STUBBORN CORNEAL ULCERS

ESSAY

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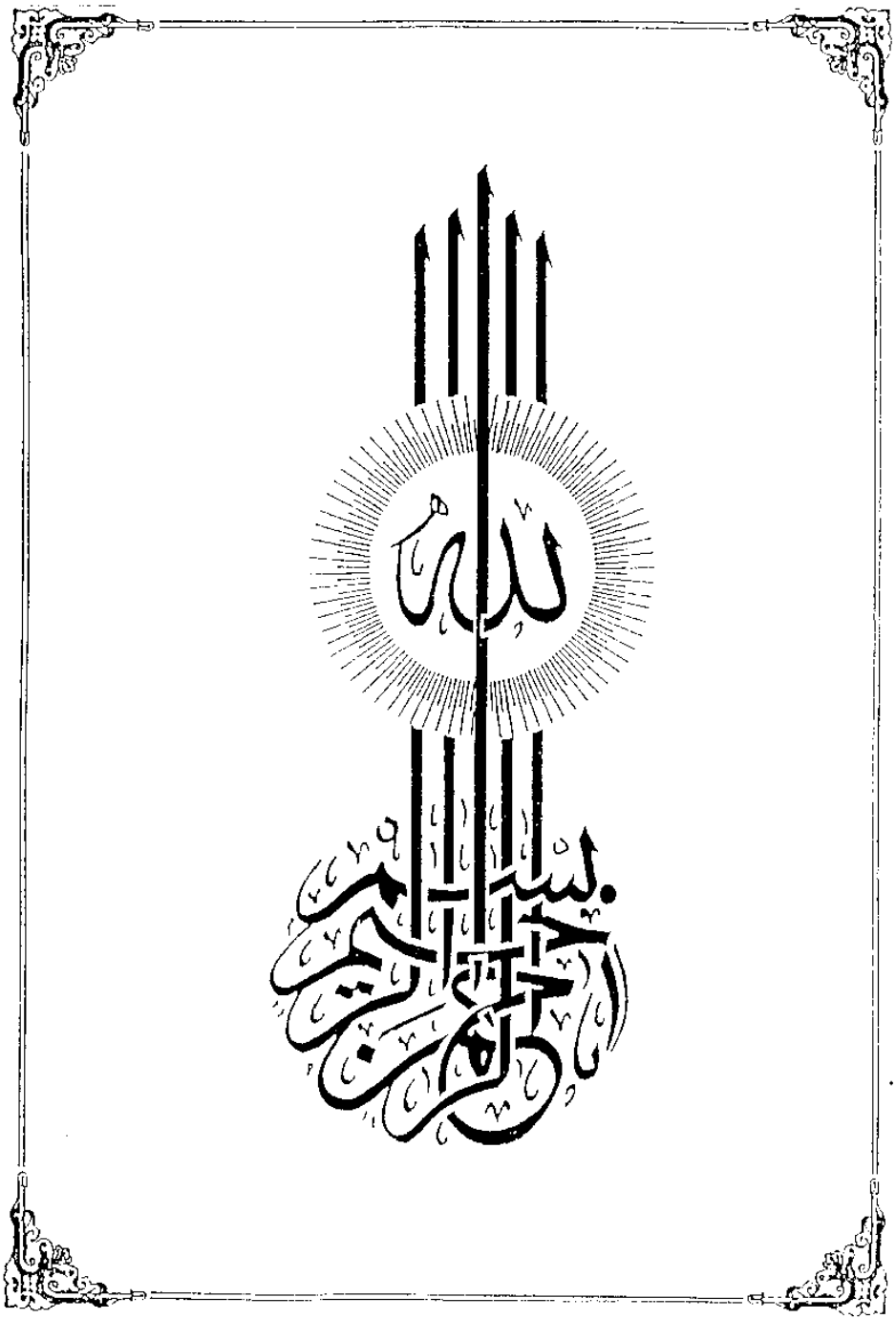

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INTRODUCTION

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Corneal ulcers and their sequelae are one of the most important causes of visual handicapping in our country. By stubborn corneal ulcers we mean those that are rapidly progressive inspite of trials of treatment as in some cases of hypopyon ulcers, as well as recurrent ulcers as in viral ulcers. Ulcers that are not properly diagnosed and hence not receiving the appropriate medications are also indolent ulcers.

For the proper management of corneal ulcers, a detailed history must be taken. This discloses the predisposing factors; corneal trauma, contact lens use eye lid disease, ocular and systemic diseases.

We divided the clinical picture of ulcers to central or marginal. Central ulcers are usually of infective origin while marginal ones are of immunological cause. Though the clinical picture of each ulcer is usually the same, one should not totaly rely on it.

For this purpose we included the set of investigations done for every type of ulceration. These investigations were divided to; conventional methods and corneal biopsy to cover the whole range of causative agents.s

Our aim is to study stubborn corneal ulcers elaborately. This will include the proper interpretation of the clinical picture of each ulcer, also following a definite scheme of investigations up to corneal biopsy, so as to reach a definitive diagnosis.

NORMAL HEALING

NORMAL HEALING

The cornea is protected and isolated from the surrounding atmosphere by the corneal epithelium. This barrier is formed as the epithelial cells move from the basal layer to the surface of the cornea. In the mean time the cells are differentiating until the superficial cells form two layers of flattened cells. Desmosomes joins these cells together, that are specially abundant in the wing cell layer, and hemidesmosomes join the basal cell layer to the basement membrane [*Gipson , 1992*].

It is assumed that epithelial cells turn over completely in 7 days [*Hanna, et al., 1961*]. The maintenance of the epithelium is achieved through either mitosis which occurs in the basal cell layer only or by migration of new basal cells into the cornea from the limbus. It therefore appears that corneal epithelium is maintained by a balance in the processes of cell migration, mitosis and shedding of the superficial cells [*Gipson , 1994*].

It has been noted in full thickness injury of the corneal epithelium, that the damaged cells adjacent to the wound edge lose their surface microvilli. Within one hour the basal cells of the corneal epithelium begins to migrate, to cover the wound, so they lose their hemidesmosomes [*Buck, 1982*].

At approximately six hours after wounding; the epithelial cells initiate wound closure by sliding into the area of defect. It was found that desmosomes are retained as the cell-cell adhesion junction during migration so, the epithelial cells move as a sheet rather than as individual cells [*Gipson, 1992*].

Fig. 1: Epithelial cells regrow over an abraded surface, using the adhesion plaques on the underside of the filopodia to maintain firm adhesion and assist the foreward movement of the cell by contraction of the contained intracellular actin-myocin network [*Pfister, 1992*].

Fifteen hours after wounding and epithelial sliding is active, as the leading cells extend pseudopodia their motility depend on the actin filaments of the cytoskeleton. As the defect is closed, contact inhibition causes cessation of cell movement and alteration in cellular configuration, as these migrating squamous cells take the cuboidal shape of the basal cells another time [*Gipson, 1994*].

After 24 to 48 hours of wounding, epithelial proliferation in the wound is at its climax and forms an epithelial plug. By 3-4 days the epithelial plug regresses and mitotic figures start to appear in the wound [*Gipson, 1994*].

Gipson and colleagues *(1989),* said that in abrasion wounds in which the basement membrane and underlying anchoring fibril net work is intact, new hemidesmosomes form over the basement membrane as soon as restratification of the epithelium occurs. In wounds, that were done for rabbits, in which the anterior portion of the stroma has been removed, resynthesis of adhesion structures occurs under restratified epithelium beginning at the wound margin and moving towards the wound center. Resynthesis of the components of the adhesion complex appears synchronous, in that ultrastructurally and immunohistochemically, hemidesmosomes, small segments of basement membrane and anchoring fibrils (collagen fibrils) appear in the same time.

As healing proceeds, the segments of the basement membrane increase in length until the adhesion complex is virtually continuous along the base of the epithelium [*Gipson et al., 1989*].

Depending on the severity of the basement damage, as long as 6 to 8 weeks may be required for complete basement membrane reconstruction. This is closely

paralleled by delayed epithelium to stroma adhesion until the intact basement membrane has been restored [*Kenyon and Chaves, 1994*].

The response of the healing cornea is not the same if the injury was severe. A study was conducted by *Dua and Forrsester (1990)* concerning re-epithelization of ocular surfaces in 17 human eyes with large corneal and conjunctival abrasions.

They have noted that large wounds which affected more than 70% of the corneal surface and more than 55% of the corneoscleral limbus, healed at a slower rate than in smaller wounds with less than 55% affection of the limbus. This would indicate that a portion of limbal cells were depleted as a result of limbal denudation and the rate of healing was consequently retarded. During limbal healing they noticed that a small recess or area staining with fluorescein was always present on the conjunctival side of the circumferentially migrating tongue shaped processes. This strongly suggests that the cells of these tongue shaped process are derived from the corneal epithelium and could represent the migration and proliferation of stem cells along the corneoscleral limbus.

These cells later develop into the centripetally migrating convex sheets, which further indicates the stem cell nature. It has also been noted that there is a zone of cells at the corneal periphery, few mm. wide, comparatively more resistant to mechanical and chemical denudation. When they are intact with a central epithelial defects they start to migrate. Also if this limbal zone was lost healing of the corneal surface corresponding to this area is delayed.

In the same study, they noted that if conjunctival epithelium migrated across the corneoscleral limbus and covered the cornea, this area was thinner and

had an irregular surface. This area also attracted new blood vessels and was the focus for recurrent erosions.

These findings were supported also by other studies advocated by *Sharpio*, and colleagues *(1981)* in which they found that the over growth of the conjunctival epithelium over the cornea is also marked by the presence of goblet cells. They have noted that the stromal neovascularization was observed mainly in the areas where goblet cells were retained.

The vascular response to various noxious stimuli is intiated by limbal capillary and venule dilatation with subsequent passage of leukocytes into the stroma with extravasation of fibrin and serum protiens. Subsequent vascular endothelial migration and proliferation occurs towards the neovascular stimulus. This could be origenated from the inflammation and may be caused by PMN's or from the corneal epithelium and its basement membrane [*Kenyon and Chaves, 1994*].

This is one of the patterns of stromal affection in wounding of the corneal epithelium, however the corneal stromal behavior to direct wounding have other patterns. After penetrating injury of the stroma, keratocytes immediately adjacent to the wound margin are killed and the defect soon fills with a fibrin clot. The stromal lamellae become oedematous and adjacent keratocytes withdraw their cytoplasmic processes [*Gipson, 1994*].

Keratocytes in the stroma adjacent to the damaged area undergo transformation into fibroblasts and migrate into the wound directly under the new epithelium. This occurs within 7 days of injury. These cells multiply over the next

few weeks to fill the space originally occupied by fibrin. Collagen is synthesized and deposited by the wound fibroblasts, but not in the characteristic parallel arrays.

Instead, collagen deposition occurs in a more haphazard lamellar pattern resembling an onion skin [*Fini et al., 1992*]. However, this early repair tissue is progressively remodeled, over a period of years, until the parallel lamellar layers are recreated across the region where the incision had interrupted them [*Davison and Galbavy, 1986*].

During this process, collagen fibril size becomes more regular and the stromal fibrils attain a more orderly arrangement. These changes are thought to contribute to the return of normal corneal transparency in the damaged area [*Fini et al., 1992*].

MODULATIONS OF HEALING

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Plasmin and its Inhibitors:

Plasminogen activation into plasmin is by far the most important mechanism of extracellular proteolysis. There is good evidence to suggest that its primary role is to degrade extracellular matrix, including components of the interstitial matrix and basement membranes as well as of fibrin clot. Plasminogen activation is a cascade like process regulated at a number of levels [*Vaheri et al., 1992*].

There are 2 plasminogen activators (PAs), urokinase type (uPA) and tissue type activators (tPA). They are both synthesized as single chain enzymes that need certain materials for their conversion into a fully active 2 chain activators [*Vaheri et al., 1992*].

Activation of plasminogen by tPA is strongly promoted by fibrin, which aligns and concentrates tPA and plasminogen with in the fibrin clot to facilitate fibrinolysis. On the other hand, uPA plasminogen actvation takes place on the cell surface when uPA is bound to its specific receptor [*Vaheri et al., 1992*].

Both tissue plasminogen activator and urokinase plasminogen activator have been demonstrated in the tear fluid. It has been suggested that the lacrimal gland and conjunctival or corneal cells are the source of tear fluid PA activity [*Tervo et al., 1992*].

Patients with corneal diseases seem to show elevated tear fluid PA activity as about 70% of patients with microbial corneal ulcers showed elevated plasmin like activity [*Berta et al., 1990*].