The X, Y, Z Hypothesis of Corneal Epithelial Maintenance

To the Editor:

For the past few years, studies of corneal epithelial healing have focused on the changes that occur in the remaining epithelial cells and their substrate following acute epithelial removal. The processes of epithelial cell sliding, proliferation, and replication have been documented in the past,1,4 and more recent work has illuminated addition details of these responses to injury.2,6 These studies have produced useful generalizations that help in understanding the pathologic processes responsible for corneal epithelial defects in humans. However, we would suggest that a fresh look at the factors involved in corneal epithelial maintenance may serve to initiate new experiments and new observations which may further advance the therapy of corneal epithelial failure.

The mass of corneal epithelium probably does not change under normal circumstances. As shown in Figure 1, the corneal epithelial cell mass can be viewed as the resultant of three separate, independent phenomena. We have termed these: X, the proliferation of basal epithelial cells; Y, the contribution to the cell mass by centripetal movement of peripheral cells; and Z, the epithelial cell loss from the surface. Corneal epithelial maintenance thus can be defined by the equation: X + Y = Z, which simply states that if the corneal epithelium is to be maintained, cell loss must be balanced by cell replacement.

The presence of the X component has been established by tritiated thymidine labeling of epithelial cells, identifying the actively dividing basal cells.3 However, there remain numerous questions to be answered with regard to X. Does the mitotic rate change in response to increased or decreased epithelial attrition? Is the rate under neuronal or pharmacologic control? What happens to the rate of basal cell proliferation in a variety of clinical circumstances, eg, inflammation, drug toxicity, denervation, or metabolic stress from contact lenses?

The Y component is an ongoing, slow, centripetal cell movement that occurs even in the absence of an acute defect. It is important not to confuse Y with another phenomenon, the rapid movement of peripheral cells in response to an acute central defect.7 While as yet not proven, there is both direct and indirect evidence for such an ongoing movement, even in the absence of a defect. Analysis of the sex chromatin in donor corneal epithelium shows that there is a loss of donor epithelium remained to react10 also indicate an active Y component. These observations have been made on surgically treated eyes. However, recent studies showing a radial pattern of hemidesmosome alignment along the basement membrane of normal murine eyes are also consistent with the concept of centripetal

cell migration. Whether in addition to cell movement from the peripheral to central cornea, there is also a continual drift of conjunctival epithelial cells across the limbus with transformation of the cell phenotype from conjunctival to corneal remains to be determined. If the later process does occur, however, its failure in disease states characterized by concurrent conjunctival and corneal involvement would explain many of the clinical phenomena in these conditions.

The ongoing, normal loss of cells from the surface, the Z component, has never been studied. It is, of course, certain that such loss occurs in the special case of failure of adhesion of the epithelium to the stroma in some abnormal conditions. Occasionally, one sees what seems to be cellular debris behind non-venting contact lenses, but to date, cell loss from the surface has not been quantitated.

Utilizing the X, Y, Z hypothesis, it is possible to categorize both diseases and therapies according to the specific component involved. Thus, an epithelial disease could be the result of inadequate basal cell proliferation (decreased X), deficient centripetal cell movement (decreased Y), or increased cell loss (increased Z). By identifying the abnormal biologic process, therapy then could be directed at correcting the abnormal component, and therapeutic endeavors could even be separated into those that affect basal cell proliferation (eg, mitogens or changes in cyclic AMP levels), those that affect centripetal cell movement (eg, conjunctival transplantation), and those that affect cell loss (eg, protective measures such as soft contact lenses and tarsorrhaphy). We suggest that investigating and observing the X, Y, and Z variables will lead to new insights into the pathogenesis and therapy of corneal epithelial disease.

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