Pathology of the corneal endothelium

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Clinical specular microscopy has indicated that human cell healing occurs by spreading, there is a limited healing reserve, and premature cell loss is the equivalent of a "premature aging" that may lead to later decompensation. This instrument has been useful in studying healing and cell damage from surgery, drugs, and special procedures such as intraocular lens insertion. It pointed out extensive cell loss at the time of intraocular lens insertion, and subsequent studies have indicated that at least part of this cell loss may be due to the methacrylate surface of the lens. Laboratory studies suggest that coating that surface can prevent this component of cell loss. The magnitude of benefits to be found from such coating requires further clinical study.

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In recent years our concept of the corneal endothelium has totally changed. Many years ago it was thought that the human corneal endothelium was similar to animals. The early experiments of Mau- menee and Kornblueth1 however, indicated that the rabbit cornea could be frozen and the endothelium presumably killed, and yet these corneas could regain their clarity.
within approximately a week. Subsequent studies in the rabbit by Kaufman, Capella, and Robbins, 6 Polack, 7 and others confirmed the fact that rabbit corneal endothelial cells could multiply, but shed little light on the human corneal endothelium.

Flat preparations of large numbers of human corneas 4 suggested, however, that the number of cells on the cornea decreased with age. They also suggested that once the cornea was injured, healing occurred by spreading but not by cell division. Such conclusions, however, were difficult to confirm until the advent of the specular microscope.

The specular microscope was first developed by Maurice 5 in 1968, and subsequently improved by Laing, Sandstrom, and Leibowitz 6 and again by Bourne and Kaufman. 7 It permits the detailed observation of the human corneal endothelium in the intact living eye, and thus opens totally new horizons for a study of this tissue. Patients can be studied at many different ages and the density of the corneal endothelial cells determined. When this is done, it becomes clear that there is a decrease in the number of corneal endothelial cells per unit area with age—despite some biological variability. After injury, even in people as young as 16 years of age, it can be seen that there is a loss of central corneal endothelial cells, and that healing occurs by sliding rather than by cell multiplication with little or no cell regeneration.

These kinds of observations have led to several new concepts which are both scientifically and clinically important in terms of an appreciation of the human corneal endothelium.

**Healing reserve.** Any damage to the corneal endothelium, whether surgical, traumatic, or drug-induced, must be compensated for by spreading of the remaining cells. Although the lower limits of cell numbers have not been defined, it seems clear that there comes a point at which adequate covering of the endothelial surface is no longer possible and corneal edema results. In conditions such as keratoplasty, where there is a wound which must be healed, or in which incidents such as immune reactions may damage some of the cells, it has become generally accepted that the more cells that are transferred to the recipient from the donor, the greater margin of safety because of the "healing reserve."

**Aging of the cornea and premature aging.** The number of endothelial cells decreases with age. In a certain proportion of people this decrease is enough so that corneal decompensation occurs and corneal edema supervenes. We believe that if the cornea is traumatized and cells are prematurely lost from such trauma, the continuing decrease in cells with age may lead to a decompensation and corneal edema many years after the original insult. There are several clinical examples which seem to exemplify this: Spencer and associates 8 described a group of patients with congenital glaucoma whose pressure had been adequately controlled and who had crystal-clear corneas for approximately 20 years after the initial episode of glaucoma and uneventful surgery. Twenty years later, these corneas became edematous—presumably because the initial cell loss from stretching in surgery had been sufficiently great so that continued cell death with time could no longer be tolerated.

Some corneal transplants remain clear for a period of years and yet become edematous and cloudy with no apparent inflammatory incident many years after the initial surgery. We believe that these donor grafts are those with marginal cell populations which can no longer cover the surface of Descemet's membrane as additional cells die with time. In the specimens of such corneas, no abnormality is seen except for corneal edema and inadequate numbers of endothelial cells.

Studies of the corneal endothelium with the specular microscope have both scientific and clinical uses. These include the examination of donor eye tissue before it is
used for corneal transplantation. The examination of patients before procedures such as intraocular lens implant is important to be certain that a reasonable number of endothelial cells are present before such surgery which might cause some increase in cell loss. Studies include the evaluation of drugs which may be used in the eye, and it now seems that any drug or any solution inserted into the eye should be checked in man to be certain that it does not cause undue loss of central corneal endothelial cells. Surgical techniques can be checked to determine whether endothelial damage is occurring, and whether modifications can be made to minimize this.

A beautiful example of the possible advantages to man of specular microscopy involves the study of intraocular lenses.

The first study of the effect of intraocular lenses on the human corneal endothelium was done by Bourne and Kaufman at the University of Florida and indicated substantial endothelial cell loss in a small number of patients. An additional cooperative study was then done by Forstot and associates from the University of Florida with Jaffe in Miami. This larger study yielded fascinating results. A prospective examination of the patients showed a substantial cell loss which appeared to occur at the time of surgery. This loss seemed to occur regardless of lens type used, and a variety of different types of intraocular lenses resulted in comparable endothelial cell loss. The comparison of intraocular lens insertion with cataract extraction in these two studies revealed an endothelial cell loss from regular intracapsular cataract extraction of 7 to 8 percent, but when aphakic eyes were compared with pseudophakic eyes, there was always a greater loss in the pseudophakic eye, and this is loss averaged greater than 40 percent. There was no evidence in this study that the retention of the lens in the eye caused progressive endothelial damage, and these studies indicated that endothelial cell damage was primarily an event occurring at the time of surgery.

This evidence of endothelial cell damage, which was much more extensive than previously believed, and the pinpointing of such damage to the time of surgery focused our attention on possible causes for such an occurrence. The most obvious place to look for such damage was in contact between the methacrylate lens and the corneal endothelium. In both rabbits and man methacrylate lenses which were wet with balanced salt solution and touched to the cornea, caused extensive corneal endothelial damage as judged both by scanning electron microscopy and by nitroblue tetrazolium staining. A careful examination of this damage indicated that its appearance was unique and it appeared as if the methacrylate surface adhered to the central corneal endothelium instantaneously and ripped off the top of the endothelial cells. In fact, examination of a lens which had been in contact with the corneal endothelial cells showed debris on the surface consistent with cell membranes stripped from the endothelial cell. Glass produces similar damage, but covering the glass with a soft contact lens (Bausch & Lomb T lens) eliminates this damage and permits a totally normal endothelium. Instantaneous touch of the unprotected intraocular lens to endothelium produces this cell destruction, but rubbing of the normal human or animal lens on the endothelial surface produces virtually no cell damage.

Because of this we thought we could biophysically alter the methacrylate surface to prevent this component of cell injury. The most effective solution tested was a polyvinyl pyrrolidone (PVP K 29-31, 40 percent, in balanced salt solution). Dipping the lens in this solution permits it to be rubbed against the endothelium without cell loss or cell injury at the time. As yet we are not certain that all surgeons obtain a comparable cell loss, nor are we certain that this is the only or
major mechanism of cell loss in human disease. To acquire such certainty, coated lenses will need to be compared with uncoated lenses from a double-blind controlled series.

In preparation for this, however, we have tested the safety of PVP in rabbit eyes, and find it to be well tolerated. It has been used in human eyes for many years to reform the anterior chamber by some surgeons who do keratoplasty without inflammation or incidence. In two patients with uneventful cataract extractions in whom lenses have been dipped in this PVP solution at the time of surgery, cell loss was 9 and 11 percent, as compared to the 7 to 8 percent cell loss seen in regular cataract extraction, or the average of 40 percent cell loss seen in intraocular lenses. This is certainly not conclusive, but provides further incentive for additional studies.

REFERENCES