The drainage of aqueous humor

In human eyes more than 80 per cent of the aqueous humor seems to be drained from the anterior chamber through the chamber angle tissue into the canal of Schlemm. This in turn is drained by collector channels into the veins of the episclera and conjunctiva. There is general agreement that a rise in the resistance in the outflow routes via Schlemm's canal is the basis for most cases of open-angle glaucoma. Discussions about the pathogenesis of this disease are hampered by the fact that there is no complete agreement on the normal anatomy of the outflow routes and the mechanism for aqueous humor drainage. The purpose of this editorial is to discuss some recent studies in this field, to analyze whether there is a need for a large pore system for aqueous humor drainage into the canal of Schlemm, and to speculate about the genesis of open-angle glaucoma.

The outflow routes

Many studies have shown that there are large openings in the uveal meshwork indicating that the aqueous humor passes from the anterior chamber through this region easily. It then flows through a layer of irregular spaces formed by the perforated sheetlike corneoscleral trabeculae. The endothelial cells of these trabeculae divide the spaces between the sheets into a large number of channels. The aqueous humor flows through these tortuous channels which may have a considerable resistance into a region that has received many names—juxtacanalicular tissue, endothelial meshwork, pore tissue, and trabeculum cribriforme. This tissue can be characterized as a kind of loose connective tissue containing endothelial cells. The channels through the tissue are not as well-defined as those through the uveal and the corneoscleral meshwork. The aqueous humor seems to seep between the endothelial cells, the elastic and collagen fibers, and the ground substance to reach the endothelial cells of the inner wall of Schlemm's canal. Particles perfused through the meshwork tend to be stopped in many of these routes.

The endothelial cells of the uveal, the corneoscleral, and the endothelial meshwork are phagocytotic and can thus remove and destroy debris entering the meshwork from the anterior chamber. After engulfing foreign material some of these cells may even leave the meshwork and move into the canal of Schlemm.

The endothelial cells of the inner wall of Schlemm's canal are rather different from those of the meshwork. They are not phagocytotic and they form a continuous layer with large invaginations from the trabecular side which makes part of the
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...cells bulge into the lumen of the canal of Schlemm.

It has been questioned whether the invaginations into the endothelial cells are due to the pressure gradient between the trabecular side and the canal of Schlemm or due to active processes in the endothelial cells themselves. VanBuskirk and Grant2 have recently reported that the invaginations can be seen in enucleated eyes perfused at 4° C. and fixed at an intraocular pressure of 25 mm. Hg. In eyes perfused at 4° C., but fixed at 0 mm. Hg, there were no invaginations. Thus at a temperature at which the cellular metabolism is very low the presence of invaginations depends on the pressure across the cells. Another argument for the importance of the pressure can be found in the reports of Inomata, Bill, and Smelser1 and Shabo, Reese, and Gaasterland.3 In both these studies the tissue was fixed in vivo. In the former study fixation was by perfusion from the anterior chamber, in the latter by perfusion from a cannulated ciliary vein. In the first study the pressure difference was in the normal direction and invaginations were observed. In the second study the pressure difference was in the opposite direction and very few invaginations were seen.

What is the significance then of the invaginations into the endothelial cells of the inner wall of Schlemm's canal? Transmission and scanning electron microscopy have shown that the walls of the invaginations are very thin and that in some of these invaginations there are one or several openings into the canal of Schlemm. These pores, first described by Holmberg, usually are 0.1 to 3 μm wide. They permit aqueous flow from the trabecular side into the canal of Schlemm. Pores also may be found in other very thin parts of the cells.1 Small particles and even blood cells may pass through the transcellular pores. The number of pores in human eyes has been reported to be about 20,000 and calculations have shown that these pores easily account for the conductance of the inner wall endothelium.4

The existence of the transcellular pores in the inner wall of Schlemm’s canal has been questioned repeatedly and it has been suggested that the aqueous humor is drained mainly through narrow routes between the endothelial cells.3 These routes were supposed to be similar to the small pores found in many capillaries. The question then arises whether such 8 nm. pores could account for a significant part of the conductance of the inner wall of Schlemm’s canal. Data for an evaluation of the role of these hypothetical 8 nm. pores are available. The total surface of the inner wall of Schlemm’s canal has been estimated to be about 40 mm². The endothelial cells are very long and have a width of about 5 μm. If the junctions are assumed to be 8 nm. wide, the total surface of the junctions can be calculated to be about 0.64 mm². If, for the sake of simplicity, 80 per cent of this surface is assumed to represent the openings of the 8 nm. pores into the canal, the number of pores is about 10⁶. If the length of the pores is assumed to be 0.3 μm, the total conductance of the pores is 0.004 μl per minute per millimeter of Hg. In normal eyes the outflow resistance is about 3 mm. Hg times minutes per microliter and 75 per cent of this resistance is known to be located between the anterior chamber and the canal of Schlemm. The conductance of this tissue is thus 0.44 μl per minute per millimeter of Hg. This tissue, as mentioned, is composed of several layers in series and the conductance of each one of these layers thus has to be higher than the total conductance. It is clear then that the 8 nm. pores can account for less than 1 per cent of the conductance of the inner wall of Schlemm’s canal. The large transcellular pores, therefore, are of overall importance for the flow of the aqueous humor into the canal of Schlemm.

Glaucoma

This discussion has shown that the structure of the chamber angle is that of a composite filter with wide meshes in the uveal part of the meshwork, finer meshes...
in the corneoscleral part, and still finer meshes in the endothelial meshwork. The openings through the endothelial cells of the inner wall of Schlemm's canal again may be somewhat larger. Small amounts of debris, of course, enter the meshwork from the anterior chamber, but under normal conditions the filter seems to be self-cleaning, the endothelial cells of the meshwork engulfing and digesting the debris that enters the filter. If the cleaning of the filter becomes insufficient due to an increased inflow of debris or an inflow of undigestible particles—material will tend to accumulate in the filter and it will clog. This seems to occur in exfoliation glaucoma, pigment glaucoma, and hemorrhagic glaucoma and explains why resistance in these diseases increases. One can speculate that an insufficiency of the endothelial cells may also be due to a subnormal function of these cells which would make a normal inflow of debris too large a burden for the filter—leading to clogging and a rise in the outflow resistance. Interestingly, corticosteroids which are known to raise outflow resistance are also known to inhibit phagocytosis. Supersensitivity of the endothelial cells to endogenous glucocorticosteroids thus might be a basis for open-angle glaucoma.

Investigators finding an accumulation of fibrous, granular, and amorphous material in the endothelial meshwork in glaucomatous eyes, also found a lack of vacuoles in the inner wall endothelium of Schlemm's canal. This fact can be explained from the results discussed above. At the places where the meshwork is clogged, there is not enough flow through this tissue to create the pressure that is necessary to produce a normal number of vacuoles in the inner wall endothelium of Schlemm's canal.

If the concept is accepted that insufficient self-cleaning of the chamber angle tissue is the basis for most cases of open-angle glaucoma, the question arises as to how a decrease in the inflow of debris may be accomplished and how phagocytosis may be stimulated. Answers to these questions might lead to new methods in the treatment of glaucoma.

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REFERENCES