

Editorial

Pharmacologic Vitreolysis

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The annals of surgery reflect numerous instances wherein widely practiced treatment modalities were replaced over time by less invasive and, eventually, atraumatic interventions. Such evolution derives primarily from increased knowledge of the basic pathogenic mechanisms of disease. Often, there is substitution of surgical therapies with medical treatment modalities and, ultimately, with approaches aimed at the prevention of the disease entirely. Consider, for example, that abscesses, once routinely treated by surgical drainage, became amenable to antibiotic regimens that are not only less traumatic and more successful, but considerably less expensive. Improved sanitary conditions and vaccines subsequently eradicated many infectious diseases that once plagued entire societies and influenced the course of history. This very type of evolution is just beginning to move beyond surgery in the area of vitreoretinal diseases.

Vitreous is an extracellular matrix that fills the center of the eye with a clear viscoelastic tissue that maintains clarity and protects against the untoward effects of eye, head, and body movements.¹ Composed 98% of water, the corpus vitreus exists in a gel state (Figure 1) because of the intricate organization of its macromolecular components. Collagen and hyaluronan are the macromolecules of import, but a number of proteoglycans, glycoproteins, and other lesser molecules may play a critical role in the organization of the two major macromolecules (Figure 2) into a three-dimensional structure^{2,3} that achieves the aforementioned functions of clarity and shock absorption.^{1,4} These intermediary molecules may or may not be the same as those responsible for the adherence of the posterior vitreous cortex to the internal limiting lamina of the retina.⁵ This

information is critical in properly designing approaches to alter vitreous on a molecular level. If the gel state and vitreo-retinal adhesion are both the result of one or a group of closely related molecule(s), then one agent will probably suffice to induce salubrious alterations in vitreous structure. If, as is likely, these two properties of vitreous are the consequences of two disparate molecules or groups of molecules, then a single agent will not suffice if there is to be any specificity to the action of the agent. In such a case, more than one agent will be needed to alter the molecular state of the corpus vitreus properly, as well as the vitreo-retinal interface.

Whereas vitreous has long been overlooked as crucial in the pathophysiology of various blinding disorders, this has begun to change in light of recent significant advances in knowledge of the structure, function, and pathobiology of this unique matrix.⁴ Advances have led to the development of an impressive array of surgical instruments, techniques, and results for conditions that permanently blinded many people just a generation or two ago. Success has engendered complacency with respect to the traumatic nature of surgery, its inherent limitations, and the enormous costs to society. As a result, involved parties have overlooked the fact that as successful as a surgical approach may seem, it can never be as beneficial as a nonsurgical treatment, both in terms of clinical outcome measures and socioeconomic aspects.

The need for a noninvasive approach to vitreoretinal disorders is beginning to be met by new methods of altering the state of the corpus vitreus, intended to eliminate untoward effects on the retina and vision. The term "pharmacologic vitreolysis" refers to the use of agents that alter the molecular organization of vitreous in an effort to reduce or eliminate

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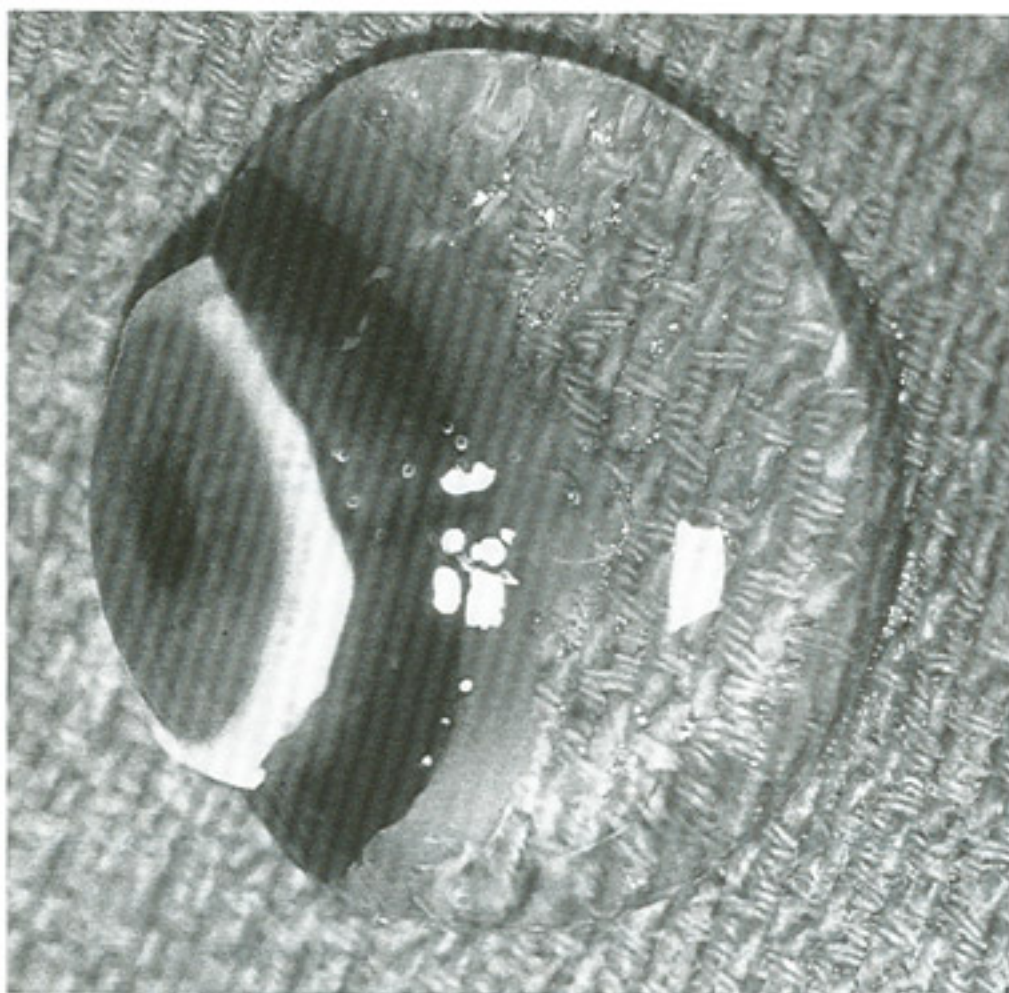


Fig. 1. Human corpus vitreus. Photograph of an eye from a 9-month-old child with the sclera, choroid, and retina dissected away, leaving the corpus vitreus attached to the anterior segment. Because of the donor's age, there is a solid gel state to this vitreous, which maintains its shape although the specimen is in room air on a surgical towel. (Specimen courtesy of The New England Eye Bank. Reprinted with permission from Springer-Verlag, New York.⁴)

its role in disease. This is achieved by liquefying the gel structure of the corpus vitreus (synchysis) and weakening the adherence of the posterior vitreous cortex to the internal limiting lamina of the retina, leading to separation and collapse of the corpus vitreus away from the retina (syneresis). In similar fashion to endogenous posterior vitreous detachment,⁶ the success of pharmacologic vitreolysis depends on inducing these two events simultaneously. Uncoupling these two processes, particularly by inducing liquefaction without weakening vitreo-retinal adherence, may worsen matters significantly. Such a state is present in many conditions that are prone to retinal detachment, such as myopia and various arthro-ophthalmopathies.⁷ Synchysis without syneresis may also induce problems at the posterior pole, such as vitreopapillopathies, vitreo-macular traction syndrome, and perhaps even macular holes.

Various agents designed to produce pharmacologic vitreolysis have been tried over the years, but none has met with sufficient success to stimulate widespread use. The table outlines the approaches currently being used. The different agents can be grouped as enzymatic and nonenzymatic. Within the enzymatic group are substrate-specific agents and nonspecific agents. The first of the agents in current use, Plasmin,⁸ is a nonspecific protease that can be isolated from the patient's own serum for use at

Table. Pharmacologic Vitreolysis

| Type of Vitreolysis | Treatment |
|----------------------------|---|
| Enzymatic | |
| Nonspecific | Plasmin ³ Dispase ⁹ |
| Substrate-specific | Chondroitinase ⁷ Hyaluronidase ^{12,13} |
| Nonenzymatic ¹⁷ | |

surgery. A phase II clinical trial of this agent is currently being organized in the United States. The other relatively nonspecific, enzymatic agent currently under investigation is Dispase (Gibco, Grand Island, NY).⁹ In this issue, this agent is described as having successfully induced posterior vitreous detachment in porcine and human eyes. No evidence of vitreous liquefaction was found, and only post-mortem eyes were studied, somewhat limiting the applicability of these findings. A substrate-specific, enzymatic agent that has been in development for a number of years is Chondroitinase. This agent lyses chondroitin sulfate, a molecule that may be important in maintenance of the gel state of the corpus

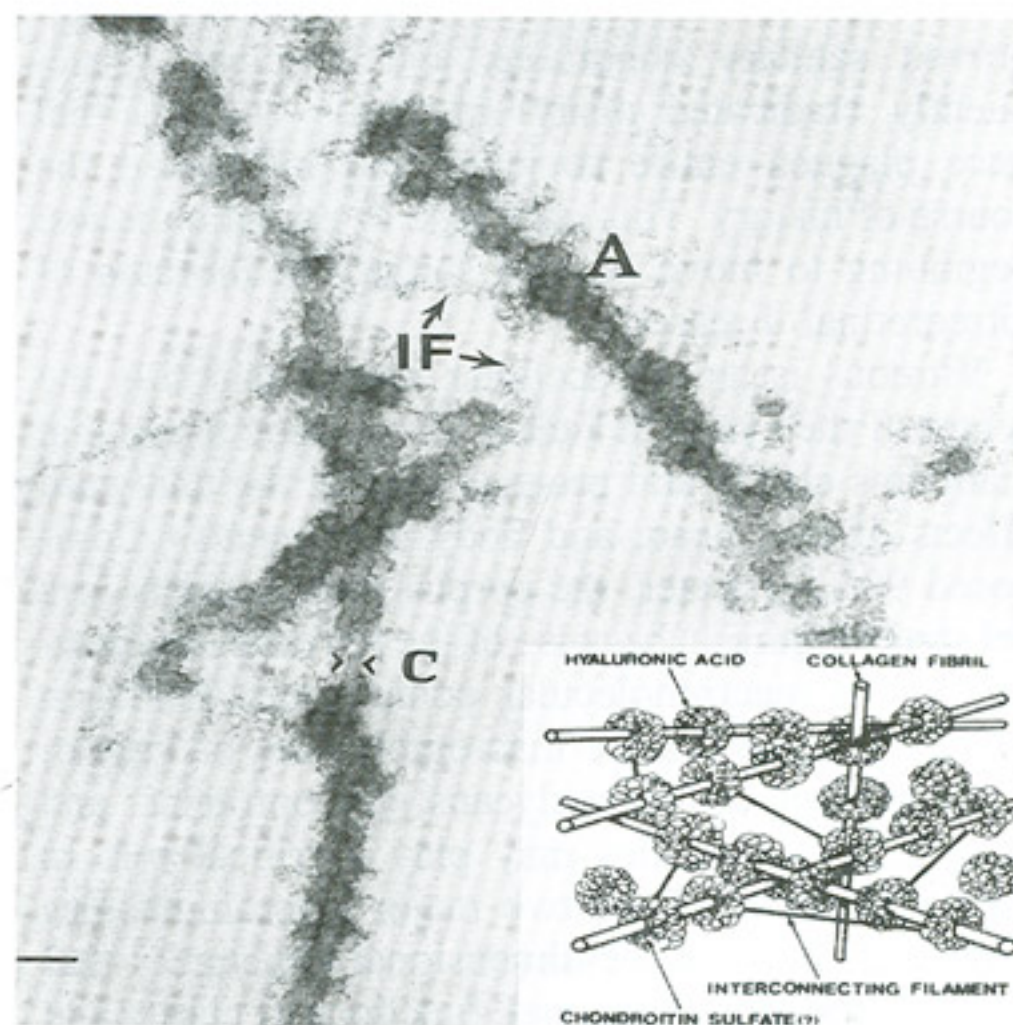


Fig. 2. Ultrastructure of hyaluronan/collagen interaction in bovine vitreous. Bovine vitreous specimen was fixed glutaraldehyde/paraformaldehyde and stained with ruthenium red. Collagen fibrils (C) are coated with amorphous material believed to be hyaluronan. Interconnecting filaments (IF) bridge between collagen fibrils and attach at sites of hyaluronan adhesion to collagen fibrils. The hyaluronan may connect to the collagen fibrils via an intermediary molecule, perhaps chondroitin sulfate. Bar, 0.1 μ m. Courtesy of Dr. Asakura. (Reprinted with permission.¹⁰)

vitreous^{2,10} and in vitreo-retinal adhesion; hence, there has been considerable interest in the use of this agent. Studies¹¹ have purported that when used as an adjunct to vitreous surgery, this agent facilitates the removal of premacular membranes. A phase I trial of this agent was completed in the United States nearly 2 years ago; the results await publication in the near future. In this trial, patients with macular holes and others with proliferative diabetic vitreoretinopathy were treated with this agent as an adjunct to vitreous surgery with no significant untoward effects.

As described, pharmacologic vitreolysis can be a useful adjunct to current vitreous surgery techniques. However, pharmacologic vitreolysis can also be performed to replace vitrectomy, as is being attempted with Hyaluronidase for nonclearing vitreous hemorrhage.¹² This application is currently the subject of a phase II clinical trial that has enrolled over 100 subjects in the United States. In this issue, an article¹³ suggests that this type of agent may be useful in the induction of posterior vitreous detachment. Should this be true, it may have considerable use in patients with diabetes who are at risk of developing proliferative diabetic vitreoretinopathy, as tremendous benefits can be garnered from inducing molecular vitreolysis before developing this advanced stage of disease.¹⁴ Liquefaction of the corpus vitreus and detachment of the posterior vitreous cortex before the onset of new vessel growth will have a better prognosis than if the vitreous were still attached to the retina.^{15,16} Inducing synchysis and syneresis of the corpus vitreus without the use of exogenous enzymes also may be possible, and perhaps safer. In this approach, nonenzymatic agents are used to alter the quaternary and perhaps even the tertiary conformation of vitreous macromolecules, thereby inducing vitreolysis.¹⁷

Although the day when vitreous surgery is replaced by noninvasive therapy remains far in the future, these new developments hold great promise. Such approaches should facilitate and enhance present methods of treating vitreo-retinal disorders. Furthermore, these new techniques will likely usher in the time when fewer patients will need the extensive invasive procedures currently being performed. The development of a simpler, cheaper, and less-invasive approach to vitreo-retinal disease eventually may make therapy available to less-privileged

people who cannot presently avail themselves of such advanced and costly care.

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