

Murray Johnstone, MD

Dr. Johnstone reflects on his early training as well as the evolution of his research on aqueous outflow.



1. What do you remember most about your training under Morton Grant, MD? According to Dr. Grant and his associates at the Howe Laboratory, success results from contributions to the field through clinical and basic research of a lasting nature. I especially remember Dr. Grant's approach to transferring knowledge. As the editor of a textbook on glaucoma and one of the most widely read people in the field, he could have simply imparted static textbook-based knowledge. Instead, he used a Socratic approach in which he more often posed questions than provided answers. He always listened politely and respectfully to students' comments and ideas and often asked new questions. Dr. Grant also placed great value on, and was quick to praise, careful observation as an effective means of finding important truths in both the clinic and the laboratory. He conveyed the message that textbook-based explanations and research findings, even his own, represent provisional approximations of the truth that are open to continual reassessment.

2. How did Dr. Grant shape your research path? Just prior to my entering the laboratory, Bruce Ellingsen, MD, and Dr. Grant published a series of perfusions and microsurgical experiments exploring what happens when the walls of Schlemm's canal come together to close the canal's lumen.¹⁻³ They concluded that the variable resistance found in normal eyes and the abnormal resistance in glaucoma result from pressure-induced structural changes that cause the trabecular meshwork to come into apposition with the unyielding external wall of Schlemm's canal.

Drs. Ellingsen and Grant's studies framed two important questions. First, how could their observations of the canal's wall collapsing be reconciled with Dr. Grant's earlier observation that removing the trabecular meshwork with a cystotome eliminates outflow resistance? Dr. Grant and I repeated the experiments, this time with histologic confirmation.

We found the same improvement in outflow he had seen previously, but we also found evidence that the technique removes all of the structures within Schlemm's canal and tears away structures at the level of the collector-channel ostia.⁴ We therefore concluded that, although the earlier work localized resistance to the region of Schlemm's canal, such studies did not provide evidence to localize resistance to the trabecular meshwork.

The second question was what type of structural changes develops in the trabecular meshwork with increasing pressure that correlates with resistance changes. Our experiments demonstrated that the trabecular meshwork is highly compliant and responds to increasing pressure by apposing the external wall of Schlemm's canal.⁵ We thus confirmed the mechanism posited by Drs. Ellingsen and Grant.

Surprisingly, we also found the trabecular meshwork to be sensitive to small changes in IOP.⁵ We concluded that progressive distention of the trabecular tissue provides a pressure-sensing or baroreceptor-like mechanism. We further concluded that the collapse of Schlemm's canal at low pressure provides a mechanism to maintain the blood-aqueous barrier. Additionally, I identified collector vessels or valves spanning Schlemm's canal.⁶ The combined findings led me to think that the trabecular tissues act as a pumping system. Dr. Grant was appropriately skeptical.

At that point, I returned to Seattle, where I fully intended to limit myself to clinical practice. Much to my surprise, Dr. Grant kept encouraging me to pursue my research. Finally, he flew to Seattle to emphasize the importance of continuing the studies. I obtained a grant from the NEI and, for some 10 years after leaving Boston, worked on outflow issues with Dr. Grant's continued interest and col-

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FAST FACTS

- Consultant in Glaucoma for the Department of Ophthalmology at the Swedish Medical Center in Seattle, 1973 to present
- Clinician with a glaucoma subspecialty referral practice, 1974 to present
- Recipient of an NEI Research Grant Award for "Factors Regulating Aqueous Outflow in Glaucoma," 1977
- Committee Member of the ASCRS Glaucoma Special Interest Group, 1997 to present
- Recipient of the AAO's Senior Honor Award, 2001

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laboration. After several failed attempts to publish my research results, I abandoned my efforts for years. Recently, I felt compelled to complete the work. Fortunately, new technologies have become available, and I found a large body of literature describing manifestations of aqueous pumping from Schlemm's canal into the aqueous veins.

3. How do you make time for both your basic research and a busy clinical practice? I do it with difficulty and not well because of time constraints. I am lucky to have an understanding wife who faces many lonely hours but remains consistently cheery and supportive, or I could not continue. I am also fortunate to have a highly competent, long-term, dedicated office manager and staff who assume almost total responsibility for financial and managerial decisions. In addition, I have had the good fortune to collaborate with Barbara Smit, MD, PhD, a talented clinician scientist, and with Robert Stegmann, MD, who couples exceptional observational skills with great intellectual curiosity.

4. How have you challenged the thinking on the aqueous outflow system? Understanding the new conceptual framework I propose⁷ requires challenging each premise of the traditional paradigm. I posit the following new premises.

First, aqueous outflow is dynamic and results from the trabecular meshwork's acting as a mechanical pump that derives its energy from IOP transients such as the ocular pulse. Second, the endothelium of Schlemm's canal resists the forces of IOP. By attachments of this endothelium to the trabecular lamellae, the entire trabecular meshwork acts as a resistance unit. Third, the juxtacanalicular space is not a rigid syncytium but instead undergoes dramatic changes in size and shape with modest changes in IOP. Fourth, outflow resistance is the result of this endothelial monolayer and the trabecular lamellae's acting as a unified structure.

Fifth, the term *giant vacuole* is an unfortunate misnomer. It suggests a metabolic process, whereas the real excitement lies in these endothelial cells' ability to undergo remarkable distention and recoil in response to moderate changes in pressure. Sixth, the flow from the juxtacanalicular space to Schlemm's canal is only through the lumen of the aqueous valves that arise from the canal's inner wall and attach to its outer wall; transcellular pores represent fixation artifacts. Seventh, the endothelial cells of Schlemm's canal control flow through mechanotransduction mechanisms like those found throughout the vasculature. These mechanisms modulate the structure of the endothelium and trabecular lamellae. Finally, the variable resistance in normal eyes and the abnormally increased variable resistance found in glaucomatous eyes result from progressive apposition of the wall of Schlemm's canal with closure of the canal's lumen.

Apposition precludes the normal function of the trabecular meshwork's pump.

5. How may your outflow system model influence new research and treatment approaches? The targeted treatment of glaucoma requires an understanding of the underlying mechanism causing the disease. The first step in understanding is to figure out how the normal system functions. The second step is to compare the normal with glaucoma to find out how the glaucomatous system fails. The third step is to find treatments that return the system to its normal state. The mechanical pump model of aqueous outflow provides a regulatory framework for controlling flow and pressure.⁷ In this model, the pump fails in glaucoma.⁸ An extensive body of evidence demonstrates that the pump's failure in glaucoma results from stiffening trabecular tissue and its progressive compression against the external wall of Schlemm's canal.⁸

Because the problem causing pump failure appears to be structural, surgical intervention seems warranted and, ideally, should focus on the surrounding tissues that participate in excursions of trabecular tissue without damaging the pump. Although incisional surgery may accomplish a desired structural change, noninvasive techniques seem preferable. Perhaps one could use a high-resolution imaging system to guide a highly focused laser stereotactically. Low levels of energy could selectively shrink tissue in the region of the scleral spur and ciliary body and thereby cause these structures to rotate posteriorly, thus opening Schlemm's canal. Such a procedure might reverse abnormality with the same specificity and safety as does laser peripheral iridotomy for angle-closure glaucoma.

The basis for new medical alternatives is that the pump's regulation relies on maintaining an optimal separation between the trabecular meshwork and the external wall of Schlemm's canal. Drug development can focus on agents that optimize the intrinsic distention and recoil of trabecular tissues, both of which ultimately control pressure and flow. □

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