A Review of the Pathogenesis of Corneal Vascularization

J.D. Jantzi *

Corneal vascularization is a subject of importance not only to research scientists but also to optometrists who in daily clinical practice are responsible for monitoring the ocular health of their patients. Contact lens patients in particular must be examined regularly and on a continuing basis for signs of pathological corneal changes such as vascularization which indicate an intolerance to their contact lenses. The purpose of this paper is to review what is presently known about the pathogenesis of corneal vascularization since an understanding of this condition may give us insight as to why it occurs in certain patients; for example contact lens wearers.

According to Duke-Elder[1], vascularization of the cornea is the response of a tissue in difficulty, primarily as a defence mechanism against disease or injury. The manner in which disease, injury of other factors may bring about blood vessel growth into the normally avascular cornea has been the subject of many investigations. Over the years a wide variety of methods have been developed to study corneal vascularization in experimental animals.[2] Typically, live rabbits are used whose anesthetized corneas are subjected to some form of injury, usually by chemical or thermal means. The response of the injured corneal tissue is then monitored by suitable laboratory techniques on living and enucleated eyes. Investigators have also studied the effect of drugs and environmental conditions on corneal vascular responses.

In one of the earliest studies, Cogan[3] observed the growth of new blood vessels into edematous corneal tissue but not into non-edamatous tissue. He concluded therefore that the decrease in compactness of the corneal stromal which occurred under conditions of corneal swelling was sufficient to allow the growth of new capillaries into the swollen stromal tissue from the limbal arcades. Expanding on this work, Campbell and Michaelson[4], Michaelson[5], Maurice, Zauberman and Michaelson[6], and Klintworth[7] showed that while edema was a necessary condition in the vascular process, it was not a sufficient stimulus per se. They postulated that corneal lesions released an unknown but essential chemical mediator or "X-factor" (perhaps as a result of anaerobic metabolism) which diffused from the site of the lesion thereby acting as a chemical stimulus to vascularization.

Ashton and Cook[8], investigating the role of tissue hypoxia, suggested that the cornea is normally in a peculiar state of "sub-oxidation" so that in the event of a decrease in tissue compactness in the limbal region for a sufficient period of time, vascularization would regularly occur. However Baum and Martola[9] subsequently demonstrated limbal edema without vascularization; and Kaiser and Klopp[10] found that vascularization was not diminished in animals exposed to hyperbaric levels of oxygen.

In a study of retinal neovascularization, Ashton[12] believed that the stimulus to neovascularization was present in hypoxic retinal tissue; probably a chemical byproduct of anaerobic metabolism. The role of one such anaerobic chemical byproduct — lactic acid — was investigated by Imre[12] who provided evidence to show that neovascularization of the retina was indeed caused by a buildup of lactic acid in hypoxic retinal tissue. Levene, Shapiro and Baum[13] went on to measure the lactic acid concentration centrally and in the region of the limbus in normal healthy corneas and in corneas which were undergoing vascularization. They discovered that normal corneas had less lactic acid peripherally than centrally, probably as a result of the proximity of the limbal vessels which would allow for greater oxygen utilization in this area and therefore less accumulation of lactic acid. In vascularized corneas however, they found that the peripheral lactic acid concentration was the same as that found centrally. This, they believed, was the result of impaired aerobic metabolism in the limbal area. Morley and McCulloch[14] reported a similar increase in peripheral corneal lactate after contact lens wear. Lactic acid then could be an example of Campbell and Michaelson's "X-factor".

Later, other chemical substances were found which also stimulated corneal vascularization. Zauberman, Michaelson, Bergmann and Maurice[15] for example, were able to stimulate blood vessel growth into the cornea by using the biogenic amines acetylcholine, histamine, serotonin and bradykinin. They thought these substances might be vasostimulating factors or the precursors of as yet unidentified vasostimulating factors. Collin[16] however showed that histamine and heparin were not directly responsible for corneal vascularization but rather were involved in the limbal inflammatory process which immediately precedes it.

Examining the role of the immune system in corneal vascularization, BenEzra and Sachs[17] found that lymphocytic inhibitors were normally present in the aqueous of rabbits: thus perhaps lymphocytes were somehow involved in the vascular process. Fromer and Klintworth[18, 19] and BenEzra[20] later found that leukocytes and possibly lymphocytes were necessary for corneal vascularization by producing one or more vasostimulating factors. However Sholley, Gimbrone and Cotran[21] demonstrated that corneal vascularization could still occur in animals whose blood leuko-

*O.D., M.Sc.
Surrey, British Columbia

cyte counts had been depleted by whole-body X-radiation, although the magnitude of the vascular response would be less than in non-leukopenic animals. Eliason[22], who later duplicated these results, suggested that the corneal epithelium itself may be the source of the vasostimulating factor. Thus the source or sources of vasostimulating factors still remains uncertain.

Corneal vascularization has been shown to be inhibted by various chemical substances. Brem et al[23] using a substance found in the vitreous, and Goren et al[24] using an extract of bovine aorta were able to inhibit the vascular response in experimental animals. Eisenstein et al[25] went on to show that bovine aortic extract not only inhibited corneal vascularization but also enhanced the regression of newly-formed vessels. Regression of newly-formed secondary and tertiary vessel branches in the rabbit cornea by the clearing action of macrophages was observed by Ausprunk, Falterman and Folkman[26] one week after the causative stimulus to vascularization had been removed. After three weeks, the primary branches were thinner and devoid of blood. They pointed out that regression of corneal blood vessels which they had observed in rabbits does not occur in humans: blood vessels may remain indefinitely as "ghost" vessels even after the causative stimulus has been removed.

Prostaglandins were later discovered to play a mediating role in vascularization by BenEzra[27, 28] who provided evidence to show that they were neovascular mediating substances. He also showed that leukocytes produced a neovascular attracting factor which he felt may be identical to "tumor angiogenesis factor" or Campbell and Michaelson's "X-factor". BenEzra[29] later went on to demonstrate that prostaglandins of the E-series were the most potent neovasculogenic activators. Additional support for the role of local prostaglandin synthesis in the pathogenesis of corneal vascularization was provided by Robin, Regis-Pacheco, Kash and Schanzlin[30] who discovered that the corticosteroid prednisolone and the non-steroids indomethacin and flurbiprofen, which were known to inhibit prostaglandin synthesis, were also potent inhibitors of corneal vascularization in experimental animals. Together, this evidence seemed to indicate that prostaglandins play an important albeit intermediate role in the pathogenesis of corneal vascularization.

Recently, Cassel and Grodin[31] introduced a new perspective on the subject of corneal vascularization by showing that experimental animals with denervated corneas experienced significantly less vascularization than animals with intact corneal nerves. Thus the possibility of a neural control of corneal vascularization must also be considered.

The results of these studies have given us a better although still incomplete understanding of the pathogenesis of corneal vascularization. In summary, it is certain that edema is a necessary condition in the vascular process although some unknown "X-factor" is also required. Lactic acid or perhaps leukocytic neovascular attracting factor may be the vasostimulating substance: the as yet unidentified "X-factor". It appeaars that the corneal epithelium itself could also be a source of this vasostimulating factor. The biogenic amine, histamine, is involved with the preliminary inflammatory phase of limbal injection which precedes corneal vascularization; and prostaglandins, in particular those of the E-series, play an intermediate role as potent neovascular mediating substances. In addition, the neural integrity of the cornea itself affects the magnitude of the vascular response. It remains for further research to explain the manner in which each of these factors relate to one another and to the overall vascularization process.

References

1. Duke-Elder, System of Ophthalmology, Vol. 8: 676
2. Henkind, P. Ocular neovascularization. *Am J Ophthal* 1978; Vol 85: 287.
3. Cogan, D.G. Vascularization of the cornea. *Arch Ophthal* 1949; Vol. 41: 406.
4. Campbell, F.W. and Michaelson, I.C. Blood vessel formation in the cornea. *Brit J Ophthal* 1949; Vol. 3: 248.
5. Michaelson, I.C. Unilateral budding in new vessel formation in the eye. *Brit J Ophthal* 1956; Vol. 40: 36.
6. Maurice, D.M., Zauberman, H. and Michaelson, I.C. The stimulus to neovascularization in the cornea. *Exptl Eye Res* 1966; Vol. 5: 168.
7. Klintworth, G.K. The hamster cheek pouch. *Am J Pathol* 1973; Vol. 73: 691.
8. Ashton, H. and Cook, C. Mechanism of corneal vascularization. *Brit J Ophthal* 1953; Vol 37: 193.
9. Baum, J.L. and Martola, E.L. Corneal edema and corneal vascularization. *Am J Ophthal* 1968; Vol. 65: 881.
10. Kaiser, R.J. and Klopp, D.W. Hyperbaric air and corneal vascularization. *Annals of Ophthal* 1973; Vol. 5: 44.
11. Ashton, N. Retinal vascularization in health and disease. *Am J Ophthal* 1957; Vol. 44: 7.
12. Imre, G. Studies on the mechanism of retinal neovascularization — role of lactic acid. *Brit J Ophthal* 1964; Vol. 48: 75.
13. Levene, R., Shapiro, A and Baum, J. Experimental corneal vascularization. *Arch Ophthal* 1963; Vol. 70: 242.
14. Morely, N. and McCulloch, C. Corneal lactate and Pyridine Nucleotides (PNS) with contact lenses. *Arch Ophthal* 1961; Vol. 66: 379.
15. Zauberman, H., Michaelson, I.C., Bergmann, F. and Maurice, D. Stimulation of neovascularization of the cornea by biogenic amines. *Exptl Eye Res* 1969; Vol. 8: 77.
16. Collin, H.B. Limbal vascular response prior to corneal vascularization. *Eye Res* 1973; Vol. 16: 443.
17. BenEzra, D. and Sachs, U. Growth factors in aqueous humor of normal and inflamed eyes of rabbits. *Invest Ophthal* 1974; Vol. 13: 868.
18. Fromer, C.H. and Klintworth, G.K. An evaluation of the role of leukocytes in the pathogenesis of experimentally induced corneal vascularization — Part 1: Comparison of experimental models of corneal vascularization. *Am J Pathol* 1975; Vol. 79: 537.
19. Fromer, C.H. and Klintworth, G.K. An evaluation of the role of leukocytes in the pathogenesis of experimentally induced corneal vascularization — Part 3: Studies related to the vasoproliferative capability of polymorphonuclear leukocytes and lymphocytes. *Am J Pathol* 1976; Vol. 82: 157.
20. BenEzra, D. Mediators of immunological reactions: function as inducers of neovascularization. *Metab Ophthal* 1978; Vol. 2: 339.
21. Sholley, M.M., Gimbrone, M.A. and Cotran, R.S. The effects of leukocyte depletion on corneal neovascularization. *Intl Acad Pathol* 1978; Vol. 38: 32.
22. Eliason, J. Leukocytes and experimental corneal vascularization. *Invest Ophthal Visual Sci* 1978; Vol. 17: 1087.
23. Brem, S., Preis, I., Langer, R., Brem, H., Folkman, J. and Patz, A. Inhibition of neovascularization by an extract derived from vitreous. *Am J Ophthal* 1977; Vol. 84: 323.
24. Goren, S.B., Eisenstein, R. and Choromokos, E. The inhibition of corneal vascularization in rabbits. *Am J Ophthal* 1977; Vol. 84: 305.
25. Eisenstein, R., Goren, S., Shumacher, B. and Choromokos, B. The inhibition of corneal vascularization with aortic extracts in rabbits. *Am J Ophthal* 1979; Vol. 88: 1005.
26. Ausprunk, D.H., Falterman, K. and Folkman, J. The sequence of events in the regression of corneal capillaries. *Intl Acad Pathol* 1978; Vol. 38: 284.
27. BenEzra, D. Neovasculogenic ability of prostaglandins, growth factors and synthetic chemoattractants. *Am J Ophthal* 1978; Vol. 86: 455.
28. BenEzra, D. Neovasculogenesis: Triggering factors and possible mechanisms. *Surv Ophthal* 1979; Vol. 24: 167.
29. BenEzra, D. Possible mediation of vasculogenesis by products of immune reaction. 2nd Intl Symposium of ocular immunology and immunopathology.
30. Robin, J., Regis-Pacheco, L., Kash, R. and Schanzlin, D. The histopathology of corneal vascularization. *Arch Ophthal* 1985; Vol. 103: 284.
31. Cassel, G. and Groden, L. New thoughts of ocular neovascularization: A neurally controlled regenerative process? *Annals Ophthal* 1984; Vol. 16: 138.