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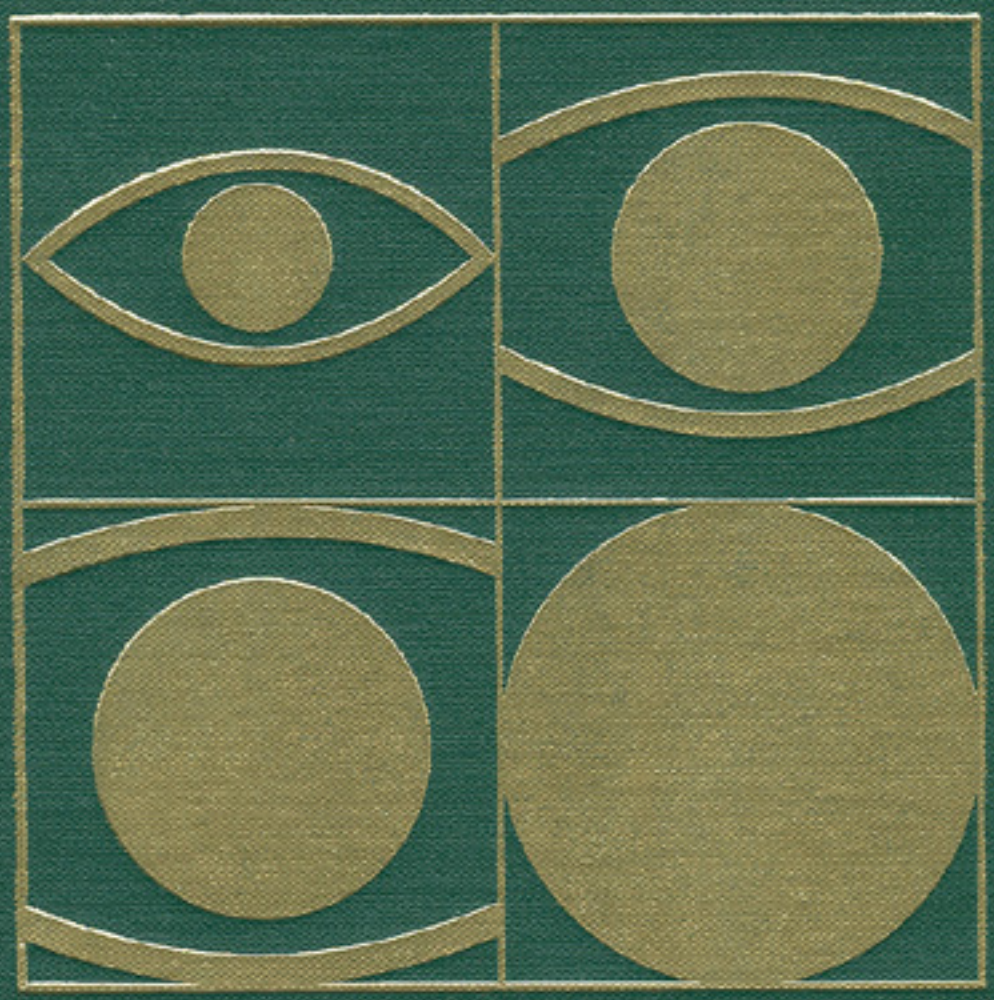
MYOPIA AND RELATED DISEASES



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Myopic vitreopathy: Significance in anomalous PVD and vitreoretinal disorders

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Myopia can be defined as a spherical equivalent refractive error of minus diopters. By this criterion, it has been estimated that the prevalence of high myopia (greater than –6 diopters) in the general population is as high as 4%.[1] Myopia is considered to be caused by both genetic and environmental factors.[2] The genetic effects upon vitreous can be considered myopic vitreous dystrophy while the effects of environmental factors are appropriately termed myopic vitreous degeneration. The combined effects are best referred to as myopic vitreopathy.

Due to various effects on vitreous and retina, myopia is one of the leading threats to vision, primarily because it contributes to retinal detachment (RD). In one study[3] the risk of rhegmatogenous RD was increased by fourfold in individuals with a spherical equivalent refractive error of –1 to –3 diopters. For individuals with greater than –3 diopters of myopia, the risk was tenfold greater than for nonmyopic controls. The investigators of that study concluded that nearly 55% of nontraumatic RD in eyes without previous ocular surgery are due to myopia. As alarming as these figures seem, they may be underestimates. As pointed out by Percival,[4] it is probably more accurate to define myopia on the basis of axial length, particularly as it relates to the posterior segment complications of this condition. In his study, Percival found that using the definition of high myopia as greater than –6 diopters yielded a 1.6% incidence of RD following cataract surgery. However, with the definition of high myopia as an axial length of greater than 26.5 mm, the incidence of RD was 4.1%.

Myopia

As stated above, myopia is believed to result from both genetic and environmental factors.[2] Vitreous is likely to contribute significantly to this process due to its role in ocular growth. This could occur either as a result of primary abnormalities in the vitreous, or vitreous could play a secondary role, mediating the effects of a primary abnormality elsewhere. It is well-known that vitreous is important in ocular growth and this was long ago suspected to be a causative factor in the development of myopia, as embodied in the ectodermal-mesodermal growth disparity theory of Vogt. Evidence in support of a primary role for vitreous in the pathogenesis of myopia derives from the observation that myopia is a common feature in patients with diseases resulting from inborn errors of type II collagen metabolism, such as Marfan syndrome, Ehlers-Danlos syndrome, and various other arthro-ophthalmopathies[5] (i.e., Wagner and Stickler syndromes[6]), although collagen type XI is probably more important in Stickler syndrome than type II. These systemic metabolic abnormalities result in abnormal collagen synthesis and vitreous structure, termed hereditary vitreopathy.[7] What is not widely appreciated is that the corpus vitreus of a highly myopic eye is not only elongated in the anteroposterior axis, but enlarged in the horizontal axis and vertically as well (Figure 1).

In 1985, Curtin[8] revised Vogt's theory to state that excess formation of vitreous by retina expands the sclera in a generalized fashion to produce

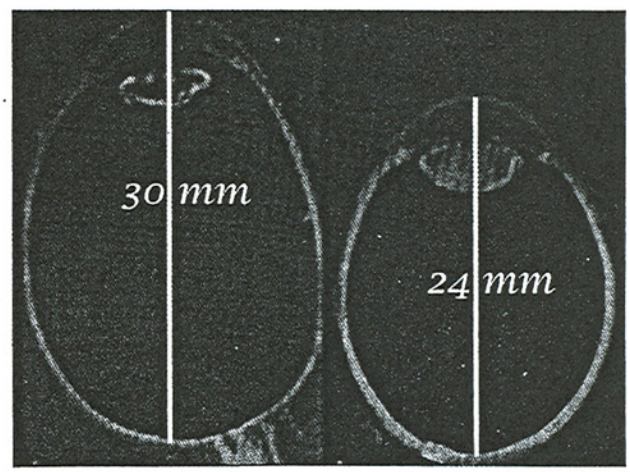

Fig. 1. Histologic cross-section of myopic eye (left) compared to emmetropic eye (right). In the myopic eye the anteroposterior (AP) dimension measured 30 mm, the horizontal axis was 26 mm, and the vertical dimension was 25 mm. In the emmetropic eye the AP length was 24 mm and both the horizontal and vertical dimensions were 23 mm. This demonstrates an overall enlargement of the myopic eye in all dimensions, not just along the AP axis. Reprinted with permission from: Spencer WH. Ophthalmic Pathology. Philadelphia: WB Saunders, 1985.

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myopia, or in a focal pattern to produce a posterior staphyloma in extreme cases. In this context, the primary abnormality is in the retina. A recent study[9] found that non-subtype-specific nicotinic antagonists chlorisondamine and mecamylamine each inhibited the development of form-deprivation myopia. Moreover, dihydro-beta-erythroidine, a relatively selective competitive inhibitor for nicotinic receptors, inhibited mainly axial elongation. The investigators concluded that retinal or retinal pigment epithelium (RPE) nicotinic cholinergic receptors regulate postnatal ocular growth. In another experimental study[10] an indirect cholinomimetic, diisopropylfluorophosphate (DFP), was demonstrated to reduce myopia by 58% in DFP-injected eyes rather than increasing myopia and elongation of the vitreous chamber as expected. The steady-state concentrations of acetylcholine and dopamine were increased by 54% and 36%, respectively, in eyes injected with DFP. As the combination of dopamine antagonists and DFP reduced myopia, the authors hypothesized that reduction is related to DFP effect on dopamine levels in the retina. Thus, primary abnormalities in retinal development could cause abnormal vitreous development, resulting in myopia, or deficient retinal metabolism in response to other factors could be the cause. For example, visual deprivation in monkeys[11] induces myopia that is due to an increase in axial length of the eye.[12] In humans, eyelid hemangiomas that occlude visual input were found to result in a 50% incidence of myopia.[13]

Normal retinal metabolism and vitreous synthesis may result in axial elongation if the sclera is abnormal. Recent in vitro studies[14] showed that ovotransferrin is synthesized and released from the chick choroid and exhibits a dose-dependent inhibition of scleral proteoglycan synthesis by 62%. In this study ovotransferrin also slowed the rate of axial elongation in a form-deprivation model of myopia. Thus, insufficient ovotransferrin synthesis by the choroid in myopic eyes could result in excess vitreous chamber elongation due to the lack of normal proteoglycan synthesis in the sclera. That there is a primary abnormality in scleral physiology and metabolism is supported by studies[15] where muscarinic receptor subtype-specific antagonists such as pirenzepine inhibited chick scleral chondrocytes synthesis of DNA and glycosaminoglycans, possibly mediated by the M1 subtype. This prompted another group of investigators[16] to examine the effect of the M4-selective antagonist, himbacine, on myopia. It was shown to have dose-dependent inhibition of induced myopia in chick eyes, thereby implicating a role for the M4 receptor.

Vitreous

Structure and Function

Vitreous is composed of water, collagen, hyaluronan (HA), and various other minor, albeit important, molecular components. The origin of the structural macromolecules of the vitreous is not clearly understood. The two leading candidates for synthesis of these macromolecules appear to be retinal Müller cells and hyalocytes.[17–19] Thus, any abnormalities including myopia-induced changes in Müller cell[8] or hyalocyte[20] function could readily result in abnormal vitreous biochemistry and structure.

During youth, there is a homogeneous distribution of the major structural components of the corpus vitreus, creating a solid gel that maintains clarity within the eye (Figure 2). Vitreous transparency depends on spreading apart collagen fibrils by at least one wavelength of incident light so as to minimize scattering. This is achieved by HA and other glycosaminoglycans, as well as several unidentified components of the unique extracellular matrix that is the corpus vitreus.

Studies have determined that the retina is primarily responsible for ocular growth[21] and most likely performs this function by controlling the degree and rate of enlargement of the corpus vitreus during development. Almost all of the growth of the eye after ages 2 or 3 years is due to expansion of the eye between the region of the ora serrata and the equator of the globe.[22] Much, if not all, of the force inducing this expansion derives from the burgeon-

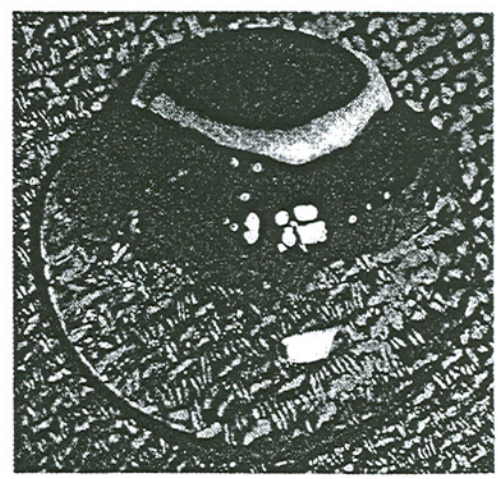

Fig. 2. Whole vitreous from a 9-month-old child. The sclera, choroid, and retina were dissected, leaving the corpus vitreus attached to the anterior segment. Because of the solid gel structure, the specimen maintains it shape while situated on a surgical towel in room air. Specimen courtesy of the New England Eye Bank. Reprinted with permission from reference 19: Sebag J. The Vitreous–Structure, Function, and Pathobiology. New York: Springer Verlag, 1989. (See color plate in Appendix.)

ing growth of the corpus vitreus. An alternative hypothesis for the control of eye growth was first proposed by Porte et al,[23] who suggested that the volume of the embryonic eye is controlled by the effects of aqueous humor synthesis on intraocular pressure. Studies by Beebe et al[24] on ciliary body synthesis of aqueous humor and vitreous proteins support this hypothesis. However, early studies by Coulombre et al[25] proposed that during development, vitreous growth was the major factor influencing intraocular pressure and eye growth. Subsequent studies[26] showed that vitrectomized eyes with normal intraocular pressure had less ocular growth than controls. Recent studies[20] showed that peripheral retinal ablation by cryopexy or laser photocoagulation in rabbits between 2 and 8 weeks of age caused significant reductions in axial length, equatorial diameter, corneal diameter, and total ocular volume. The investigators hypothesized that these effects were due to interference with peripheral retinal control of eye growth or destruction of hyalocytes with elimination of their synthesis of vitreous macromolecules, particularly the structural component HA. Studies[27] in humans who underwent peripheral retinal cryoablation for retinopathy of prematurity confirmed the finding of decreased eye growth in treated cases. Thus, because vitreous plays such an important role in eye growth, it may have an important contribution in the origins of myopia.

Anomalous Posterior Vitreous Detachment (PVD)

True PVD can be defined as a separation of the posterior vitreous cortex from the internal limiting lamina (ILL) of the retina. PVD results from weakening of the vitreous cortex/ILL adhesion, in conjunction with rheologic changes within the corpus vitreus that lead to liquefaction. Dissolution of the vitreous cortex/ILL adhesion at the posterior pole allows liquid vitreous to enter the retrocortical space via the prepapillary hole and perhaps the premacular vitreous cortex as well. There may be biochemical effects of liquid vitreous upon the vitreoretinal interface that contribute to weakened adhesion. With rotational eye movements, liquid vitreous dissects a plane as a wedge between the vitreous cortex and the ILL, leading to true PVD. This volume displacement from the central vitreous to the preretinal space causes the observed collapse of the vitreous body (syneresis). Critical to the development of PVD without untoward effects is the concurrence of vitreous liquefaction (synchysis) and vitreoretinal dehiscence. There must be sufficient weakening at the vitreoretinal interface when the gel vitreous is liquefied enough to collapse so that the separation of vitreous away from retina is innocuous.

Autopsy and clinical studies have estimated that two out of three individuals over the age of 65 have PVD. It is more common in women and individuals with myopia, occurring 10 years earlier than in emmetropia and hyperopia. Cataract extraction in myopic patients introduces additional effects, causing PVD in even more patients. In a large number of cases, however, this PVD is not innocuous. Anomalous PVD results when there is vitreous liquefaction without concurrent dehiscence at the vitreoretinal interface. The resulting anomalies can be grouped into one of two categories: disruption of retina or disruption of vitreous.

Retinal Disruption

Anomalous PVD can injure the retina via vitreous traction, with the resulting pathology differing based upon where the vitreous is most adherent. Minimal vitreous hemorrhage occurs in 13 to 19% of cases with PVD. This finding is generally considered to be an important risk factor for the presence of a retinal tear. Retinal tears result from traction upon foci of firm vitreoretinal adhesion, such as lattice degeneration and rosettes. In these examples of anomalous PVD there was sufficient vitreous liquefaction to promote collapse of the corpus vitreus, but insufficient dehiscence at the vitreoretinal interface overlying blood vessels, in the case of vitreous hemorrhage, and in the peripheral fundus, in the case of retinal tears, to result in an innocuous PVD.

In 1979, Maumenee[5] characterized several disorders of inborn errors in type II collagen metabolism with autosomal dominant inheritance and identified them as single-gene diseases with dysplastic connective tissues resulting in joint laxity and various other skeletal abnormalities. Marfan, Ehlers-Danlos, and Stickler are the best known of these syndromes. Advanced vitreous liquefaction at a young age is typical in these patients. Since there is no concomitant dehiscence at the vitreoretinal interface, anomalous PVD results and there is a high incidence of RD due to large, posterior tears. Myopic vitreous dystrophy is likely to be similar to these conditions, which often have excess axial elongation as well.

Vitreous Disruption

A frequently unrecognized form of vitreoretinal separation that can mimic true PVD is known as vitreoschisis (Figure 3). This condition is characterized by forward displacement of the anterior portion of the posterior vitreous cortex leaving part or all of

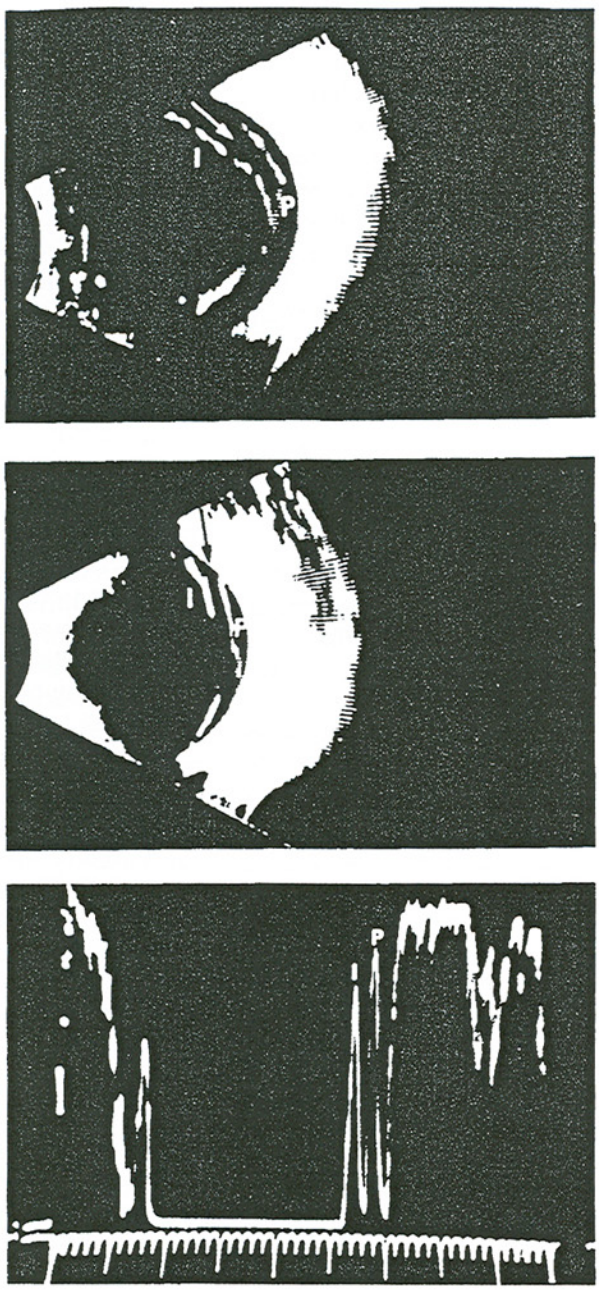

Fig. 3. B-scan ultrasonography of posterior vitreoschisis. Splitting of the posterior vitreous cortex (white arrow) can mimic posterior vitreous detachment. The tissue that remains attached to the macula (P) can induce macular pucker or macular holes (I = inner wall of vitreoschisis cavity; P = outer wall). Reprinted with permission from: Green RL, Byrne SF. Clinical ultrasonography. In: Ryan SJ, ed. Retina. St. Louis: Mosby, 1989.

the posterior aspect of the vitreous cortex still attached to the retina.

Posterior vitreoschisis has recently been found in proliferative diabetic vitreoretinopathy,[28] and may play an important role in the pathophysiology of this condition.[29] Cases of premacular membranes with macular pucker and cases of macular holes may also result from persistent attachment of part or all of the posterior vitreous. These manifestations of anomalous PVD may be more frequent and particularly severe in highly myopic eyes.

Posterior Segment Effects of Myopia

Vitreous

In myopia, the corpus vitreus is liquefied and contains filaments with localized nodules.[8] Biochemical studies[30] in myopic humans found decreased collagen content and concentration in the central vitreous. Hexosamine concentration, an index of HA, was not only decreased in the central vitreous but in the posterior vitreous cortex as well. Confirmatory studies[24] in experimental models of myopia found a decrease in vitreous protein concentration. Other studies[31] determined that the decrease in protein concentration in the liquid vitreous was concurrent with an increase in the protein concentration of the gel vitreous. More recent studies[32] of both the volumes of the gel and liquid compartments of the corpus vitreus as well as the protein content in these compartments found that although overall vitreous volume increased in experimental myopia, the volume of gel vitreous remained the same, and there was a marked increase in liquid vitreous volume. Comparing the liquid and gel vitreous of myopic eyes to controls with respect to protein content as well as the spectrum of proteins resolvable by polyacrylamide gel electrophoresis showed that whereas the protein profiles of the gel and liquid vitreous were similar on the day of hatching, they differed by day 14 after hatching. The investigators concluded that the accumulation of liquid vitreous in the myopic eye is not a dilution phenomenon, but rather the result of active synthesis of liquid vitreous. This is different from the degenerative liquefaction seen in aging in which the increase in liquid vitreous volume occurs in synchrony with a decrease in gel volume.[17–19] Abundant synthesis of liquid vitreous could be the source of increased intraocular pressure, or perhaps more importantly, an increase in the pressure gradient differential between the corpus vitreus and the suprachoroidal space[33] that results in elongation of the eye and myopia. Another important consideration is that because the corpus vitreus in myopia is far more liquid than in an emmetropic eye, the different physical characteristics inherent to such a composition may interfere with the feedback regulatory signals

that would normally modulate the process of vitreous synthesis and thereby limit the forces that influence growth of the eye. Such altered feedback regulation may be an important component in the pathogenesis of myopia.

In a retrospective, histopathologic study[34] of 308 eyes with pathologic myopia, nonspecific degenerative changes of the vitreous were detected in 35.1%. These investigators likely were describing a prominence of liquid vitreous, erroneously likening this finding to the degeneration seen in aging. Stirpe and Heimann[35] found that in 10% of 496 highly myopic eyes, there was extensive vitreous liquefaction and condensation of the vitreous base, resulting in giant retinal tears in 70% of these patients. There were 87 eyes (17.5%) with a prominent posterior vitreous lacuna; i.e., a large pocket of liquid vitreous. These eyes had more prominent posterior staphylomata and a thin posterior vitreous cortex that was firmly adherent to the ILL of the retina. Posterior retinal breaks, including macular holes, were present in 56% of these cases.

Anomalous Posterior Vitreous Detachment in Myopia

In myopia, the accumulation of liquid vitreous that induces the increase in vitreous size and elongates the eye also markedly destabilizes the corpus vitreus and threatens the retina, as this vitreous liquefaction does not occur concurrently with sufficient dehiscence at the vitreoretinal interface. It is known[36] that in youth there is strong adhesion of the posterior vitreous cortex to the ILL of the retina. Consequently, the finding[37] that the incidence of vitreous liquefaction and PVD is greater in people with high myopia (greater than –6 diopters) and that this occurs 5 to 10 years earlier than in emmetropic eyes[38,39] portends risk. Given the discordance between the processes of vitreous liquefaction and dehiscence at the vitreoretinal interface that exists in cases with anomalous PVD, the occurrence of PVD in a myopic eye at a relatively young age is a dangerous event. Furthermore, there are frequently distinct peripheral retinal lesions in myopia that make PVD in the myopic eye particularly ominous.

Retina

In a study[40] based on preoperative evaluation of 165 eyes with pathologic myopia undergoing cataract extraction, lattice degeneration was found in 9.7%, and retinal holes and tears in 3.6%. Histopathologic evaluation[34] of 308 eyes with pathologic myopia revealed peripheral retinal degeneration in 30.6%, with cobblestone degeneration in 14.3% and, somewhat surprisingly, lattice degeneration in only 4.9%. However, a variant of this type of degeneration was present in an additional 11.4%, bringing the total closer to the prevalence of 16.5% found in a clinical study[41] of 436 eyes with myopia ≥–6 diopters. Interestingly, this clinical study found the highest prevalence of lattice degeneration in eyes with –6 to –8.7 diopters (63/154 eyes; 40.9%) with an axial length of 26 to 26.9 mm, and the lowest prevalence (5/71; 7%) in eyes with more than –24 diopters (axial length ≥32 mm). The authors suggest that this may explain why RD following cataract surgery is seen more commonly in patients with moderate myopia than those with severe myopia. Contradictory results were obtained in a recent study[42] involving a random sample of 200 eyes where the highest frequency of lattice degeneration was in myopic patients with axial length between 29 and 30 mm (greater than 15 diopters) and those with 25 to 27 mm (between 3 and 10 diopters). The reasons for these disparate findings are not clear.

Retinal Detachment

The incidence of RD in the general population ranges between 0.005 and 0.01%.[43] RD occurs far more frequently in patients with myopia. The Eye Disease Case-Control Study Group[3] found that subjects with a spherical equivalent refractive error of –1 to –3 diopters had a fourfold greater risk of RD than a nonmyopic individual. For refractive errors greater than –3 diopters, the risk was tenfold greater. Another study[44] retrospectively compared 1166 eyes with RD to 11,671 eyes without RD. Myopia was present in 82.2% of RD patients as compared to 34.4% of controls. There was a relative frequency of RD equal to 0.83 in patients with myopia in the range of –0.75 to –2.75 diopters. This is likely due to myopic vitreous dystrophy (as described), younger age at onset of PVD in myopic individuals, relatively high incidence of peripheral retinal pathology, and abundance of liquid vitreous available to access the subretinal space and detach the retina. A variety of factors related to cataract surgery can further increase the risk of RD (Table 1).

RD After Cataract Surgery in Myopia

Vitreous undergoes considerable molecular and structural changes following cataract surgery.[45] These abnormalities add to the risk for developing RD already in effect as a result of myopia. Consequently, a study[46] comparing 291 patients with RD with 870 matched controls found that the odds ratio of RD increased by 0.92 for each diopter of myopia and by 1.21 for each mm of axial length greater than emmetropia. This again demonstrates the underesti-

Table 1. Incidence of retinal detachment (RD) in certain patient groups

Patient group	Incidence of RD (%)
General population[43]	0.01
ICCE[43]	1.74
ECCE[43]	0.62
ECCE and YAG[8]	Four- to fivefold increase over ECCE
Myopia (−1 to −3 diopters)[3]	0.04
Myopia (>−3 diopters)[3]	0.1
Myopia + ICCE[43]	11.11
Myopia + ECCE[40]	5.5
Myopia + ECCE + YAG[40]	11

ICCE = intracapsular cataract extraction; ECCE = extracapsular cataract extraction; YAG = Nd:YAG laser capsulotomy.

mate that results when defining myopia in terms of refractive error as opposed to axial length.[4] Jaffe et al[47] noted that after intracapsular cataract extraction in high myopia, the rate of RD is ninefold greater than after extracapsular surgery. Performing extracapsular cataract extraction in high myopia without implanting an intraocular lens doubles the incidence of postoperative RD.[48] The incidence of postoperative RD in high myopia also doubles after YAG laser capsulotomy (Table 1).

In recent years, there has been an increasing trend of extracting clear lenses as therapy for high myopia. The foregoing observations and considerations seem to suggest that this approach may be fraught with hazards. A 7-year follow-up study[49] reveals that the incidence of RD after clear lens extraction (CLE) for high myopia (greater than −12 diopters) was 8.1% (4/49 eyes), almost double the estimation for those with myopia greater than −10 diopters who do not undergo CLE. Furthermore, PVD occurred in 16.3% of the studied eyes. These results are even more striking when one takes into consideration that prior to surgery, photocoagulation was performed on patients with lattice degeneration and retinal breaks.

RD After LASIK Surgery for Myopia

As laser in situ keratomileusis (LASIK) has increasingly been performed for the correction of myopia, its effects on the vitreous and subsequent RD have to be considered. In a clinical study[50] of 100 eyes, 50 with low myopia (<4 diopters) and 50 with high myopia (>7 diopters), partial or total PVD was discovered in 4% of the former and 24% of the latter group. This suggests that vitreoretinal changes following LASIK mainly occur in patients with high myopia. In a study[51] consisting of 31,739 myopic eyes, rhegmatogenous RD occurred in 20 eyes after LASIK, a frequency of 0.06%. The mean preoperative myopia in these eyes was −7.02 diopters. The authors concluded that rhegmatogenous RD following LASIK for correcting myopia is infrequent. Similarly, another study[52] involving 38,823 myopic eyes that underwent surgical correction found that rhegmatogenous RD developed in 33 eyes (frequency of 0.08%) postoperatively. The pre-LASIK myopia in these eyes was a mean of −8.75 diopters.

Prophylaxis of Retinal Detachment

There have been various attempts to decrease the inherent risks in surgical approaches to myopia. In one study[53] of 49 eyes in 28 patients with high myopia of −12 diopters or more, prophylactic peripheral retinal laser photocoagulation was performed before cataract extraction with intraocular lens implantation. After 4 years of follow-up, the incidence of RD was only 1.9%. However, in another study[54] of 41 eyes in 39 patients with high myopia of −14 diopters or more who had undergone CLE and developed postoperative RD, 26 (63%) had undergone prophylactic laser photocoagulation therapy before lens surgery. Such observations have prompted one group of authors[55] to state that CLE is contraindicated in the young, in eyes with axial lengths greater than 29 mm, and in eyes with peripheral chorioretinal degeneration. Another author[56] stated that "the possible optical benefits of clear lens extraction in axial myopia are usually outweighed by the severity of the risks and by the availability of safer alternatives." Future developments in the field of refractive surgery may provide additional therapeutic options to substantiate this position further. Alternatively, refractive surgery could be combined with vitreous therapy to make the surgery safer.

Pharmacologic Vitreolysis

Coined[57] in 1998, this term refers to the use of exogenous (to the vitreous) agents to alter the biochemical and biophysical states of the macromolecules responsible for maintaining vitreous structure and vitreoretinal adhesion. The goals of pharmacologic vitreolysis are thus to induce liquefaction of the gel and promote dehiscence of the vitreous from the retina. It is important to note that the success of pharmacologic vitreolysis depends upon inducing these two events simultaneously, or at least insuring that liquefaction does not progress without sufficient vitreoretinal dehiscence. Uncoupling these two processes, particularly by inducing liquefaction without weakening vitreoretinal adherence, may worsen matters significantly by provoking, rather

than preventing or ameliorating, anomalous PVD and its untoward sequelae: vitreopapillopathies, vitreomaculopathies, and peripheral retinal traction.

There have been a variety of approaches attempted to date. Albeit unsuccessfully, hyaluronidase was employed as early as 1949 and collagenase in 1973. Table 2 outlines the approaches that are currently being developed. The different pharmacologic agents can be broadly grouped as enzymatic and nonenzymatic. Within the enzymatic group there are substrate-specific agents and nonspecific agents.

Early observations of the effects of blood on vitreous laid the groundwork for approaches based upon extracting active agents from blood for pharmacologic vitreolysis. Plasmin is a nonspecific protease that can be isolated from the patient's own serum for use at surgery. It has been tested in rabbits and several small series of pediatric and adult patients undergoing vitrectomy by Trese and colleagues.[58] This agent is primarily advocated as an adjunct to vitreoretinal surgery. A phase II clinical trial of autologous plasmin agent is currently being organized in the United States. There are also other, so-called exogenous, sources of plasmin. Studies[59] have shown that effective intravitreal levels of plasmin can be generated by injecting tissue plasminogen activator and breaking down the blood-retinal barrier with cryopexy or laser photocoagulation. Other studies[60] have used combinations of human recombinant plasminogen and urokinase. Recently, a human recombinant fragment of plasmin, called microplasmin, has been shown to induce PVD in porcine eyes.[61]

Another relatively nonspecific protease currently under investigation is Dispase. The first investigations[62] used Dispase to induce PVD in enucleated porcine and human cadaver eyes, noting no untoward effects upon retinal histology and ultrastructure. Subsequent studies[63] were successful in using this agent in vivo to remove cortical vitreous during vitreous surgery in the pig. Since Dispase has proteolytic activity against type IV collagen and fibronectin, there is some concern that the ILL of the retina might be adversely affected by this agent. Yet the histologic studies[62] in porcine and human cadaver eyes found that only the lamina rara externa of the ILL was affected, with lesser effects upon the lamina densa. Although subsequent animal studies found that this agent did not alter the electroretinogram in vivo, and no neuroretinal ultrastructural abnormalities were detected postmortem,[63] other studies[64] in rabbits and humans detected retinal toxicity.

Table 2. Pharmacologic vitreolysis

I. Enzymatic vitreolysis
A. Nonspecific
1. Plasmin
a. Autologous (patient's blood)
b. Tissue plasminogen activator (tPA + blood-retinal barrier breakdown)
c. Plasminogen-urokinase (combine in patient's eye)
d. Microplasmin (human recombinant)
2. Dispase
B. Substrate-specific
1. Chondroitinase
2. Hyaluronidase
3. Collagenase
II. Nonenzymatic vitreolysis

A substrate-specific enzyme that has been in development for a number of years by Drs. Greg Hageman and Steve Russell is chondroitinase. This agent lyses chondroitin sulfate, a molecule that may be important in the maintenance of both the gel state of vitreous[65] and vitreoretinal adhesion; hence, there has been considerable interest in the use of this agent. Indeed, studies[66] have purportedly shown that when used as an adjunct to vitreous surgery, chondroitinase facilitates the removal of premacular membranes. Several years ago, a phase I trial using this agent during vitreous surgery in patients was completed in the United States, yet the results still await publication. In this trial, patients with macular holes and others with proliferative diabetic vitreoretinopathy were treated with chondroitinase during vitreous surgery, with no untoward effects. Phase II studies of efficacy have yet to be undertaken.

In addition to facilitating vitreoretinal surgery as currently performed, pharmacologic vitreolysis could possibly replace vitrectomy, as was proposed with hyaluronidase to clear vitreous hemorrhage without vitrectomy. However, in the phase III Food and Drug Administration trial undertaken in the United States, this drug was not found to be effective. This may be due to the fact that the trial included patients with both type I and type II diabetes. In the former group the patients are younger and more likely to have an attached vitreous without a weakened vitreoretinal interface. Thus, although the enzyme may have decreased the viscosity of vitreous gel and facilitated the outflow of red blood cells, the persistent attachment of the posterior vitreous cortex to the retina and to any neovascular complexes arising from the retina and optic disk would cause recurrent vitreous hemorrhage, and possibly RD. Indeed, there has been some discussion of using this agent to induce PVD in patients with nonproliferative diabetic retinopathy, since liquefaction of the vitreous body and detachment of the posterior vitre-

ous cortex away from the retina prior to the onset of new vessel growth into the vitreoretinal interface (see below) will have a far better prognosis than if the vitreous were still attached. However, hyaluronidase is not likely to induce vitreoretinal separation and PVD, at least on theoretical grounds. Indeed, studies[67] in experimental animal models have shown contradictory results in this regard, with the most recent studies[68] finding no such effect. On the other hand, combining hyaluronidase with SF_6 has purportedly induced PVD in the rabbit.[69] It is plausible that the expanding gas, and not the enzyme, is responsible for these effects, since many years ago Lincoff and Machemer reported similar effects with expanding gas alone.

Ideal Solutions for Pharmacologic Vitreolysis

It is important to note that in the Dispase studies, there was no evidence of vitreous liquefaction. With hyaluronidase there is no vitreo-retinal separation. This underscores the concept that few, if any, single agents alone can achieve both of the desired components of effective pharmacologic vitreolysis: liquefaction of the gel and vitreoretinal dehiscence. Dispase causes dehiscence but not liquefaction. Hyaluronidase liquefies vitreous gel but without gas probably does not induce PVD. Chondroitinase may do both but the depolymerization of HA and chondroitin sulfate only results in a reduction of vitreous gel wet weight and not gel destruction.[70] Collagenases would probably be needed to achieve such effects. Indeed, vitreous molecular morphology is so complex and there are so many different changes that occur with aging and various diseases that the future will probably see the use of a mixture of agents whose relative concentrations will need to be adjusted in consideration of the patient's age, disease, and the desired effect. Ideally this would begin by inducing vitreoretinal dehiscence, and then be followed by liquefaction of the gel vitreous.

References

1. Coscas G, Soubrane G. Severe myopia or myopia disease? Rev Pratique 1993;43:1768-1772.
2. Mutti DO, Zadnik K, Adams AJ. Myopia: the nature versus nurture debate goes on. Invest Ophthalmol Vis Sci 1996;37:952-957.
3. The Eye Disease Case-Control Study Group. Risk factors for idiopathic rhegmatogenous retinal detachment. Am J Epidemiol 1993;137:749-757.
4. Percival SP. Redefinition of high myopia: the relationship of axial length measurement to myopic pathology and its relevance to cataract surgery. Dev Ophthalmol 1987;14:42-46.
5. Maumenee IH. Vitreoretinal degeneration as a sign of generalized connective tissue diseases. Am J Ophthalmol 1979;88:432-449.
6. Richards AJ, Martin S, Yates JR, et al. COL2A1 exon 2 mutations: relevance to the Stickler and Wagner syndromes. Br J Ophthalmol 2000;84:364-371.
7. Snead MP. Hereditary vitreopathy. Eye 1996;10:653-663.
8. Curtin BJ. The Myopias: Basic Science and Clinical Management. Philadelphia: Harper & Row, 1985.
9. Stone RA, Sugimoto R, Gill AS, Liu J, Capehart C, Lindstrom JM. Effects of nicotinic antagonists on ocular growth and experimental myopia. Invest Ophthalmol Vis Sci 2001;42:557-565.
10. Cottriall CL, Brew J, Vessey KA, McBrien NA. Diisopropylfluorophosphate alters retinal neurotransmitter levels and reduces experimentally-induced myopia. Naunyn Schmiedebergs Arch Pharmacol 2001;364:372-382.
11. Weisel TN, Raviola E. Myopia and eye enlargement after neonatal lid fusion in monkeys. Nature 1977;266:66.
12. Weisel TN, Raviola E. Increase in axial length of the macaque monkey eye after corneal opacification. Invest Ophthalmol Vis Sci 1979;18:1232.
13. Robb RM. Refractive errors associated with hemangiomas of the eyelids and orbit in infancy. Am J Ophthalmol 1977;83:52.
14. Rada JA, Huang Y, Rada KG. Identification of choroidal ovotransferrin as a potential ocular growth regulator. Curr Eye Res 2001;22:121-132.
15. Lind GJ, Chew SJ, Marzani D, Wallman J. Muscarinic acetylcholine receptor antagonists inhibit chick scleral chondrocytes. Invest Ophthalmol Vis Sci 1998;39:2217-2231.
16. Cottriall CL, Truong HT, McBrien NA. Inhibition of myopia development in chicks using himbacine: a role for M(4) receptors? Neuroreport 2001;12:2453-2456.
17. Sebag J. The vitreous. In: Hart WM Jr., ed. Adler's Physiology of the Eye. St. Louis: CV Mosby, 1992:268-347.
18. Sebag J. Macromolecular structure of vitreous. In: Chirila T, ed. Polymer Science and the Eye. London: Elsevier Science, 1998.
19. Sebag J. The Vitreous—Structure, Function, and Pathobiology. New York: Springer Verlag, 1989.
20. Whitmore WG, Curtin BJ, Fox D. The modulation of ocular growth in rabbits with peripheral retinal ablation. Ophthalmology 1993;100:1003-1008.
21. Erlich D, Sattayasai J, Zappia J, Barrington M. Effects of selective neurotoxins on eye growth in the young chick. In: Boch G, Widdows K, eds. Myopia and the Control of Eye Growth. New York: John Wiley & Sons, 1990:63-84.
22. Streeten B. Development of the human retinal pigment epithelium and the posterior segment. Arch Ophthalmol 1969;81:383-394.
23. Porte A, Stockel MD, Brini A, et al. Structure et differentiation du corps ciliare et du feuillet pigmente de la retine chez le poulet. Arch Ophthalmol 1968;28:259-282.
24. Beebe DC, Latker CH, Jebens HAH, et al. Transport and steady-state concentration of plasma proteins in the vitreous humor of the chicken embryo: implications for the mechanism of eye growth during early development. Dev Biol 1983;114:361-368.
25. Coulombre AJ, Steinberg SN, Coulombre JL. The role of intraocular pressure in the development of the chick eye. V. Pigmented epithelium. Invest Ophthalmol Vis Sci 1963;2:83-89.
26. Arcienegas A, Amaya LE, Ruiz LA. Myopia: a bioengineering approach. Ann Ophthalmol 1980;12:805.
27. Pulido J, Byrne SF, Clarkson JG, et al. Evaluation of eyes with advanced stages of retinopathy of prematurity using standardized echography. Ophthalmology 1991;98:1099-1104.
28. Chu TG, Lopez PF, Cano MR, et al. Posterior vitreoschisis. An echographic finding in proliferative diabetic retinopathy. Ophthalmology 1996;103:315-322.

29. Sebag J. Diabetic vitreopathy (guest editorial). Ophthalmology 1996;103:205-206.
30. Berman ER, Michaelson IC. The chemical composition of the human vitreous body as related to age and myopia. Exp Eye Res 1964;3:9-15.
31. Balazs EA, Toth LZJ, Jutheden GM, Collins BA. Cytological and biochemical studies of the developing chicken vitreous. Exp Eye Res 1965;4:237.
32. Pickett-Seltner RL, Doughty MJ, Pasternak JJ, Sivak JG. Proteins of the vitreous humor during experimentally induced myopia. Invest Ophthalmol Vis Sci 1992;33:3424-3429.
33. Van Alphen GWHM. Emmetropization in the primate eye. In: Boch G, Widdows K, eds. Myopia and the Control of Eye Growth. New York: John Wiley & Sons, 1990:115-125.
34. Grossniklaus HE, Green WR. Pathologic findings in pathologic myopia. Retina 1992;12:127-133.
35. Stirpe M, Heimann K. Vitreous changes and retinal detachment in highly myopic eyes. Eur J Ophthalmol 1996;6:50-58.
36. Sebag J. Age-related differences in the human vitreo-retinal interface. Arch Ophthalmol 1991;109:966-971.
37. Singh A, Paul SD, Singh K. A clinical study of the vitreous body in emmetropia and refractive errors. Oriental Arch Ophthalmol 1970;8:11.
38. Novak MA, Welch RB. Complications of acute symptomatic posterior vitreous detachment. Am J Ophthalmol 1984;97:308-314.
39. Akiba J. Prevalence of posterior vitreous detachment in high myopia. Ophthalmology 1993;100:1384-1388.
40. Barraquer C, Cavelier C, Mejia LF. Incidence of retinal detachment following clear-lens extraction in myopic patients. Arch Ophthalmol 1994;112:336-339.
41. Celorio JM, Pruett RC. Prevalence of lattice degeneration and its relation to axial length in severe myopia. Am J Ophthalmol 1991;111:20-23.
42. Sanchez M, Roldan PM. Myopia: frequency of lattice degeneration and axial length. Arch Soc Esp Oftalmol 2001;76:291-296.
43. Jaffe NS. Retinal detachment in aphakia and pseudophakia. In: Klein EA, ed. Cataract Surgery and its Complications. 5th ed. St. Louis: CV Mosby, 1990:653-665.
44. Ogawa A, Tanaka M. The relationship between refractive errors and retinal detachment: analysis of 1,166 retinal detachment cases. Jpn J Ophthalmol 1988;32:310-315.
45. Sebag J. Vitreous effects of cataract surgery and YAG laser capsulotomy: role in postoperative retinal detachment. In: Stirpe M, ed. Anterior and Posterior Segment Surgery: Mutual Problems and Common Interests. ACTA of the Fifth International Congress on Vitreoretinal Surgery (Rome, Sept. 24-27, 1997). New York: Ophthalmic Communications Society, 1998:85-88.
46. Tielsch JM, Legro MW, Cassard SD, et al. Risk factors for retinal detachment after cataract surgery: a population-based case-control study. Ophthalmology 1996;103:1537-1545.
47. Jaffe NS, Clayman HM, Jaffe MS. Retinal detachment in myopia eyes after intracapsular and extracapsular cataract extraction. Am J Ophthalmol 1984;97:48-52.
48. Badr IA, Hussain HM, Jabak M, Wagoner MD. Extracapsular cataract extraction with or without posterior chamber intraocular lenses in eyes with cataract and high myopia. Ophthalmology 1995;102:1139-1143.
49. Colin J, Robinet A, Cochener B. Retinal detachment after clear lens extraction for high myopia: seven-year follow-up. Ophthalmology 1999;106:2281-2284.
50. Luna JD, Artal MN, Reviglio VE, Pelizzari M, Diaz H, Juarez CP. Vitreoretinal alterations following laser in situ keratomileusis: clinical and experimental studies. Graefes Arch Clin Exp Ophthalmol 2001;239:416-423.
51. Arevalo JF, Ramirez E, Suarez E, Cortez R, Ramirez G, Yepez JB. Rhegmatogenous retinal detachment in myopic eyes after laser in situ keratomileusis: frequency, characteristics, and mechanism. J Cataract Refract Surg 2001;27:674-680.
52. Arevalo JF, Ramirez E, Suarez E, Cortez R, Ramirez G, Yepez JB. Retinal detachment in myopic eyes after laser in situ keratomileusis. J Refract Surg 2002;18:708-714.
53. Colin J, Robinet A. Clear lensectomy and implantation of a low-power posterior chamber intraocular lens for correction of high myopia: a four-year follow-up. Ophthalmology 1997;10:73-77.
54. Ripandelli G, Bili B, Fedeli R, Stirpe M. Retinal detachment after clear lens extraction in 41 eyes with high axial myopia. Retina 1996;16:3-6.
55. Rodriguez A, Guiterrez E, Alvira G. Complications of clear lens extraction in axial myopia. Arch Ophthalmol 1987;105:1522-1523.
56. Goldberg MF. Clear lens extractions for axial myopia. An appraisal. Ophthalmology 1987;94:571-582.
57. Sebag J. Pharmacologic vitreolysis. Retina 1998;18:1-3.
58. Verstraeten T, Chapman C, Hartzer M, Winkler BS, Trese MT, Williams GA. Pharmacologic induction of PVD in the rabbit. Arch Ophthalmol 1993;111:849.
59. Hesse L, Nebeling B, Schroeder B, Heller G, Kroll P. Induction of posterior vitreous detachment in rabbits by intravitreal injection of tissue plasminogen activator following cryopexy. Exp Eye Res 2000;70:31-39.
60. Unal M, Peyman GA. The efficacy of plasminogen-urokinase combination in inducing posterior vitreous detachment. Retina 2000;20:69-75.
61. Valmaggi C, Willekens B, de Smet M. Microplasmin induced vitreolysis in porcine eyes. Invest Ophthalmol Vis Sci (ARVO) 2003; poster 3050.
62. Tezel TH, Del Priore LV, Kaplan HJ. Posterior vitreous detachment with Dispase. Retina 1998;18:7-15.
63. Oliviera LB, Tatebayashi M, Mahmoud TH, et al. Dispase facilitates posterior vitreous detachment during vitrectomy in young pigs. Retina 2001;21:324-331.
64. Jorge R, Oyamaguchi EK, Cardillo JA, et al. Intravitreal injection of dispase causes retinal hemorrhages in rabbit and human eyes. Curr Eye Res 2003;26:107-112.
65. Hageman GS, Johnson LV. Lectin-binding glycoproteins in the vertebrate vitreous body and inner limiting membrane: tissue localization and biochemical characterization. J Cell Biol 1984;99:179a.
66. Hageman GS, Russell SR. Chondroitinase-mediated disinsertion of the primate vitreous body. Invest Ophthalmol Vis Sci 1997;38(ARVO):S662.
67. Harooni M, McMillan T, Refojo M. Efficacy and safety of enzymatic posterior vitreous detachment by intravitreal injection of hyaluronidase. Retina 1998;18:16-22.
68. Hikichi T, Masanori K, Yoshida A. Intravitreal injection of hyaluronidase cannot induce posterior vitreous detachment in the rabbit. Retina 2000;20:195-198.
69. Hikichi T, Yanagiya N, Kado M, Akiba J, Yoshida A. Posterior vitreous detachment induced by injection of plasmin and sulfur hexafluoride in the rabbit vitreous. Retina 1999;19:55-58.
70. Bishop PN, McLeod D, Reardon A. Effects of hyaluronan lyase, hyaluronidase, and chondroitin ABC lyase on mammalian vitreous gel. Invest Ophthalmol Vis Sci 1999;40:2173-2178.