

# Outflow Resistance

An analysis of early and recent research.

BY MURRAY JOHNSTONE, MD



Welcome to Glaucoma Today's new column, "Bench to Bedside: How Laboratory Studies May Better Explain Why Procedures Work and Why They Fail." The essence of this series is to explain the "why" of the clinical quandaries we glaucoma specialists often face. The clinical quandary addressed in this first edition is why canal-based surgery does not lower IOP to episcleral venous pressure. One would think it should, but on average, it does not. Why? Basic laboratory experiments may improve our understanding.

We asked three basic and clinician scientists critical questions about outflow to bridge the gap of this clinical puzzle from bench to bedside. In this first installment, Murray Johnstone, MD, provides an important historical viewpoint in his answers to four questions about outflow. Stay tuned for responses from Arthur J. Sit, MD, and Haiyan Gong, MD, in future editions of "Bench to Bedside."

—Ronald L. Fellman, MD, and Davinder S. Grover, MD, MPH, section editors

## CLINICAL PUZZLE

Canal-based surgery does not lower IOP to episcleral venous pressure, which is reported to be around 10 mm Hg. Why?

**The classic outflow experiment by Rosenquist et al<sup>1</sup> found greater downstream resistance to aqueous outflow than Grant's classic study.<sup>2</sup> Why? Does this article at least partially explain IOP control after canal-based surgery?**

Grant's 1958 and 1963 laboratory research demonstrated that a 360° trabeculotomy eliminated 75% of outflow resistance.<sup>2,3</sup> This finding resulted in the hypothesis that 75% of resistance is in the trabecular meshwork (TM). This theory was recorded in textbooks along with the additional assumption that most of the resistance was in the juxtacanalicular tissue (JCT) space. Although Grant removed the uveal meshwork with no appreciable effect on resistance,<sup>3</sup> he did not conduct microsurgical studies separating the corneoscleral lamellae from the JCT space. Accordingly, the JCT resistance hypothesis could not be derived from Grant's microsurgical studies. Within a few years of his research, however, the TM and JCT resistance hypothesis was regarded as axiomatic with the supposition that it was no longer necessary to examine the underlying evidence.

There is a fundamental problem! Grant and colleagues published later studies<sup>4-8</sup> that incorporated newer empirical evidence about outflow resistance and

generated a different conclusion and an alternative outflow hypothesis. Specifically, they hypothesized that the measured resistance to aqueous outflow depends on pressure-dependent TM motion and distal resistance. These later studies by Grant et al further explained why canal-based surgery might not lower IOP to episcleral venous pressure level.

In a critically important comparative study involving the removal of either the TM or the external wall of Schlemm canal (SC), Ellingsen and Grant made two very important observations. First, they demonstrated that, at IOPs of 5 and 10 mm Hg, trabeculotomy eliminated only 14% and 27% of resistance, respectively.<sup>4</sup> (The low pressures simulate normal differentials across SC in vivo, because episcleral venous pressure is approximately 8 mm Hg.) Similar to results in earlier outflow studies,<sup>2,3</sup> at higher IOPs of 20 to 50 mm Hg, 62% to 82% of resistance was eliminated in this later study.<sup>4</sup>

Ellingsen and Grant's second observation was that removing the external wall of SC also eliminated approximately 75% of the resistance, leaving only 25% to be explained by the TM (based on the same IOP parameters as in Grant's earlier studies<sup>4</sup>). The investigators reconciled these findings by concluding that it was the resultant pressure-dependent movement of the TM to the external wall of SC that accounted for much of the increasing resistance as IOP rose, not just the TM. Per Ellingsen and Grant, "as intraocular pressure increases, the outward stretching of the trabecular meshwork and inner wall would normally be limited by the fairly rigid overlying sclera."<sup>4</sup>

Further support for these conclusions derives from studies using microsurgical manipulations of the lens to move TM tissue away from the external wall of SC through both chamber deepening<sup>4</sup> and lens depression.<sup>6,7</sup> The TM motion resulting from the scleral spur's pulling the TM away from SC's external wall caused a profound reduction in resistance, completely eliminating the increasing resistance previously found with rising IOP.

These findings point to the movement of the TM to SC's external wall as a cause of resistance, particularly in glaucomatous eyes. According to Ellingsen and Grant, "glaucomatous eyes ... differed not only in having an abnormally high resistance to outflow but also in responding with abnormally steep increase of resistance to elevated pressure."<sup>5</sup> Grant and I later explored pressure-dependent motion. We showed that the configuration of TM tissue is highly pressure dependent, with apposition to SC's external wall occurring at relatively low pressures.<sup>8</sup> None of these findings has been refuted or challenged.

Because the premise of much research on outflow resistance is based on Grant's work, citing his earlier study in isolation may inadvertently lead to incomplete awareness and understanding of causal factors in outflow resistance. Rosenquist et al<sup>1</sup> replicated Ellingsen and Grant's trabeculotomy studies by using a similar lower (7 mm Hg) and higher (25 mm Hg) IOP, and they reported resistance reductions of 49% and 75%, respectively. Epstein also believed this was because the TM did not artificially close the canal at lower perfusion pressures.<sup>9</sup> These studies by Rosenquist et al and Epstein emphasize the need to refer to Grant's early work as well as the additional in-depth studies<sup>5-8</sup> when considering sites of outflow resistance.

One might ask why Grant's early work is cited extensively to support the concept of the TM and even the JCT space as the source of resistance, whereas the far more complete understanding provided by Grant and colleagues' later studies<sup>4-8</sup> are rarely mentioned. Authorities investigating the history of science claim such citation omissions are the norm in scientific endeavors large and small.<sup>10</sup> Once a hypothesis becomes an established basis for research efforts, rival hypotheses are systematically excluded to provide the scientific community with a seamless narrative, a stable framework for future research.<sup>10</sup> A hypothesis once elevated to the level of axiom defines the limits of acceptable solutions and the steps necessary to obtain them. Citing only Grant's early work with regard to the JCT and omitting the later, far more informative studies prevent both researchers and microsurgeons from accessing a complete and balanced framework

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within which to pose questions and find appropriate solutions.

**If distal outflow resistance is higher than initially anticipated, is most of the resistance coming from deep in the sclera, or is it more superficial?**

Experimental microsurgical studies by Grant and Ellingsen anticipated a major role for distal outflow resistance.<sup>4</sup> The first successful clinical sinusotomy or externalization of SC in the United States was performed by Ellingsen under the watchful eyes of Chandler and Grant at Massachusetts Eye and Ear Infirmary—a remarkable bench-to-bedside story achieved in less than a year. Grant described the removal of two-thirds of the scleral wall without an appreciable change in resistance, thus placing the distal resistance close to the region of collector channel entrances.<sup>11</sup>

Identifying collagen flaps at collector channel entrances as an important source of resistance, Rohen's classic study also notes that the flaps are held open by attachments to the TM.<sup>12</sup> Researchers at the University of Washington recently developed high-resolution optical coherence tomography and optical microscope platforms that permit the real-time observation of collector channel motion. My colleagues and I have observed pressure-dependent opening and closing of highly mobile tissue flaps at collector channel entrances and adjacent intrascleral collectors, as anticipated by Rohen.<sup>13</sup>



**What is outflow facility, and how is it measured? What is the correlation between outflow facility and outflow resistance?**

Aqueous outflow resistance represents the sum of factors that limit the rate of flow from the eye. Facility is the inverse of resistance. Such measurements help clinicians understand the disease process. Various methods of

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measurement are available, although each is “highly variable and fraught with limitations and assumptions,” as Carol Toris, PhD, and others have pointed out.<sup>14</sup>

### In your opinion, why is circumferential flow in SC limited, and does this influence canal-based surgery?

Evidence indicates that the entire aqueous outflow apparatus is pre-stressed and tensionally integrated by the force of IOP, which allows it to act as a pressure-sensing, pressure-responsive, and pressure-regulating system.<sup>15-17</sup> Evidence also indicates that the TM is effectively spring loaded, with the inner wall of SC poised just short of its external wall at physiologic pressures in normal eyes. According to Ellingsen and Grant, “The capacity of the trabecular meshwork and the inner wall of Schlemm’s canal to stretch with a pressure gradient across it, as well as the apparent lack of circumferential flow in Schlemm’s canal, suggests that appositional closure of the canal probably exists even at low pressures.”<sup>3</sup> The TM and collector channel tissues are remarkably sensitive to pressure. Recent evidence by optical coherence tomography demonstrates millisecond-level motion sensitivity, which enables the tissues to respond easily to ocular transients like those generated by the ocular pulse.<sup>13,18,19</sup>

Glaucoma may result from changes in the elasticity and compliance of outflow system tissues that reduce their ability to sense, respond to, and thus regulate IOP. Collapse of SC is described as resulting from such a change in tissue properties.<sup>8,15</sup> Rather than simply create a communication with SC, surgery directed at maintaining the patency of the collector channel ostia may be important. Additionally, canal-based surgery that focuses on maintaining or restoring the spring-loading properties of the TM may provide a new focus for the next generation of surgical innovators. ■

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