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Topical aldose reductase inhibitor

Polymegathism is a term used to describe increased variability in the size of corneal endothelial cells. Polymegathism came to notice when the advent of the clinical specular microscope made the close examination of the corneal endothelium a relatively simple clinical procedure. With the addition of digital morphometric analysis systems to clinical specular microscopes, quantification of variations in cell size and shape also became simple and reliable. Polymegathism and pleomorphism (increased variability in cell shape) occur with age,¹⁻³ after trauma (including cataract surgery),^{4,5} with contact lens wear,⁶⁻¹⁰ with a number of disorders affecting the anterior segment of the eye,¹¹⁻¹⁴ and after keratorefractive procedures.¹⁵⁻¹⁷ They also occur in diabetes.¹⁸⁻²⁰

Polymegathism is often seen in diabetics when no other ocular disease is apparent. The precise mechanism is yet to be determined. It has been attributed to the accumulation of sorbitol in endothelial cells which in turn has been linked to the presence in corneal endothelial cells of aldose reductase, the rate limiting enzyme in the polyol pathway associated with the conversion of glucose to sorbitol.²¹⁻²³ In addition to corneal endothelial cells, the enzyme is present in the lens and the retina.²⁴⁻²⁶ Experiments in diabetic animals have implicated sorbitol accumulation with osmotic changes and the development of cataracts.^{27,28} A similar process is proposed to explain irregularities in the size of corneal endothelial cells. When blood glucose levels are high, there is sufficient substrate for the polyol pathway to become important and for the intracellular osmolarity to rise and water to accumulate and alter cell size and shape. Whatever the mechanism, inhibition of aldose reductase reverses endothelial polymegathism.^{21, 22, 29, 30}

It has been demonstrated that galactose fed dogs developed polymegathism and that the concomitant administration of aldose reductase inhibitors prevented this.²² Furthermore, it has also been shown that topical administration of aldose reductase inhibitors could reverse polymegathism in animals.^{21, 23, 29, 30} More recently it has been shown that corneal epitheliopathy and decreased sensation in human diabetics can be reversed using the same therapeutic approach.^{31, 32} The paper by Ohguro *et al* in this issue of the *BJO* (p 1074) confirms that endothelial polymegathism will also respond to this treatment.

The clinical significance of endothelial polymegathism is uncertain. Although it is generally acknowledged that polymegathism occurs in diseased corneas, the precise pathology has not been identified. Until now nobody has been able to relate polymegathism to essential endothelial structures such as pump sites. There is some evidence, at least at an anecdotal level, that corneas exhibiting polymegathism have a reduced functional reserve capacity and that they are more prone to develop oedema after cataract

surgery.⁴ The decreased functional reserve has also been demonstrated in controlled experiments on humans subjected to hypoxic stress.¹ Uncertainty about the clinical significance of polymegathism is due to the paucity of reports of corneal disease associated with the phenomena. Polymegathism is common in contact lens wearers and in diabetics, but it is very unusual for patients with polymegathism as a result of hard contact lens wear to go on to develop corneal failure and bullous keratopathy, or for patients with diabetes and polymegathism to suffer a similar fate.

The findings set out in the paper by Ohguro *et al* may have direct clinical benefits. If the decreased functional reserve capacity ascribed to patients with polymegathism is real then the risk of anterior segment surgery to the cornea may be reduced by the use of topical preparations of aldose reductase inhibitors. However, the importance of the observations may go beyond this.

Firstly, there is the prospect of the development of pharmacology relevant to the complicated and important metabolism of the corneal endothelium pump; even though the precise physiological mechanisms of this are not fully understood, the prospects of pharmacological manipulation are tantalising. Secondly, the prospect of reducing the systemic complications of diabetes by medical means opens the way to new opportunities on a broader front.²⁸

If we are to explore these possibilities further, more needs to be known about the basic biology of the cornea. Much has been learned recently, but much more remains unknown.

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