the vitreoretinal interface are less well understood.
3. Pathology from posterior vitreous detachment results from liquefaction without concurrent vitreoretinal interface dehiscence, known as *anomalous posterior vitreous detachment*.

Electronic supplementary material Supplementary material is available in the online version of this chapter at 10.1007/978-1-4939-1086-1_9. Videos can also be accessed at http://www.springerimages.com/videos/978-1-4939-1085-4.

K. Tozer, MD
Doheny Eye Institute, Los Angeles, CA, USA

VMR Institute for Vitreous Macula Retina, 7677 Center Avenue, Suite 400, Huntington Beach, CA 92647, USA

Department of Ophthalmology and Visual Sciences, Kellogg Eye Center, University of Michigan, 1000 Wall Street, Ann Arbor, MI 48105, USA
e-mail: ktozer@med.umich.edu

M.W. Johnson, MD
Department of Ophthalmology and Visual Sciences, Kellogg Eye Center, University of Michigan, 1000 Wall Street, Ann Arbor, MI 48105, USA
e-mail: markwj@med.umich.edu

J. Sebag, MD, FACS, FRCOphth, FARVO (✉)
Doheny Eye Institute, Los Angeles, CA, USA

VMR Institute for Vitreous Macula Retina, 7677 Center Avenue, Suite 400, Huntington Beach, CA 92647, USA
e-mail: jsebag@VMRinstitute.com

J. Sebag (ed.), *Vitreous: in Health and Disease*,
DOI 10.1007/978-1-4939-1086-1_9, © Springer Science+Business Media New York 2014

I. Introduction

Vitreous undergoes dramatic changes with age, the most notable called "synchysis senilis," which refers to the liquefaction of the gel with age. An understanding of synchysis from molecular to macroscopic levels is crucial because it is directly responsible for many important pathologic conditions that form a large and diverse group of ocular diseases. Remarkably, these changes start in the first few years of life and thus, untoward consequences are not confined to the elderly, but have the potential to afflict anyone. The most important event that is directly related to vitreous aging is posterior vitreous detachment (PVD). This seminal event is the ultimate outcome of a series of vitreous changes that occur throughout life in two locations: in the gel vitreous body and at the vitreoretinal interface. Although remarkably common and usually harmless, PVD is the single most important factor underlying pathology that results from the aging process in the vitreous body [see chapter III.B. Anomalous posterior vitreous detachment and vitreoschisis].

II. Molecular Composition of Vitreous

Understanding the process of aging in the vitreous requires knowledge of the molecular components that are ultimately responsible for the changes on a macroscopic level. A more detailed review of all aspects of vitreous biochemistry is available elsewhere in this book [see chapters I.A. Vitreous proteins; I.F. Vitreous biochemistry and artificial vitreous].

A. Collagens

Type II collagen comprises 60–70 % of all vitreous collagen [1]. Alternative splicing within the second exon creates two different forms, IIA and IIB [2]. Mutations in exon 2, such as in Stickler syndrome, result in significant ocular pathology that includes very liquefied vitreous [3] and a substantially higher risk of retinal detachment arising from large posterior retinal breaks [see chapter I.C. Hereditary vitreoretinopathies]. Type IX collagen comprises 20–25 % of vitreous collagen [1, 4]. Unlike type II, it is a heterotrimer and cannot form fibrils, but it does interact with the fibrils of other collagens. Alterations in the quantity and location of type IX collagen have been proposed as a reason for some of the most important age-related vitreous changes [5, 6]. Type V/XI collagen makes up about 10–15 % of all vitreous collagen [2]. Type II and the hybrid type V/XI collagen combine to form a heterotypic fibril. Type IX collagen attaches to the COL2 domain of type II collagen and helps keep the fibrils spaced from one another [2].

Current evidence suggests that during life vitreous collagens change dramatically in structure, with both aggregation and enzymatic cleavage, but there is also evidence of collagen turnover. Advanced glycation end products (AGEs), specifically pentosidine, have been documented, suggesting vitreous turnover [7]. Based on rate of accumulation of pentosidine in nondiabetic individuals, the average half-life of vitreous collagen is likely around 15 years, similar to that of skin [7]. In diabetes, there are significant increases in vitreous AGEs [8, 9] [see chapter I.E. Diabetic vitreopathy].

B. Non-collagenous Components

Hyaluronan (HA) is a highly hydrophilic glycosaminoglycans (GAG) [see chapter I.F. Vitreous biochemistry and artificial vitreous] that keeps vitreous collagen sufficiently spaced to minimize light scattering [10]. Loss of this HA-collagen association has been implicated as an important part of vitreous aging [11]. Other important non-collagenous molecules include chondroitin sulfate (CS) and heparin sulfate, as well as opticin, a structural protein. CS and HS both attach to protein cores to form proteoglycans [2]. CS interacts with type IX collagen and may be important in fibril aggregation with aging [5, 6], while HS is also found at the vitreoretinal interface [2]. Opticin, which is not a GAG, is found at the vitreoretinal interface as well as on the surface of heterotypic collagen fibrils [12, 13]. Its role may be important in vitreoretinal adhesion and in preventing neovascularization [see chapter IV.C. Vitreous and iris neovascularization].

III. Vitreous Structure

A. Vitreous Body

Comprised mostly of water, the vitreous body is important in maintaining both optical clarity and structural integrity of the eye. For transparency, collagen fibrils are spread apart in youth by association with HA molecules. The collagen fibers attain their highest concentration at the vitreous base and lowest concentration in the central vitreous body. At the vitreous base the fibers course perpendicular to the eye wall which results in strong mechanical vitreoretinal adhesion in the periphery [14, 15].

B. Posterior Vitreous Cortex

The posterior vitreous cortex is the outer shell of the vitreous that extends from the vitreous base posteriorly to adhere to the entire posterior retina. Similarly, there is an anterior vitreous cortex that courses anteriorly from the vitreous base and adheres to the posterior lens surface. The posterior vitreous cortex varies in thickness between 100 and 110 μm [16] and is actually absent over the optic disc (i.e., the prepapillary

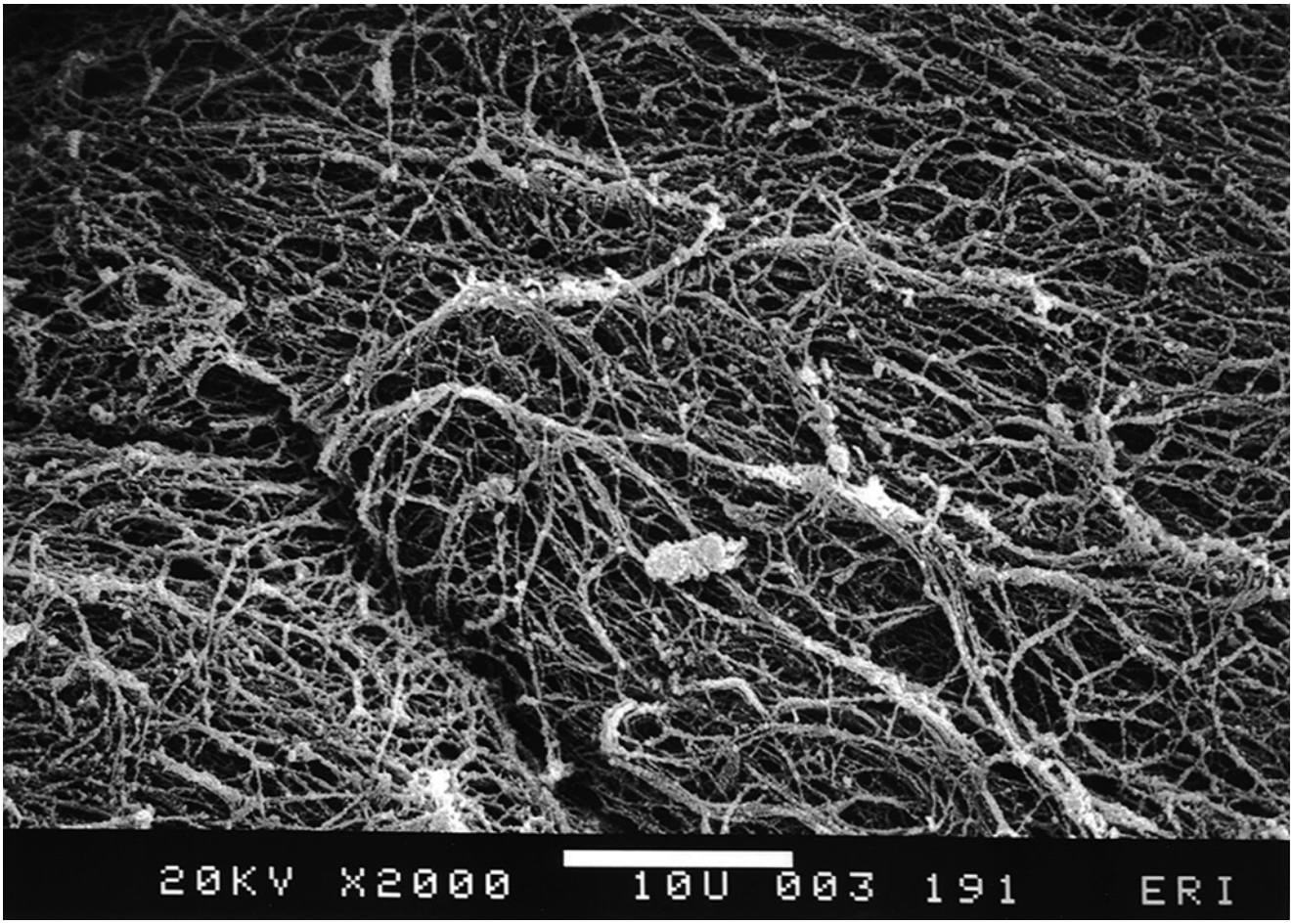

Figure II.C-1 Scanning electron micrograph demonstrating the dense matrix of collagen fibrils in the human posterior vitreous cortex

hole) [15, 17]. The cortex is thinnest in the fovea and increases in thickness as it extends outward [18] [see chapter III.E. Vitreo-papillary adhesion and traction]. Unlike at the vitreous base, the collagen fibrils in the posterior vitreous cortex run parallel to the plane of the retina (Figure II.C-1). This orientation does not allow any direct insertion into the retina and accounts for the weaker adhesion along this zone [15, 19].

An important structural feature of the posterior vitreous cortex is its lamellar organization. Much like an onion, the posterior vitreous cortex is comprised of layers that are potential cleavage planes through which the structure can split, a phenomenon known as "vitreoschisis" which can occur endogenously or during membrane peel surgery [see chapter III.B. Anomalous posterior vitreous detachment and vitreoschisis]. Indeed, Gupta et al. [20] showed that vitreoschisis is present in a much higher percentage of patients with macular hole and macular pucker than normal controls [see chapters III.F. Vitreous in the pathobiology of macular pucker; III.C. Pathology of vitreomaculopathies]. Another unique feature of the posterior vitreous cortex is that hyalocytes are embedded within it. These cells, which are located approximately 20–50 μm from the retina, form a monolayer in the posterior vitreous cortex [10]. Their main function is to serve as important immunomodulating cells and help maintain vitreous clarity through their phagocytic activity. Pathologically, they are likely to be important in early stages of a number of disease entities involving preretinal membranes, like macular pucker, and serve as the main contractile elements by differentiating into myofibroblasts [see chapters II.D. Hyalocytes: essential vitreous cells in vitreoretinal health and disease; III.F. Vitreous in the pathobiology of macular pucker].

C. Vitreous Base

The vitreous base "anchors" the vitreous body and is the point of insertion for vitreous collagen fibrils. Its anterior border is approximately 2 mm anterior to the ora serrata, and the posterior border, which extends posteriorly over time, is between 1 and 3 mm posterior to the ora serrata [21, 22]. Additionally, the vitreous base is not a flat structure but actually extends into the anterior vitreous body as well. As mentioned above, the vitreous base is the location of highest collagen concentration and the only zone where collagen fibers course perpendicular to the retina. These fibers insert anterior and posterior to the ora serrata (Figure II.C-2) forming a dense doughnut-like structure that straddles the ora

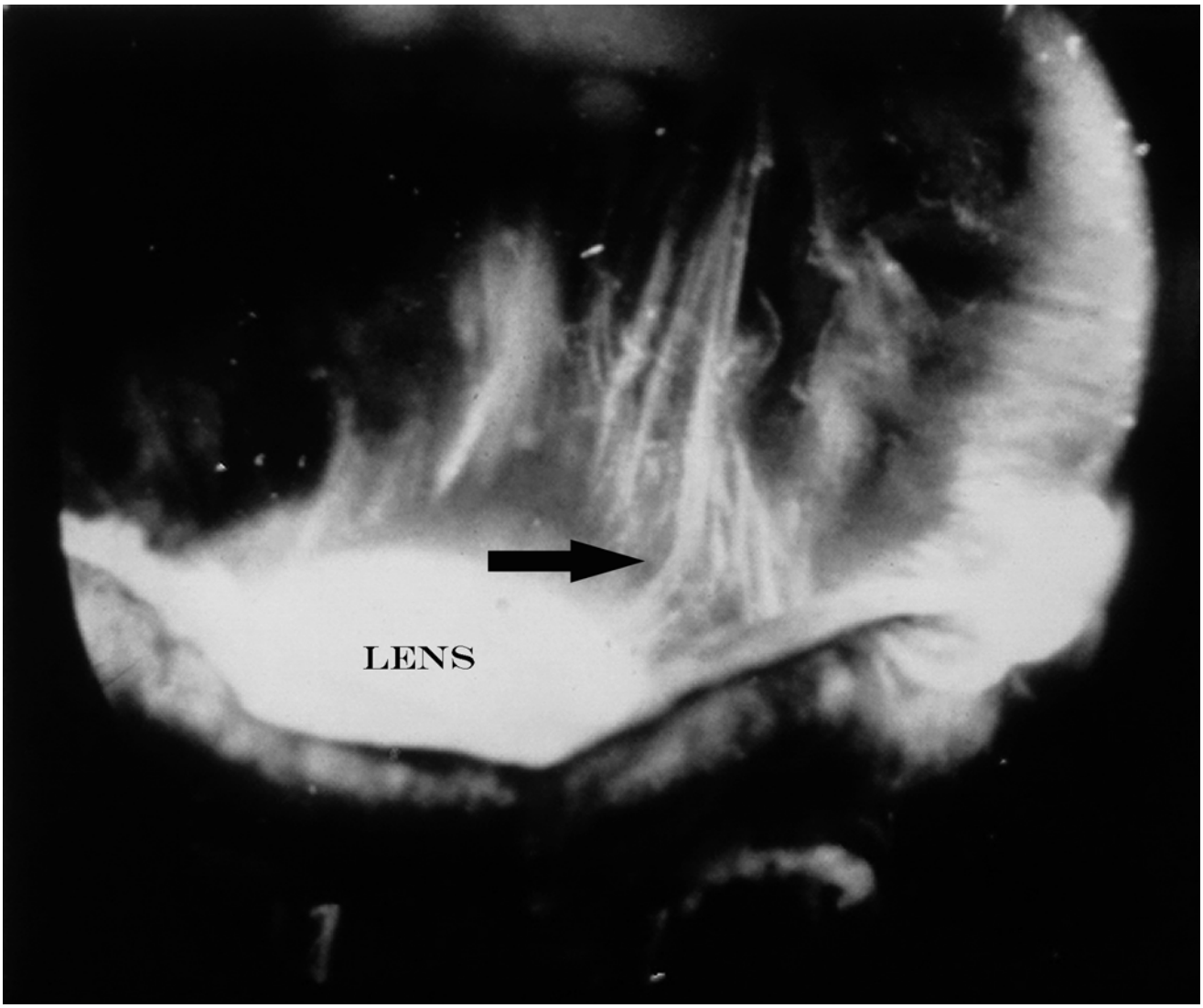

Figure II.C-2 Dark-field slit micrograph demonstrating the collagen fibrils of the vitreous base inserting anterior and posterior to the ora serrata (*arrow*). The posterior aspect of the lens is seen [24]

serrata. While biochemical interactions may underlie vitreoretinal adhesion elsewhere in the fundus, mechanical insertion is a unique property of the vitreous base where vitreous collagen fibrils directly interdigitate with the nonpigmented epithelium of the ciliary body and the neuroglia of the peripheral retina. This strong mechanical adhesion is likely responsible for persistent attachment along the vitreous base [15] despite PVD elsewhere and explains the propensity for retinal tears to occur at the posterior border of the vitreous base [see chapter III.H. Peripheral vitreo-retinal pathologies].

D. Vitreoretinal Interface

Possibly the most complex region of the vitreous is the narrow zone of adhesion between the vitreous and the retina, known as the vitreoretinal interface. The vitreoretinal interface is made of three distinct components: the posterior vitreous cortex (see above), the inner limiting membrane of the retina [see chapter II.E. Vitreoretinal interface and inner limiting membrane], and the extracellular matrix between the two. The inner limiting membrane (ILM) is the basal lamina of the retina and serves as the basement membrane for the Müller cells. Over the optic disc, the ILM actually ceases and transitions to the inner limiting membrane of Elschnig and the membrane of Khunt [10, 15, 23] [see chapter III.E. Vitreo-papillary adhesion and traction]. These topographical variations are important because numerous studies have demonstrated an inverse relationship between strength of vitreoretinal adhesion and ILM thickness [15, 24]. Studies [25] demonstrated that there were persistent remnants of vitreous cortex in the fovea after spontaneous posterior vitreous detachment with diameters of approximately 500 and 1,500 μm, both areas with thin ILM.

The other important component of the vitreoretinal interface is the extracellular matrix (ECM), also called the

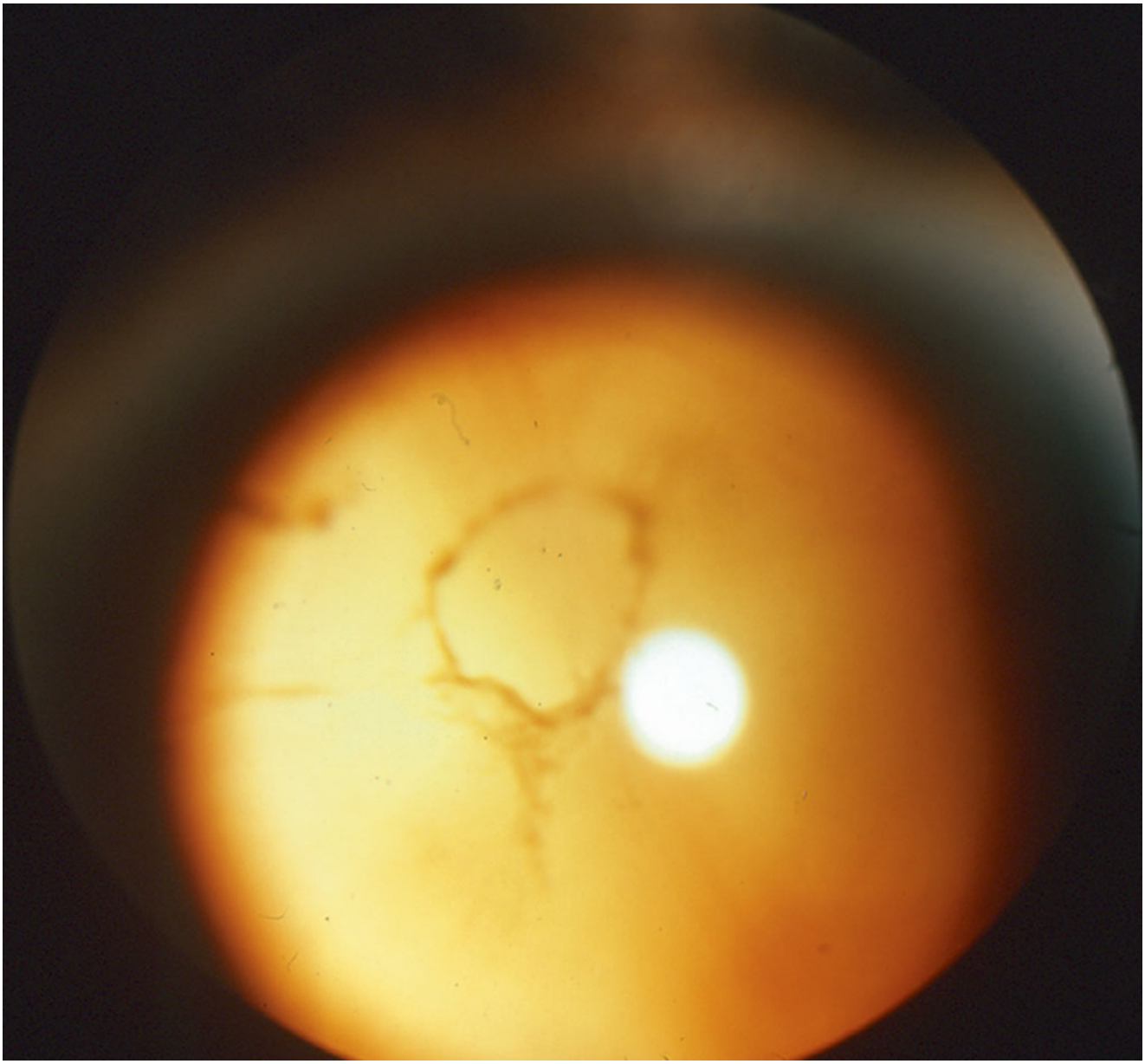

Figure II.C-3 Slit-lamp photo of a Weiss ring in the posterior vitreous cortex following PVD

vitreoretinal border region of Heegaard. The ECM functions as the biochemical glue that keeps the two structures adherent in the absence of mechanical adhesions. The molecular components of the ECM are numerous but are known to include fibronectin, laminin, opticin, and chondroitin sulfate proteoglycans. Russell [12] proposed a model by which the ECM maintains integrity of the vitreoretinal interface. In his theory a 240-kDa protein core is bound to the type IV collagen of the ILM. Attached to the protein core are a series of chondroitin sulfate glycosaminoglycans (GAG) that are present on the vitreal side of the ILM. The GAGs bind to a fibrillar protein, most likely opticin, which then interacts with type II collagen of the cortical vitreous. Through this chain of interaction, ILM to core protein to GAG to opticin to cortical vitreous, a relatively strong biochemical adhesion is formed [12]. This type of biochemical adhesion appears to present throughout the retina, not just along the posterior pole. Evidence for this fact comes from studies examining the effect of ABC chondroitinase on the vitreoretinal interface. Chondroitinase causes an enzymatic destruction of the chondroitin sulfate adhesion process, and exposure to it caused complete dissociation of the vitreous from the retina, even along the vitreous base [26, 27] [see chapter VI.H. Chondroitinase as a vitreous interfactant: vitreous disinsertion in the human].

Another important consideration in the topographical variations of the vitreoretinal adhesion is the optic disc. Over the optic disc head, there is no posterior vitreous cortex and no inner limiting membrane, only the very thin membranes of Elschnig and Khunt [28]. Along the borders of the optic

disc, however, there are strong vitreoretinal adhesions. The nature of these adhesions likely falls somewhere between the biochemical adhesions of the remaining posterior pole and mechanical insertions of the vitreous base. What is known is that this peripapillary adhesion is often the last area of the retina, other than the vitreous base, to separate during a posterior vitreous detachment. Additionally, this separation is often associated with a rim of neuroglial tissue coming off the retina along with the vitreous, a finding clinically identified as a Weiss ring [29] (Figure II.C-3).

That PVD can tear away peripapillary tissue suggests a strong adhesion between the fibers of the vitreous cortex and glial tissue of the optic nerve head. In fact, cortical vitreous fibers have been shown to mechanically intertwine with the basal lamina and astroglial epipapillary membranes present in that area [30]. Whether this adhesion is purely mechanical or a mixture of mechanical and biochemical remains to be determined. Interestingly, in diabetic patients the peripapillary vitreous often remain persistently attached. The mechanism for this is likely related to the presence of neovascular membranes that preferentially proliferate through the prepapillary hole in the vitreous cortex [31]. These membranes function as additional anchors strengthening peripapillary vitreoretinal adhesion [see chapter III.E. Vitreo-papillary adhesion and traction].

IV. Aging Changes in the Vitreous Body

Vitreous aging is characterized by two separate processes that occur in parallel: gel liquefaction and vitreoretinal interface weakening. Each contributes to the principal aging event of the adult vitreous, posterior vitreous detachment.

A. Liquefaction

The first appearance of liquid vitreous is actually in childhood [32, 33]. Age-related liquefaction is called "synchysis senilis"; however, liquid vitreous has been documented at all ages (Figure II.C-4). In many young individuals a major cause of vitreous liquefaction is myopia which is known to lead to PVD at an earlier age than in emmetropia. Yonemoto [34] found that 0.91 years could be subtracted from the average age of PVD development (61 years) for each diopter of myopic refractive error. This is presumably at least in part related to precocious vitreous liquefaction. The pathway through which myopia affects PVD may be a decrease in HA concentration [35]. Others have suggested that in myopic eyes there may actually be an increase in synthesis of liquid vitreous more so than an increase in liquefaction of existing gel vitreous [36, 37]

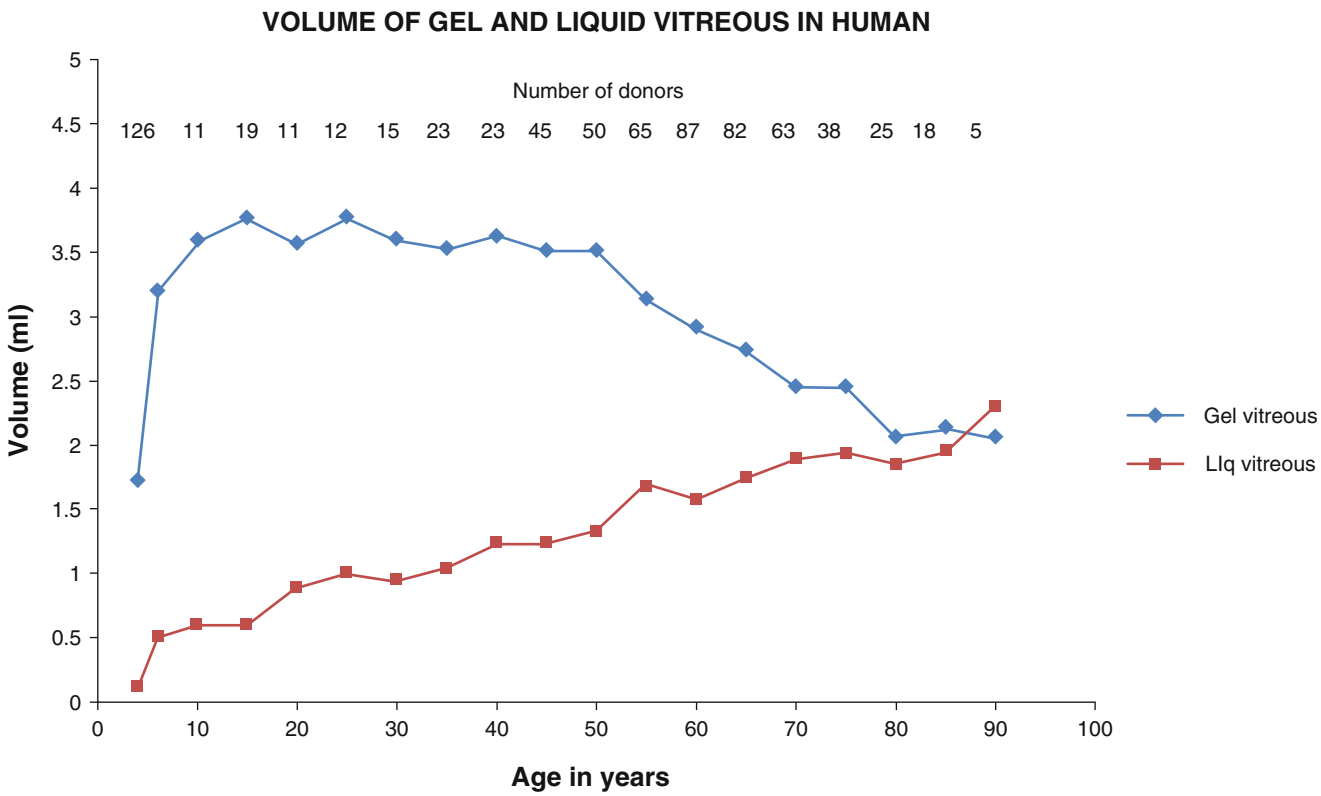

Figure II.C-4 Graph depicting the volume of gel and liquid vitreous throughout life. Note that liquid vitreous begins appearing, albeit in small quantities, during the first 5 years of life. Each data point represents the average derived from the number of eyes listed across the top of the graph

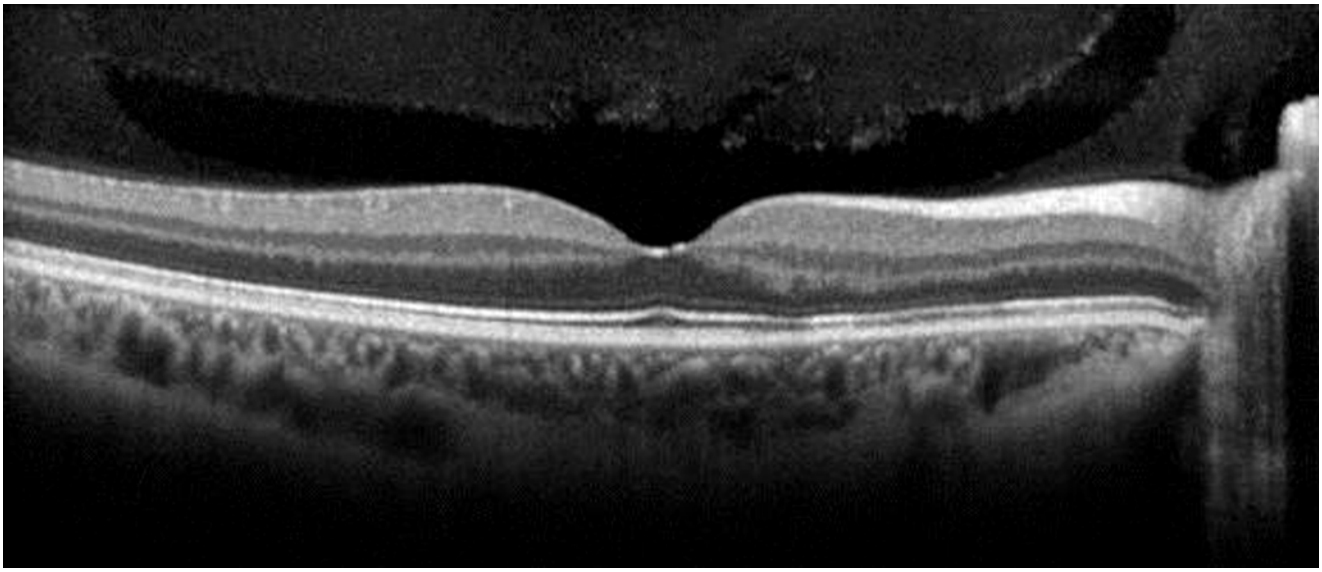

Figure II.C-5 Optical coherence tomography image demonstrating a premacular lacuna in the posterior vitreous of a 22-year-old female

[see chapter II.B. Myopic vitreopathy]. In addition, there are number of conditions that may cause increased liquefaction at an earlier age, most related to inborn errors of collagen metabolism. Collagen disorders such as Marfan, Ehlers-Danlos, Stickler [38], and Knobloch syndromes [39] all have substantial ocular manifestations usually associated with advanced vitreous liquefaction [see chapter I.C. Hereditary vitreoretinopathies].

With advancing vitreous liquefaction, pockets of liquid vitreous called lacunae form within the gel. As originally described by Worst [40], the first lacunae form in the premacular vitreous (Figure II.C-5). The reason for this specific location is unclear, but several theories exist. One is that the macula is the site that the majority of the light, and therefore light radiation, is focused. Visible light radiation exposure is thought to produce free radicals [41] that predispose the premacular vitreous to breakdown at a younger age than other parts of the vitreous body [42, 43]. A second theory is similarly reliant on free-radical damage but posits that the free radicals are a byproduct of being located near the highly metabolically active macula [44]. It is also plausible that like Cloquet's canal, this bursa is an embryologic vascular remnant.

By the teenage years, 20 % of the total vitreous has undergone synchysis [32], and by 70 years of age, this increases to 50 % [45]. Importantly, it is usually around the age of 40 that enough vitreous has liquefied to produce findings evident on clinical slit-lamp biomicroscopy as gray linear structures and pockets of liquid vitreous devoid of any light scattering. Dark-field slit microscopy has documented the presence of fibers in the adult human vitreous and characterized their distribution (Figure II.C-6a). Transmission electron microscopy has determined that these visible fibers are aggregated vitreous collagen fibrils organized into bundles [46] (Figure II.C-6b). Indeed, all theories of vitreous liquefaction maintain a central role for collagen. Although there is evidence of vitreous collagen turnover throughout life (see section I above), turnover alone would not account for the dramatic structural changes that vitreous undergoes. Three theories to be discussed include changes in the hyaluronan-collagen association, loss of type IX collagen from the surface of heterotypic collagen fibrils, and enzymatic collagen destruction.

One of the leading theories explaining vitreous liquefaction explores the role of hyaluronan (HA). As described above HA is a hydrophilic glycosaminoglycans that is important in short- and long-range spacing of collagen fibrils [see chapter I.F. Vitreous biochemistry and artificial vitreous]. While the collagen provides the matrix, HA draws the water that effectively provides the matrix structure by hydrating it [47, 48]. In theory, if the nature of the HA-collagen interaction were to change, either through loss of HA or another mechanism, the collagen matrix would collapse and the liquid inside would form pockets. Following HA dissociation from collagen, the collagen fibrils cross-link with one another and undergo lateral fusion into larger aggregates. Increasing the collagen content in the residual gel vitreous while simultaneously decreasing it elsewhere leads to liquid lacunae (Figure II.C-6c). This theory is supported by the finding that eyes with posterior vitreous detachment had a lower concentration of HA than eyes with an intact vitreous [11]. Circumstantial evidence derives from the observation that as HA concentration decreases the volume of the vitreous gel decreases as well [6]. There may also be HA structural changes that alter its interaction with collagen. Free-radical

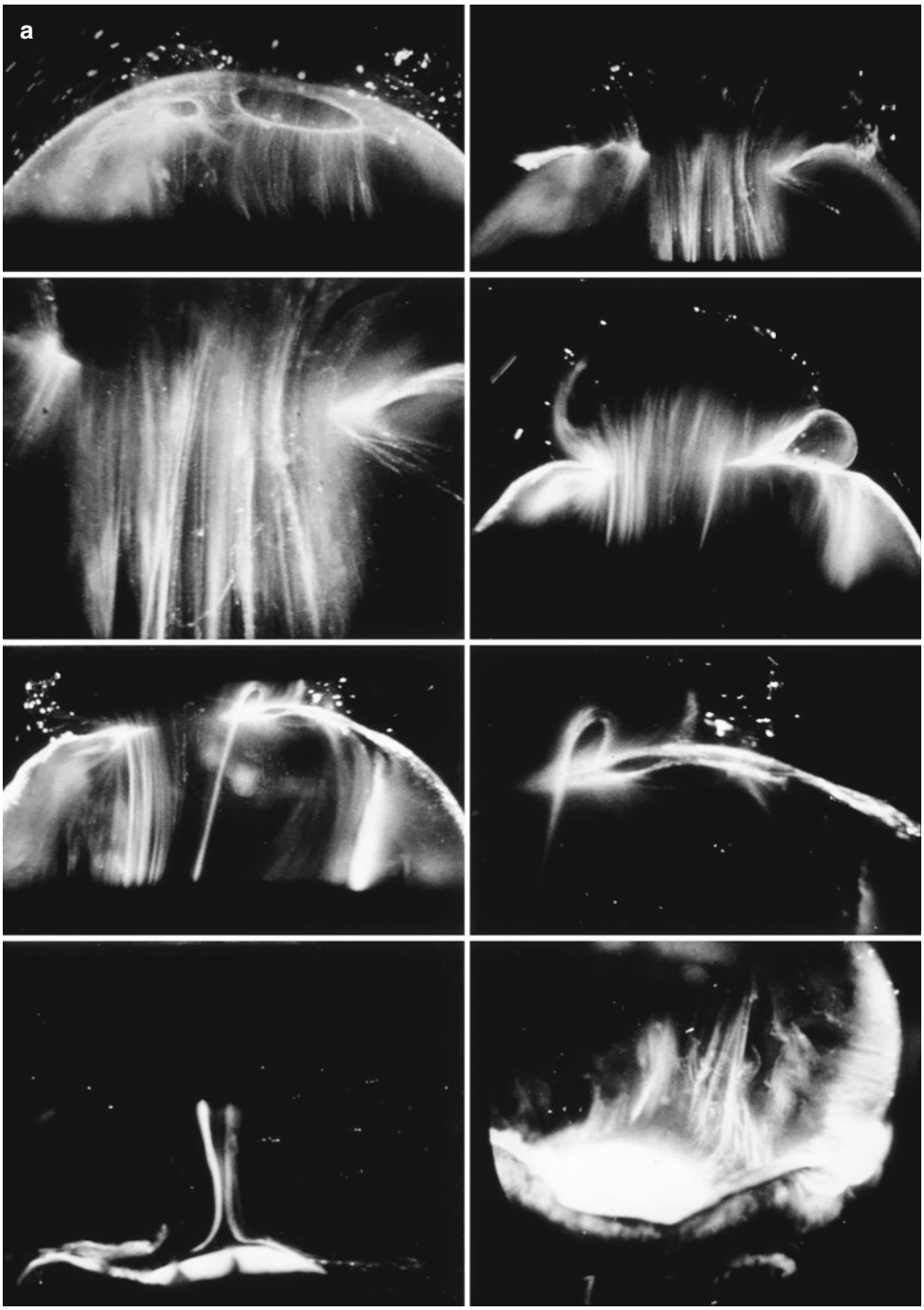

Figure II.C-6 (**a**) Dark-field slit microscopy of human vitreous structure. The sclera, choroid, and retina were dissected off the vitreous body which is left attached to the anterior segment. Illumination is provided by a slit-lamp beam shining in from the side, creating a horizontal optical section through the eye. All photographs are oriented with the anterior segment below and the posterior pole above. *Top left*: Posterior vitreous in the left eye of a 52-year-old man. The vitreous body is enclosed by the vitreous cortex. There is a hole in the prepapillary (small, to the *left*) vitreous cortex. Vitreous fibers are oriented toward the premacular region. *Top right*: Posterior vitreous in a 57-year-old man. A large bundle of prominent fibers is seen coursing anteroposteriorly and entering the retrocortical space by way of the premacular vitreous cortex. *Row 2 left*: Same photograph as top right, at higher magnification. *Row 2 right*: Posterior vitreous in the right eye of a 53-year-old woman. There is posterior extrusion of vitreous out the prepapillary hole (to the *right*) and premacular (large extrusion to the *left*) vitreous cortex. Fibers course anteroposteriorly out into the retrocortical space. *Row 3 left*: Horizontal optical section of the same specimen as row 2 right at a different level. A large fiber courses posteriorly from the central vitreous and inserts into the premacular vitreous cortex. *Row 3 right*: Same view as row 3 left at higher magnification. The large fiber has a curvilinear appearance because of traction by the vitreous extruding into the retrocortical space. However, because of its attachment to the posterior vitreous cortex, the fiber arcs back to its point of insertion. *Bottom left*: Anterior and central vitreous in a 33-year-old woman. The canal of Cloquet is seen forming the retrolental space of Berger. *Bottom right*: Anterior and peripheral vitreous in a 57-year-old man. The specimen is tilted forward to enable visualization of the posterior aspect of the lens and the peripheral anterior vitreous. To the right of the lens, there are fibers coursing anteroposteriorly that insert into the vitreous base. These fibers splay out to insert anterior and posterior to the ora serrata (From Sebag [24])

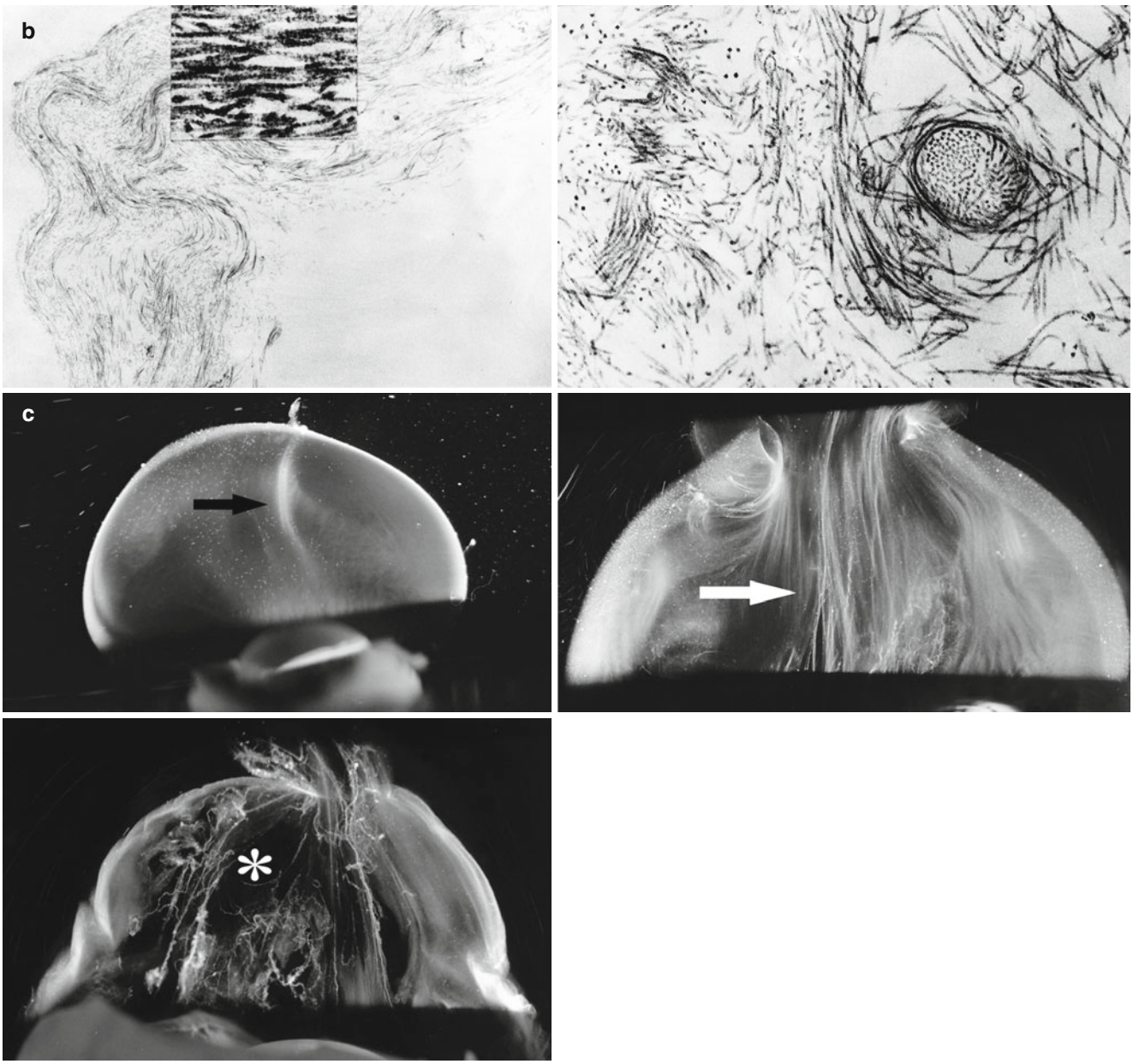

Figure II.C-6 (continued) (**b**) Transmission electron microscopy of human vitreous detected bundles of collagen fibrils shown longitudinally to the left and in cross section to the right. The inset in the left image is a high magnification of the bundle of fibrils demonstarting their collagenous nature [46]. (**c**) Left image (*middle*) shows the homogenous gel vitreous of a 33-week gestational age human. The only light-scattering structure is the remnant of the hyaloid artery (*black arrow*). *Right image* demonstrates the formation of central vitreous fibers (*white arrow*) in a 59-year-old subject. *Bottom left image* shows the extensive degeneration of the gel structure in an 88-year-old human with dense fibrous aggregation and adjacent gel liquefaction, sometimes forming lacunae (*asterisk*)

damage has been shown to change the average molecular weight of HA [49]. Additionally, the chromatographic elution profile and optical properties of HA have been shown to be different in gel versus liquefied vitreous [50], suggesting that changes in structural properties play an important role in vitreous liquefaction. Additionally, it provides a plausible explanation for the development of more extensive vitreous liquefaction earlier in life in diabetic patients compared to nondiabetics. Since diabetes increases glucose concentration in the vitreous [51], collagen is more likely to develop nonenzymatic glycation [8, 52] and with free-radical damage to HA [49] lead to earlier vitreous liquefaction [see chapter I.E. Diabetic vitreopathy].

One problem with the HA theory, however, is that experimental studies showed that even with almost complete removal of HA, vitreous did not liquefy. Although the volume of the gel did decrease, there was not extensive gel liquefaction even after over 90 % of the HA had been

depolymerized using *Streptomyces* HA lyse [6]. Thus, another mechanism that has been proposed for the liquefaction of vitreous over time is the loss of type IX collagen from the surface of the heterotypic collage fibrils [5, 53]. As described above, type IX collagen binds to the type II collagen in the heterotypic collagen fibrils. This is important in maintaining spacing between collagen fibrils because unbound type II collagen has a natural propensity to aggregate with other type II collagen molecules. Studies [53] have shown that type IX collagen has shorter half-life (approximately 11 years), as compared to other forms of collagen. Additionally, loss of type IX collagen has been shown to cause type II collagen aggregation. This has been proven by enzymatically cleaving the CS chains of type IX collagen using ABC lyase and observing subsequent type collagen bundling [53].

While most of the prevailing theories on vitreous liquefaction involve collagen aggregation, a third theory actually proposes that collagen breakdown is the primary cause. Los and colleagues [54] demonstrated an increase in collagen fragments associated with aging. Further studies on the topic suggested that enzymatic breakdown, possibly from matrix metalloproteinases or other enzymes, is responsible specifically for collagen type II destruction over time.

B. Structural Changes

1. Fibrous Aggregation

As vitreous liquefies, collagen aggregates into bundles (Figure II.C-6b) that become visible with biomicroscopy [32, 46] (Figure II.C-6a, c). Liquefaction and concomitant dehiscence at the vitreoretinal interface results in entry of liquid vitreous between the inner limiting membrane of the retina and posterior vitreous cortex. This volume displacement from within the vitreous body to the space forming between vitreous and retina results in collapse ("syneresis") of the vitreous body, an important event in vitreous aging. Aside from being a crucial step in the process of posterior vitreous detachment, to be discussed below, the rheological changes caused by liquefaction play an important role in ocular physiology [see chapter IV.A. Vitreous physiology] and many disease entities, ranging from nuclear sclerotic cataract formation to primary open-angle glaucoma and proliferative diabetic retinopathy. The critical pathway by which liquefied vitreous affects these disease states is oxygen diffusion [see chapter IV.B. Oxygen in vitreoretinal physiology and pathology]. Oxygen is known to move from retinal arterioles into [55] the vitreous via diffusion. However, oxygen in gel vitreous can only reach other parts of the vitreous via further diffusion, a relatively slow process. Once the vitreous has liquefied, however, fluid currents generated by eye movements quickly disperse the oxygen throughout the entire vitreous, greatly altering the geographical oxygen concentration gradients in the vitreous [56]. Additionally, as vitreous liquefies it consumes less oxygen than it does in its gel state [57]. This results in a higher oxygen concentration in the vitreous cavity. It is this alteration in oxygen distribution and consumption that has been proposed as the cause of pathological changes in the eye associated with vitreous liquefaction [55, 57].

2. Vitreous Base Migration

Like the vitreous body and vitreoretinal interface, the vitreous base undergoes changes over time. The most significant change is that the posterior border of the vitreous base migrates posteriorly. At birth the posterior border of the vitreous base is usually at or minimally past the posterior edge of the ora serrata. As the vitreous ages, however, this border migrates farther posteriorly into the peripheral retina itself [21]. This process is possibly due to synthesis of new collagen in the anterior retina that migrates through the ILM and intertwines with existing vitreous collagen [22]. Interestingly, this process appears to happen to a greater extent on the temporal side as compared to the nasal side. This fact may explain the phenomenon that retinal tears occur with greater frequency temporally rather than nasally.

3. Vitreoretinal Interface Weakening

Gel liquefaction with vitreous body collapse can only result in an innocuous posterior vitreous detachment (PVD) if there is concurrent weakening of the vitreoretinal interface. Foos demonstrated that despite a substantial part of the vitreous being liquefied earlier, posterior vitreous detachment rarely occurred before the age of 60, a fact that has been attributed to persistent vitreoretinal adhesion [45]. While the vitreoretinal interface does weaken, and often dehisce, one area that does not separate is the vitreous base, where strong mechanical adhesions prevent vitreoretinal separation, even in the setting of complete PVD. Other sites of firm adhesion are at the optic disk, macula, and along retinal blood vessels but is important to appreciate that rather than just focal adherence at these locations, vitreous adheres to the entire posterior pole in a fascial manner (Figure II.C-7a). At times, the circular edge of the central zone of the premacular vitreous cortex is the site of membrane formation in proliferative diabetic retinopathy or the site of vitreo-macular traction (larger circle to the right in Figure II.C-7b and Video II.C-1).

There are many theories about the mechanisms underlying vitreoretinal interface weakening. One theory states that Müller cells play an important role. Müller cells are known

to synthesize some of the extracellular matrix components of the vitreoretinal interface. Kloti and colleagues demonstrated that Müller cell infarction led to dissolution of the attachment between the ILM and the PVC and hypothesized that this was underlying mechanism behind age-related vitreoretinal interface changes [59]. Along a similar line of reasoning, other studies have hypothesized that it is thickening of the ILM over time [60] that mechanically prevents Müller cells from getting ECM proteins into the vitreoretinal interface [58]. Progressive ILM thickening over time is a well-documented phenomenon and thus provides at least a temporal association with vitreoretinal interface weakening [see chapter II.E. Vitreoretinal interface and inner limiting membrane].

Another popular theory centers on the collagen content, specifically type XVIII, in the ECM [61, 62]. As mentioned above, vitreoretinal adhesion involves the interaction of GAGs, collagen, and opticin. Type XVIII collagen has been proposed as one of the crucial collagens in that chain of interactions because it forms a heparin sulfate proteoglycan which binds to opticin [2, 13]. In fact, knock-out mice deficient in type XVIII collage have increased vitreoretinal disinsertion. Opticin knock-out mice, however, do not appear to have increased rate of dehiscence [62].

V. Posterior Vitreous Detachment

Posterior vitreous detachment (PVD) is the final step in the long process of vitreous aging. It is defined as a complete separation of the vitreous from the retina in all areas posterior to the vitreous base (Figure II.C-8). It occurs without untoward sequelae if both liquefaction and vitreoretinal dehiscence have occurred in a sufficient amount and is instigated by static and dynamic forces associated with eye movement. Although PVD is a natural part of aging and usually does not result in any problems, PVD can be the inciting event for numerous vitreoretinal pathologies. Studies suggest up to 24 % of symptomatic PVDs result in retinal complications [34, 63, 64] [see chapter III.B. Anomalous posterior vitreous detachment and vitreoschisis]. Thus, understanding the process of PVD is helpful in defining the pathophysiology behind many important clinical conditions.

A. Epidemiology

PVD is one of the most common events that occur in vitreous. Autopsy studies [45] show that by the seventh decade of life, PVD is present in 51 % of all eyes and by the eighth decade the prevalence increases to 63 %. Similarly, clinical studies have shown a prevalence of 65 % after the age of 65 [65]. Overall, the average age of onset is approximately 61 years [34]. Comparing prevalence to degree of liquefaction shows a significant increase in PVD when over 60 % of the vitreous has liquefied as compared to only 50 % liquefaction [45]. Several other factors can influence the onset of PVD. One interesting factor is female gender. The average age of onset for females has been shown to be statistically significantly earlier than males [34, 45, 66]. The mechanism for the age disparity has been attributed to postmenopausal loss of estrogen [63]. The decrease in estrogen may cause a decrease in hyaluronan synthesis leading to increased liquefaction as described above [11, 45]. This theory is supported by animal evidence showing a decrease in hyaluronan with decreased exposure to sex hormones [67]. Another proposed pathway is that the antioxidant and insulin-dependent glucose regulation roles of estrogen are affected by menopause. Van Deemter et al. showed that females accumulate advanced glycation end products (AGEs) at a faster rate than men, particularly after menopause [7].

Another risk factor for earlier PVD is myopia [63]. Yonemoto et al. [34] found that 0.91 years could be subtracted from the average age of PVD (61 years) for each diopter of myopic refractive error. That study included eyes that had undergone either complete posterior vitreous detachment or partial PVD with residual retinal adhesions. The pathway through which myopia affects PVD is likely related to a decrease in hyaluronan concentration [35]. Others have suggested that in myopic eyes there may actually be an increase in synthesis of liquid vitreous more so than an increase in liquefaction of existing gel vitreous [36, 37].

Additionally, many disorders of collagen metabolism affect PVD incidence. As mentioned above, increased vitreous liquefaction is seen in Marfan, Stickler, Ehlers-Danlos, and other collagen disorders [see chapter I.C. Hereditary vitreoretinopathies]. An important distinction for this group of disorders is that the liquefaction occurs at a rate far out of proportion to vitreoretinal dehiscence. Due to that fact, patients with these collagen disorders often have persistent vitreoretinal adhesion even after near complete vitreous liquefaction and thus may not undergo an innocuous PVD. Other factors that have been shown to increase vitreous liquefaction and PVD are trauma, aphakia, inflammation, retinal vascular diseases, and vitreous hemorrhage [68].

B. Pathophysiology

The most important processes in the pathophysiology of PVD are gel liquefaction and vitreoretinal dehiscence. While

these are necessary, they may not be sufficient since there are other events that contribute to complete PVD. One important event is that liquid vitreous must enter the retrocortical/preretinal space, essentially the vitreoretinal border region of Heegaard [23]. The path through which the gel obtains access to this area is unclear. One widely accepted route is through the prepapillary hole in the posterior vitreous cortex. The presence of this hole is documented on numerous histologic studies and provides a logical explanation for liquid vitreous entry into the retrocortical/preretinal space [24, 45, 69]. However, as pointed out by Johnson [29], vitreopapillary adhesion is usually the last to release during PVD. Thus, another possible route is through the premacular vitreous cortex. While a "hole" can sometimes be seen in the premacular vitreous cortex after vitreo-macular separation (Figure II.C-7b), it was long ago pointed out by Sebag and recently confirmed by OCT imaging [29, 70, 71] that such a hole usually does not exist *in vivo*. In some cases of PVD, there can be a prolapse of vitreous through this region, as first proposed by Jaffe in 1968 [72] and as identified by Kishi who found an oval-shaped defect in the premacular cortex through which vitreous herniated in 10/36 cases at autopsy [33]. Indeed, Gärtner likened this to herniation of the intervertebral disk and questioned whether the two events were

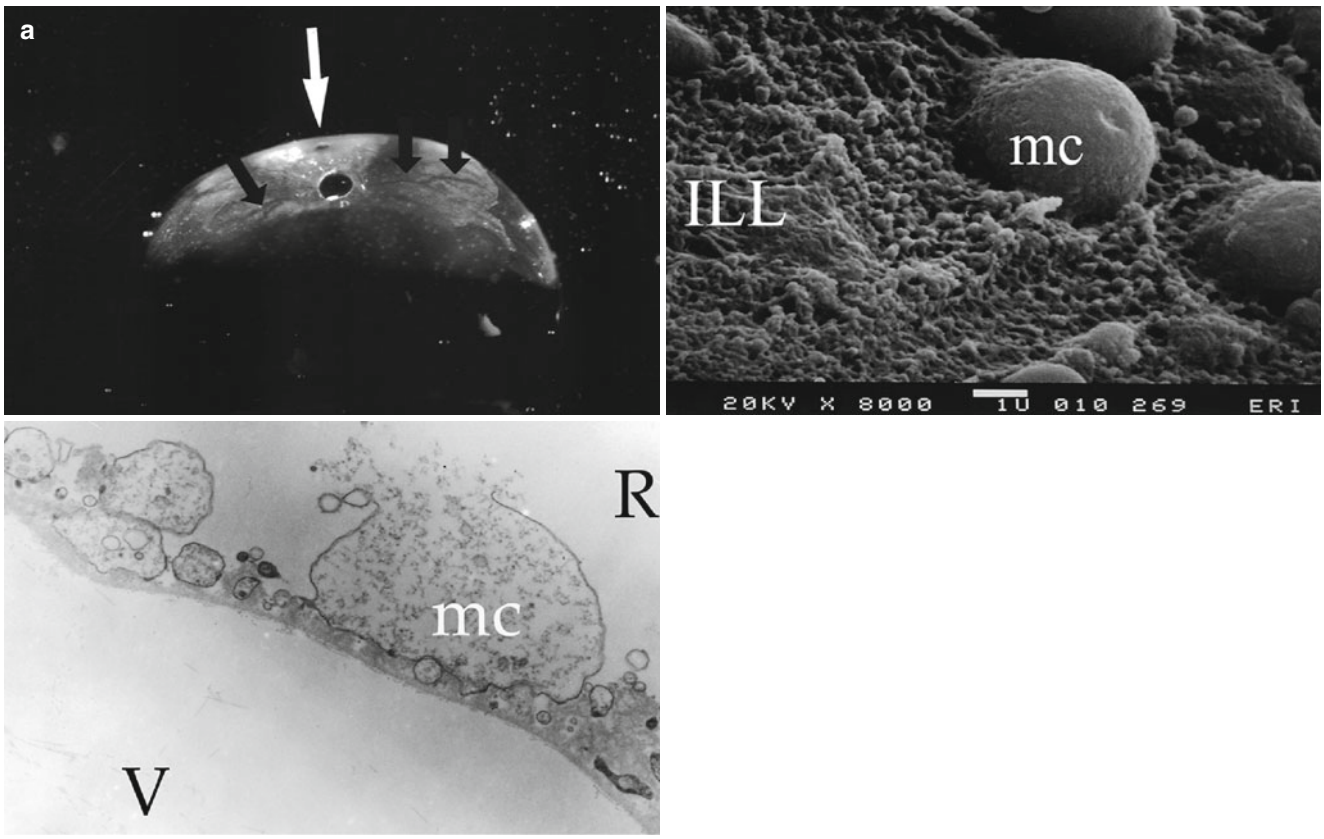

Figure II.C-7 Age-related differences at the vitreoretinal interface. There is firm adhesion of vitreous to the vitreous base, optic disc, macula, and along retinal blood vessels. In addition, there is strong adhesion throughout the posterior pole in a fascial (rather than focal) distribution. This is demonstrated by the different appearance of the posterior pole following peeling of the retina off the posterior vitreous in young subjects (**a**) as compared to middle-aged subjects (**b**). (**a**) Imaging of the posterior vitreous cortex in youth. After peeling the retina off the posterior vitreous, there is a different appearance from that obtained in all middle-aged subjects (see Figure II.C-7b). By dark-field slit microscopy, there appears to be an additional layer of tissue adherent to the posterior vitreous (*top left image*, this page). Within this tissue is a hole corresponding to the prepapillary posterior vitreous with linear branching structures that have a pattern identical to retinal blood vessels (*black arrows*). The *white arrow* indicates the site corresponding to the fovea. This tissue was processed for scanning electron microscopy (*upper right image*) which revealed the presence of mound-like structures (*mc*) adherent to the inner limiting membrane (ILL). Transmission electron microscopy (lower left *image*) identified these mounds as the inner segment footplates of Müller cells (*mc*) adherent to the ILM [*R* retina, *V* vitreous]. Thus, in youth the adhesion of vitreous to retina was stronger than the Müller cells themselves. This occurred only in subjects younger than 20 years of age and only in the posterior pole (From Sebag [58]). (**b**, see next page) Dark-field slit microscopy imaging of the posterior vitreous cortex in middle age. Demonstrated are the peripapillary hole (smaller "hole" to the left; *black arrows*) with extruding vitreous (*white arrows*) and the premacular hole (larger "hole" to the right) with extruding vitreous fibers. Hyalocytes appear as bright punctate structures embedded within the peripheral and posterior vitreous cortex

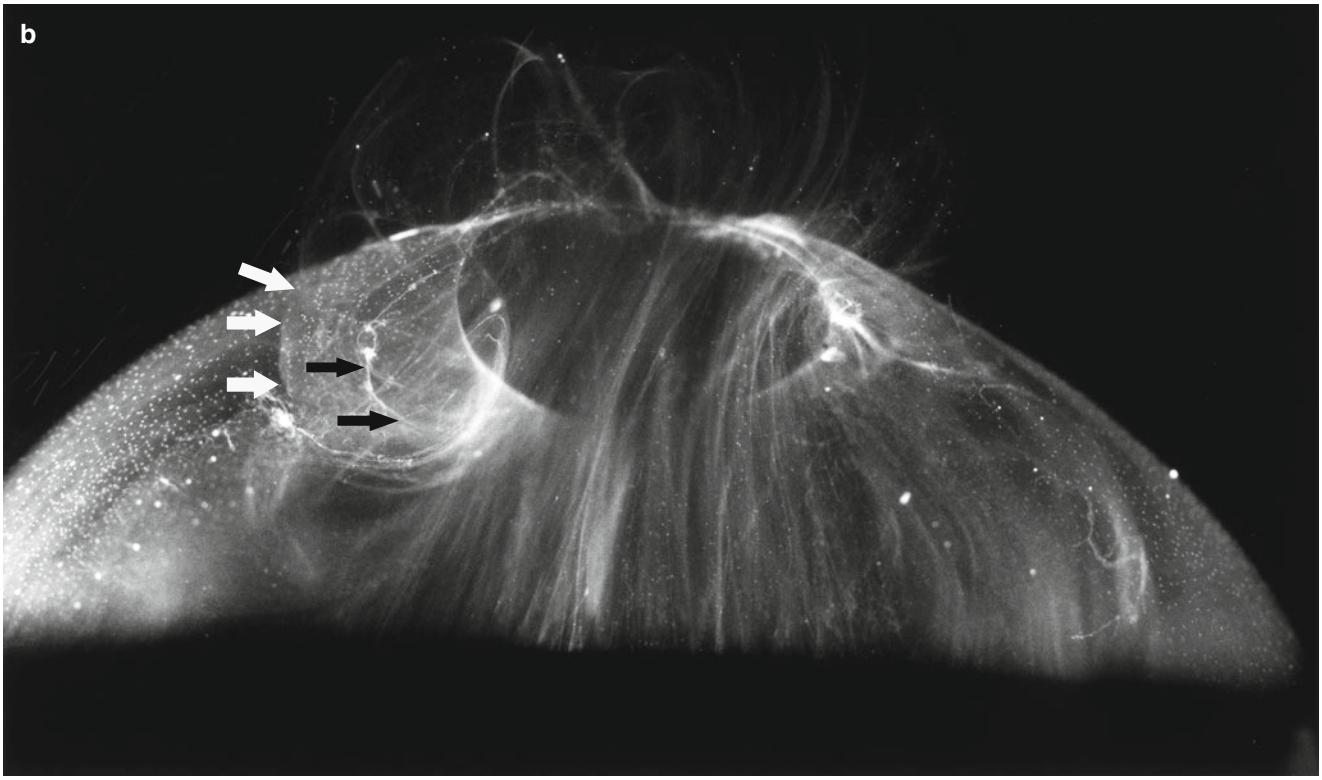

Figure II.C-7 (continued)

not somehow related [73]. Given the biochemical similarities between vitreous and joints [see chapter I.F. Vitreous biochemistry and artificial vitreous], this is plausible. Even if a true hole is not present, the premacular vitreous cortex likely does play a role in liquid vitreous dissection of a plane between the posterior vitreous cortex and the ILM since as the vitreous liquefies this region of the cortex becomes thin and thus more prone to microscopic defects [68, 74].

Once liquid vitreous enters the retrocortical/preretinal space, it begins to hydrodissect a plane separating vitreous from retina. Extensive mathematical modeling has been done to explore the role of saccadic eye movements on vitreous movement. Most early models failed to account for the unique geometry of the eye. For instance, early work by Lindner [75] and later Rosengren [76] utilized a cylindrical chamber to model the complex fluid dynamics of the eye. A more recent model presented by David et al. [77] assumed a spherical shape for the vitreous body. That model, while more accurate, failed to account for lens-induced flattening of the anterior vitreous. Even so, it presented an interesting representation and directly related shear stress on the retina induced by vitreous movement to axial length of the eye. Finally, the most recent model, as described by Abouali, accounted for lens geometry while also comparing the effect of changing viscosity in the aging vitreous. This model suggested that as vitreous liquefies the intensity of secondary flow increases by as much as 500 % as compared to a complete gel state. This suggests that the movement of vitreous, particularly near its boundaries, increases dramatically as the vitreous liquefies [78]. Other work that used a similar anatomically correct model for the eye showed that this effect is not so much influenced by the amplitude of saccadic eye movements as it is frequency of movement [79]. This suggests that is the frequent smaller movements that play the largest role in moving the liquefied vitreous.

The process of hydrodissection often follows a well-defined sequence that is influenced by previously described areas of increased vitreoretinal adhesion. This sequence has been described by Johnson [68, 80] as a 5-stage process (Stages 0–4; Figure II.C-9). Stage 0 is complete attachment throughout the fundus. Stage 1 involves detachment of the perifoveal posterior vitreous cortex, probably because this is the area where the liquefied gel first gains access to the retrocortical/preretinal space. Although there is perifoveal vitreous detachment, there is persistent vitreo-foveal adhesion at this early stage. As described above, studies have documented a 500-μm diameter area of strong vitreoretinal

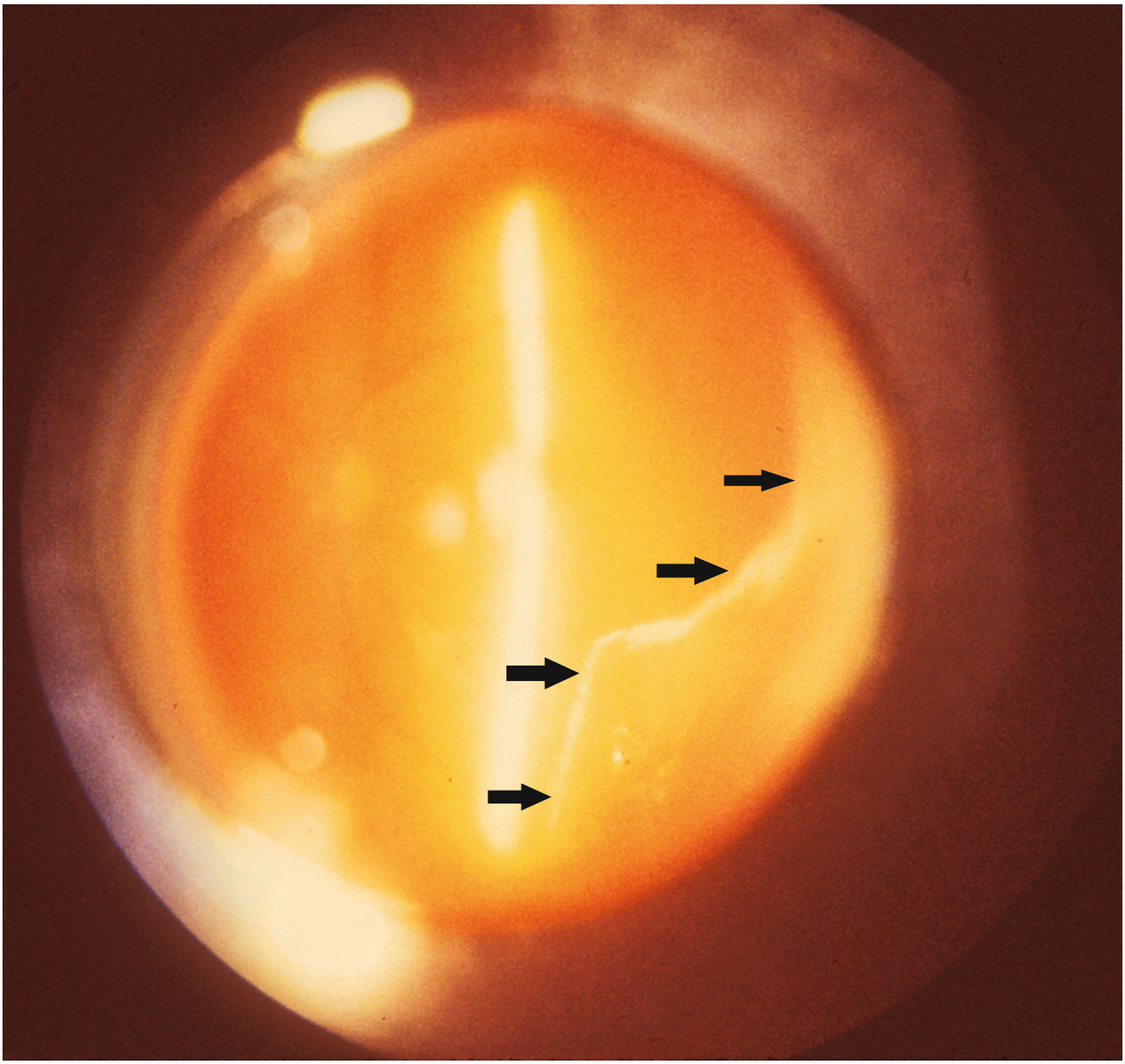

Figure II.C-8 Preset lens biomicroscopy of posterior vitreous detachment *in vivo*. The posterior vitreous cortex (*black arrows*) is detached away from the disc (to the left), macula, and retinal vessels (seen emanating from the optic disk). Commonly seen on clinical ultrasonography, the typical sigmoid configuration of the detached posterior vitreous is due to the effects of gravity upon the superior vitreous which descends inferiorly after detaching from the retina (Courtesy of Clement Trempe, MD)

adhesion in the foveola [25]. This strongly adherent foveolar zone does not detach until stage 2, at which point there is complete macular separation. In stage 3, there is a near-total PVD involving the entire retina except for the vitreo-papillary zone. Apart from the vitreous base, the immediate peripapillary zone is the area of strongest vitreoretinal adhesion and thus is the last site of vitreoretinal separation in the posterior fundus. In stage 4, there is release of the vitreo-papillary adhesion and total PVD. It is this last stage that is most often the clinically recognized event [29, 68].

C. Clinical Presentation

When describing the clinical presentation of PVD, it is important to make a distinction about where in the process of

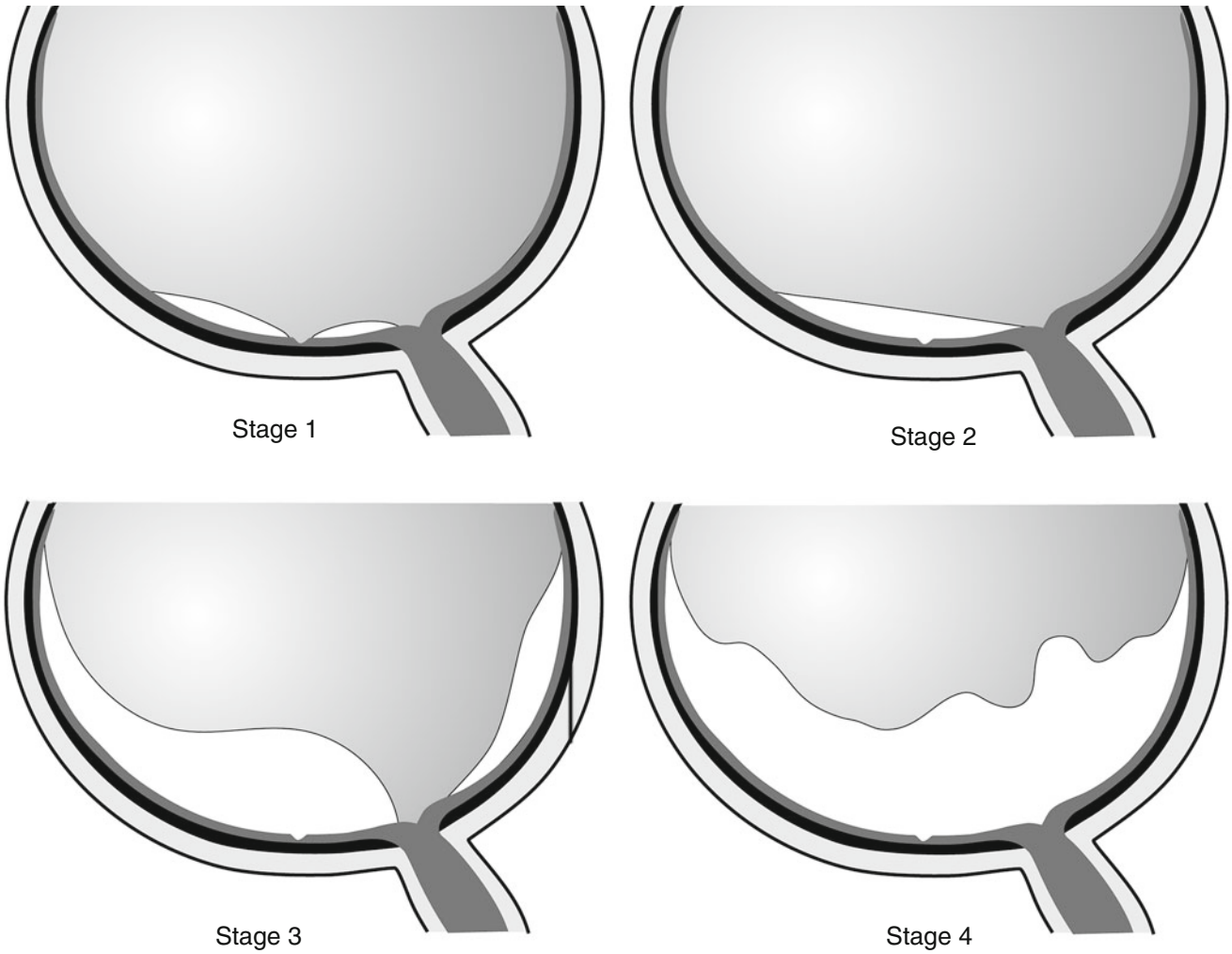

Figure II.C-9 Schematic representation of the last 4 stages (stage 0 not shown) of posterior vitreous detachment (d'après Johnson [68])

PVD symptoms occur. Barring a complication in an early stage (as described below), PVD is usually asymptomatic until the final stage of vitreo-papillary dehiscence. Even then, many PVDs occur with no symptoms at all. The symptoms described in this section are only those caused by a complete PVD and not those caused by all previous stages, which will be discussed later.

The most common symptom resulting from PVD is *floaters* [see chapter V.B.8. Vitreous floaters and vision: current concepts and management paradigms]. Floaters can result from shadows cast by Weiss ring, intravitreal blood, or condensed vitreous fibers. Their movement during saccadic eye movements is characterized by over-damping which creates a noticeable visual phenomenon in many patients. Recent studies suggest that these symptoms have a significantly negative impact on patients' quality of life [81, 82]. Since the floaters have a different acoustic reflectivity than normal gel vitreous, they can be visualized on B-scan ultrasound and are represented by increased speckling of the image. B-scan image speckle density has been shown to increase with age. Additionally, by quantifying the motion of the speckles on ultrasound, the movement and viscosity of the vitreous can be measured *in vivo* [83] [see chapter II.F. Imaging vitreous].

Another common clinical symptom in PVD is photopsia or Moore's light flashes. Symptomatic flashes occur in between 27 and 42 % of PVD cases [72]. These are thought to result from either traction [84] or impact [85] exerted by the vitreous onto the retina and may signify a higher risk of retinal tears [72]. It is especially useful to query patients whether photopsia can be triggered by head movement or ocular saccades. If this is the case and the photopsia are described as a c-shaped arc of light that flashes off to the side, then it is likely they are experiencing vitreous traction

upon the peripheral retina with an increased risk of retinal tears. Interestingly, mathematical models of vitreous motion have shown that eyes with longer axial length experience larger sheer forces exerted onto the retina by the movement of vitreous during saccadic eye movements. This is another possible explanation for the increased incidence of retinal tears and detachments in myopic individuals [77]. Similar traction upon retinal or optic disk blood vessels [72, 86] can induce hemorrhage, noted in 21 % of eyes with symptomatic PVD [66].

1. Time Course

PVD has long been perceived as a relatively acute process that occurs following a long process of gel liquefaction and weakening of the vitreoretinal adhesion. However, this is only true of the final stage of PVD, i.e., vitreo-papillary separation. With only perpendicular B-scan ultrasonography [70, 87], true high-resolution documentation of early PVD was difficult [88, 89]. With the advent of optical coherence tomography (OCT) (Figure II.C-10), however, early PVD can now be reliably identified [89]. Consequently, PVD is now perceived as a slow process occurring over the course of many years. In healthy, asymptomatic adults over the age 30, over 62 % of people have been found to have between a stage 1 and stage 3 PVD [90], suggesting a very high prevalence of early PVD. In eyes with various vitreoretinal pathologies the prevalence may be as high as 90 % [29]. Also, longitudinal studies have documented a very slow progression of PVD. Over the course of 30 months, 10 % of eyes with stage 1 or 2 PVD progressed to complete PVD [29]. Even progression from stage 1 to stage 2 PVD occurred in only 29 % of patients observed over 24 months [91]. While the process maybe slow, it is largely bilateral and occurs at approximately the same rate in each eye. After development of acute PVD in one eye, PVD will occur in 47 % of fellow eyes within 18 months and 90 % of fellow eyes within 36 months [92].

D. Anomalous PVD

Although early PVD often goes undetected, the clinical implications of these early stages have recently been defined. Several authors have described events that may occur prior to a complete PVD that can result in substantial vitreoretinal pathology. One such description by Sebag [10, 93] utilizes the concept of "anomalous PVD" (APVD) [see chapter III.B. Anomalous posterior vitreous detachment and vitreoschisis]. Sebag's APVD theory states that pathology arises from a disconnection between liquefaction and gel dehiscence. This can be the result of any number of underlying conditions, such as inborn errors of type II collagen metabolism, myopia, or diabetes, or may occur in the absence of underlying systemic conditions. Therefore, in this model, the term "anomalous" does not necessarily imply the presence of an underlying condition affecting vitreous liquefaction, such as Marfan or high myopia, but simply means that a disconnection between liquefaction and interface dehiscence exists. Within the APVD theory framework, the exact pathological manifestation of APVD is determined by a few factors. First, the location of persistent gel adhesion is important. For example, persistent adhesion at the macula results in vitreo-macular traction syndrome, while persistent adhesion at the disk or over blood vessels may cause vitreo-papillary traction or retinal hemorrhage, respectively. The second important consideration is the structural integrity of the vitreous cortex. Known to have lamellar structure, the posterior vitreous cortex can split (*vitreoschisis*) during early PVD resulting in the more posterior layers remaining adherent to the retinal surface [see chapter III.B. Anomalous posterior vitreous detachment and vitreoschisis].

Johnson [29, 68, 80] has further advanced our understanding of early PVD by grouping the manifestations of early PVD according to the anatomical site of persistent adhesion. Utilizing the 500- and 1,500-μm regions of increased vitreo-macular adhesion described by Kishi [25], Johnson gathered seemingly disparate conditions into two categories based on the size of the adhesion. With smaller adhesion sizes (500 μm or less), the tractional force is very localized, resulting in high stress over a small area of the central macula. This may cause full-thickness macular hole, pseudo-operculum, lamellar macular hole, or vitreo-foveolar traction syndrome. Macular microhole and most cases of foveal red spot syndrome are likely due to the smallest zones of adhesion (50–150 μm), which result in even higher force per unit area traction stress. Conversely, larger adhesion zones (typically 1,500 μm or greater) disperse the traction force over a larger area. This lower traction stress is unlikely to result in macular hole states but can cause vitreo-macular traction syndrome or traction diabetic macular edema and can exacerbate myopic traction maculopathy [94] and possibly neovascular age-related macular degeneration [95]. Premacular membranes, which most likely develop from vitreoschitic remnants on the retinal surface, can begin to form as soon as there are areas of vitreoretinal separation and may therefore be seen in eyes with or without residual vitreo-macular adhesions [68]. Johnson's model also discusses the nature of the traction forces being applied to the persistent vitreoretinal adhesion. He describes both static and dynamic forces as being important contributors. Static traction results from the inherent trampoline-like elasticity of the detaching posterior vitreous cortex and possibly from gravitational forces acting on the partially separated vitreous body. Dynamic traction forces are generated by

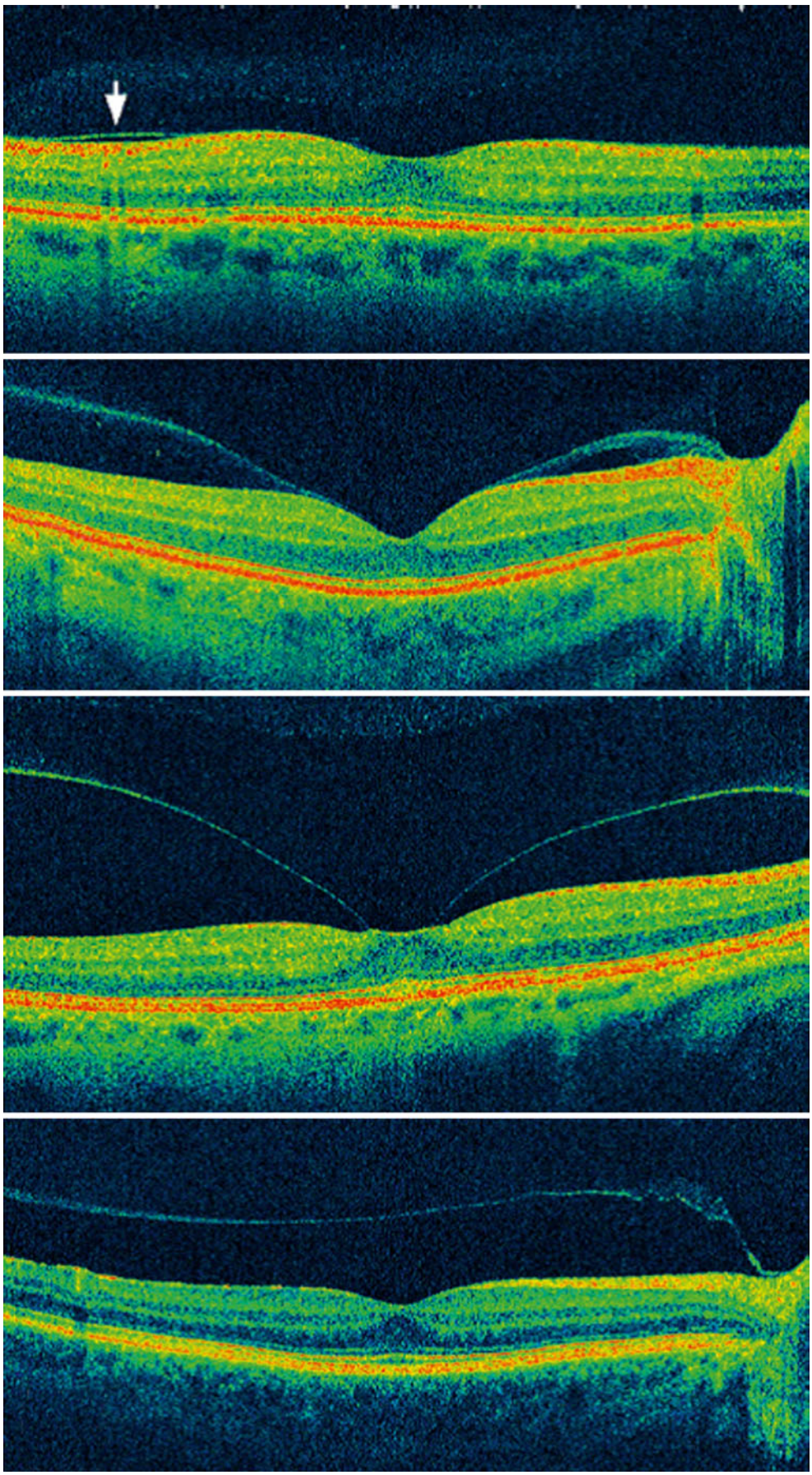

Figure II.C-10 Optical coherence tomography (OCT) images of the early stages of posterior vitreous detachment. Many of the early stages were undetectable prior to the advent of OCT imaging [see chapter II.F. To see the invisible - the quest of imaging vitreous]. The top panel demonstrates the appearance of the posterior vitreous cortex (*arrow*) slightly elevated off the inner limiting membrane (*ILM*) of the retina. The third panel down demonstrates anomalous PVD with vitreo-macular traction, defined by the 2013 IVTS classification system as persistent vitreo-macular adhesion with structural alteration of the retina, in this case slight elevation of the fovea. The bottom panel demonstrates PVD with persistent attachment to the optic disc [68]

ocular saccades. It is likely the dynamic forces that are responsible for the greater part of the tractional stress placed on the retina [29, 68, 80].

The two models share many similarities. Both models contrast physiologic, uncomplicated PVDs with PVDs that are complicated by vitreoretinal pathology. Both Sebag and Johnson ascribe vitreoretinal pathology to age-related vitreous degeneration and detachment in the presence of persistent focal vitreoretinal adhesions. Both recognize that the macular and peripapillary areas are the most common sites of adhesion and that slight variations in the size and strength of the adhesion can determine the resulting retinal pathology. Johnson's model emphasizes the evolution and complications of the early stages of PVD, and Sebag emphasizes the role of vitreoschisis, particularly with respect to the pathogenesis of macular pucker [see chapter III.F. Vitreous in the pathobiology of macular pucker] and macular hole [see chapter III.B. Anomalous posterior vitreous detachment and vitreoschisis]. Both models suggest that most late complications of PVD (e.g., retinal tear, retinal detachment, vitreous hemorrhage) occur only after vitreo-papillary separation, which allows for large saccadic movements of the vitreous body and increased dynamic traction forces [68]. Other late complications of PVD, like cataract formation, are likely due to changes in oxygen tension in the vitreous cavity [57]. In summary, both descriptions serve to underscore the pathogenic role of early PVD stages in the development of many serious vitreoretinal pathologies.

Abbreviations

AGEs	Advanced glycation end products
APVD	Anomalous posterior vitreous detachment
CS	Chondroitin sulfate
ECM	Extracellular matrix
GAG	Glycosaminoglycans
HA	Hyaluronan
HS	Heparan sulfate
ILM	Inner limiting membrane
PVC	Posterior vitreous cortex
PVD	Posterior vitreous detachment

References

1. Bishop P, Crossman M, McLeod D, Ayad S. Extraction and characterization of the tissue forms of collagen types II and IX from bovine vitreous. Biochem J. 1994;299(Pt 2):497.
2. Le Goff M, Bishop P. Adult vitreous structure and postnatal changes. Eye. 2008;22(10):1214–22.
3. Richards AJ, Martin S, Yates JRW, Scott JD, Baguley DM, Pope FM, et al. COL2A1 exon 2 mutations: relevance to the Stickler and Wagner syndromes. Br J Ophthalmol. 2000;84(4):364–71.
4. Bishop P, McLeod D, Ayad S. Extraction and characterisation of the intact form of bovine vitreous type IX collagen. Biochem Biophys Res Commun. 1992;185(1):392–7.
5. Bos K, Holmes D, Meadows R, Kadler K, McLeod D, Bishop P. Collagen fibril organisation in mammalian vitreous by freeze etch/rotary shadowing electron microscopy. Micron. 2001;32(3):301–6.
6. Bishop PN, McLeod D, Reardon A. Effects of hyaluronan lyase, hyaluronidase, and chondroitin ABC lyase on mammalian vitreous gel. Invest Ophthalmol Vis Sci. 1999;40(10):2173–8.
7. Van Deemter M, Ponsioen T, Bank R, Snabel J, Van der Worp R, Hooymans J, et al. Pentosidine accumulates in the aging vitreous body: a gender effect. Exp Eye Res. 2009;88(6):1043–50.
8. Sebag J, Buckingham B, Charles MA, Reiser K. Biochemical abnormalities in vitreous of humans with proliferative diabetic retinopathy. Arch Ophthalmol. 1992;110(10):1472.
9. Sebag J, Nie S, Reiser K, Charles MA, Yu NT. Raman spectroscopy of human vitreous in proliferative diabetic retinopathy. Invest Ophthalmol Vis Sci. 1994;35(7):2976–80.
10. Sebag J. Vitreous – from biochemistry to clinical relevance. In: Tasman W, Jaeger E, editors. Duane's foundations of clinical ophthalmology. Philadelphia: Lippincott Williams & Wilkins; 1998. p. 1–34.
11. Larsson L, Österlin S. Posterior vitreous detachment. Graefes Arch Clin Exp Ophthalmol. 1985;223(2):92–5.
12. Russell SR. What we know (and do not know) about vitreoretinal adhesion. Retina. 2012;32:S181–6.
13. Hindson VJ, Gallagher JT, Halfter W, Bishop PN. Opticin binds to heparan and chondroitin sulfate proteoglycans. Invest Ophthalmol Vis Sci. 2005;46(12):4417–23.
14. Bishop PN. Structural macromolecules and supramolecular organisation of the vitreous gel. Prog Retin Eye Res. 2000;19(3):323–44.
15. Foos RY. Vitreoretinal juncture; topographical variations. Invest Ophthalmol Vis Sci. 1972;11(10):801–8.
16. Balazs E. Molecular morphology of the vitreous body. The structure of the eye. New York: Academic Press; 1961. p. 295.
17. Theopold H, Faulborn J. Scanning electron microscopy of the vitreous body. Graefes Arch Clin Exp Ophthalmol. 1979;211(3):259–64.
18. Sebag J. Anatomy and pathology of the vitreo-retinal interface. Eye. 1992;6(6):541–52.
19. Balazs EA. Fine structure of the developing vitreous. Int Ophthalmol Clin. 1975;15(1):53.
20. Gupta P, Yee KMP, Garcia P, Rosen RB, Parikh J, Hageman GS, et al. Vitreoschisis in macular diseases. Br J Ophthalmol. 2011;95(3):376–80.
21. Teng C, Chi H. Vitreous changes and the mechanism of retinal detachment. Am J Ophthalmol. 1957;44(3):335.
22. Wang J, McLeod D, Henson DB, Bishop PN. Age-dependent changes in the basal retinovitreous adhesion. Invest Ophthalmol Vis Sci. 2003;44(5):1793–800.
23. Heegaard S. Morphology of the vitreoretinal border region. Acta Ophthalmol Scand Suppl. 1997;222:1.
24. Sebag J. The vitreous: structure, function, and pathobiology. New York: Springer; 1989.
25. Kishi S, Demaria C, Shimizu K. Vitreous cortex remnants at the fovea after spontaneous vitreous detachment. Int Ophthalmol. 1986;9(4):253–60.
26. Hageman GS, Johnson LV. Biochemical characterization of the major peanut agglutinin binding glycoproteins in vertebrate retinae. J Comp Neurol. 1986;249(4):499–510.
27. Hageman G, Russell S. Chondroitinase-mediated disinsertion of the primate vitreous body. Invest Ophthalmol Vis Sci. 1994;35(4):1260.

28. Heegaard S, Jensen O, Prause J. Structure of the vitread face of the monkey optic disc (Macacca mulatta). Graefes Arch Clin Exp Ophthalmol. 1988;226(4):377–83.
29. Johnson MW. Perifoveal vitreous detachment and its macular complications. Trans Am Ophthalmol Soc. 2005;103:537.
30. Foos RY, Roth A. Surface structure of the optic nerve head. 2. Vitreopapillary attachments and posterior vitreous detachment. Am J Ophthalmol. 1973;76(5):662.
31. Kroll P, Wiegand W, Schmidt J. Vitreopapillary traction in proliferative diabetic vitreoretinopathy. Br J Ophthalmol. 1999;83(3): 261–4.
32. Balazs EA, Denlinger J. Aging changes in the vitreous. Aging and human visual function. New York: Alan R Liss; 1982. p. 45–7.
33. Kishi S, Shimizu K. Posterior precortical vitreous pocket. Arch Ophthalmol. 1990;108(7):979–82.
34. Yonemoto J, Ideta H, Sasaki K, Tanaka S, Hirose A, Oka C. The age of onset of posterior vitreous detachment. Graefes Arch Clin Exp Ophthalmol. 1994;232(2):67–70.
35. Berman E, Michaelson I. The chemical composition of the human vitreous body as related to age and myopia. Exp Eye Res. 1964;3(1): 9–15.
36. Balazs EA, Toth LZ, Jutheden GM, Collins B-A. Cytological and biochemical studies on the developing chicken vitreous. Exp Eye Res. 1965;4(3):237–IN26.
37. Pickett-Seltner R, Doughty M, Pasternak J, Sivak J. Proteins of the vitreous humor during experimentally induced myopia. Invest Ophthalmol Vis Sci. 1992;33(12):3424–9.
38. Maumenee IH. Vitreoretinal degeneration as a sign of generalized connective tissue diseases. Am J Ophthalmol. 1979;88(3 Pt 1):432.
39. Knobloch WH. Inherited hyaloideoretinopathy and skeletal dysplasia. Trans Am Ophthalmol Soc. 1975;73:417.
40. Worst J. Cisternal systems of the fully developed vitreous body in the young adult. Trans Ophthalmol Soc U K. 1977;97(4):550.
41. Ueno N, Sebag J, Hirokawa H, Chakrabarti B. Effects of visible-light irradiation on vitreous structure in the presence of a photosensitizer. Exp Eye Res. 1987;44(6):863–70.
42. Akiba J, Ueno N, Chakrabarti B. Mechanisms of photo-induced vitreous liquefaction. Curr Eye Res. 1994;13(7):505–12.
43. Kakehashi A, Ueno N, Chakrabarti B. Molecular mechanisms of photochemically induced posterior vitreous detachment. Ophthalmic Res. 1994;26(1):51–9.
44. Sebag J. Ageing of the vitreous. Eye. 1987;1(2):254–62.
45. Foos R, Wheeler N. Vitreoretinal juncture. Synchysis senilis and posterior vitreous detachment. Ophthalmology. 1982;89(12): 1502–12.
46. Sebag J, Balazs E. Morphology and ultrastructure of human vitreous fibers. Invest Ophthalmol Vis Sci. 1989;30(8):1867–71.
47. Comper W, Laurent TC. Physiological functions of connective tissue polysaccharides. Physiol Rev. 1978;58:255.
48. Scott JE. The chemical morphology of the vitreous. Eye. 1992; 6(6):553–5.
49. Deguine V, Menasche M, Ferrari P, Fraisse L, Pouliquen Y, Robert L. Free radical depolymerization of hyaluronan by Maillard reaction products: role in liquefaction of aging vitreous. Int J Biol Macromol. 1998;22(1):17–22.
50. Armand G, Chakrabarti B. Conformational differences between hyaluronates of gel and liquid human vitreous: fractionation and circular dichroism studies. Curr Eye Res. 1987;6(3):445–50.
51. Lundquist O, Österlin S. Glucose concentration in the vitreous of nondiabetic and diabetic human eyes. Graefes Arch Clin Exp Ophthalmol. 1994;232(2):71–4.
52. Stitt AW, Moore JE, Sharkey JA, Murphy G, Simpson D, Bucala R, et al. Advanced glycation end products in vitreous: structural and functional implications for diabetic vitreopathy. Invest Ophthalmol Vis Sci. 1998;39(13):2517–23.
53. Bishop PN, Holmes DF, Kadler KE, McLeod D, Bos KJ. Age-related changes on the surface of vitreous collagen fibrils. Invest Ophthalmol Vis Sci. 2004;45(4):1041–6.
54. Los LI, van der Worp RJ, van Luyn MJA, Hooymans JMM. Age-related liquefaction of the human vitreous body: LM and TEM evaluation of the role of proteoglycans and collagen. Invest Ophthalmol Vis Sci. 2003;44(7):2828–33.
55. Beebe DC, Holekamp NM, Siegfried C, Shui Y-B. Vitreoretinal influences on lens function and cataract. Philos Trans Roy Soc B: Biol Sci. 2011;366(1568):1293–300.
56. Stocchino A, Repetto R, Siggers JH. Mixing processes in the vitreous chamber induced by eye rotations. Phys Med Biol. 2010;55(2):453.
57. Holekamp NM. The vitreous gel: more than meets the eye. Am J Ophthalmol. 2010;149(1):32–6.e1.
58. Sebag J. Age-related differences in the human vitreoretinal interface. Arch Ophthalmol. 1991;109:966–71.
59. Klöti R. Experimental occlusion of retinal and ciliary vessels in owl monkeys: I. Technique and clinical observations of selective embolism of the central retinal artery system. Exp Eye Res. 1967;6(4): 393–IN28.
60. Kohno T, Sorgente N, Ishibashi T, Goodnight R, Ryan SJ. Immunofluorescent studies of fibronectin and laminin in the human eye. Invest Ophthalmol Vis Sci. 1987;28(3):506–14.
61. Ponsioen TL, Hooymans JMM, Los LI. Remodelling of the human vitreous and vitreoretinal interface – a dynamic process. Prog Retin Eye Res. 2010;29(6):580–95.
62. Fukai N, Eklund L, Marneros AG, Oh SP, Keene DR, Tamarkin L, et al. Lack of collagen XVIII/endostatin results in eye abnormalities. EMBO J. 2002;21(7):1535–44.
63. Chuo JY, Lee TY, Hollands H, Morris AH, Reyes RC, Rossiter JD, et al. Risk factors for posterior vitreous detachment: a case–control study. Am J Ophthalmol. 2006;142(6):931–7.e1.
64. Hikichi T, Trempe CL. Relationship between floaters, light flashes, or both, and complications of posterior vitreous detachment. Am J Ophthalmol. 1994;117(5):593.
65. Favre M, Goldmann H. Zur Genese der hinteren Glaskörperabhebung. Ophthalmologica. 1956;132(2):87–97.
66. Novak M, Welch R. Complications of acute symptomatic posterior vitreous detachment. Am J Ophthalmol. 1984;97(3):308–14.
67. Larsen G. The hyaluronic acid in the rabbit vitreous body: variations following hormonal treatment. Arch Ophthalmol. 1958; 60(5):815.
68. Johnson MW. Posterior vitreous detachment: evolution and complications of its early stages. Am J Ophthalmol. 2010;149(3): 371–82.
69. Sebag J. Age-related changes in human vitreous structure. Graefes Arch Clin Exp Ophthalmol. 1987;225(2):89–93.
70. Johnson MW, Van Newkirk MR, Meyer KA. Perifoveal vitreous detachment is the primary pathogenic event in idiopathic macular hole formation. Arch Ophthalmol. 2001;119(2):215.
71. Tanner V, Chauhan D, Jackson T, Williamson T. Optical coherence tomography of the vitreoretinal interface in macular hole formation. Br J Ophthalmol. 2001;85(9):1092–7.
72. Jaffe NS. Complications of acute posterior vitreous detachment. Arch Ophthalmol. 1968;79(5):568–71.
73. Gärtner J. Photoelastic and ultrasonic studies on the structure and senile changes of the intervertebral disc and of the vitreous body. Bibl Ophthalmol. 1969;79:136.
74. Kishi S, Hagimura N, Shimizu K. The role of the premacular liquefied pocket and premacular vitreous cortex in idiopathic macular hole development. Am J Ophthalmol. 1996;122(5):622–8.
75. Lindner K. Uber die Herstellung von Modellen zu Modellversuchen der Netzhautabhebung. Klin Monatsbl Augenheilkd. 1933;90: 289–300.

76. Rosengren B, Österlin S. Hydrodynamic events in the vitreous space accompanying eye movements. Ophthalmologica. 1976; 173(6):513–24.
77. David T, Smye S, Dabbs T, James T. A model for the fluid motion of vitreous humour of the human eye during saccadic movement. Phys Med Biol. 1998;43(6):1385.
78. Abouali O, Modareszadeh A, Ghaffariyeh A, Tu J. Numerical simulation of the fluid dynamics in vitreous cavity due to saccadic eye movement. Med Eng Phys. 2012;34(6):681–92.
79. Repetto R, Stocchino A, Cafferata C. Experimental investigation of vitreous humour motion within a human eye model. Phys Med Biol. 2005;50(19):4729.
80. Johnson MW. Posterior vitreous detachment: evolution and role in macular disease. Retina. 2012;32:S174–8.
81. Wagle AM, Lim W-Y, Yap T-P, Neelam K, Au Eong K-G. Utility values associated with vitreous floaters. Am J Ophthalmol. 2011; 152(1):60–5.e1.
82. Sebag J. Floaters and the quality of life. Am J Ophthalmol. 2011;152(1):3–4.e1.
83. Walton KA, Meyer CH, Harkrider CJ, Cox TA, Toth CA. Age-related changes in vitreous mobility as measured by video B scan ultrasound. Exp Eye Res. 2002;74(2):173–80.
84. Wise G. Relationship of idiopathic preretinal macular fibrosis to posterior vitreous detachment. Am J Ophthalmol. 1975;79(3):358–62.
85. Verhoeff F. Are Moore's lightning streaks of serious portent? Am J Ophthalmol. 1956;41(5):837.
86. Lindner B. Acute posterior vitreous detachment and its retinal complications. Acta Ophthalmol. 1966;87:1–108.
87. Van Newkirk M, Gass J, Callanan D, Byrne S, Hughes JR. Follow-up and ultrasonographic examination of patients with macular pseudooperculum. Am J Ophthalmol. 1994;117(1):13–8.
88. Sebag J. Imaging vitreous. Eye. 2002;16(4):429–39.
89. Mirza RG, Johnson MW, Jampol LM. Optical coherence tomography use in evaluation of the vitreoretinal interface: a review. Surv Ophthalmol. 2007;52(4):397–421.
90. Uchino E, Uemura A, Ohba N. Initial stages of posterior vitreous detachment in healthy eyes of older persons evaluated by optical coherence tomography. Arch Ophthalmol. 2001;119(10):1475.
91. Niwa H, Terasaki H, Ito Y, Miyake Y. Macular hole development in fellow eyes of patients with unilateral macular hole. Am J Ophthalmol. 2005;140(3):370–5.
92. Hikichi T. Time course of posterior vitreous detachment in the second eye. Curr Opin Ophthalmol. 2007;18(3):224–7.
93. Sebag J. Anomalous posterior vitreous detachment: a unifying concept in vitreo-retinal disease. Graefes Arch Clin Exp Ophthalmol. 2004;242(8):690–8.
94. VanderBeek BL, Johnson MW. The diversity of traction mechanisms in myopic traction maculopathy. Am J Ophthalmol. 2012; 153(1):93–102.
95. Krebs I, Brannath W, Glittenberg C, Zeiler F, Sebag J, Binder S. Posterior vitreomacular adhesion: a potential risk factor for exudative age-related macular degeneration? Am J Ophthalmol. 2007; 144(5):741–6.e1.