UVA–Riboflavin Collagen Cross-Linking: A Misnomer
Perhaps, but It Works!

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The mechanisms underlying the success of UVA-riboflavin collagen cross-linking (CXL) to arrest or allay corneal ectasia are not well understood. One observation that may shed light on the underpinnings of CXL: the cornea thins after the procedure for at least several months.1 Thinning produces a more compact and stiffer tissue. Normally, corneal thickness is controlled by endothelial active transport of solute into the aqueous humor. This lowers the osmotic pressure within the corneal stroma to balance the swelling tendency of the glycosaminoglycan-rich hydrophilic ground substance. If CXL were to reduce this tendency by modifying the hydrophilic nature of the stromal glycosaminoglycans rather than by cross-linking collagen, one would theorize a reduction in swelling pressure and corneal thinning. This is precisely what Søndergaard and colleagues2 report; CXL reduces stromal swelling pressure in pig and human corneas in vitro. They conclude this may be why CXL seems to help control edema in patients whose corneas are swollen from pathology. But the observation may also shed light on a mechanism of action of CXL. It has been well established that binding the stromal glycosaminoglycans in the interfibrillar matrix with cetylpyridinium chloride, or lowering the pH, reduces the swelling pressure of the cornea, whereas reducing the ionic strength increases it.3 The latter two conditions do not involve chemical bonds at all; rather they shield or promote fixed-charge Donnan effects of the matrix macromolecules. Several processes have been developed to tan animal hide to produce leather. Not all of them involve collagen cross-linking. Because cross-linking between or within corneal collagen fibers has not been demonstrated after CXL, it is likely that its action is extrafibrillar, and corneal collagen cross-linking is a misnomer. Be that as it may, multiple published clinical trials in the literature support the fact that CXL is able to stabilize corneas that develop ectasia; it does work!

References