British Journal of Ophthalmology, 1979, **63**, 1–2

Editorial: Outflow pathways

The conventional outflow pathway through the trabecular meshwork and Schlemm's canal to the episcleral venous system is the major route by which aqueous humour leaves the intraocular cavities of the eye and accounts for some 90% of total drainage in the human. The fluid which passes by this route must negotiate the intratrabecular and extracellular spaces of the meshwork to reach the endothelium of Schlemm's canal. These spaces become progressively narrower and more tortuous as Schlemm's canal is approached. In the narrowest and most tortuous portion of the system, called the *endothelial meshwork*, the trabecular organisation is lost and is replaced by a loose connective tissue. The extracellular spaces through which the aqueous humour flows contain both coarse framework (collagen and elastic-like components) and fine framework (mucopolysaccharides) extracellular materials. It is this tissue which is thought to offer the greatest resistance to aqueous outflow in the normal eye (Bill and Svedbergh, 1972) and has been implicated as a likely site at which abnormally increased resistance develops in the early stages of primary open-angle glaucoma.

The precise pathway by which the aqueous humour crosses the endothelium lining the trabecular aspect of Schlemm's canal to enter the lumen of this vessel has long been a subject of extensive investigation and much controversy. Certainly it seems to be the case that the endothelial cells are connected to each other by junctions which are not physiologically 'tight', and, as a consequence, some aqueous must leak through the monolayer by this route. However, it has been estimated that the intercellular pathway can account for only 1% of drainage at normal levels of intraocular pressure (Bill, 1975). There is a broad consensus of opinion that the major outflow pathway is a series of temporary transendothelial pores (Bill, 1975; Tripathi, 1977; Grierson, *et al.*, 1978, for reviews). The pores are usually, but not exclusively, found in bizarre outpouchings of the endothelium which are a characteristic feature of this tissue and have been called *giant vacuoles*. These structures are not vacuoles as such, because the vast majority can be shown to be blind invaginations from the meshwork surface of the endothelium. A small proportion also have an opening on the luminal surface of the endothelial cells and are therefore the channels which have been implicated in the transendothelial transfer of fluid. The reason why only a small proportion of the vacuoles are through-and-through channels is poorly understood, but a possible explanation has been provided by Tripathi (see Tripathi (1977) for a recent review). He has suggested that the transcellular channel is a stage in a cyclical process whereby an invagination forms, expands, and becomes a transcellular channel, and then eventually this channel collapses. Little is yet known about the morphogenesis of these structures, but it would seem highly probable that the two factors of greatest importance are (*a*) the pressure head across the endothelium acting as the driving force for vacuolation (Inomata *et al.*, 1972; Grierson and Lee, 1975; Tripathi, 1977), and (*b*) the resilience of the endothelial cell to resist the distorting effect of vacuole formation (Grierson and Lee, 1975).

The conventional outflow system has a high facility of aqueous outflow, that is, it is particularly pressure-sensitive. By way of comparison the uveoscleral subsidiary drainage pathway, which drains aqueous laterally between the bundles of the ciliary muscle to the suprachoroid and accounts for most of the remaining 10% of outflow from the human eye, has a very low facility of aqueous outflow. In an experiment conducted on the cynomolgus monkey Bill (1966) found that, when intraocular pressure was increased from 11 to 22 mmHg, flow through the conventional drainage pathway increased 5-fold, whereas the increase in flow through the uveoscleral pathway was minimal.

Experimental studies of the effects of various levels of intraocular pressure on the morphology of the conventional pathway provide an explanation for its high facility. With stepwise increases of the intraocular pressure within the near physiological range the meshwork, and in particular the endothelial meshwork, becomes progressively distended, and thus the pathways for the passage of fluid become wider. In addition there is a progressive increase in the incidence of giant vacuoles and vacuolar transcellular channels. Therefore when the intraocular pressure is increased the meshwork adopts a configuration which is conducive to the easier passage of fluid through the system. This valve action seems to be purely a passive response, because the changes in both the configuration of the meshwork and the numbers of giant vacuoles can be produced equally well in vitro (Johnstone and Grant, 1973) as in vivo (Grierson and Lee, 1974).

That the pliability of the cells and extracellular elements are important to the normal functioning of the outflow system is highlighted by flow studies

through aldehyde-fixed tissue. Aldehyde fixation reduces pliability of the meshwork cells, turns the ground substances of the endothelial meshwork into a cross-linked immobile network, and presumably 'freezes' the vacuole and pore populations of the canal endothelium. Under such circumstances the rate of aqueous outflow and the facility are drastically reduced (Johnstone and Grant, 1973). On the other hand the perfusion of cytochalasin B (which disrupts intracellular microfilament systems) into the anterior chamber results in a marked increase in the facility of aqueous outflow. Interestingly the morphological effect of the drug is to produce distension of the endothelial meshwork and enlarged vacuoles and more numerous pores in the endothelium of Schlemm's canal (Svedbergh *et al.*, 1978).

Clearly the cytoskeletal framework of the cells of the conventional outflow system plays a key role in the pressure-sensitive valve action of this tissue. It is therefore of importance that the actin microfilament, intermediate filament, and microtubule systems of both the canal endothelial cells (giant vacuole formation) and the trabecular meshwork cells (general pliability) are investigated in some detail (see Ringvold, 1978; Grierson and Rahi, 1979). Indeed, the possibility that subtle qualitative or quantitative changes to these cytoskeletal elements, which would radically alter the mechanical properties of the cells, may be a factor in the development of open-angle glaucoma is worthy of consideration.

References

Bill, A. (1966). Conventional and uveoscleral drainage of aqueous humour in the cynomolgus monkey (*Macaca irus*) at normal and high intraocular pressures. *Experimental Eye Research*, **5**, 45–54.

Bill, A. (1975). The drainage of aqueous humour. *Investigative Ophthalmology*, **14**, 1–3.

Bill, A., and Svedbergh, B. (1972). Scanning electron microscopic studies of the trabecular meshwork and the canal of Schlemm—an attempt to localize the main resistance to outflow of aqueous humour in man. *Acta Ophthalmologica*, **50**, 295–320.

Grierson, I., and Lee, W. R. (1974). Changes in the monkey outflow apparatus at graded levels of intraocular pressure. A qualitative analysis by light microscopy and scanning electron microscopy. *Experimental Eye Research*, **19**, 21–33.

Grierson, I., and Lee, W. R. (1975). Pressure-induced changes in the ultrastructure of the endothelium lining Schlemm's canal. *American Journal of Ophthalmology*, **80**, 863–884.

Grierson, I., Lee, W. R., and Abraham, S. (1978). Pathways for the drainage of aqueous humour into Schlemm's canal. *Transactions of the Ophthalmological Societies of the United Kingdom*, **97**, 719–725.

Grierson, I., and Rahi, A. H. S. (1979). Microfilaments in the cells of the human trabecular meshwork. *British Journal of Ophthalmology*, **63**, 3–8.

Inomata, H., Bill, A., and Smelser, G. K. (1972). Aqueous humour pathways through the trabecular meshwork and into Schlemm's canal in the cynomolgus monkey (*Macaca irus*). An electron microscopic study. *American Journal of Ophthalmology*, **73**, 760–789.

Johnstone, M. A., and Grant, W. M. (1973). Pressure-dependent changes in structures of the aqueous outflow system of human and monkey eyes. *American Journal of Ophthalmology*, **75**, 365–383.

Ringvold, A. (1978). Actin filaments in trabecular endothelial cells in eyes of the vervet monkey. *Acta Ophthalmologica*, **56**, 217–225.

Svedbergh, B., Lutjen-Drecoll, E., Ober, M., and Kaufman, P. L. (1978). Cytochalasin B-induced structural changes in the anterior ocular segment of the cynomolgus monkey. *Investigative Ophthalmology*, **17**, 718–734.

Tripathi, R. C. (1977). The functional morphology of the outflow systems of ocular and cerebrospinal fluids. *Experimental Eye Research*, Supplement, 65–116.