The term pharmacologic vitreolysis first appeared in the world’s literature one decade ago in the pages of the journal *Retina*. The coining of this term formalized a new field and was predicated on a premise and a promise. The premise was that we now understood enough about the molecular organization, structure, and physiology of vitreous and its role in retinal disorders, and that this knowledge could be used to enhance vitreoretinal surgery with pharmacologic adjuncts. The promise was that this novel form of therapy could one day supplant surgery by mitigating the pathophysiology of vitreous at the earliest stages of disease and also improve ocular physiology and metabolism. Although there have been many interesting developments during the first decade, most recently the results of MIVI III (Microplasmin Intravitreous Injection III, a Phase IIb multicenter, randomized, controlled clinical trial evaluating microplasmin, which showed the release of vitreo-macular traction without surgical intervention in 30% of patients), too few of these objectives have been met to date. There are important lessons to be learned in considering why there has not been more rapid progress.

Vitreous is believed to play an important role in ocular health and disease. Posterior vitreous detachment (PVD) is characterized by gel liquefaction (synchisis) and vitreoretinal dehiscence with collapse (syreresis) of the posterior vitreous away from the retina. It is plausible that much like the phenomenon of apoptosis, PVD is preprogrammed to happen, because PVD occurs in the overwhelming majority of individuals. Furthermore, it is currently believed that in a variety of diseases, such as diabetic retinopathy and age-related macular degeneration, complete PVD protects against more advanced stages of disease. In a minority of cases, however, liquefaction occurs without sufficient dehiscence at the vitreoretinal interface to allow for clean separation of the posterior vitreous cortex from the retina. This is known as “anomalous PVD.” The sequelae of anomalous PVD vary depending on where the gel is most liquefied and where the posterior vitreous cortex is most firmly adherent to the retina. The clinical setting is also extremely important insofar as anomalous PVD may have very different effects in an individual with diabetes as compared with a nondiabetic patient, or in the setting of a genetic predisposition to certain forms of age-related macular degeneration. Thus, the interplay of these multiple factors is an important consideration.

Histopathologic studies have shown that vitreoschisis is present in 80% of eyes with proliferative diabetic retinopathy. Clinical investigations using combined optical coherence tomography and scanning laser ophthalmoscopy have detected vitreoschisis in half of the eyes with macular holes and macular pucker. The various permutations of anomalous PVD are diagrammed in Figure 1. As can be appreciated, seemingly disparate diseases can in fact be perceived as different consequences of the same initiating event, i.e., anomalous PVD.

Our enhanced understanding of the role of vitreous in retinal disorders has led investigators to use pharmacologic vitreolysis in diseases such as diabetic retinopathy, macular holes, retinopathy of prematurity, and even congenital retinoschisis. Since initial attempts all used enzymes as adjuncts to surgery, the term “enzymatic vitreolysis” prevailed in the early literature. However, in 1998, the term “pharmacologic vitreolysis” was proposed, so that vitreolytic agents could be grouped according to their mechanism of action as either “enzymatic” or “nonenzymatic.” Furthermore, it was proposed that these agents could be grouped, as either nonspecific agents, such as tissue plasminogen activator, plasmin, microplasmin, and nattokinase, or substrate-specific agents, such as chondroitinase, dispase, and hyaluronidase. Although this perspective does have intellectual appeal on theoretical grounds, the original classification system seems to have little relevance today, because other than two nonenzymatic approaches (urea/vitreosolve and Arginine-Glycine-Aspartate (RGD) peptides), the overwhelming ma-
The majority of drugs that have been tested during the first decade are enzymes. It would seem, therefore, that in the next decade of pharmacologic vitreolysis an alternative classification might be more useful. Rather than basing this new classification system on the properties of the agents themselves, grouping could be organized on the basis of the biologic effects of the different agents, in particular whether they induce liquefaction ("liquefactants") or whether they induce dehiscence at the vitreoretinal interface ("interfactants"). Table 1 lists the different pharmacologic vitreolysis agents currently in development classified on the basis of biologic activity.

Another important consideration for the future of pharmacologic vitreolysis research and development is that when implemented clinically, pharmacologic vitreolysis will be performed on the eyes with abnormal vitreous. This is not only true for all the ophthalmic conditions identified in Figure 1, but also systemic conditions such as diabetes. It is known, for example, that diabetes induces significant biochemical and structural effects on vitreous, resulting in diabetic vitreopathy, termed by some diabetic vitreoretinopathy. Because diabetic vitreous is so different from normal vitreous, studies on the effects of pharmacologic vitreolysis on normal vitreous may fail to result in effective implementation of this therapy in pathologic conditions. This consideration might partly explain why hyaluronidase (developed as Vitrase, ISTA Pharmaceuticals, Irvine, CA) failed in Phase III Food and Drug Administration clinical trials for treating vitreous hemorrhage in diabetic retinopathy. No preclinical studies were done using Vitrase on diabetic vitreous. Although this agent did clear vitreous hemorrhage in 32.9% of cases, the saline control also cleared the blood in 25.5% of cases. Another explanation for the failure of Vitrase relates to the fact that hyaluronidase is not an interfactant, only a liquefactant (Table 1). Thus, although hyaluronidase will liquefy gel vitreous, it will not induce vitreoretinal dehiscence. In proliferative diabetic retinopathy, this will result in persistent traction on neovascularization with subsequent recurrent hemorrhages and vision loss. Previous studies have found similarly disappointing results with hyaluronidase.

A notable exception to the foregoing precedent is the study of Zhiliang et al, published in this issue of Retina. These investigators studied the effects of pharmacologic vitreolysis in diabetic rats. The results showed that hyaluronidase alone did not induce PVD in any of the 10 subjects tested, confirming previous studies. Plasmin alone induced only a partial PVD in 10 of 10 subjects (100%). Although previous investigations using plasmin and microplasmin claimed to induce total PVD, these experiments were performed in nondiabetic vitreous. Pilot clinical studies in diabetic eyes without controls found that plasmin was effective as an adjunct to surgery for diabetic vitreoretinopathy, but there were no studies using plasmin in diabetic eyes without surgery. Thus, further work needs to be undertaken with diabetic eyes using plasmin in a nonsurgical setting. This is important, because past studies have shown that a partially detached vitreous carries the worst prognosis for progressive diabetic retinopathy. The results of the studies presented herein suggest that plasmin alone would not only fail to achieve effective pharmacologic vitreolysis in diabetic vitreopathy, but might even worsen the prognosis by inducing a partial (anomalous) PVD. Interestingly, the combination of plasmin and hyaluronidase in the studies by Zhiliang et al induced a total PVD in 8 of 10 eyes. Of course, these studies were in an animal model of diabetic vitreous.
vitreopathy and the results need to be corroborated in humans.

Zhiliang et al are to be congratulated for having brought to reality the previously proposed\textsuperscript{29,41} concept of combination pharmacologic vitreolysis, because combining plasmin with hyaluronidase was indeed effective in achieving a total PVD in 80\% of cases. Thus, not only did these investigators appropriately study pharmacologic vitreolysis in a diabetic model, but they also used combination therapy to attain a therapeutic outcome that neither agent alone could achieve. It is likely that in these studies the liquefying hyaluronidase induced gel liquefaction whereas the interfactant properties of plasmin induced sufficient dehiscence at the vitreoretinal interface to induce total PVD in a much higher percentage of cases than has been observed to date in any clinical trials. Future clinical trial protocols might thus benefit from incorporating combination therapy whose value was previously suggested in theory\textsuperscript{41} and has been proven in practice in nondiabetic vitreous\textsuperscript{29} and now in experimental models of diabetic vitreopathy. Including outcome measures of ocular physiology and metabolism would also test the hypothesis that pharmacologic vitreolysis can induce salubrious effects on ocular metabolism.\textsuperscript{42,43}

J. Sebag, MD, FACS, FRCOphth
VMR Institute, Huntington Beach
University of Southern California
Los Angeles, California

References

28. Hikichi T, Kado M, Yoshida A. Intravitreal injection of hyal-

Copyright © by Ophthalmic Communications Society, Inc. Unauthorized reproduction of this article is prohibited.