Glaucoma filtration surgery is over 100 years old,\textsuperscript{1,2} so I am very enthusiastic about novel surgical techniques\textsuperscript{3} directed at the site of abnormal resistance at or near the inner wall of Schlemm canal.\textsuperscript{4} The scientific rationale for Schlemm canal surgery, however, dates back approximately 50 years to the exquisite dissection and perfusion studies of W. Morton Grant, MD.\textsuperscript{4} The field has not progressed as much as one might believe, and my purpose in this article is to remind Glaucoma Today's readers of Grant's experiments\textsuperscript{4} and what he actually discovered. Many have misinterpreted his findings, and there is no clear rationale for some of the proposed surgical procedures aimed at Schlemm canal. I urge readers to critically examine the rationale for all novel surgical procedures targeting this site with Grant's work in mind.

**FILTRATION SURGERY VERSUS SCHLEMM CANAL SURGERY**

Filtration surgery totally bypasses the conventional outflow pathway and basically connects the anterior chamber to the subconjunctival space (guarded by an intervening scleral flap), where it is believed that the pressure is 0 to 1 mm Hg (B.A. Ellingsen, unpublished data, 1969). The surgeon is fistulizing the inside of the eye to the outside. If wound healing does not induce resistance to the subconjunctival flow of fluid (as typically happens gradually over the first several postoperative weeks), the procedure results in very low pressures and often hypotony, especially immediately postoperatively.

In contrast, manipulating or operating on Schlemm canal leaves its outer wall as well as the more distal structures intact. Significant remaining distal resistance\textsuperscript{4,5} results in a higher IOP than would bypassing these distal structures to directly access the subconjunctival space.

**WHAT DR. GRANT REALLY FOUND**

In what I consider to be one of the greatest single publications of multiple experimental manipulations of the aqueous outflow system ever published\textsuperscript{4}—and one that I hand out to all of my fellows and residents—Grant progressively dissected the trabecular meshwork in enucleated human eyes such that the depth of dissection was correlated with perfusion of the same eye to measure outflow facility. He observed no change in outflow resistance until he penetrated the inner wall of Schlemm canal. He thus found that approximately 75% of the resistance to aqueous outflow was either at or just proximal to the inner wall of the canal in both healthy human eyes and those with open-angle glaucoma (OAG).\textsuperscript{4} In other words, in glaucomatous eyes, he eliminated both normal and abnormal glaucomatous resistance by incising the inner wall of Schlemm canal.

These findings are all well known, but it is important to recognize that 25% of the normal resistance to outflow was located somewhere between the outer wall of Schlemm canal and distally. (Furthermore, this distal resistance was the same in both healthy and glaucomatous eyes, thus providing no evidence—albeit only in a small number of diseased eyes—of distal outflow pathway glaucoma.) Residual distal resistance after most of the new canal surgeries results in a higher IOP than does a glaucoma filtration operation, where the anterior chamber is short-circuited and bypassed to the subconjunctival space, which has low resting pressure.

The most significant detail of Grant’s experiments is often overlooked. He perfused these eyes at elevated pressures, and the results are consistent with the “OUTFLOW EXPERIMENT” hypothesis. The lack of a change in facility at the inner wall of Schlemm canal predicts that the aqueous outflow resistance was still present, but this resistance was bypassed. Thus, one might correctly postulate that the site of abnormal resistance is not the inner wall of Schlemm canal, but instead is in the more distal drainable portion of Schlemm canal. (On the other hand, Grant’s observations also support the thesis that the inner wall of Schlemm canal is the site of resistance. Some authors have argued that the distal resistance is located in the inner wall of Schlemm canal, but Grant’s findings suggest the distal resistance is located somewhere else.)

"There is significant outflow resistance from the outer wall of Schlemm canal distally."
IOP (approximately 35 mm Hg) in order to accurately measure outflow resistance (his constant-pressure outflow apparatus required high levels of flow). I remember awakening in the middle of the night worrying that this choice of perfusion pressure might have increased resistance by compressing Schlemm canal or the trabecular meshwork, so my colleagues and I repeated these experiments at a much lower perfusion pressure. Fortunately, Grant’s summary findings and conclusions held true with one exception. We found that the distal outflow resistance from Schlemm canal outward represented an even higher percentage of normal outflow resistance (approaching 40%) in normal eyes in the same internal trabeculotomy experiments.

From Grant’s experiments, one can tentatively conclude that all of the glaucomatous outflow resistance is at or proximal to the inner wall of Schlemm canal and that normal and glaucomatous eyes therefore have similar distal outflow pathways and resistance. The morphological correlate of this distal resistance is really unknown, because the collector channel vessels appear to have open lumens. Johannes Rohen (unpublished data, 1989) has hypothesized that there may be sphincters immediately behind the ostia of the collector channels in the outer wall of Schlemm canal, but the exact cause of the distal resistance in both normal and glaucomatous eyes remains unclear. By performing excimer laser dissections from the sclera inward to the outer wall of Schlemm canal, Schuman has shown that the distal resistance is very close to the outer wall.

I would also like to highlight Grant’s exact dissection technique. He had to incise the inner wall of Schlemm canal for the total 360º of the angle (all 12 clock hours), because outflow pathway resistance behaves segmentally. There is minimal circumferential flow in the canal, so a 1-to-2-hour internal trabeculotomy (incising or disrupting the inner wall) produces only a proportional amount of the 75% reduction in resistance. Of note, only six eyes with primary open-angle glaucoma (POAG) were studied in this way, and Grant issued a plea for further study. I am aware of perhaps six additional POAG eyes studied by myself or others that, fortunately, demonstrated findings similar to Grant’s. Still, there could be some unique (POAG) eyes where the abnormal resistance derives from another location. The entire proximal corneal-scleral trabecular meshwork or the distal outflow pathway beyond the outer wall of Schlemm canal could be the locus of any added abnormal outflow resistance in other secondary or even primary glaucomas. That is, the cause of glaucoma could be increased abnormal resistance at a site where normally there is no significant resistance. This certainly may be the case in many secondary OAGs (eg, exfoliation glaucoma).

**TRABECULECTOMY**

Cairns originally devised the trabeculectomy not to be a guarded scleral flap filtration operation but rather to remove the site of Grant’s abnormal glaucomatous resistance. Based on the details of Dr. Grant’s work already presented, it is clear that such a localized surgical procedure would not eliminate resistance when Grant had to incise 360º of the angle to achieve that effect. Interestingly, for a while after the procedure’s introduction, there was vigorous debate over whether a trabeculectomy was a filtration operation or not. The cause of discussion was case examples of low postoperative IOP without an apparent bleb. The original dissection technique of Cairns, however, involved the excision of the scleral spur in order to include the total abnormal trabecular meshwork (and the aqueous humor is believed to exit primarily from the posterior half of the trabecular meshwork closest to the scleral spur). I therefore strongly suspect that many of these blebless cases achieved low IOPs due to the formation of cyclodialysis clefts.

The history of trabeculectomy might be summarized as the right operation for the wrong reason.

**ELIMINATING PROXIMAL RESISTANCE**

The outflow pathway behaves segmentally, because there is limited circumferential flow in Schlemm canal (Figure 1). With the canal’s outer wall exposed, why does the aqueous humor not flow out through the collector channels (or go around the lumen of Schlemm canal)? One answer might be that, in a form of Ohm’s law, it does. Increased flow through a lumen with resistance (either the collector channel or Schlemm canal’s lumen) raises pressure in the lumen. This is totally different than entirely bypassing the conventional outflow pathway and Schlemm canal in a filtering operation and allowing communication between the anterior chamber and subconjunctival space, where there is very low pressure. Alternatively, from the observations of Rohen, one might just think of the ostia of the collector channels (or the collapsed, cut ends of Schlemm canal) as functionally having sphincters.

How many 1-hour effective trabeculotomies, then, would eliminate all of the proximal resistance? My interest in this question arose when it became feasible to use YAG goniopuncture to treat glaucoma. How many holes in Schlemm canal and with what spacing could eliminate resistance? My colleagues and I repeated Grant’s classic experiments using a series of 1-hour incisional internal trabeculotomies. Except for certain secondary glaucomas, such as juvenile OAG and glaucoma due to juvenile rheumatoid arthritis, YAG laser therapy to the trabecular meshwork proved ineffective.
because the tissue healed,\textsuperscript{10,11} which we did not understand at the time.

Our data are shown in Figure 2.\textsuperscript{5} Consistent with Grant’s findings, whether at low or high pressure, 1 clock hour of trabeculotomy was notably suboptimal for eliminating the outflow resistance. Despite some differences with larger extents of trabeculotomy, whether perfused at high or low pressure, our general impression was that four equidistant 1-hour trabeculotomies would eliminate almost all of the proximal resistance at the inner wall of Schlemm canal. Of course, in a glaucomatous eye (which we did not study), one might expect to get more bang for the buck with fewer 1-hour trabeculotomies, because with each hole made in Schlemm canal, one is bypassing the extra glaucomatous resistance (Figure 3). The point, however, is that one would still wind up with a relatively higher IOP in such eyes, because the remaining distal resistance should be similar to that of the normal eye.

These considerations are of great practical importance, despite the failure of YAG trabeculopuncture. For example, both Grant’s\textsuperscript{4} and Rosenquist’s\textsuperscript{5} studies would predict further lowering of IOP postsurgically if more than one iStent Trabecular Micro-Bypass Stent (Glaukos Corporation)\textsuperscript{14,15} were placed in Schlemm canal, especially spaced as far apart as possible. Douglas Johnson’s group studied this experimentally in cultured human anterior segments,\textsuperscript{16} and my interpretation of their data is that they confirmed this concept. There also seem to be preliminary data from human surgical experience indicating that more than one iStent provides additional IOP lowering.\textsuperscript{17} These findings are predictable based on Grant’s experiments.\textsuperscript{4}

\section*{HOW DO SCHLEMM CANAL PROCEDURES WORK?}

When analyzing the newest Schlemm canal operations, surgeons need to remember Grant’s scientific work.\textsuperscript{4,5} They also need to ask for a specific rationalization of the mechanism of efficacy for these procedures in the context of that research. Just as trabeculectomy turned out to be the right operation for the wrong reason, if these procedures work, then it may not matter what the concept is. I would think, however, that one
might be able to devise an optimal novel Schlemm canal surgical procedure by using Grant’s observations and principles. For example, septae connect the outer and inner walls of the canal. As shown by two different groups, disrupting the outer wall can inadvertently rupture the inner wall (and therefore eliminate some of the proximal resistance).16,19 As with YAG goniotommy,18,19,20 the general problem with internal trabeculotomy procedures is healing over time. I would therefore expect the IOP effects not to be long-lasting. Also, disrupting the Descemet window is unlikely to provide the needed circumferential flow in Schlemm canal. Rather, this likely creates a guarded filter to short-circuit the anterior chamber to the subconjunctival space, perhaps through an intervening scleral lake.19 Of course, one might wonder whether the scleral lake would alter the distal resistance as an inadvertent benefit. Canaloplasty21 is an intriguing surgical procedure that involves 360° of manipulation of Schlemm canal, but the mechanism of action is unclear, especially when vigorous tightening of the suture is required for maximum efficacy. A full discussion of possible mechanisms is beyond the scope of this article, but could this procedure be causing breaks in the inner wall of Schlemm canal?18,19 Could the distension of the trabecular meshwork as a result of this suture tightening cause a greater filtration area in the trabecular meshwork with an effect similar to that of pilocarpine?22 Have surgeons underappreciated the role of Schlemm canal’s collapse in glaucoma?23

The subject of the canal’s collapse as a primary or secondary mechanism in glaucoma has been controversial. Most have thought that, although the canal’s diameter decreases in POAG,23 the septae—which preferentially bridge the inner wall of Schlemm canal to its outer wall near the ostia of the collector channels18,19—might prevent total collapse. Much remains to be explained. As far as stents in Schlemm canal, there is likely only minimal circumferential flow beyond the two ends of the stent, which must also be fashioned not to occlude the ostia of the collector channels. I predict that the future may bring about the combination of Schlemm canal surgery with pharmacological therapy to its inner wall.24 Novel drugs are currently in human testing25 that are believed to affect the entire circumference of the canal’s inner wall.26

CONCLUSION

The point of this article was to remind readers of Grant’s seminal findings4 and to stimulate them to think creatively about how to implement these scientific observations to develop a better surgical procedure for glaucoma directed at Schlemm canal. It is important to remember that these operations may not get the IOP as low as desired. The main reason, as Grant’s work demonstrated,4,5 is a lack of circumferential flow in Schlemm canal and the presence of significant distal (ie, outer-wall) resistance.

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