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Basic Sciences in Clinical Glaucoma

How Does Nonpenetrating Glaucoma Surgery Work? Aqueous Outflow Resistance and Glaucoma Surgery

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Summary: Histologic, experimental, and theoretical studies of the aqueous outflow pathways point toward the juxtacanalicular region and inner wall of Schlemm's canal as the likely site of aqueous outflow resistance in the normal eye. At least 50% of the aqueous outflow resistance in the normal eye and the bulk of the pathologically increased resistance in the glaucomatous eye resides in the trabecular meshwork and the inner wall of Schlemm's canal. The uveoscleral, or uveovortex, pathway, which accounts for perhaps 10% of the aqueous drainage in the healthy aged human eye, can become a major accessory route for aqueous drainage after pharmacologic treatment. Surgeries designed to incise or remove the abnormal trabecular meshwork of glaucoma address the pathologic problem of the disease. Surgeries that unroof Schlemm's canal or expand the canal, such as viscocanalostomy, probably cause inadvertent ruptures of the inner wall and juxtacanalicular tissue, thus relieving the abnormal outflow resistance of glaucoma. This review is a summary of current thought on the pathophysiology of aqueous outflow resistance in glaucoma and, in light of this, provides an interpretation of the mechanism of pressure reduction created by these new surgeries.

Key Words: Aqueous outflow resistance—Glaucoma—Nonpenetrating surgery—Viscocanalostomy.

The advent of a new surgical procedure for glaucoma often raises the question of how the procedure lowers intraocular pressure (IOP), especially given the conventional understandings of the site of outflow resistance in glaucoma. Trabeculectomy was introduced in 1968 as a means of bypassing the clogged trabecular meshwork, allowing aqueous to enter Schlemm's canal directly through the cut ends of the canal.[1] Later experience found trabeculectomy most successful in cases in which a filtration bleb developed, giving rise to the understanding that it functions as a guarded filtration procedure.[2,3] IOP can be lowered in the absence of a visible filtration bleb, indicating that the procedure may well allow aqueous to enter Schlemm's canal directly in some cases or that subclinical transconjunctival filtration of aqueous can occur.

Viscocanalostomy and deep sclerectomy are new operations for glaucoma that have been designed to avoid the complications of filtering blebs and also the shallow or flat anterior chambers sometimes seen after trabeculectomy.[4,5] Both procedures involve fashioning a partial-thickness scleral flap, removing a second layer of sclera deep to the initial flap, and exposing Descemet's membrane. Descemet's membrane is said to act as a semipermeable layer of tissue, allowing aqueous to percolate through it. Schlemm's canal is also unroofed during the removal of the second, deep scleral layer. In viscocanalostomy, the cut ends of the canal are then expanded with a viscoelastic material. Viscoelastic is also injected into the region of excised sclera, or "scleral lake," to prevent healing. By never entering the anterior chamber or removing trabecular meshwork, hypotony, hyphema, and other complications are said to be avoided.[4] Deep sclerectomy is similar in that Schlemm's canal is unroofed and Descemet's membrane is exposed by the

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removal of the second, deeper layer of sclera. Variations of these procedures include removing the inner wall of Schlemm's canal and adjacent meshwork, but leaving the inner meshwork intact, or placement of a collagen implant or drainage device in the filtration bed.[5] Do these operations relieve the specific pathologic problem of primary open-angle glaucoma? Or do they function as simply another way to make a hole in the eye? This review is a summary of current thought on the pathophysiology of aqueous outflow resistance in glaucoma and, in light of this, provides an interpretation of the mechanism of pressure reduction created by these new surgeries. The review does not attempt to be comprehensive in scope, but rather to present a synopsis of current conventional wisdom regarding aqueous outflow resistance.

AQUEOUS OUTFLOW RESISTANCE

The increased IOP found in glaucoma is caused by an increase in aqueous outflow resistance in the drainage pathways, not excess secretion of aqueous humor.[6,7] Thus, understanding the mechanism by which outflow resistance is generated in the normal eye and how this resistance is increased in the glaucomatous eye has been the subject of intense research for more than 100 years. Aqueous humor passes from the anterior chamber through the outflow pathway as a bulk flow driven by a pressure gradient. Neither metabolic poisons[8] nor temperature[9] affect this bulk flow (outside of an effect on the viscosity of the fluid), and thus, the outflow system does not involve active transport. There is consensus that the bulk of outflow resistance in the normal eye resides near or within the inner wall of Schlemm's canal; however, there is no such consensus about where the increased outflow resistance characteristic of primary open-angle glaucoma is localized, although it appears not to reside in the aqueous veins. We begin by reviewing the basis for these conclusions.

Two pathways for aqueous drainage have been found to exist. The conventional pathway through the trabecular meshwork was discovered first. Early experiments showed that dye injected into the anterior chamber enters the episcleral veins and can be seen exiting at the limbus. These limbal vessels on the surface of the eye, the "aqueous veins," contain aqueous humor.[10] On histologic examination, these aqueous veins originate as collector channels in the outer wall of Schlemm's canal. Casting techniques show that the trabecular meshwork, Schlemm's canal, the collector channels, aqueous veins, and the episcleral veins form a continuous pathway.[11]

The unconventional or uveoscleral pathway originates at the angle of the eye. Aqueous passes through the ciliary body and ciliary muscle, enters the supraciliary and suprachoroidal spaces, and finally passes through the sclera[12–14] or is reabsorbed by the vortex veins.[15,16] In lower animals, the origin of this pathway is the ciliary cleft. The ciliary cleft becomes progressively smaller as the ciliary muscle enlarges and accommodative ability of the animal increases. The unconventional outflow may account for 30% of aqueous outflow in young monkeys and young humans.[17] With age, uveoscleral outflow becomes reduced, decreasing to perhaps 10% of the total outflow in monkeys and humans.[18] It is difficult to study the amount of aqueous drainage by this route, however, and studies must use radioactive tracers or microspheres to understand the dynamics of fluid flow in this pathway. In humans, these methods cannot be performed, and studies must use tonography or aqueous humor fluorophotometry. These methods make a number of assumptions in the calculation of uveoscleral flow, which make the interpretation of results tenuous.[19]

TRABECULAR MESHWORK (CONVENTIONAL OUTFLOW)

The conventional aqueous outflow system in the human eye comprises the trabecular meshwork, Schlemm's canal, and the aqueous veins (Fig. 1). The trabecular meshwork has two major regions: the uveal and corneoscleral region and the juxtacanalicular region.

The resistance of the trabecular meshwork to aqueous outflow was assessed by Grant[20] nearly half a century ago. In a now classic experiment, a modified scalpel was used to incise the trabecular meshwork of enucleated normal eyes, measuring outflow resistance before and after each cut. Incision of the uveal and proximal corneoscleral meshwork did not affect outflow resistance. A

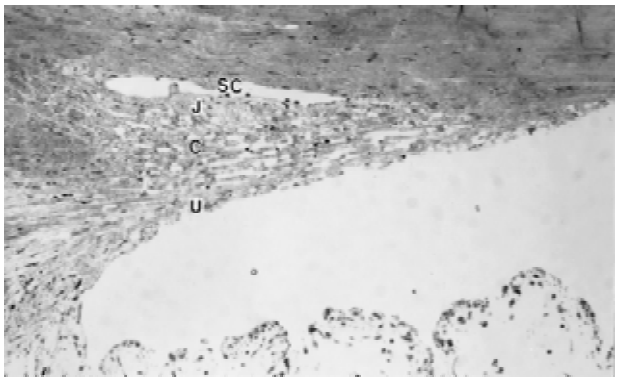

FIG. 1. Trabecular meshwork. Schlemm's canal (SC) appears as a large, single-lumen channel in this section. Aqueous spaces between lamellae are visible. U, uveal meshwork; C, corneoscleral meshwork; J, juxtacanalicular tissue. Light microscopy, toluidine blue stain (original magnification, ×400).

deeper incision through the entire meshwork and into Schlemm's canal, however, eliminated 75% of the normal outflow resistance.[20]

Other investigators have confirmed the finding that an appreciable fraction of outflow resistance (25–50%) is distal to the trabecular meshwork and Schlemm's canal.[21,22] Not all studies agree, however, micropuncture techniques that measure the pressure distribution in the outflow pathway conclude that less than 10% of the outflow resistance is distal to the inner wall. Although this discrepancy has not been resolved, all studies agree that at least half of aqueous outflow resistance is generated proximal to the aqueous veins. Grant[20] also studied a series of eight enucleated glaucomatous eyes and found that an incision through the meshwork into Schlemm's canal eliminated all the abnormal glaucomatous outflow resistance. The remaining scleral resistance was similar to that found in normal eyes. This finding of the abnormal outflow resistance of glaucoma residing proximal to the aqueous veins is supported by the success of trabeculotomy, goniotomy, and direct removal of the trabecular meshwork (goniocurettage) in adults with primary open-angle glaucoma.[23–28] Although the success of these procedures may diminish with time, their initial success in lowering IOP shows that the meshwork is the site of the abnormally high outflow resistance in primary open-angle glaucoma. In addition, laser trabeculoplasty also reduces outflow resistance in the glaucomatous eye.[29]

Because no incision is made during laser trabeculoplasty, inadvertent fistula formation through the sclera cannot occur, as could potentially happen after trabeculotomy. Although it is unclear how laser trabeculoplasty actually works in the meshwork to lower this abnormal outflow resistance,[30,31] its application to the trabecular meshwork strongly suggests a local meshwork effect. Evidence exists for contraction of the meshwork around the lasered spots, stimulation of trabecular cell replication, and induction of matrix metalloprotease enzymes that digest the extracellular matrix.[32–35]

Uveal and Corneoscleral Meshwork Regions

The uveal and corneoscleral regions are composed of a series of sheets or lamellae of collagenous tissue covered by a nearly continuous lining of endothelial cells. The uveal meshwork contains small, thin, cordlike lamellae (Fig. 2). The corneoscleral meshwork has wider, flatter lamellae that contain oval windows between layers (Fig. 3). The aqueous spaces between the uveal cords are large and become smaller in the subsequent layers of the corneoscleral region. The number and size of these

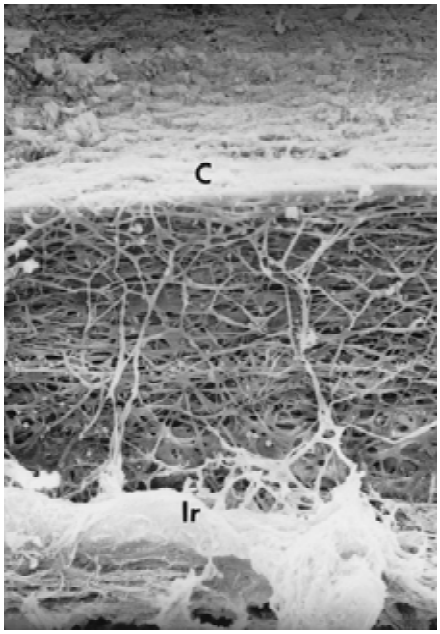

FIG. 2. Uveal meshwork as seen from the anterior chamber in a view similar to clinical gonioscopy. Round cords of tissue form the first layer of the meshwork, nearest the anterior chamber. Deeper layers appear as wider, flatter lamellae. C, cornea; Ir, iris. Scanning electron microscopy (original magnification, ×250).

openings are large enough that the uveal and corneoscleral meshwork can be expected to create negligible resistance to flow. Poiseuille's law predicts that a single pore 100 μm long (the thickness of the trabecular meshwork from the anterior chamber to Schlemm's canal) with a diameter of 20 μm can carry the entire aqueous outflow (2 μL/minute) with a pressure decrease of 5 mm Hg. Because the uveal and corneoscleral regions of the meshwork have numerous openings of this size and larger,[36] it can be concluded that the pressure decrease through this region is negligible. Experimental support for this proposition was provided by Grant,[20] who cut through the proximal regions of the meshwork and found no effect on outflow resistance. In the latter stages of open-angle glaucoma, collapse and fusion of the trabecular lamellae have been described in these regions in some eyes, but are not generally considered a prominent feature of the glaucomatous process.[37–40]

Juxtacanalicular Region

The second major region of the trabecular meshwork is the loose tissue near Schlemm's canal, known as the juxtacanalicular connective tissue (JCT). This region contains relatively free cells in an extracellular matrix (Fig. 4). The cells are interconnected by thin arms to one

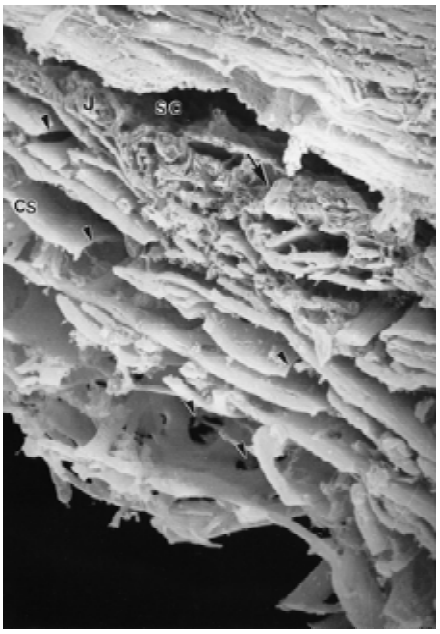

FIG. 3. Trabecular meshwork. Corneoscleral lamellae consist of broad, flat sheets of tissue with oval windows (arrowheads) allowing aqueous to pass between layers. Juxtacanalicular connective tissue has irregular arrangement of tissue, without organized lamellae. Two erythrocytes are present (arrow), probably displaced during tissue dissection. CS, corneoscleral lamellae; JCT, juxtacanalicular connective tissue; SC, Schlemm's canal. Scanning electron microscopy (original magnification, ×250).

another, to the cells of the inner wall of Schlemm's canal, and to fine collagen and elastic fibrils and fibers in this region. These cells differ from those of the endothelial lining of Schlemm's canal in that they have a more fibroblastic appearance and only patches of surrounding basal lamina.[41] The intervening extracellular matrix, or ground substance, contains basement membrane material, including collagen IV, laminin, fibronectin, proteoglycans, and glycosaminoglycans. Tendonlike extensions from the ciliary muscle pass through this region[42] and insert into the wall of Schlemm's canal (Fig. 5). These connections are responsible for the effects of ciliary muscle contraction on outflow resistance.[43]

The Outflow Resistance of the Juxtacanalicular Connective Tissue and the Role of the Extracellular Matrix

With its small openings and tortuous flow pathways, the JCT is expected to be the principal site of outflow resistance.[44,45] Using microcannulation techniques, Maepea and Bill[46] found that most of the outflow resistance was localized in the JCT of living monkeys, within several micrometers of the inner wall endothelium. Although this technique is difficult and subject to artifact, the results are consistent with the expected site of outflow resistance reported by other studies.[37–40,44,45]

Studies are not unanimous that the site of outflow resistance is in the JCT. Alternative sites have been proposed, including a layer of cells between the corneoscleral meshwork and JCT,[47] fusion of the trabecular lamellae,[48] or collapse of Schlemm's canal.[49]

Theoretical calculations suggest the JCT contains too much optically empty space to account for the measured outflow resistance of the eye.[44,45,47,50] In addition, the configuration of the JCT changes with IOP, appearing

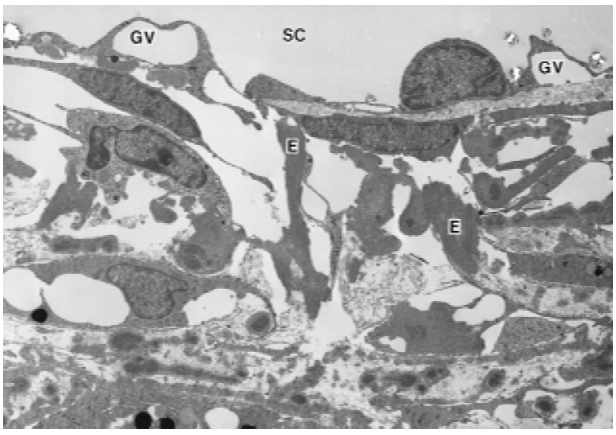

FIG. 4. Juxtacanalicular tissue. Schlemm's canal endothelial lining is a continuous sheet of cells, which contain giant vacuoles (GV). Juxtacanalicular connective tissue appears as loose arrangement of extracellular matrix. Elastic tendons (E), which will insert into the inner wall of the canal, are visible (original magnification, ×6,250).

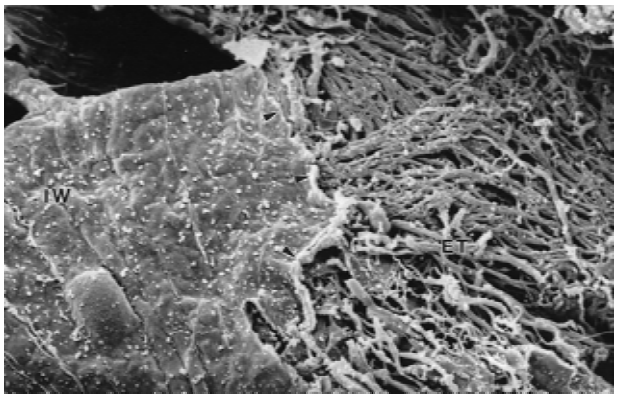

FIG. 5. The inner wall of Schlemm's canal and underlying juxtacanalicular tissue. Schlemm's canal has been unroofed by removing the outer wall of canal. Inadvertent damage occurred to some inner wall cells, removing them and exposing the elastic tendons of the juxtacanalicular connective tissue. The boundary of damaged cell layer is indicated by arrowheads. IW, inner wall cells; ET, elastic tendons. Scanning electron microscopy (original magnification, ×1,800).

collapsed at low pressures and expanded at higher pressures.[50–52] This expansion of the JCT with higher pressures does not fit the measured increase in aqueous outflow resistance that occurs as IOP increases. This increase is approximately 1% per millimeter of mercury of pressure, and is termed the "outflow obstruction coefficient (Q)"[53] Conventional thought suggests that partial collapse of the canal accounts for this increase in resistance with increased pressure. Lens depression, which prevents canal collapse, eliminates Q.[54]

Theoretical calculations[44,45,47,50] of the flow resistance of the JCT indicate that the aqueous channels, as viewed with conventional electron microscopy, would generate an insignificant fraction of outflow resistance. If the JCT were filled with an extracellular matrix gel, such as glycosaminoglycans and proteoglycans, sufficient outflow resistance would be created to match that measured in the eye.[44] Glycosaminoglycans and proteoglycans are known to be present in the meshwork and JCT.[55–60] Glycosaminoglycans generate flow resistance in other connective tissues[61] and could create flow resistance in the eye.

Proteoglycans consist of glycosaminoglycans attached to a core protein. They are poorly visualized with conventional histochemical techniques.[62] Glycosaminoglycans are highly negatively charged molecules that hold significant amounts of water and occupy large volumes of space as a consequence of their charge and hydration. Conventional histochemical preparation techniques use cationic ions that collapse these macromolecules, and thus, they are not well visualized on standard electron micrographs. The result would be large areas of empty space on electron micrographs. Large amounts (up to 40% of total area) of such empty spaces are seen in the JCT on conventional electron micrographs.[44,45,47,50] Because it is not known whether these empty regions were truly empty in life before fixation and processing of the tissue or whether they were filled with proteoglycans that were lost in processing, the empty spaces are termed optically empty spaces.

ENDOTHELIAL LINING OF SCHLEMM'S CANAL

Whereas the JCT contains large areas of optically empty space as seen with electron microscopy, a continuous anatomic barrier to aqueous outflow exists. This barrier is the endothelial lining of Schlemm's canal. This endothelial lining has several unique aspects, which appear to represent a specific engineering solution to a unique physiologic situation: movement of fluid into the lumen of a vessel across an intact endothelium down a pressure gradient, without collapsing the lumen, rather than from the lumen into the surrounding tissue. Venous capillaries also have fluid movement into them, from the surrounding tissue, but this is the result of the higher oncotic pressure in the lumen, which draws in the tissue fluid. As in other endothelia, the endothelial cells that line Schlemm's canal are attached to one another by tight junctions.[41,63] One of the unique aspects of this endothelium is the appearance of outpouchings or invaginations in the endothelial lining, termed "giant vacuoles"[41,64] (Fig. 4 and 6). Giant vacuoles can form in one cell or between neighboring cells. On their basal side is an opening that connects with the underlying aqueous spaces of the JCT. They are not formed by metabolic processes and do not require energy to form.[8,9] Current thought indicates that these structures form passively as a result of the pressure decrease across the inner wall endothelium.[64,65] Tripathi suggested that the giant vacuoles might be transient structures and proposed a process by which vacuolar formation could occur as a cyclic process.[64]

A second unique characteristic of the endothelium of Schlemm's canal is the appearance of small pores passing through these cells (Fig. 6). The pores are predominantly intracellular, but a significant fraction of them are also intercellular[66] and may correspond to a paracellular

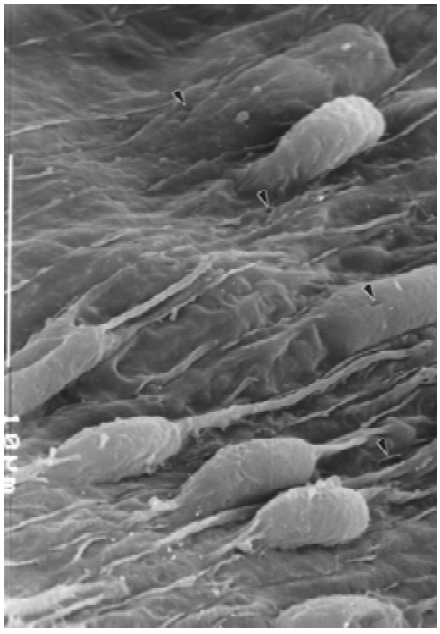

FIG. 6. The inner wall of Schlemm's canal. In contrast to Figure 5, cellular monolayer is intact. Bulging structures are presumably giant vacuoles, although they cannot always be distinguished from prominent nuclei. Pores (arrowheads) are found in presumed giant vacuoles and also in flat areas between cells. Scanning electron microscopy (original magnification, ×3,700).

pathway described recently by Epstein and Rohen.[67] The tight junctions between the endothelial cells become less complex with fewer junctional strands, as IOP increases.[63] This loosening of the junctions could make the formation of intercellular pores more likely at higher pressures and could serve as a means of self-regulation of IOP by the meshwork. The pores have an average diameter of approximately 1 μm (range, 0.1 to more than 3 μm),[68] and their density in the inner wall ranges between 1,000 and 2,000 pores per mm^2, or roughly 0.2 to 1 pores per cell.[68–74]

Scanning electron microscopy shows that between 13% and 29% of giant vacuoles have pores, consistent with this estimate.[70,72,73] The nature of the pores is not fully understood because the number of pores may increase if fixative is perfused through an eye, suggesting that some pores may be fixation artifacts.[66,68] The finding of pores by numerous laboratories, however, using both scanning and electron microscopy, suggest they are real structures.[64,66,69,71,73,74]

The Outflow Resistance of the Endothelium

Another unique aspect of the endothelium of Schlemm's canal is its leakiness; it has the highest hydraulic conductivity of any endothelium in the body (Table 1). Endothelia of relatively high hydraulic conductivity are usually fenestrated (e.g., glomerulus), whereas the endothelium of Schlemm's canal is not, yet the hydraulic conductivity of the canal endothelium is almost 10 times higher than that of the renal glomerulus.

In addition, the intercellular spaces are composed of tight junctions, which greatly limit fluid flow through the intercellular spaces. In other endothelia, fluid passes between the cells through the cells' junctional complexes,[75] or through fenestra if the endothelia is fenestrated.[76] Compared with other endothelia that have tight junctions, the large hydraulic conductivity of the endothelium of Schlemm's canal is even more exceptional.

From this, we can conclude that fluid likely passes through the endothelium of Schlemm's canal by a different mechanism than what occurs in other endothelia. The pores of the endothelium of Schlemm's canal appear to be this difference. Pores are numerous enough that the outflow resistance has been calculated to be at most 10% of the total outflow resistance of that measured in the eye.[71] Furthermore, it has been found that an increase in the IOP increases the number of inner wall pores.[73,77] This increase is not associated with a decrease in outflow resistance.[53] This provides further evidence that the inner wall endothelium accounts for only a small part of the outflow resistance.

Giant vacuoles and pores allow the endothelium of the canal to function as a one-way valve; they decrease greatly in number when the pressure in the canal becomes higher than that in the eye.[73,78] This prevents reflux of blood from the canal into the eye during periods when the episcleral venous pressure is increased, such as with bending or Valsalva maneuvers. This unique physiologic requirement is also necessary in the drainage pathways for cerebrospinal fluid, in which giant vacuoles and pores are also seen.[79,80]

Although the pores of the endothelium of Schlemm's canal are numerous enough that the endothelium is predicted to have a low resistance to aqueous outflow, it is interesting that disruption of the endothelium nonetheless can greatly decrease outflow resistance. Perfusion with agents that interfere with the cytostructural protein actin (e.g., cytochalasins and latrunculins) or that interfere with cell-to-cell contacts (e.g., ethylenediaminetetraacetic acid) causes ruptures of the inner wall that reduce outflow resistance.[81–88] This change is more than what would be predicted based on the calculated resistance of the inner wall pores.[66,68,71] Removal of these agents leads to a reversal of the inner wall ruptures and a return of resistance toward baseline.

Assuming that these agents affect the cytoskeleton as expected and as shown by histologic studies,[84,86,87] four explanations are possible. 1) The inner and outer walls of Schlemm's canal may have more resistance than theorized. 2) Disruption of the endothelial cells also disrupts the underlying basement membrane and extracellular matrix. 3) Cytoskeletal agents affect other cells in the meshwork, particularly the cells of the JCT. These cells

TABLE 1. *Hydraulic conductivity (L_p) of endothelia*

Type	Endothelium	L_p (cm^2 sec/g) × 10	References
Not fenestrated	Brain capillary	0.03	117
	Cornea	1.6	116
	Lung capillary	3.4	117
	Skeletal muscle capillary	2.5–7	117
	Aorta	9	118
	Mesentery, omentum	50	53,117
Fenestrated	Intestinal mucosa	32–130	53,117
	Synovium (knee)	120	53
	Renal glomerulus	400–3,100	53,117
Not fenestrated	Aqueous outflow pathway	4,000–9,000	*

* Flow rate of 2 μl/min driven by a pressure decrease of 5 mm Hg through a cross-sectional area between 0.054 and 0.13 cm^2 (canal width of 150–350 μm; canal length around the eye of 3.6 cm). Note that this is not necessarily the L_p for the inner wall endothelium because this calculation is based on the entire pressure decrease through the outflow pathway; the L_p for the inner wall endothelium is likely higher than this value.

have junctional complexes that connect to adjacent JCT cells, to the JCT extracellular matrix, and to the endothelium of the canal. Disruption of these connections could relax the juxtacanalicular–Schlemm's canal network, loosen the tethering of the inner wall, expand the canal wall, and increase the draining surface, permitting more extensive flow through the meshwork.[89] 4) The inner wall acts in conjunction with the underlying extracellular matrix to modulate outflow resistance. In this potential hydrodynamic interaction, termed funneling, the endothelial pores themselves contribute negligible flow resistance, but because they force the fluid to funnel through those regions of the JCT nearest the pores, their number and size can greatly increase the effective outflow resistance of the JCT.[90] Disruption of cells, or separation of inner wall cells from their underlying attachments, would eliminate the funneling effect and decrease outflow resistance. This may explain the results of several studies[81,84,86,89] that found that disruption of the inner wall cells decreases outflow resistance.

Collapse of Schlemm's Canal

Schlemm's canal is a continuous channel oriented in a circumferential direction. The canal is oval in shape, with dimensions of approximately 280 μm by 30 μm at low IOP.[50,78,91,92] A lumen of this size is too large to generate an appreciable outflow resistance. As IOP increases, the trabecular meshwork expands into the lumen of the canal and causes a concomitant narrowing of the lumen,[78] raising the possibility that this collapse might cause a significant increase in outflow resistance. Throughout the canal, however, especially near the collector channels, septae are present between the inner and outer wall. The proximity of these structures to the collector channels suggests they will prevent collapse of the canal and occlusion of the collector channels as IOP increases.[78,91,93] At an IOP of 40 mm Hg, the canal is predicted to be largely collapsed, except at the sites of the septae.[91] Nesterov[49] postulated that canal collapse could cause the increased outflow resistance characteristic of primary open-angle glaucoma and designed an operation to unroof the canal to remedy this problem. Although outflow resistance is increased by collapse of the canal, resistance levels at high IOPs are not as high as found in glaucoma; in healthy eyes, facility changed from a baseline of 0.40 μl/minute/mm Hg at 10 mm Hg to a facility of 0.28 μl/minute/mm Hg at 50 mm Hg, whereas the facility of eyes with primary open-angle glaucoma is usually less than 0.13 μl/minute/mm Hg.[53,91] Assuming that Q, the obstruction of outflow with increasing IOP, is caused by collapse of the canal, the underlying problem in glaucoma must therefore involve more that just collapse of Schlemm's canal. Although collapse of Schlemm's canal is not the primary cause of glaucoma, if it occurs it can worsen the problem of increased IOP. Pilocarpine, which decreases outflow resistance, increases ciliary muscle tone, acts to expand the trabecular meshwork and JCT, and may also open the canal.[94]

Collector Channels and the Aqueous Veins

After entering the canal, the aqueous humor travels circumferentially around the eye until it reaches one of the 30 or so collector channels that join Schlemm's canal. Fluid flows from the collecting channels into aqueous veins that ultimately drain into the episcleral venous system. The aqueous veins have an average diameter of 50 μm and a length of approximately 1 mm.[21] Use of Poiseuille's law indicates that the resistance of the aqueous veins should be negligible if the veins are neither collapsed nor compressed.

Measurement of the pressure in Schlemm's canal in live monkeys supports this conclusion.[46,95] Experimental evidence in the human eye, however, indicates that some resistance does occur in the collector channel–aqueous vein system. The trabeculotomy experiments previously mentioned have shown that between 25% and 50% of the total outflow resistance is distal to Schlemm's canal, presumably in the aqueous veins. However, most studies suggest the abnormal increase in outflow resistance found in glaucoma is not found in the aqueous veins or in Schlemm's canal.[20,23,91]

ABNORMAL OUTFLOW RESISTANCE IN THE GLAUCOMATOUS EYE

Several pieces of evidence indicate that the trabecular meshwork is the site of the abnormally increased outflow resistance of primary open-angle glaucoma, as discussed above. Surprisingly, however, histologic examination of the meshwork does not show specific abnormalities or ultrastructural changes that could account for the increase in IOP.[37–40] The few changes found appear to be an exaggeration of aging changes found in the normal eye. A small increase in the amount of tendon and tendon-sheath material in the JCT is found, increasing from 15% to 22% in primary open-angle glaucoma, as compared with aged healthy eyes.[37,38] This increase in tendon and tendon-sheath material does not occur early in the disease process; IOP can be increased even with normal amounts of the tendon and tendon-sheath material.[39] The increase in tendon and tendon-sheath material is not

enough to obstruct aqueous channels.[44,45,47,50] Studies have also examined glycosaminoglycans and proteoglycans of the meshwork in primary open-angle glaucoma, phagocytosis by trabecular cells, and the size of Schlemm's canal.[59,60,92,96] Elucidation of the pathophysiologic mechanism of primary open-angle glaucoma remains an area of intense research.

UVEOSCLERAL OUTFLOW (UNCONVENTIONAL PATHWAY)

The uveoscleral, or uveovortex, pathway originates at the angle of the eye, passes through the ciliary body and ciliary muscle, enters the supraciliary and suprachoroidal spaces, and finally passes through the sclera.[12,13] Aqueous humor and aqueous proteins seep through sclera and episclera, pass into the orbit, and are absorbed there by blood vessels. Aqueous may also be absorbed osmotically by the vortex veins.[15,16] The unconventional outflow is relatively insensitive to IOP and increases only a small amount with increases of pressure.[14]

The ciliary muscle probably represents a major site of flow resistance along this pathway. Pilocarpine, which causes ciliary muscle contraction and decreases the size of spaces between the muscle bundles, decreases outflow through this pathway. Atropine, which relaxes the ciliary muscle, does the converse.[97] Furthermore, $PGF_{2\alpha}$, recently shown to increase unconventional outflow,[98–101] may act by decreasing the extracellular matrix between ciliary muscle bundles.[102]

THE MECHANISMS OF LASER AND GLAUCOMA SURGERY

Laser Trabeculoplasty

Since laser trabeculoplasty was first described,[29] it has been recognized that this procedure decreases outflow resistance by a mechanism other than simply making holes in the trabecular meshwork. When holes are created, they quickly heal shut (even with an yttrium–aluminum–garnet laser).[29,103] Wise and Witter[29] hypothesized that laser trabeculoplasty worked mechanically by shrinking collagen or through the formation of scar tissue that later contracts. Such contraction or shrinkage would lead to tension on the remaining trabecular meshwork, which then would open the intertrabecular spaces[29] or prevent collapse of Schlemm's canal.[31] Melamed et al.[104] provided support for this hypothesis by showing that the actual sites of the laser burns appeared to be nonfiltering, with aqueous flow being diverted to the remaining meshwork.

Laser-induced shrinkage of the trabecular tissues does not lead to an immediate change in outflow facility in enucleated human eyes.[30,31] This is consistent with the clinical observation that it takes approximately 3 to 6 weeks after laser treatment for outflow facility to improve.[29] Although it could be that scarring caused by the laser takes several weeks to occur and affect outflow facility, another mechanism of laser action could be a change in the activity of the trabecular cells.[30,31,105,106]

Increased phagocytic activity, activation of cells leading to altered metabolic activity, increased levels of cell division, or a tissue remodeling between the lasered spots may occur. However, no conclusive experiment has been performed to elucidate the mechanism by which improvements in outflow facility occur after laser treatment.

Trabeculectomy

The original concept of trabeculectomy was to bypass the trabecular meshwork and allow aqueous humor to enter Schlemm's canal.[1] Healing and fibrosis occur, however, and it is likely that the cut ends of the canal become closed with scar tissue.[2,107,108] The development of a filtering bleb is strong evidence that aqueous humor bypasses the meshwork and canal and exits through the surgical fistula. The advantage to this procedure over a full-thickness filter is the prevention of low pressures provided by the scleral flap. Once the eye has healed, aqueous continues to seep through the fistula and enter the filtration bleb.

Nonpenetrating Surgery

Viscocanalostomy

Unroofing Schlemm's canal (i.e., removing the outer wall of the canal) can cause damage to the inner wall of the canal (Fig. 5 and 7).[109,110] The septae, which bridge the inner and outer walls, can easily damage the inner wall when they are pulled away during the unroofing procedure. Injection of a viscoelastic substance into the ends of Schlemm's canal is designed to enlarge the canal,[4] but it is likely that this injection ruptures the inner and outer endothelial walls of the canal as shown in monkeys.[110] These ruptures probably extend into the JCT and may also rupture some of the meshwork itself. The operation likely functions as a gentle trabeculectomy, allowing aqueous to bypass the site of abnormal outflow resistance, the JCT, and enter the canal through

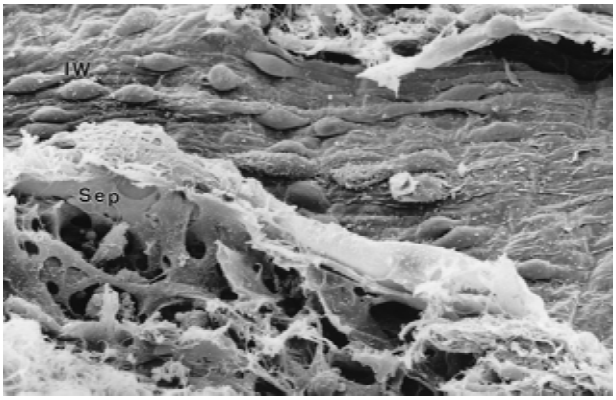

FIG. 7. The inner wall of Schlemm's canal and ruptured septa. The canal has been unroofed by removing the outer wall. One of the septae that bridge the inner and outer walls has been inadvertently damaged, showing the loose arrangement of cells within. IW, inner wall cells; Sep, ruptured septa. Scanning electron microscopy (original magnification, ×3,700).

these presumed and inadvertent ruptures. In addition, excising a deep layer of sclera and exposing Descemet's membrane may also create a route for aqueous drainage that bypasses the meshwork. Studies in rabbits, however, indicate that Descemet's membrane is not permeable enough to allow relief of the increased IOP of glaucoma.[111,112] If the ruptured regions of the JCT and canal heal with time, surgery may fail in those eyes that did not develop filtration blebs.

There is no theoretical basis for relieving increased IOP by expanding the lumen of Schlemm's canal. Injection of a viscoelastic substance certainly will dilate the canal lumen, but the viscoelastic itself will probably not remain in the canal long enough to prevent healing of the cut ends of the canal. The high-molecular-weight viscoelastic substance used in this procedure has not been shown to retard healing.

The creation of a "scleral lake" under the partial-thickness scleral flap has no theoretical effect on the abnormal outflow resistance found in glaucoma. Ultrasonic measurements of the area of the lake found no relationship to IOP in a series of human eyes.[113] A small effect on pressure may occur by removing a segment of the aqueous veins in that region and eliminating some of the normal resistance created by these aqueous veins. If the cut ends of the aqueous veins did not heal shut but remained open, this might lower IOP by a few millimeters of mercury.

Deep sclerectomy

During conventional trabeculectomy, many surgeons do not actually remove a piece of the trabecular meshwork at all, but rather a piece of cornea anterior to the meshwork. Deep sclerectomy takes this approach, with the exception of leaving Descemet's membrane intact.[5] Descemet's membrane is semipermeable and therefore creates some resistance to aqueous drainage into the surgical fistula, but Descemet's membrane is not permeable enough to relieve the increased IOP of glaucoma.[111,112] Deep sclerectomy appears to be another variation of a guarded filter, adding a second guard to that of the partial-thickness scleral flap, which is still used in this surgery. The operation also unroofs Schlemm's canal, and aqueous percolates through the remaining trabeculo-Descemet's membrane. Damage to the inner wall of the canal is highly likely to occur during the removal of the outer wall when unroofing the canal (Fig. 5 and 7). Such damage to the inner wall and underlying JCT would allow aqueous a new route into Schlemm's canal.

Trabecular Aspiration

Application of a high vacuum to the meshwork region is reported to lower IOP in pseudoexfoliative glaucoma but have little effect on primary open-angle glaucoma.[114,115] If the suction were strong enough to break the endothelial lining of the canal and rupture the JCT, IOP would be lowered. This would be expected to lower pressure in primary open-angle glaucoma and pseudoexfoliation glaucoma. If the suction were not that strong, it might function in removing the accumulations of pseudoexfoliative material that occur in the meshwork.[116]

Goniotomy

Although successful in infant eyes with abnormally developed meshworks, goniotomy and trabeculotomy have been generally disappointing in adult eyes.[3,117,118] Trabeculotomy and goniotomy make excellent theoretical sense in that the surgical incision through the trabecular meshwork and JCT into Schlemm's canal allows aqueous to bypass the abnormal portions of the meshwork. Because the aqueous veins may have some outflow resistance, IOP should not decrease too much. Clinical studies find pressure to stabilize in the high teens.[117,118] Blood reflux into the eye from Schlemm's canal could occur if the episcleral venous pressure was increased during a cough or Valsalva maneuver or if the patient were to bend over. This would probably be an acceptable, minor side effect if the operation otherwise kept IOP normal, avoiding a filtration bleb and all its attendant problems.

Healing of the goniotomy incision has been the main problem in adult eyes.[107,108,117–119] Why healing does not occur more frequently in the infant eye is unknown,

but may be related to the elastic condition of infant eye tissues. Infant sclera retracts when cut, sometimes making it difficult to make a trabeculectomy scleral flap cover the surgical bed from which it was dissected. This same elastic property may be the reason infant eyes become larger when IOP is increased. Such buphthalmos occurs until approximately 2 years of age, which is about the same age at which goniotomies are no longer effective in children. In the infant eye undergoing goniotomy, the cut ends of the meshwork may retract enough because of the elastic nature of the infantile tissues that the incision gapes, and does not heal together. In the adult eye, such elastic retraction would not occur, allowing the cut ends of the meshwork to lie in apposition to each other and thus allowing healing of the incision.

A recent study of goniotomy in adults has suggested that incision of the meshwork near Schwalbe's line, anterior to the usual site of incision in goniotomy, may overcome this problem. Success in adult eyes has been reported with this anterior incision.[120]

Goniocurettage

An operation related to goniotomy involves removal of the trabecular meshwork. Using a sharpened curette to scrape away the meshwork for approximately 90° of the circumference of the eye, Jacobi et al.[121–123] reported success in lowering IOP. An ab interno incision is used, and a filtration bleb is not created. Damage to the collector channels during the removal of meshwork could limit the effectiveness of this procedure, which is the most promising of the new glaucoma surgeries. IOP is lowered into the high teens and does not reach as low a level as after conventional filtration surgery.

FUTURE GOALS

Our understanding of aqueous outflow mechanisms is incomplete, especially in understanding the pathogenesis of primary open-angle glaucoma. Although ideas abound and a working hypothesis has been presented in this review, much remains unsolved. The ideal surgical procedure would address the as-yet-unknown site of pathology in glaucoma and leave the eye otherwise intact. In practice, however, any procedure that is effective in lowering IOP, that has minimal complications and side effects, and that provides long-term success in pressure control would be helpful in the management of glaucoma. The current practice of filtration surgery, especially with the use of antifibrotic agents such as mitomycin C, creates eyes that can develop conjunctival leaks, infection, and problems from filtration blebs. We look forward to improvements in the surgical control of pressure in the new millennium.

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