CORNEAL EPITHELIAL CELL MIGRATION IN HUMANS: 'HURRICANE AND BLIZZARD KERATOPATHY'

H. S. DUA[1,2], N. J. WATSON[2], R. M. MATHUR[3] and J. V. FORRESTER[2]
Philadelphia, Aberdeen and Ontario

SUMMARY

Replicative turnover of the corneal epithelium is believed to occur from a population of stem cells located at the corneo-scleral limbus. During the healing of corneal epithelial wounds, sheets of epithelial cells move centripetally from the limbus and circumferentially along the limbus to cover the defect. A whorled or vortex pattern, similar to that seen in cornea verticillata, has been reported to occur on the corneal surface as an effect of topical steroid medication, during the healing of grafted corneas. This condition has been termed 'hurricane keratopathy'. We have noted this appearance in 6 patients who did not have corneal grafts. In all our patients the whorled pattern was best visible on fluorescein staining. This feature differentiates 'hurricane keratopathy' from cornea verticillata secondary to deposition of substances in corneal epithelial cells. Further, in all our patients the vortex was clockwise. Examination of illustrations of 'hurricane keratopathy' and cornea verticillata reported in the literature reveals that the whorled pattern is almost always clockwise. We believe that this specific pattern is likely to be due to the effect of the electromagnetic fields of the eye on the migrating epithelial cells and present a theory to explain this phenomenon. In 3 eyes of 2 other patients with chronic epitheliopathies we observed a random distribution of cells that did not conform to any specific pattern. We have termed this condition 'blizzard keratopathy'.

A whorled or vortex distribution of cells often occurs in the epithelium of corneal grafts. Mackman *et al.*[1] reported this observation in 15 patients with full-thickness corneal grafts and called the condition 'hurricane keratitis'. They believed it to be a toxic effect of topically applied dexamethasone. They did not, however, observe this toxicity in post-cataract corneas and therefore suggested that the epithelium of corneal grafts was highly sensitive to topical medication. Using colour specular microscopy, Lemp and Mathers[2] studied the epithelial surface of 31 healing corneal grafts and reported a vortex pattern in 71% of the eyes studied. They suggested that this was due to the radial movement of epithelial cells between sutures. In their study, corneas of patients with keratoconjunctivitis sicca and neurotrophic keratitis and those of extended contact lens wearers did not show this pattern. It is suggested in the above reports that 'vortex keratopathy' or 'hurricane keratitis' is peculiar to the healing of donor corneal epithelium following keratoplasty.

We report 6 cases of 'hurricane keratopathy' that developed in eyes with no previous history of corneal graft surgery but 5 of which were on long-term topical steroid therapy. We also report our observations in 3 eyes of 2 patients, one with a corneal graft, where a bizarre distribution of the healing epithelial cells occurred. On the basis of our observations, supported by evidence from the current literature, an explanation for these occurrences is proposed.

PATIENTS

Eight patients, 4 females and 4 males, between the ages of 35 and 82 years, attending the Eye Outpatients' department of the Aberdeen Royal Infirmary, are included in this report. Six of these patients showed a whorled distribution of corneal epithelial cells in their symptomatic eye, on one or more occasions, during the course of their ailment. Clinical details and treatment of these patients are summarised in Table I. The other patients showed an apparently disorganised, random distribution of the corneal epithelial cells. Clinical details and treatment of these patients are summarised in Table II.

OBSERVATIONS

All 6 patients with 'hurricane keratopathy' showed a clockwise vortex or spiral pattern on the corneal surface. The pattern was always clockwise in both right and left eyes (Figs. 1 and 2). The cells that formed the pattern were arranged radially for 2–3 mm at the limbus and then

From: [1]Wills Eye Hospital, Philadelphia, USA; [2]Department of Ophthalmology, University of Aberdeen, UK; [3]Faculty of Engineering Science, University of Western Ontario, London, Canada.

Correspondence to: Dr. H. S. Dua, Research Division, Wills Eye Hospital, 900 Walnut Street, Philadelphia, PA 19107, USA.

Eye (1993) 7, 53–58

Table I. Clinical details of patients with 'hurricane keratopathy'

No.	Sex	Age (yr)	Eye	Clinical diagnosis	Topical medication	Duration of treatment before hurricane keratopathy
1.	F	61	L	Recurrent idiopathic iridocyclitis	Betamethasone, dexamethasone and atropine	16 months[a]
2.	F	82	R	Post-operative uveitis (extracapsular cataract)	Betamethasone	4 weeks
			R[b]	Herpes zoster kerato-uveitis	Dexamethasone, betamethasone and chloromycetin	10 weeks
3.	M	42	R	Idiopathic anterior uveitis	Betamethasone	8 weeks
4.	M	55	L	Herpes simplex disciform keratitis	Betamethasone and dexamethasone	12 weeks
5.	M	35	R	Chemical corneal abrasion with anterior uveitis (detergent cleaning fluid)	Prednisolone, betamethasone and cyclopentolate	5 weeks
6.	M	43	L	Form fruste keratoconus, hard contact lens wear (over 14 hours a day)	Nil	

[a]This patient was on steroid medication intermittently over 16 months with the longest duration being 6 months.
[b]This patient had recurrent hurricane keratopathy: first whilst being treated for post-operative uveitis and for the second time when she developed herpes zoster kerato-uveitis 1 year following the operation.
Patients 1, 2 and 5 also had small central corneal epithelial defects. In all patients the hurricane keratopathy healed between 3 weeks and 6 months after discontinuing steroid medication.

curved to the left. The curve became gradually more pronounced as the cells spiralled towards the apex of vortex. Although the fine lines of the vortex pattern were visible by slit lamp examination in all patients, they were best visualised after staining with 1% sodium fluorescein. The corneal epithelial cells that formed the vortex were highlighted by fluorescein stain, with intervening areas remaining unstained. It was, however, not possible to determine whether the staining was intercellular or whether it was the cells themselves that stained. The staining intensity was maximal at the apex of the vortex. In 3 cases there was an epithelial defect at the apex (Fig. 1).

In 5 of the 6 cases with 'hurricane keratopathy' the pattern became obvious after 4 weeks to 16 months of commencing topical steroid medication with betamethasone or dexamethasone sodium phosphate. Discontinuation of topical steroids corresponded with a disappearance or attenuation of the keratopathy over 3 weeks to 6 months. The central epithelial defect when present was the first to heal. Resolution of 'hurricane keratopathy' commenced at the limbus and progressed centripetally. The process was not uniform; one area of the cornea cleared considerably while the other still showed remnants of the original whorled pattern (Fig. 3). The sixth patient, who did not have any steroid medication, wore a hard contact lens for mild keratoconus. His presenting symptom was mild ocular irritation. The whorled pattern, 'hurricane keratopathy', was still present 6 months after his initial presentation.

In the other 2 patients similar epithelial cells, highlighted with fluorescein stain, were seen but did not conform to any pattern and were scattered irregularly over the entire surface of the cornea much like 'snow flakes tossed in a blizzard' ('blizzard keratopathy'). A tendency for the cells to be arranged in radial lines or small whorls was apparent (Figs. 4 and 5).

Symptoms experienced by these patients were principally those of the primary disease condition. However, mild ocular irritation, a foreign body sensation, lacrimation and photophobia were experienced by patients in the presence of 'hurricane keratopathy' and 'blizzard keratopathy' even when the underlying disease process was quiescent.

Table II. Clinical details of patients with 'blizzard keratopathy'

No.	Sex	Age (yr)	Eye	Clinical diagnosis	Topical medication	Duration of treatment before blizzard keratopathy
1.	F	56	L	Corneal graft for HSV keratitis. Epithelial rejection. Epithelium surgically removed and soft bandage lens placed	Prednisolone and betamethasone	2 weeks
2.	F	80	R and L	Bilateral chronic open angle glaucoma. Kerato-conjunctival reaction to topical 1% adrenaline drops	Prednisolone	Less than 6 weeks[a]

[a]When this patient presented with a keratoconjunctival reaction suspected to be secondary to topical antiglaucoma medication, the adrenaline drops were discontinued and oral acetazolamide with topical prednisolone commenced. The patient did not return until 6 weeks following this and was noted to have 'blizzard keratopathy'.

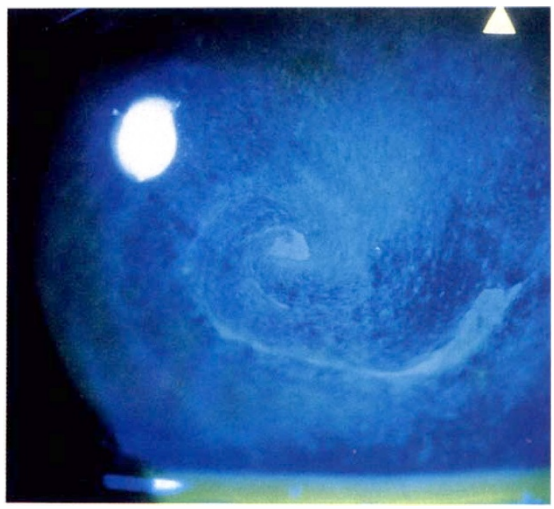

Fig. 1. *Clockwise whorled pattern seen on the corneal surface of patient 1 (Table I). The cornea has been stained with fluorescein. Note the small central epithelial defect.*

DISCUSSION

Cornea verticillata or vortex keratopathy was first described by Fleischer[3] in 1910. Since then it has been reported in several diverse clinical conditions such as Fabry's disease, amiodarone keratopathy, chloroquine keratopathy, band keratopathy and striate melanocytosis.[2,4] In these conditions the whorled pattern becomes visible due to intracellular deposition of a variety of substances such as pigment, iron, drug metabolites, glycogen or sphingolipid. These whorls do not stain with fluorescein.

Vortex keratopathy seen in the above group of conditions is essentially different from 'hurricane keratopathy' seen in corneal grafts and those reported here. In 'hurricane keratopathy' the whorl of epithelial cells stains brightly with fluorescein and visible deposition or accumulation of pigment or iron is not significant. Similar small localised whorled patterns around Y-shaped contact lines formed by advancing epithelial sheets during the healing of corneal epithelial abrasions have also been reported.[5] The exact mechanism by which a whorled pattern forms on the corneal surface is not clear. However, as suggested by Bron[4] the very diversity of clinical conditions and situations where this pattern develops would indicate that it is dependent upon the multiplication and migration properties of the corneal epithelium rather than on any specific stimulus or disease process.

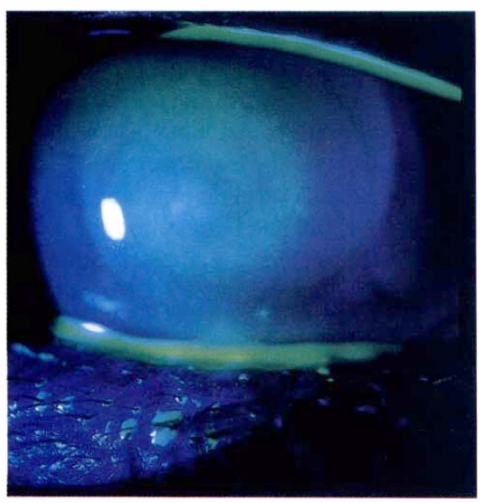

Fig. 2. *Clockwise whorled pattern seen on the corneal surface of patient 6 (Table I). The cornea has been stained with fluorescein. This patient wore a hard contact lens for keratoconus but had never received topical steroid medication.*

Studies on corneal epithelial wound healing have shown that the source of cell proliferation and migration is located at the corneal periphery, in the limbus.[6] Stem cells of the corneal epithelium are situated in the basal cell layer of the limbus and show a high mitotic index.[7,8] There is a general centripetal movement of cells from this site of maximal cell multiplication at the periphery towards the centre of the cornea.[9,10] This centripetal streaming of cells occurs constantly in the normal renewal of corneal epithelium and is accentuated after epithelial cell loss as in abrasions.[5,10–12] Furthermore, a zone of cells at the limbus of human corneas has been reported to show a preferential circumferential migration along the limbus.[13] This circumferential movement at the periphery would introduce a 'spiralling' or 'torsional' effect on the centripetally or radially migrating epithelial cell sheets and could be a factor contributing to the formation of a whorled pattern. This would not, however, explain why the whorled pattern always shows a clockwise predisposition.

All patients with 'hurricane keratopathy' presented here had clockwise whorls. Although never commented upon, illustrations of 'hurricane keratopathy' or 'vortex keratopathy' given by various authors in several publications over the years almost always show the direction of the whorl to be clockwise irrespective of the eye involved.[1,2,4,14,15] This observation is significant and could hold the key to understanding the mechanism by which whorled patterns develop.

We propose that the clockwise whorled distribution of corneal epithelial cells is determined by the electromagnetic fields of the eye and occurs during normal corneal epithelial cell turnover. The pattern becomes visible by the

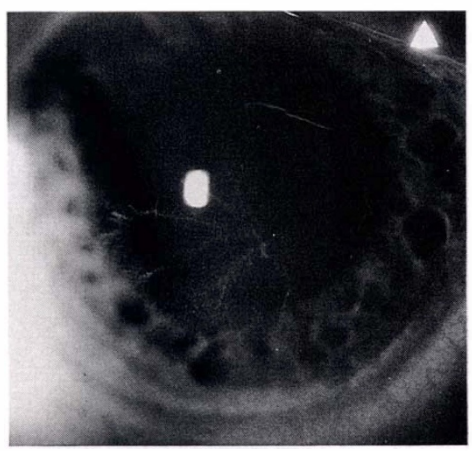

Fig. 3. *Resolving 'hurricane keratopathy' in patient 5 (Table I). A small part of the whorl remains in the inferior temporal quadrant. The pattern is visible without fluorescein staining.*

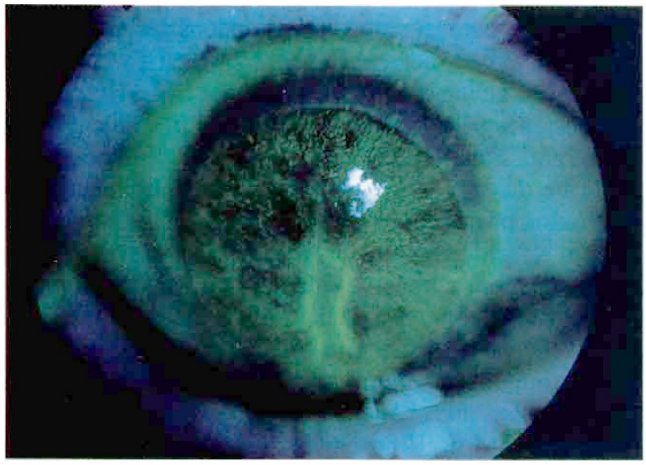

Fig. 4a

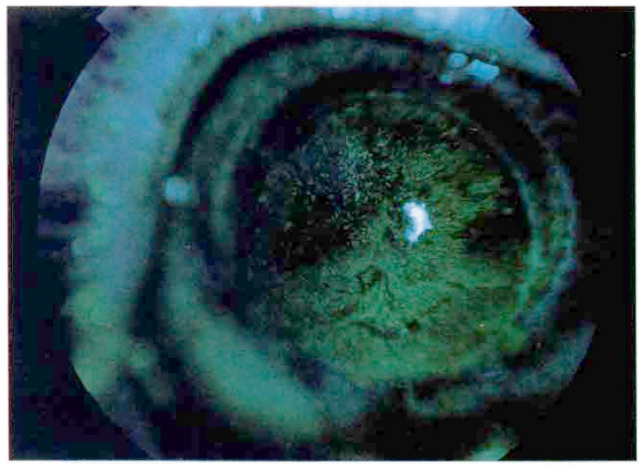

Fig. 4b

Fig. 4. *(a) 'Blizzard keratopathy' developing on the surface of a corneal graft where the epithelium was surgically removed (fluorescein-stained cornea of patient 1, Table II). (b) The random pattern persists after the epithelial defect has healed. The pattern is highlighted with fluorescein stain.*

deposition of substances in the cells (vortex keratopathy), in which case fluorescein staining does not highlight the whorled pattern; or when the epithelial turnover is exaggerated, as after corneal grafts or as in the patients described in this study. In the latter situation the pattern is highlighted by fluorescein staining. One possible explanation for this could be that the rapidly migrating cells do not form tight intercellular adhesions and are outlined with fluorescein stain either singly or in small groups.

As early as 1848 Du Bois-Reymond[16] reported that a difference in electric potential of about 6 mV exists between the cornea and the back of the eye. The human eye behaves like a dipole, oriented along its anteroposterior axis with the cornea positive to the posterior pole.[16] Fig. 6(a) illustrates the electric field (E-field) in the eye. The electric fields that the corneal epithelial cells would experience on the corneal surface are illustrated in Fig. 6(b). Electric and magnetic fields are related. Presence of electric fields gives rise to electric currents in the medium across which the electric field exists. The magnitude of resulting current and its distribution depend on the dimensions and conductivity of the medium. The distribution of electric current in the eye would be as illustrated in Fig. 7(a). The corresponding electromagnetic field generated by the current would be distributed as illustrated in Fig. 7(b), with the magnetic flux lines being clockwise and the flux density gradually increasing from the apex of the cornea to the periphery (Fig. 7c).

Epithelial cells are known to experience force and movement when placed in an electric field. Nuccitelli[17]

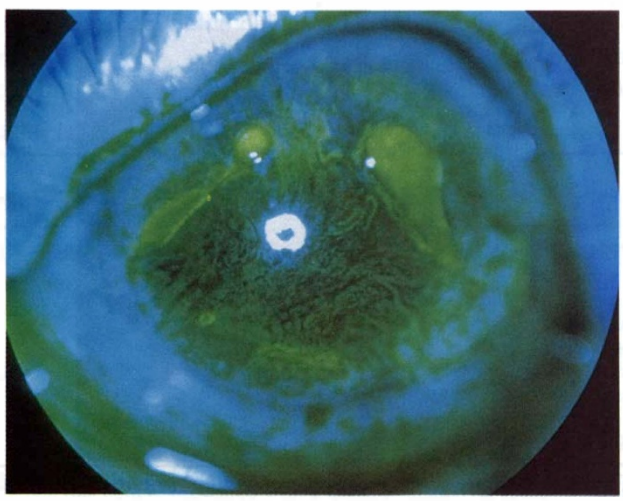

Fig. 5. *'Blizzard keratopathy' as seen in patient 2 (Table II).*

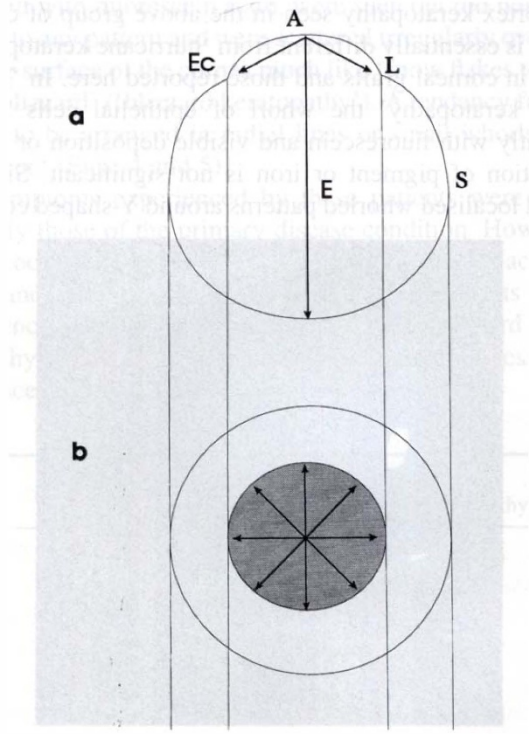

Fig. 6. *(a) The electric field of an eye (E) in the anterior posterior direction and (Ec) tangentially across the cornea. A, apex of cornea; L, limbus; S, sclera. (b) Electric field on the corneal surface as would be experienced by the corneal epithelial cells.*

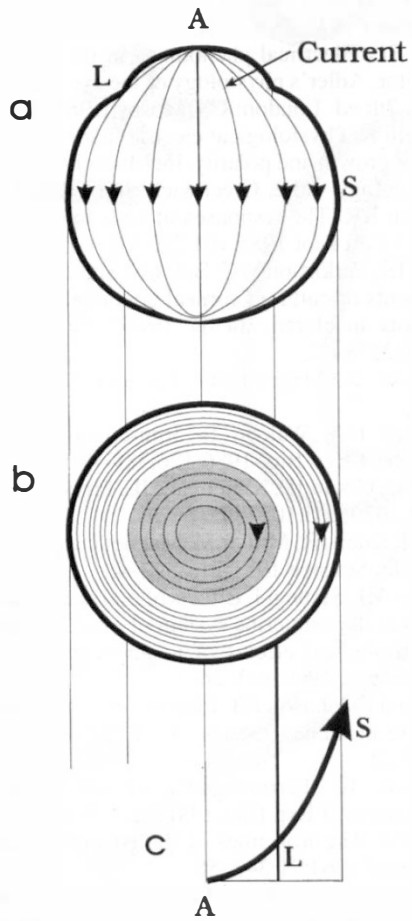

Fig. 7. *Distribution of electric current and the resulting magnetic field in a human eye. (a) Current distribution. A, apex of cornea; L, limbus; S, sclera. (b) Magnetic field distribution. Notice that the magnetic flux density (force of the magnetic field) is clockwise. (c) Flux density distribution on the ocular surface. The flux density gradually increased from the apex of the cornea (A) through the limbus (L) to the sclera (S).*

and Robinson[18] have shown that many types of cells, including epithelial cells, react to weak direct-current-induced E-fields (field strengths as low as 1–10 mV) with a galvanotropic and galvanotaxic response. Galvanotropism is the polarised shifting of cellular orientation in an E-field whereas galvanotaxis is the migration of a cell in an E-field. These responses are very significantly manifested during embryogenesis and wound healing.[17,18] Soong *et al.*[19] experimented on cultured corneal epithelial cells and corneal stromal fibroblasts. They demonstrated that galvanotropism and galvanotaxis were manifested in both cell types by elongation of the cell bodies into spindle-shaped somata that became oriented orthogonally to the E-field lines. Epithelial cells migrated towards the cathode. Given the distribution of E-fields on the corneal surface (Figs. 6 and 7), corneal epithelial cells would tend to organise in concentric circles (Fig. 8a). During the healing of corneal abrasions or when epithelial cell turnover is otherwise increased the radial centripetal movement of epithelial cells from the limbal stem cell zone on one hand and the tendency of the E-field to organise them in concentric circles on the other, would lead to the formation of clockwise whorls.

Several cells and organisms are known to respond to magnetic fields. Such cells and organisms almost universally contain magnetite (iron oxide), a ferromagnetic mineral. Magnetotactic bacteria, honey bees, homing pigeons and dolphins' heads contain deposits of magnetite which are believed to be associated with receptors for geomagnetic fields.[20–23] Mouse adrenal glands are prone to degeneration in magnetic fields and this has been related to the presence of magnetite.[24] Significant amounts of this substance are present in human tissues such as the lungs and adrenals.[25,26] Although studies to demonstrate this substance in human corneal epithelial cells have not been undertaken there is evidence that these cells contain abundant iron. In a histochemical study Gass[27] reported that 'localised iron deposits were present in the epithelium of the paracentral cornea in all the "normal" autopsy eyes and in all but 3 of the 50 eyes with associated pathology.' Iron, like magnetite, being ferromagnetic and a good conductor of electricity, would also interact strongly with electric and magnetic fields. The presence of intracellular ionic currents and iron ions would render corneal epithelial cells capable of responding to magnetic and electric fields in similar manner. Galaktionova[28] has shown that long-term intermittent exposure to a static magnetic field induced profound phase fluctuations in the mitotic index of murine corneal epithelium. The index normalised rapidly after cessation of exposure. Skrinnik[29] has shown that the reparative process of post-traumatic corneal epithelial defects could be hastened and favourably influenced by continuous magnetic field therapy.

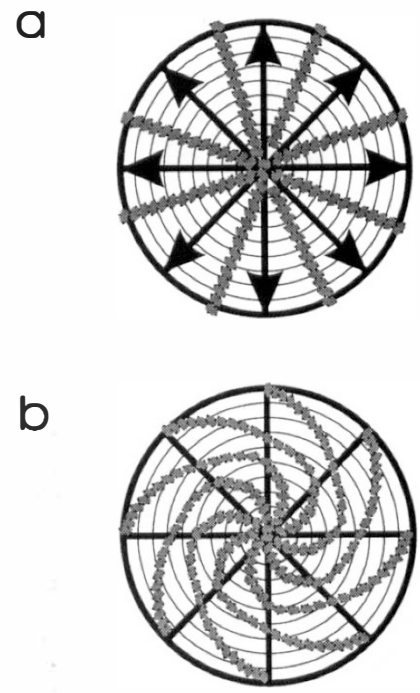

Fig. 8. *(a) Concentric distribution of the combined electromagnetic fields. (b) The torsional effect of the combined electromagnetic fields on the centripetal radial migration of epithelial cells to produce a clockwise whorled pattern.*

The electromagnetic field on the surface of the cornea being concentric and clockwise, the combined effect of electric and magnetic fields on centripetally migrating cells would be to arrange them in clockwise whorls (Fig. 8b).

REFERENCES

1. Mackman GS, Polack FM, Sydrys L. Hurricane keratitis in penetrating keratoplasty. Cornea 1983;2:31–4.
2. Lemp MA, Mathers WD. Corneal epithelial cell movement in humans. Eye 1989;3:438–45.
3. Fleischer B. (1910). Quoted by Bloch FJ. Vortex-shaped dystrophy of the cornea. Arch Ophthalmol 1940;23:825–8.
4. Bron AJ. Vortex patterns of the corneal epithelium. Trans Ophthalmol Soc UK 1973;93:455–72.
5. Dua HS, Forrester JV. Clinical patterns of corneal epithelial wound healing. Am J Ophthalmol 1987;104:481–9.
6. Thoft RA, Wiley LA, Sundarraj N. The multipotent cells of the limbus. Eye 1989;3:109–13.
7. Tseng SCG. Concept and application of limbal stem cells. Eye 1989;3:141–57.
8. Hanna C, O'Brien JE. Cell production and migration in the epithelial layer of the cornea. Arch Ophthalmol 1960;64: 536–9.
9. Friedenwald JS, Buschke W. Some factors concerned in the mitotic and wound-healing activities of the corneal epithelium. Trans Am Ophthalmol Soc 1944;42:371–83.
10. Ebato B, Friend J, Thoft RA. Comparison of central and peripheral human corneal epithelium in tissue culture. Invest Ophthalmol Vis Sci 1987;28:1450–6.
11. Buck RC. Cell migration in repair of mouse corneal epithelium. Invest Ophthalmol Vis Sci 1979;18:767–84.
12. Kuwabara T, Perkins DG, Cogan DG. Sliding of the epithelium in experimental corneal wounds. Invest Ophthalmol Vis Sci 1976;15:4–14.
13. Dua HS, Forrester JV. The corneoscleral limbus in human corneal epithelial wound healing. Am J Ophthalmol 1990; 110:646–56.
14. Duke-Elder S. In: System of ophthalmology: Normal and abnormal development, vol III, part 2, Congenital deformities. London: Henry Kimpton, 1964:531–3.
15. Bloch FJ. Vortex-shaped dystrophy of the cornea. Arch Ophthalmol 1940;23:825–8.
16. Berson EL. Electrical phenomena in the retina. In: Moses RA, editor. Adler's physiology of the eye and clinical applications. 7th ed. London: CV Mosby, 1981:507–9.
17. Nuccitelli R. Physiological electric fields can influence cell mobility, growth and polarity. In: Miller K, editor. Advances in cell biology, vol 2. Greenwich: JAI Press, 1988;213–34.
18. Robinson KR. The responses of cells to electrical fields: a review. J Cell Biol 1985;101:2023–7.
19. Soong HK, Parkinson WC, Bafna S, Sulik GL, Huang SCM. Movements of cultured corneal epithelial cells and stromal fibroblasts in electric fields. Invest Ophthalmol Vis Sci 1990;31:2278–82.
20. Blakemore R. Magnetotatic bacteria. Science 1975;190: 377–9.
21. Kuterbach DA, Walcott B. Iron-containing cells in the honey bee. J Exp Biol 1986;126:389–401.
22. Walcott C, Gould JL, Kirschvink JL. Pigeons have magnets. Science 1979;205:1027–9.
23. Zoeger J, Dunn JR, Muller M. Magnetic material in the head of dolphin. Science 1981;213:892–4.
24. Barnothy MF, Sumegi I. Effects of magnetic field on internal organs and the endocrine system of mice. In: Barnothy MF, editor. Biological effects of magnetic fields, vol 2. New York: Plenum, 1969:103–26.
25. Moatamed F, Johnson FB. Identification and significance of magnetite in human tissues. Arch Pathol Lab Med 1986; 110:618–21.
26. Kirschvink JL. Ferromagnetic crystals (magnetite?) in human tissues. J Exp Biol 1981;92:333–5.
27. Gass JDM. The iron lines of the superficial cornea. Arch Ophthalmol 1964;71:348–58.
28. Galaktionova GV. Nature of the cellular proliferation of the corneal epithelium of mice in various regimens of exposure to permanent magnetic fields. Vopr Kurortol Fizioter Lech Fiz Kult 1985;6:45–8.
29. Skrinnik AV. Effect of a permanent magnetic field on reparative post-traumatic regeneration of the cornea. Oftalmol Zh 1980;35:361–3.