Cultivating a cure for blindness

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Damaged corneas can often be repaired using donor grafts, but if the damage is too great the graft will be rejected. This may change with the development of a method to inhibit rejection which uses cultivated cells.

The human cornea has a special property known as immune privilege, which allows tissue grafts from donors to be carried out without the usual problems of immune rejection. However, immune privilege is lost at the perimeter of the cornea — the limbus of the eye — where the transparent corneal stroma meets the opaque sclera (Fig. 1). So, if too large a corneal button is grafted and it approaches the limbus of the recipient, the graft is usually rejected. Similarly, the prognosis is not good if the recipient's cornea is so badly damaged that there is no sign of healthy corneal tissue.

A solution to these problems may now be at hand with the publication of a report by Pellegrini *et al.*[1] in *The Lancet*. They have extended immune privilege in an unexpected way with the aid of human stem cells, and their results promise a wider use of corneal transplantation in what are currently thought to be relatively untreatable conditions.

The outer layer of the cornea comprises the regularly dividing and sloughing corneal epithelial cells. Studies into the origin of these cells showed that they are not derived by self-perpetuation — instead they come from stem cells in the limbal epithelium[2,3], which occupies an annulus (ring) about 1.5 mm wide between the corneal epithelium and the conjunctival epithelium (Fig. 1). The transition from corneal to limbal epithelial cells is quite abrupt, but whereas the corneal epithelium can mould a smooth apical and basal surface, the limbal epithelial stem cells do not form such a smooth surface.

If the corneal epithelium is lost it can be functionally regenerated by the limbal stem cells. But if both the corneal and limbal epithelia are lost, the corneal surface is re-colonized by the other neighbour of the limbal epithelium — the conjunctival epithelium[3–5]. After a cornea has been grafted into a recipient, its outer surface will eventually be covered by a host-derived epithelium that migrates in from the limbus. So, if the recipient has limbal epithelial cells, a normal corneal epithelium is generated. But if the eye has been severely damaged and the recipient's limbal epithelium is missing, the donor cornea will be covered, by cell migration, with cells from the conjunctival epithelium. Conjunctival epithelia and corneal/limbal epithelia represent two different cell lines[6], and the conjunctival epithelium cannot form smooth apical and basal surfaces if it is allowed to colonize the cornea. The result is a loss of visual acuity by scarring of the stroma, as well as severe discomfort.

Pellegrini *et al.*[1] now describe a method for using limbal stem cells to advantage in corneal epithelial grafts. Two patients, who each had one severely damaged cornea that was covered with conjunctival epithelium, were willing subjects after conventional grafting had failed. Limbal epithelial cells were taken in a 1-mm^2 biopsy from the good eye, then they were cultured and, on second passage, they formed a tightly packed and communicating (confluent) monolayer of cells. For grafting, the conjunctival epithelium was completely removed from the cornea and limbus of the recipient eye, and replaced with a slightly larger monolayer of cultured limbal epithelium. The eyes were then covered with therapeutic soft contact lenses, and tightly patched for several days.

The results after the limbal epithelial graft were very promising. The grafted epithelium was stable, transparent, multi-layered and smooth. One of the patients had suffered an alkali burn to his left eye ten years earlier, and had undergone three previous unsuccessful corneal grafts. Before the treatment he had continual severe corneal vascularization (development of blood vessels) and persistent ulceration, and the eye was painful and blind. But after the conjunctival epithelium that was covering his cornea was replaced with cultured limbal epithelium, a stable and transparent corneal epithelium was reconstituted, and there were no further problems. His vision improved so much that he could count fingers from one metre away. However, because of his previous experiences he refused the next logical step, which was to check whether his cornea had recovered its immune privilege and could now take a full-thickness graft.

The other patient, whose epithelial graft using the new method had also been a success, agreed to a second operation of a full-thickness graft. The result was excellent — the eye that had been blind for many years, and had been perforated after an earlier unsuccessful graft, was restored to a visual acuity of a high enough standard to allow him to drive a vehicle safely using the restored eye alone. His previously untreatable blindness was cured after 29 years.

The clinical results are surprising and encouraging. Clearly, much of the cornea's immune privilege is vested in the limbal/corneal epithelium, and other epithelial cell lines seem to be unable to inherit this privilege. It would be nice to see the development of limbal epithelial allografts (for which tissue matching would be necessary), to find out whether they could also extend the immune privilege of the cornea. It could then be possible to restore full vision to millions of totally blind people through limbal epithelial primary grafts. □

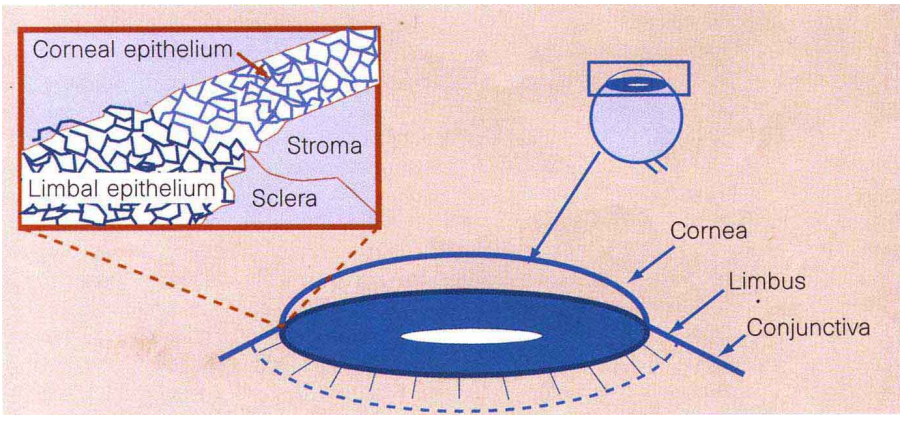

Figure 1 **Donor grafts can often be used to repair damaged corneas, as the donor's corneal epithelium can be replaced by stem cells of the limbal epithelium. If the recipient's cornea is too badly damaged and the neighbouring limbal epithelial cells are also lost, conjunctival epithelium will extend to replace the corneal epithelium and the grafted cornea's 'immune privilege' will be compromised. Pellegrini *et al.*[1] have now developed a method to inhibit rejection, by restoring the corneal surface using sheets of cultivated host limbal epithelium as a primary graft prior to full-thickness grafting.**

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