# THE EFFECTS OF CONTACT LENS WEAR ON THE MORPHOLOGY OF CORNEAL SURFACE CELLS IN THE HUMAN*

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## INTRODUCTION

THE DEVELOPMENT OF CONTACT LENSES OVER THE LAST FOUR DECADES has resulted in the largely successful fitting and wearing of contact lenses by over 20 million individuals in the US. Lenses worn successfully include soft, hydrophilic lenses, both for daily wear and on an extended wear basis, silicone soft lenses, rigid gas permeable lenses and the original rigid polymethylmethacrylate lenses. Each of these types of lenses has effects on a variety of parameters of corneal physiology and all of these lenses result in some degree of corneal hypoxia.[1] While major attention has focused on the long-term changes in corneal endothelial morphology associated with contact lens wear, effects on the corneal epithelium have been noted both in humans and in animal models. These epithelial changes include a decrease in corneal sensitivity,[2-4] significant biochemical alterations,[5] changes in the rate of surface cell exfoliation,[6] the development of intraepithelial microcysts[7,8] and a variety of surface cell abnormalities including dendritiform lesions.[9] In recent years an increasing number of reports of infectious keratitis associated with contact lens wear have appeared.[10-12] A recent epidemiologic study has demonstrated substantially increased risk for infectious keratitis associated with the wearing of contact lenses.[13]

In a previously reported study from our institution, we have described morphologic changes in the corneal epithelium associated with the wear-

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ing of soft hydrophilic contact lenses, on an extended wear basis.[14] These changes included a statistically significant shift to large presumably older surface cells implying delayed exfoliation and possible susceptibility to bacterial invasion. Recent modifications of this technology include the introduction of computerized morphometric analysis of cell morphology.[15] In this study, we have used this newer modification to study central corneal surface cell morphology in patients wearing a variety of different contact types, in an attempt to differentiate possible deviations from normal values with specific types of contact lens wear.

## METHODS AND RESULTS

Patients were selected from the Contact Lens Service of the Center for Sight, Georgetown University, for inclusion in this study and specular microscopy on the corneal epithelium was performed on one or both eyes of each patient. The technique for this procedure has been previously described.[16] Briefly, each eye was anesthetized with one drop of topical anesthetic. Immediately after the removal of the contact lens, the tip of an 18X cone was applied to the center of each cornea while careful lid retraction was performed by an assistant who monitored the position of the cone on the eye. Specular photographs were taken with the Keeler Conan Polington specular microscope while the cone was moved over the central cornea. Only the central one third of the corneal surface was examined in this study. We used 100 ASA T-MAX film and developed it at ASA 400. The best, sharpest negative which showed the most number of cells was selected by a masked observer and enlarged to an 8 × 10 black and white print. The photograph was then digitized by a second masked observer, manually outlining each clearly identified cell and entering the information (Epicalc by Bio-optics). We were able to digitize 49 ± cells from each photograph. Area, perimeter and shape factor are calculated for each case by the program and the mean and standard deviation are tabulated for each eye.

Eighty-four eyes of 48 patients were included in this study. These were divided into seven groups by the type of contact lens worn. Patients with hard polymethylmethacrylate (HCL), extended soft (EWSCL), rigid gas permeable (RGP), or daily wear soft contact lenses (DWS) were age (by decade) and sex matched and compared with a group of normals who were of the same average age (29 years). Aphakic extended wear soft contact lens patients (AEWSCL) were older (average age, 64 ± 4 years) and were compared with a second group of nonaphakic normal older patients of similar age (Table I).

TABLE I

| GROUP | NAME | MEAN AREA ($\mu m^2$) | SD | PATIENTS | |
|---|---|---|---|---|---|
| | | | | NO (eyes) | PATIENTS |
| 1 | AEWSCL | 818.3 | ± 186.5 | 6 | 4 |
| 2 | HCL | 516.8 | ± 52.0 | 8 | 5 |
| 3 | EWS | 633.8 | ± 180.6 | 12 | 6 |
| 4 | RGP (DW) | 612.1 | ± 87.2 | 7 | 4 |
| 5 | DWS | 511.2 | ± 145.1 | 15 | 8 |
| 6 | NL-young controls | 509.6 | ± 75.3 | 23 | 12 |
| 7 | NL-old controls | 616.5 | ± 218.9 | 13 | 7 |

Using one-way analysis of variance, the patients with AEWSCL, group 1, had significantly larger cells (818 ± 186 $\mu m^2$) (Fig 1) than all other groups and were significantly larger than their age matched controls, group 7 (616 ± 218 $\mu m^2$, $P < 0.002$). We also found that the older normal patients in group 7 had cells which were significantly larger than the normal young patients, group 6 (509 ± 75 $\mu m^2$) (Fig 7). There were two additional groups of contact lens patients with cells significantly larger than normal: the EWSCL patients, group 3 (633 ± 180 $\mu m^2$) (Fig 3) and

FIGURE 1
Specular microscopy of epithelial cells from a patient wearing an AEWSCL.

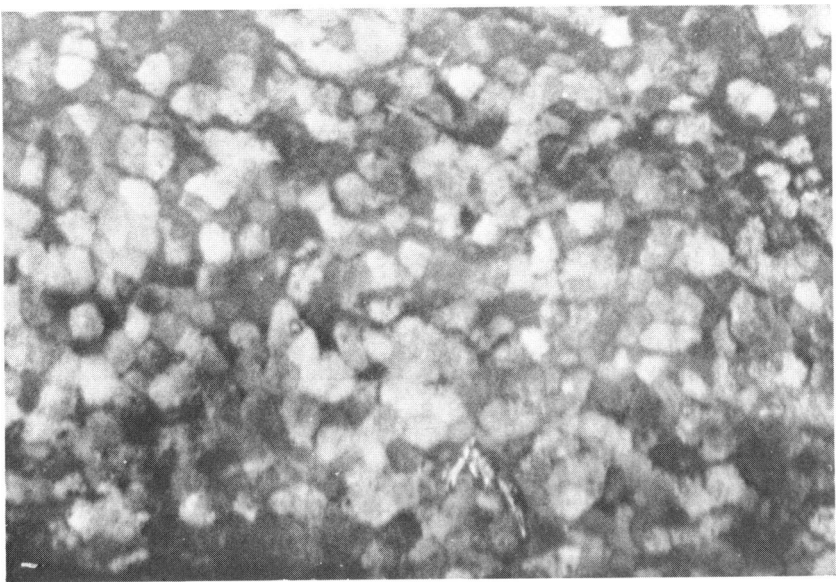

FIGURE 2
Specular microscopy of epithelial cells from a patient wearing a HCL.

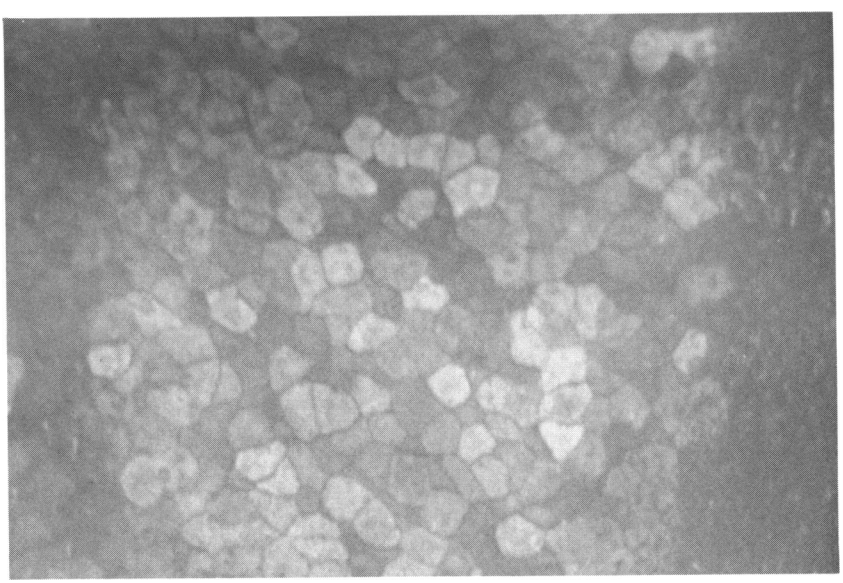

FIGURE 3
Specular microscopy of epithelial cells from a patient wearing an EWSCL.

the daily wear RGP contact lens patients, group 4 (612 ± 87 $\mu m^2$) (Fig 4). In addition we found that these EWSCL patients' cells were larger than DWS patients' cells (633 ± 180 $\mu m^2$ *vs* 511 ± 145 $\mu m^2$) (Fig 5). The *P* values of these comparisons are statistically significant at a *P* value of 0.05. We found no significant difference between DWS patients (group 5, Fig 6), HCL patients (group 2, Fig 2), and young normal patients (group 6, Fig 6).

## DISCUSSION

The development of the original corneal contact lens employing polymethylmethacrylate (PMMA) material opened an era in which the successful fitting of millions of patients with corneal contact lenses was ushered in. From 1949 to the late 1960s, PMMA lenses represented the only contact lens material available. Despite large numbers of successful fits, a significant number of patients, were still contact lens intolerant. Overwearing of contact lenses and tight fits were associated with acute corneal epithelial swelling and pain, the so-called overwearing syndrome associated with acute corneal hypoxia.[17] PMMA is impermeable to oxygen transmission. An exchange of oxygen-containing tears beneath the

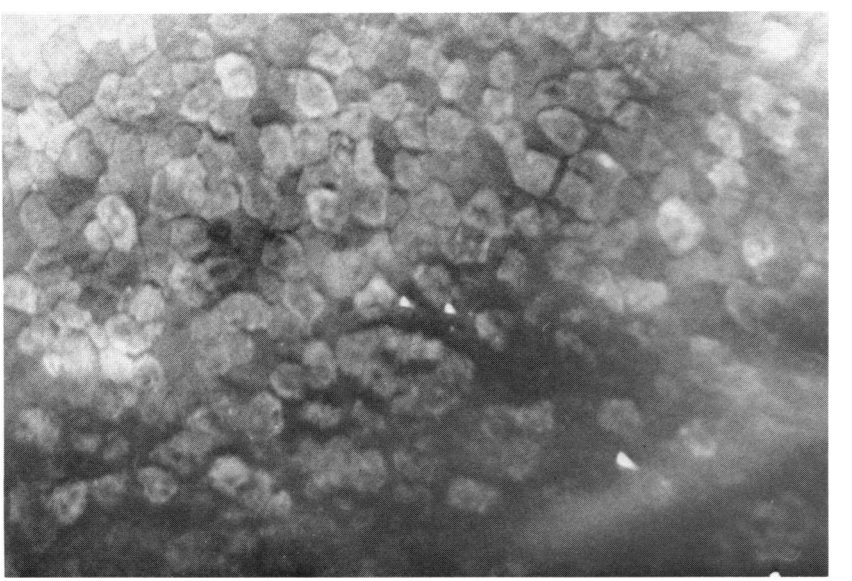

FIGURE 4
Specular microscopy of epithelial cells from a patient wearing a daily wear RGP contact lens.

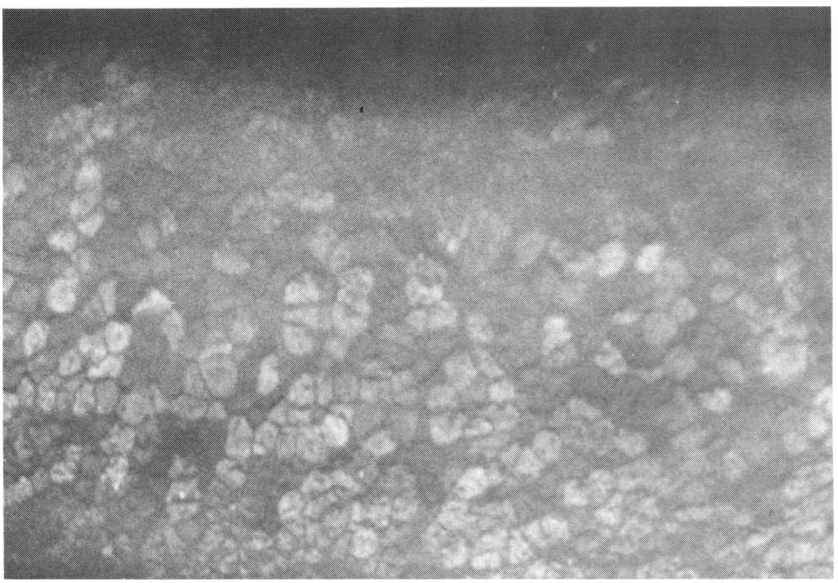

FIGURE 5
Specular microscopy from a patient wearing a DWS contact lens.

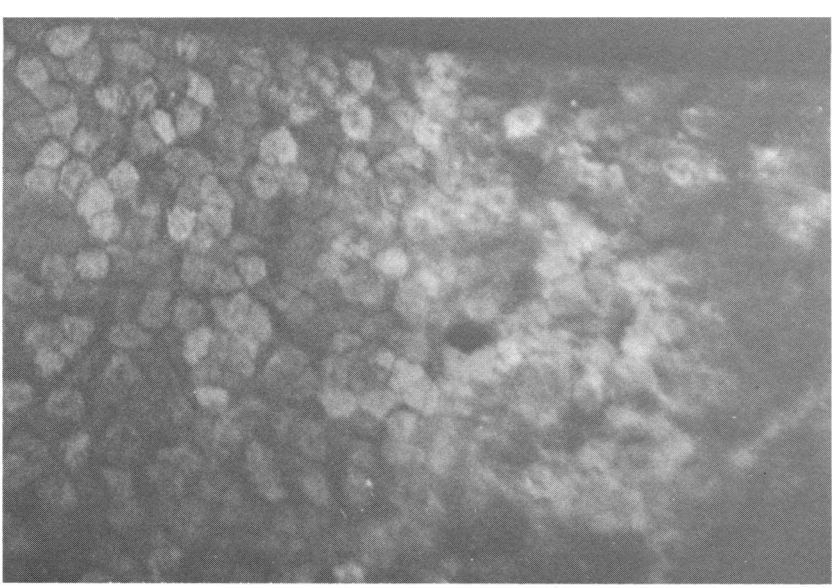

FIGURE 6
Specular microscopy from a normal young control group.

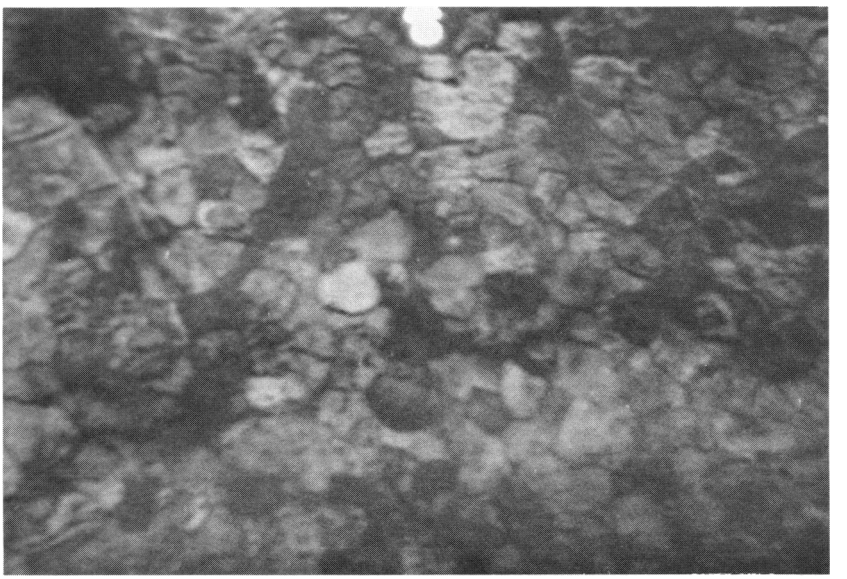

FIGURE 7
Specular microscopy from a normal old control group.

rigid PMMA lens depends upon an adequate fit and good lid blinking to assure mixture of tears beneath the lens. In the late 1960s the advent of hydrophilic materials for contact lens wear introduced an entirely new class of compounds and fitting characteristics for contact lenses. Soft hydrophilic lenses have varying degrees of oxygen transmissibility depending upon their water content. Moreover, they have been shown to have very little exchange beneath these lenses and this is in contrast to rigid lenses.[18] Transmissibility of oxygen through hydrophilic lenses is dependent upon the water content of the lens and the thickness of the lens.[19] As has been recently demonstrated, there is no type of hydrophilic soft contact lens which adequately meets the oxygen demand of the cornea and some degree of corneal swelling is associated with contact lens wear.[1] The recent development of materials for the construction of rigid contact lenses which permit a much higher degree of oxygen transmissibility through them has permitted successful contact lens adaptation for many patients who were previously contact lens intolerant.[20]

Wearing of contact lenses is also associated with a decrease in corneal sensitivity.[2] This is associated with a so-called adaptation phenomenon and is a feature of both rigid and soft contact lenses. This decrease in

corneal sensitivity is independent of corneal hypoxia and reversible upon cessation of contact lens wear.[3] This is thought to be the result of sensory adaptation to a mechanical stimulant and may be mediated by altered intraepithelial metabolism. In animal models, it has been demonstrated that there are biochemical alterations induced by contact lens wear including glycogen depletion and an increase in lactic acid.[5] A prominent clinical observation in contact lens wearers, particularly those wearing hydrophilic lenses on an extended wear basis, is that of epithelial microcysts.[7,9] Some series have reported 100% of patients with extended wear lenses showing these microcystic inclusions within the corneal epithelium.[9] Recent reports have demonstrated a variety of surface cell abnormalities associated with contact lens wear including dendritiform lesions of the cornea.[9,21-23] The mechanism by which these changes are affected remains unclear.

In previous studies, we have employed color specular microscopy to study the morphology of surface cells in a normal human cornea.[6] We delineated three populations of surface cells on the basis of size. Extrapolating from the scanning electron microscope studies in rabbit corneas by Pfister,[24] we have interpreted small cells to represent newly emerged surface cells which are, therefore, younger; older cells are resident for a longer period of time on the corneal surface. Newly emerged cells on the ocular surface which are small are probably small either by virtue of the fact that they emerge on the surface as small cells and gradually enlarge as they are resident for longer periods of time or by virtue of the fact that they are initially only partially exposed but as overlying cells partially covering them exfoliate from the surface, they reveal their full size after a longer resident time on the surface. In earlier studies, we discerned a statistically significant shift to small cells in patients with keratoconjunctivitis sicca.[25] Conversely, in patients wearing EWSCL, there was a statistically shift to large cells.

In more recent studies employing specular microscopy of the corneal epithelium, we have employed a computerized program which studies cell area, perimeter and shape.[15] The previous distinction between small, medium, and large cells represented a convenient classification system. Morphometric analysis, however, reveals that the cell size on the corneal surface is a continuum. Employing this new technique, we have recently studied the morphology of surface cells in anesthetic corneas that have demonstrated a statistically significant shift from normal central cell areas to larger cells than the anesthetic cornea. This is presumably due to sensory denervation which is characterized by a loss of cytoskeletal structures, decreases in cellular adhesions, an increase in intercellular spaces, and changes in epithelial permeability.

In this study, we have demonstrated a statistically significant shift in the mean cell area of central corneal cells from normal values in relatively young patients with those wearing hydrophilic lenses on an extended wear basis. These findings are consistent with our previously published data. Comparing aphakic patients that were age-matched for nonaphakic patients wearing extended wear lenses, there was also a statistically significant shift to large central cells. There may be two explanations for this: (1) The EWSCL may retard exfoliation and increase the cell size. (2) Aphakic patients have partially denervated corneas. This denervation would increase cell size as stated above. We have previously demonstrated this effect in our earlier study which found more large cells in aphakic patients than normal patients.[14] These findings with EWSCL are in contrast to the findings in patients with DWS in which there was no statistically significant difference in mean cell size from age-matched normal subjects. Similar findings were seen in patients wearing rigid PMMA lenses. In patients wearing RGP lenses, there was also a statistically significant increase in mean cell size.

The pathogenetic mechanisms by which these surface cell changes are effected under contact lens wear remains unclear. It is tempting to relate these changes to putative changes in corneal sensitivity occurring under soft contact lens wear. This would correlate well with similar changes reported in anesthetic corneas.[15] What is not clear, however, is why such changes should be present under RGP lenses but not under rigid PMMA lenses.

The marked morphologic changes demonstrated in this study, however, suggest a delayed exfoliation of cells from the surface of the cornea in certain contact lens situations. This explanation would be consistent with the suggestion by Hamano and Hori,[26] suggesting a suppression of mitotic activity in the corneal epithelium under soft contact lens wear. Older cells with changes in the density of microvilli might well present areas facilitating attachment of bacteria and may well be at least partially related to the increased risk for infectious keratitis associated with contact lens wear.

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## *DISCUSSION*

Dr R. Linsy Farris. Doctor Lemp and co-workers have extended previous in vivo human corneal epithelial studies using color specular microscopy by using

black and white photography of central corneal epithelial cells in contact lens wearers. A computer program has been used to measure the hand traced cell outlines of approximately 50 central corneal epithelial cells and to convert the measurements to a mean cell area in square microns. Subjects with various types of contact lenses and various modes of wear were compared to age, sex matched controls.

The mean cell area of the central corneal epithelial cells were found to be significantly larger in AEWSCL wearers compared to normal subjects, 818 ± 186 $\mu m^2$ compared to 616 ± 219 $\mu m^2$ which was significant at a $P$ value of less than 0.002. A comparison of the older and a younger group of control subjects yielded a difference of 616 ± 219 $\mu m^2$ compared to 509 ± 75 $\mu m^2$.

Additional significant differences were found in phakic extended contact lens wearers (633 ± 180 $\mu m^2$) and RGP daily wear contact lens patients (612 ± 87 $\mu m^2$). No differences were found between DWS patients, HCL patients and young normal patients.

Previous studies of Lemp and Gold have shown that aphakic individuals in EWSCL have a larger number of large surface corneal epithelial cells compared to aphakic patients wearing spectacles. No difference was demonstrated in that study between normal and aphakic patients with regard to the frequency of larger cells. Only extended wear of contact lenses in aphakia and myopia was associated with a greater frequency of large surface corneal epithelial cells.

These color photographs of central corneal epithelium were loaned to me by Doctor Koester of the Edward S. Harkness Eye Institute at Columbia. He was one of the first to report the use of this technique of corneal surface photography. One can see in a neuroparalytic and exposure keratitis enlarged cells.

The question in all of our minds is "Why more large cells in older individuals and contact lens wearers, particularly those using extended wear overnight?".

Accepting the fact that larger epithelial cells are older cells and are retained in central cornea, we need to keep in mind that only the appearance of approximately 50 central cells in the middle third of the cornea have been photographed in this study after instilling topical anesthetic. Peripheral zone differences, particularly in contact lens wearers are likely to occur, especially if an aphakic wears an extended wear lens until they develop deposits of varying degree. Doctor Lemp has reported zonal differences in previous studies but confines this report to only central changes.

No doubt one of the reasons I was aksed to discuss this paper was that my AOS thesis was about tear analysis in contact lens wearers and the tears are the watery environment of the cells we are discussing.

By using a microcapillary collection technique and the Clifton Technical Physics Micro-osmometer, we could freeze extremely small, nanoliter-size tear samples of tears. We found that dry eyes and contact lens wearers have hypertonic tears. Gilbard and I with Rose bengal staining and later Gilbard and associates in Boston with cell cultures showed that hypertonic tears are associated with cell degeneration and aging.

The present study convincingly demonstrates differences in corneal epithelial cell size with measuring methods proven in corneal endothelial studies and confirms earlier work using more rudimentary techniques of counting cell populations. I commend Doctor Lemp's group in perfecting the technique and developing a firmer belief in the earlier findings.

Nevertheless, I would still like to see some studies in unanesthetized corneas. Contact lens wearers are use to having objects placed on their corneas without anesthetics. The anesthetic could have been responsible for some older cells falling off so that the differences may even be greater. I would also like to see the results of these new measurements on aphakia patients without contact lens wear and zonal studies such as performed by Doctor Lemp in patients after keratoplasty. Contact lenses have movement on the cornea with greatest movement perhaps across the central zone where the counts are obtained. Extended wear RGP contact lenses would also be of interest since their movement is much different from EWSCL and less generally than PMMA hard contact lenses.

Contact lens movement offers an explanation for the fact that large cells were not found in HCL and DWS patients. Exfoliation would be encouraged by the more mobile, usually smaller diameter PMMA hard contact lens and also the thicker, firmer daily soft contact lenses compared to the higher water content or thinner EWSCL. Certainly the daily removal of lenses would also encourage exfoliation of the larger cells.

I am sure these studies are all forthcoming with the new use of digitized specular microscopy of the corneal epithelium. Greater numbers of eyes, now limited to no more than 12 eyes in six patients in the groups found to have significant differences, and zonal comparisons in the cornea will give more reason to discover the cause of larger central surface corneal epithelial cells in certain types of contact lens wear.

If the larger, presumably older cells are less resistant to bacterial invasion or provide greater opportunity for bacterial attachment, these studies may have revealed a major mechanism for production of corneal ulcers in contact lens wearers.

I congratulate Doctor Lemp and co-workers on the occasion of this presentation of their most recent good work and look forward to their future studies of the cornea.

DR RICHARD C. TROUTMAN. Have you correlated the surface cell changes with endothelial cell changes in these patients, in particular in patients with aphakia where 10% to 15% of the endothelial cells can be lost and there may be an increase in corneal thickness as well? Also, have you correlated your findings with different methods of cataract extraction? Do you get more cell loss with a 10 mm incision than with a phako incision? Following penetrating keratoplasty we try to avoid contact lenses because the epithelium often does not do well in the almost totally anesthetic donor cornea.

DR MICHAEL A. LEMP. Thank you for those comments, Doctor Farris, I would like to thank you for your very thorough discussion. Just picking up on a couple of threads that you have pointed out — the effect of topical anesthetics. We know that these are lipids in the cell walls and anesthetics adversely affect these; they can, therefore, have profound effects on the corneal epithelium. The question is, in the technique of doing this, is the effect immediate because we do this immediately after you anesthetize the eye? We have found that we get better quality photographs in our institution using our particular machine without any contact lens. I know that Doctor Koester has been using contact lens — he is using a slightly different kind of machine and this may account for the differences that we have.

Your question about zonal changes I think is very important at least from a research point of view. We have done these studies, in noncontact lens wearers and have reported a year ago at ARVO in a poster and have a manuscript in preparation now. What we think is a significant finding is that there are statistically significant differences in cell sizes from the central cornea to the peripheral cornea. We think that there is a preferential loss of cells in the center of the cornea probably secondary to the shearing action of the lid over the dome of the cornea. This preferential loss of cells from the center of the cornea is driven by the force of the lid; there are substantial posterior forces from the lid onto the surface of the eye. We think that this is one of the driving forces for the centripetal movement of cells from the periphery of the cornea to the center. It may also be driven from the back in terms of cell pressure. This preferential loss of cells in the center is reflected in a statistically significant decrease in cell size with newer, smaller cells there. We may well see the same thing in contact lens wearers.

Doctor Troutman, you asked me about the endothelial changes. We have not been able to correlate this. It is a very good point and something that probably needs to be looked at. We haven't looked at the difference between phakos *vs* the larger incisions; the ones that I reported were not phakos, they were more standard size incisions in which you would have a more profound degree of anesthesia at the cornea. In this presentation we did not have a normal aphakic group but we had historical controls previously described and the cells are statistically larger in aphakia. They are not as large as the ones in aphakics wearing extended wear lenses but they are statistically significantly larger than we find in nonaphakics but that certainly is a very good point.