Glaucoma

Edited by

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and

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Glaucoma

This book is dedicated to our wives whose loyal and unwavering support has made possible the time commitment required.

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Preface

For many years the glaucomas were a part of ophthalmology which generated little enthusiasm among students, residents and teachers alike. Associated with a pessimistic outlook and lifetime attendance, outpatient glaucoma clinics were rather depressing affairs. Greater understanding of the pathophysiology of the disease, coupled with the introduction of laser surgery and safer, more consistent operative procedures, has revolutionized the treatment of glaucoma. Accompanying the ophthalmologist's expanding arsenal are more interest and excitement than have been seen in glaucoma to date.

This book is a product of that ground swell of information and enthusiasm. While in no way pretending to replace comprehensive textbooks or collate the myriad of scientific papers extant, the editors have attempted to sift and highlight the recent advances in understanding the glaucomas. From these advances more logical approaches to management have developed, greatly enhanced by the exploding technology of our age. The rapid expansion of ophthalmic knowledge makes it difficult for even sub-specialists to keep up. We hope that this book will not only advance the reader to the forefront of glaucoma knowledge, but infuse in him our zeal for the challenge glaucoma represents.

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Contents

1
Alterations in the outflow system in chronic simple glaucoma

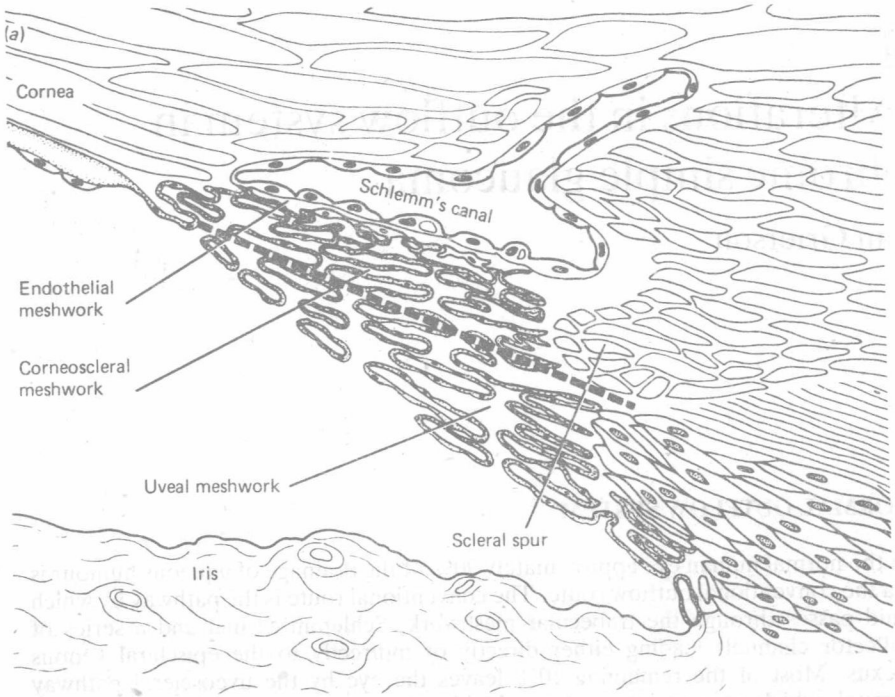
Ian Grierson

NORMAL OUTFLOW SYSTEM

In the normal human eye approximately 90% of the drainage of aqueous humour is via the conventional outflow route. The conventional route is the pathway by which fluid passes through the trabecular meshwork, Schlemm's canal and a series of collector channels leading either directly or indirectly to the episcleral venous plexus. Most of the remaining 10% leaves the eye by the uveoscleral pathway through which aqueous passes from the chamber angle and the iris root, via the ciliary muscle to the suprachoroid or across the sclera. Ultimately the aqueous leaving the eye by this rather ill-defined route enters the vortex veins (Bill and Phillips, 1971). Drainage through the outflow pathways is by bulk flow and, as such, flow rate depends on the pressure head across the pathways opposed by the intrinsic resistance in the tissue. It is thought that progressive increase in outflow resistance leads to the pathologically elevated intraocular pressure (IOP) associated with chronic simple glaucoma. However, the nature of the early lesion in the drainage system associated with the initial development of chronic simple glaucoma remains obscure. Indeed the precise location of the main resistance to flow through the normal drainage pathway is still a matter of some controversy.

The trabecular meshwork of the conventional pathway consists of two main regions, the uveal and the corneoscleral meshwork (*Figure 1.1*). The uveal meshes are cord shaped and are composed of a collagenous core surrounded by an endothelial cover. They are situated closest to the chamber angle, link directly with the ciliary muscle and have openings for aqueous passage which are up to 70 μm in diameter. This tissue is thought to offer little resistance to aqueous outflow (Bill and Svedbergh, 1972). The bulk of the trabecular meshwork consists of sheet-like trabeculae and these corneoscleral trabeculae are so called because they insert into the scleral spur. Openings for fluid passage at this site are considerably smaller than in the uveal meshwork (Bill and Svedbergh, 1972; Svedbergh, 1976).

Adjacent to Schlemm's canal is a narrow but important zone of loose connective tissue where trabecular organization is absent (*Figure 1.2*). This region has several names including, for example, juxtacanalicular connective tissue, cribriform tissue and endothelial meshwork. None of the names is totally satisfactory but I will use the term 'endothelial meshwork' which is as good as any. The endothelial



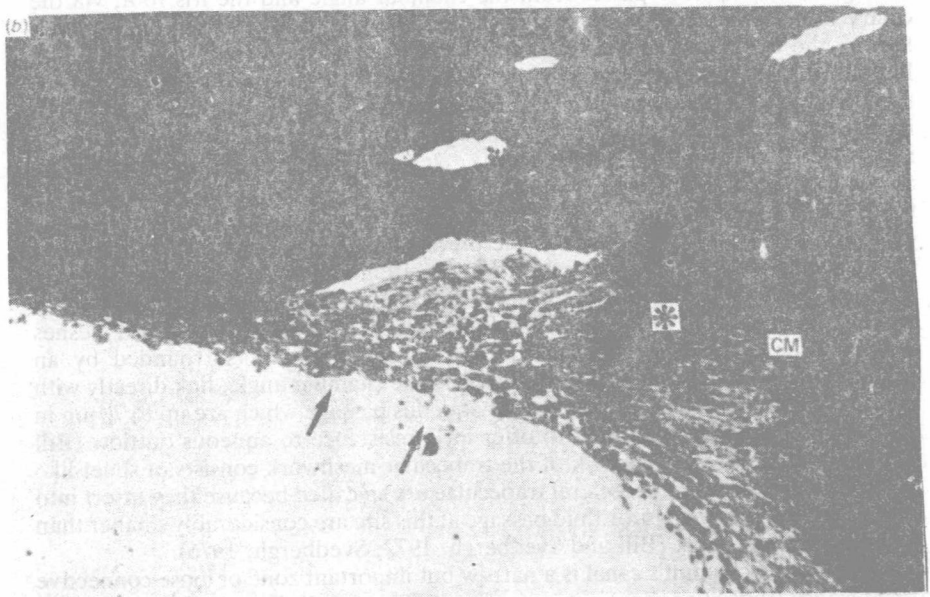


Figure 1.1 (*a*) Various regions in the meshwork; (*b*) light micrograph of the angular region – the ciliary muscle (CM), scleral spur (*), meshwork (arrows) and Schlemm's canal can be identified (×250)

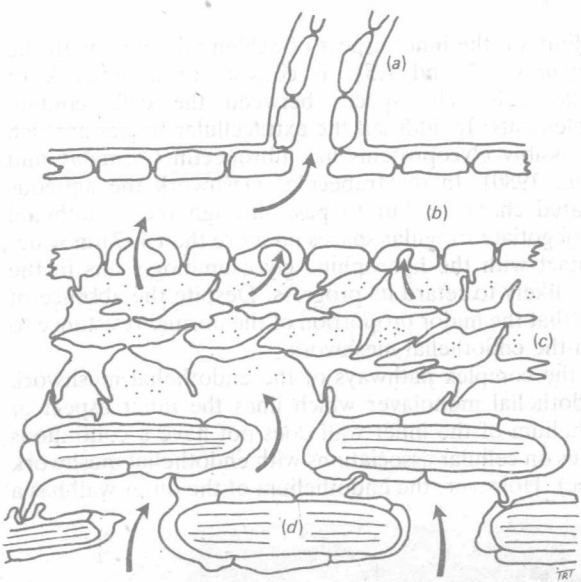


Figure 1.2 Pathway for fluid drainage from the trabecular meshwork and into Schlemm's canal: (*a*) collector channel; (*b*) Schlemm's canal; (*c*) endothelial meshwork; (*d*) corneoscleral meshwork

Figure 1.3 Transmission electron micrograph of part of the meshwork adjacent to Schlemm's canal (SC). The endothelial meshwork is demarcated by arrows, and giant vacuoles (*) can be identified (×1500)

meshwork links the endothelium on the inner aspect of Schlemm's canal with the corneoscleral trabeculae (*Figures 1.2* and *1.3*). It consists of a network of interconnecting fibroblast-like cells. The spaces between the cells contain collagenous and elastic-like elements. In addition the extracellular spaces are rich in glycosaminoglycans and possibly glycoproteins like fibronectin (Armalay and Wang, 1975; Rodrigues *et al.*, 1980). In the trabecular meshwork the aqueous passes through well-demarcated channels, but to pass through the endothelial meshwork the aqueous must negotiate irregular spaces no more than 4–7 μm wide. Also the fluid comes in contact with the hydrophilic glycosaminoglycans in the extracellular spaces which are likely to retard its progress. Despite the absence of direct evidence, it is probable that the major proportion of the normal resistance to aqueous passage is located in the endothelial meshwork.

After percolating through the complex pathways of the endothelial meshwork the aqueous reaches the endothelial monolayer which lines the inner aspect of Schlemm's canal. The endothelium of the inner wall does not have a continuous basement membrane, but relies on cellular associations with endothelial meshwork cells for support (cf. lymphatic). However, the endothelium of the outer wall has a

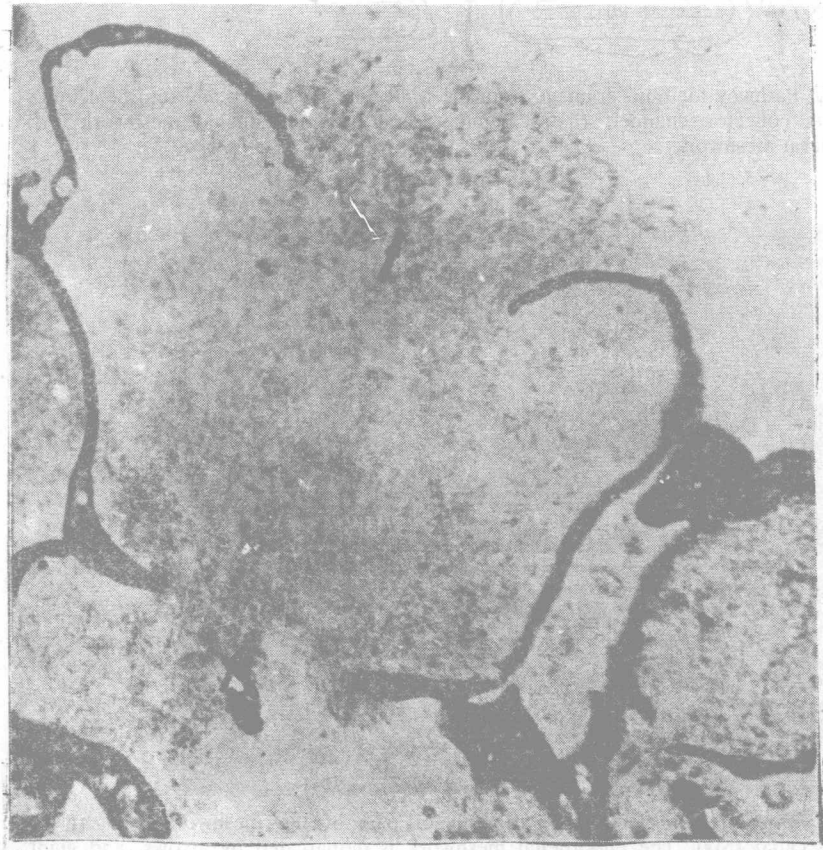


Figure 1.4 Arrows indicate extracellular material at the meshwork and luminal openings of a vacuolar transcellular channel leading into Schlemm's canal (×25 000)

distinctive and continuous basement membrane which cements the endothelial cells to a support tissue which is rich in collagen but contains relatively few cells (cf. capillary). The absence of a basement membrane on the inner aspect of the canal is likely to be an adaptation to drainage.

The precise route by which fluid passes from the endothelial meshwork to Schlemm's canal through the inner wall endothelium has always been controversial. It is probable that some aqueous passes between adjacent endothelial cells via the leaky cell-to-cell junctions. However, it is thought by many but not all (see Tripathi, 1974 and Grierson *et al.*, 1981 for reviews) that the bulk of the drainage is by way of a series of relatively large transcellular channels. Large vesicular-like structures (*Figure 1.3*) are evident in the canal endothelium which have been called 'giant vacuoles' (Tripathi, 1974). It has been shown that the term 'giant vacuole' is unfortunate as these structures are invaginations or infoldings of the endothelial cytoplasm and none of them are intracytoplasmic vacuoles (Svedbergh, 1976; Grierson *et al.*, 1981). Nevertheless these structures have been referred to as 'giant vacuoles' for so long that the name will probably persist and I will use it in this text. A proportion of the infoldings (giant vacuoles) have an opening on their luminal side and as such they constitute transcellular channels. These vacuolar channels (and there are also some non-vacuolar channels) serve as the transendothelial pathways for fluid drainage (*Figure 1.4*).

It was once thought that the pathways were sufficiently infrequent to make the canal endothelium a high resistance zone (Tripathi, 1974). However, it has been shown recently from scanning electron microscopic studies that channels are far more frequent than previously considered. Calculations of aqueous conductance based on channel size and frequency indicate that the resistance in the endothelial monolayer at normal intraocular pressure is less than one-sixth of that in the meshwork (Bill and Svedbergh, 1972; Grierson *et al.*, 1979). If this is true then the endothelial meshwork, where the pathways for the egress of aqueous are particularly tortuous, is likely to be the major site of resistance in the normal eye accounting for as much as three-quarters of total outflow resistance (Bill and Svedbergh, 1972).

PRESSURE SENSITIVITY

Since the conventional outflow pathway is a bulk flow route, it is pressure sensitive. Increase in the pressure differential (pressure head) across the system is associated with an increased rate of drainage. Of course, we express this pressure sensitivity in terms of facility of aqueous outflow. Unlike the uveoscleral outflow pathway which is the main subsidiary outflow route, the conventional pathway is particularly pressure sensitive. It has an intrinsically high outflow facility because the tissues of the meshwork are extremely pliable. When IOP is elevated experimentally in primates including man, the meshwork distends. Distension is most pronounced in the outer corneoscleral meshwork and endothelial meshwork where the normally narrow and tortuous pathways for fluid passage become enlarged. In addition more giant vacuoles and transcellular channels develop in the canal's endothelial monolayer. When IOP is at non-physiologically high levels the distension is so severe that Schlemm's canal can be blocked. If IOP is dropped below normal, the meshwork tissues become compacted and the numbers of giant vacuoles and transcellular channels decrease (Johnstone and Grant, 1973; Grierson and Lee, 1975, Svedbergh, 1976).

Thus the conventional system has the ability to act as a passive valve since it can change from a low flow configuration with narrow meshwork pathways, few giant vacuoles and a paucity of transendothelial channels to a high flow configuration with wide meshwork pathways, many giant vacuoles and an abundance of transendothelial channels (and vice versa). It may not be unreasonable to consider the outflow system as a 'dampening device' capable of dampening out excessive pressure fluctuation in IOP in response to altered aqueous dynamics. If this is the case then it follows that an outflow system with a high facility differs from that with a low facility in the ease by which configurational changes can take place for a given alteration in IOP. We know in chronic simple glaucoma that in addition to mean IOP increase there is also a wider range of diurnal fluctuation in pressure. Perhaps loss of intrinsic pliability of the meshwork tissue may be as important as structural blockage of the trabecular filter *per se*.

When the endothelial meshwork is examined at high IOP there is an obvious loss of ground substance from the distended extracellular spaces (Grierson and Lee, 1975; Svedbergh, 1976). We have conducted a detailed study of this phenomenon and we were able to show that even at pressure within the near physiological range, extracellular materials could be observed in passage through the transcellular channels of the canal's endothelial lining (Grierson and Lee, 1977). Because the endothelial monolayer on the inner aspect of Schlemm's canal does not have an effective basement membrane but does have relatively large intracellular pores, it is conceivable that even at normal levels of IOP there is a continuous washout of ground substances which would require replacement by the native cells (*Figure 1.4*). Not surprisingly, endothelial meshwork cells have more mitochondria, better developed rough endoplasmic reticulum and more prominent Golgi saccules than ordinary trabecular meshwork cells (Tripathi, 1974; Rohen and Lutjen-Drecoll, 1982).

BIOLOGY OF MESHWORK CELLS

As Alvarado, Murphy and Juster (1984) have stated: 'It is likely that trabecular cells perform a variety of important activities for the maintenance of the structural integrity and normal function of the aqueous outflow pathway. Alterations in the density of these cells, as well as their functional ability, could result in a reduced outflow facility or other abnormalities.' Among these activities we could include (a) synthesis of extracellular matrix materials, (b) phagocytosis of debris present in the circulating aqueous, and (c) possibly the maintenance of trabecular hydration levels.

Until recently the importance of the biological behaviour of meshwork cells was ignored and the idea that the trabecular meshwork was merely a 'mechanical filter' prevailed. To a large extent a change in attitude has been brought about by the work of Rohen and associates (Rohen and Lutjen-Drecoll, 1982) and the establishment of primate meshwork cells in tissue culture by several research centres (see Polansky *et al.*, 1984). Rohen has demonstrated *in vivo* that meshwork cells can engulf a wide variety of materials and therefore they are capable of cleaning out debris present in the aqueous humour which otherwise might block up the narrowest of the drainage pathways. Whether meshwork cells should be considered as the reticulo-endothelial system of the eye (Rohen and Lutjen-Drecoll, 1982) or merely as facultative macrophages remains to be established.

In tissue culture at least, meshwork cells produce glycosaminoglycans, fibronectin and laminin and incorporate the precursors necessary for collagen synthesis. Analysis of meshwork cell lysosomes show they are rich in enzymes involved in glycosaminoglycan degradative pathways (Polansky *et al.*, 1984). Undoubtedly tissue culture techniques are giving us new insights into meshwork cell behaviour and metabolism which may eventually further our understanding of disease mechanisms involved in glaucoma.

In response to a variety of insults including enzyme infusion, surgical trauma, deposition of large amounts of particulate material, exposure to cytochalasin B and laser trabeculoplasty, the meshwork cells undergo a remarkable change. The cells have greatly increased amounts of rough endoplasmic reticulum, little heterochromatin in the nucleus, abundant mitochondria, many ribosomes and a well-developed Golgi system. Frequently they are seen to be in the process of detaching from the trabeculae, detached from the trabeculae or even in transit through the endothelium of Schlemm's canal. They have been called 'activated cells' (Rohen and Lutjen-Drecoll, 1982) and the process is somewhat similar to the development of metaplastic retinal pigment epithelium observed after retinal detachment. Activated meshwork cells engulf large amounts of debris and are (on the basis of their morphology) presumed to be vigorously involved in synthetic and catabolic processes. Some supportive evidence is provided by tissue culture studies where cells with the morphological characteristics associated with activation incorporate proline and glucosamine far more avidly than cells which resemble 'normal' meshwork cells. Despite the reactivity of the meshwork cells to insult, the trabecular meshwork in many situations has only a limited capacity for regeneration.

AGE CHANGES

What replicative capacity trabecular meshwork cells have *in vivo* remains unknown, but it would seem to be extremely limited so that for all intents and purposes the complement of trabecular meshwork cells we are born with is more or less all we ever have. By 20 years of age the estimated cell population is 750 000, whereas by 80 years the numbers have decreased to fewer than 400 000 cells with a loss rate of 6000 cells per year. Even Schlemm's canal is not spared, having about 77 000 at 20 years reducing to 55 000 by 80 years. The figures quoted are from our own quantitative analysis of 46 human eyes of various ages from the first to the tenth decade and this study is in progress at the moment. However, the data from other laboratories, although it may not be in precise agreement with our actual estimates of cell numbers, does describe a similar trend of progressive cell loss from the outflow system with increasing age (Alvarado *et al.*, 1981, 1984).

Wear and tear, produced by the repeated alteration of the configuration of the delicate drainage tissues either by changes in aqueous flow rates or in response to the pull of the ciliary muscle during accommodation, may contribute to the decline in the meshwork cell population. Another factor could be activation of the meshwork cells in response to accumulating debris. The major contaminant of aqueous humour is pigment from the iris epithelium which is released in progressively greater amounts as we age. This pigment is phagocytosed by meshwork cells (see previous section) so that less than 3% of meshwork cells contain melanin granules in the young eye, whereas the figure can be of the order