Pathogenesis of the ICE syndrome

'Iridocorneal endothelial (ICE) syndrome' was the term proposed in 1979 by Yanoff to embrace a group of rare diseases with similar characteristics. Progressive essential iris atrophy,2 Chandler’s syndrome,1 and iris naevus syndrome1 all showed abnormalities of the cornea, anterior chamber angle, and iris. In the past 15 years interest has centred on the cornea, for it appears that it is an abnormality of the corneal endothelial cells that is fundamental to the three conditions and that accounts for the other manifestations: the cells can migrate across the angle, occluding it, and on to the anterior iris surface, where contraction of a sheet of cells, or its subjacent abnormal ‘Descemet’s membrane’, can distort the pupil, thin the iris, and pull holes in it. If on the cornea the pump function of these abnormal cells fails (Bourne and Brubaker found their barrier function to be greater than normal7) corneal oedema results.

It became apparent to the pioneer clinical specular microscopists including Bourne8 and Neubauer et al9 that areas of both ICE cells and apparently normal endothelial cells could co-exist on the same posterior corneal surface, though confusion arose when a similar appearance was ascribed by Hirst and Waring6 to posterior polymorphous dystrophy (PPD). The specular microscopical variants have now been described in detail by Sherrard et al10 and Laganowski et al,11 but the assent of all workers has not been achieved.11 Lee et al, whose paper appears in this issue of the journal, propose that both cell types of the dual cell population are abnormal; the normal appearing cells, having failed to control water movement across the posterior corneal surface, transform to ICE cells in an attempt to regain control.

The literature now contains many descriptions of the ICE syndrome cornea using clinical specular microscopy, light microscopy, transmission and scanning electron microscopy, cytokeratin expression, immunohistochemical staining, and many other methods. Naturally, these have given rise to a number of theories of the pathogenesis of the condition.

For some time it has been held that ICE cells have epithelial characteristics. These were cited by Hirst et al12 as comprising (in their example) increased intercellular interdigitations, microvillous surface projections, bundles of 10 nm intracytoplasmic filaments, desmosome formation, and positive staining with rabbit antikeratin antibody. They differed from the epithelium-like cells seen in PPD and after epithelial ingrowth in that they did not form more than two layers on the cornea. Whether these epithelium-like cells were a congenital variant or an acquired change was not known.

Neither Rodrigues et al13 nor Alvarado et al14 found epithelial characteristics in the abnormal endothelial cells of their specimens, and for some time it was generally assumed that the clinical confusion of ICE syndrome with PPD had earlier given rise to a misunderstanding; but the more recent cytokeratin work of Kramer et al14 and of Levy et al15 strongly suggests that ICE cells do indeed have epithelial characteristics. Levy et al, furthermore, have identified a close similarity between ICE cells and limbal conjunctival epithelium, and they propose that ICE cells may arise from a heterotope of the ocular surface epithelium.

The other main current theory of the pathogenesis of the ICE syndrome is that expounded by Alvarado et al16 who propose a viral aetiology. The evidence they adduce includes the presence of inflammatory cells (believed by some other workers to be merely 'passengers'), a patchy form of cell necrosis known as apoptosis, the tendency of some viral diseases to have a single locus of primary infection and to be predominantly unilateral, and the acquired, rather than congenital, nature of the condition. This last characteristic is justified by 'archaeological' studies of the abnormal Descemet’s membrane produced by ICE cells (Alvarado et al17). Recently, Alvarado’s group tested ocular tissues and cell cultures from ICE patients for viral DNA using the polymerase chain reaction and found four of 11 positive for herpes simplex virus (HSV 1).18 No specimens were positive for herpes zoster virus or for Epstein-Barr virus. The latter finding was unexpected, as Tsai et al19 found IgG antibodies to Epstein-Barr virus capsid antigen raised in 12 seropositive ICE patients, compared with 12 race, age, and sex-matched controls. New work by Alvarado’s group has shown 10 of 17 ICE samples to be HSV 1 positive.20

A further contribution to our understanding of this condition, with particular reference to the collagen types found within the abnormal Descemet’s membrane, features in the work by Lee and colleagues. The pathogenesis of ICE syndrome remains a mystery, but evidence continues to accumulate rapidly. We might have the answer by the end of the millennium.

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Mechanisms governing the passage of aqueous humour through the trabecular meshwork

Ascher’s discovery of aqueous veins half a century ago was the crucial factor in recognising that aqueous humour is a circulating fluid draining from the anterior chamber, and a few years later Ashton demonstrated continuity between the canal of Schlemm and aqueous veins. The trabecular meshwork at the irido-corneal angle was the obvious route for drainage, yet for this to be so the continuous endothelial layer constituting the inner wall of the canal of Schlemm had to be breached. With the aid of electron microscopy, Holmberg and Tripathi advanced the concept that this was achieved by means of giant vacuole transport (earlier light microscopic observations had suggested the possibility). Pores on the abluminal surface develop into giant vacuoles up to 5 μm in diameter, contact the luminal surface, and discharge into the canal. The incidence and size of giant vacuoles are intraocular pressure dependent, and measurement of pressure in each of the structures involved in aqueous drainage confirmed the meshwork as the principal site of resistance to outflow. Some paracellular drainage through the leaky gap junctions of the inner wall is likely but probably very limited. The juxta-canalicular tissue adjacent to the inner wall, consisting of a mesh of endothelial cells within a loose fibrous matrix, may have the major role in trabecular resistance to aqueous humour outflow. According to this view the facility of passage through the juxta-canalicular tissue determines access of aqueous to the inner wall and, consequently, the rate of formation and discharge of giant vacuoles. Provided the wide channels of the deeper parts of the meshwork are maintained, their potential for obstruction appears negligible, especially when the spacing of the beams is viewed with the scanning electron microscope. But Carreras and his colleagues have reopened the debate of the significance of mucous cover of trabecular cell membranes by identifying a substantial mucous lining of the posterior and anterior chambers in humans, thickest at the filtration angle. They suggest that its glycosaminoglycan composition, containing long hyaluronic acid molecules, is capable of trapping and holding virtually any of the macromolecules suspended in aqueous and so plays a part in the regulation of aqueous outflow.

Recently, attention has been directed to the subject of endothelial cell permeability and in particular to the role of negatively charged domains (anionic sites) on membrane surfaces. Sialic acid groups, highly charged anions, are the terminal constituents of many cell surface glycoconjugates—for example, gangliosides and glycoproteins such as fibronectin and laminin. Consequently, they are important in the maintenance of structural relations between endothelium and matrix and they are thought to be factors in the stabilising of cell membranes. Using cationic ferritin and colloidal iron labelling coupled with neuraminidase digestion, sialic acid groups have been identified on each side of the lining endothelium of Schlemm’s canal. Labelling was heavy on the luminal surface but random and sparse on the abluminal or basal surface. In this issue of the journal Chapman and colleagues report their work confirming a concentration of sialyl groups on the luminal surface and, furthermore, employing a method using different cationic probes to distinguish two sialyl glycosides, one of them disposed mainly on the luminal aspect of the lining endothelium and in the cytoplasm of juxta-canalicular tissue cells. The other was localised predominantly to the extracellular fibrillar material of this region. The demonstration of different sialyl glycosides occupying distinct sites in the trabecular meshwork adds further encouragement to the proposal that they are of significance in the regulation of aqueous outflow.

The argument is presented that absence or sparseness of sialated molecules on the abluminal surface of the lining endothelium reduces membrane stability, facilitating initiation of the macropmculation process and, thus, aqueous passage. Interest is heightened by the observation of increased labelling on both sides in glaucoma, presumably increasing stability and reducing capacity for giant vacuole formation. Observations in other studies are not consistent with this result and it becomes clear that the effects of differences in tissue preparation must be understood before there is further progress. Future monitoring of the responsiveness to selective manipulation of these and other anionic sites and the potential for their therapeutic regulation are exciting prospects.

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