position-related nonlinearities of retinal or eye motion feedback or of predictive inputs to the smooth pursuit system might explain the effects of orbital eccentricity on sinusoidal pursuit gain in our study.

We identified no effect of head position on horizontal sinusoidal pursuit when targets were kept centered with respect to the orbit. This implies that static proprioceptive inputs from the neck do not normally influence smooth pursuit maintenance. This result also suggests that the effects of eye position on sinusoidal smooth pursuit are not caused by changes in the spatial position of targets with respect to the trunk; responses to stimuli centered 60° from the midline of a trunk-centered (somatotopic) reference frame were indistinguishable from those centered at the somatic midline. The relative effects of eye and head positions we recorded with regard to smooth pursuit maintenance are comparable to those observed with respect to perceptual localization of targets in space. The accuracy of finger pointing toward a visual stimulus is impaired when the target is viewed in peripheral eye positions compared to primary position. The influence of eccentric head position on this task, if any, is much smaller than that of eccentric eye position. Declines in the accuracy of smooth pursuit and target localization that occur when the eyes are deviated from the orbital midline might be explained by inaccuracies of a central neural representation of spatial position for visual stimuli. Such a representation could be formulated in cerebral cortex; eye position information that would be necessary for this process is known to be encoded by some posterior parietal neurons.

**Key Words**

eye movements (vertical), eye position, head position, pursuit initiation, smooth pursuit

**Acknowledgments**

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**References**


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**Central Corneal Endothelial Cell Changes Over a Ten-Year Period**

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**Purpose.** To obtain longitudinal data to estimate long-term morphometric changes in normal human corneal endothelia.

**Methods.** Ten years after an initial study, the authors rephotographed the central corneal endothelium of 52 normal subjects with the same contact specular microscope. The findings for the 10 subjects younger than 18 years of age at the initial examination were considered separately. For the remaining 42 adult subjects, the time between examinations averaged 10.6 ± 0.2 years (range, 10.1 to 11 years). At the recent examination, these subjects' ages averaged 59.5 ± 16.8 years (range, 30 to 84 years). Outlines of 100 cells for each cornea were digitized.

**Results.** For the 42 adult subjects, the mean endothelial cell density decreased during the 10.6-year interval from...
The SC of the normal population is necessary not only for comparison to other time-dependent changes but also for the latter is usually expressed as the standard deviation of the differences between paired measurements on the same persons at two different times (S_{d}). SC cannot be obtained from cross-sectional data; longitudinal studies are required. In 1985, we conducted an investigation of normal corneal endothelia of normal humans aged 50 (27 females, 40 males, 10 per decade in age). Because of the relative stability of the population in Olmsted County, Minnesota, we were able to repeat the study 10 years later and to obtain longitudinal morphologic data on the corneal endothelia of normal persons.

**METHODS.** Of the 80 subjects in the 1985 study, six died and 17 either could not be contacted or refused to return; 57 returned for repeat measurements. This study followed the tenets of the Declaration of Helsinki. Five of the 57 subjects who returned were excluded because of occurrences during the 10-year interval (three wore contact lenses, one now had diabetes, and one had undergone bilateral cataract extraction). The remaining 52 subjects (27 female, 25 male) gave informed consent for the study, which was approved by our institutional review board. All subjects were white, reflecting the local population in 1985. We conducted brief ophthalmic examinations, which included visual acuity, slit lamp examination, tonometry, and undilated fundus examination. One eye in each of seven subjects was excluded because of occurrences during the past 10 years (unilateral cataract extraction and lens implantation in three subjects; unilateral retinal surgery, lens surgery, eye injury, and contact lens wear in one subject each). All remaining eyes were normal and had undergone no ophthalmic surgery. The 52 subjects underwent bilateral central endothelial photography and pachometry with the same Schulte specular microscope (Product Research Organization, Tustin, CA) used 10 years earlier. We took repeat calibration photographs of a micrometer slide with the microscope set at a corneal thickness of 0.54 mm, as previously described.²

From the photographic negatives, we digitized the apices of 100 cells for each eye with a video analyzer (BioOptics, Arlington, MA). The 1985 calibration photographs were used to calibrate the magnification for the repeat analyses of the 1985 photographs, and the 1995 calibration photographs were used for the 1995 data. The two calibrations were identical, indicating no shrinkage or expansion of the 1985 photographic negatives during the subsequent 10 years. The computer algorithm calculated the mean cell area and its reciprocal, the cell density, the coefficient of variation of cell area (mean/standard deviation), and the percentage of hexagonal cells on the assumption that the cell sides were straight lines connecting the apices. The specular microscopic measurement method is reproducible within 7%, of which approximately one third is the result of the precision of the technique and the remaining two thirds is the result of the variance of the endothelial cell population measured.³ Either a two-tailed paired t-test or Wilcoxon signed-rank test (depending on the distribution of the data) was used to test for differences between the 1995 and the 1985 examinations. Pearson correlation coefficients were computed to test for associations between continuous variables. One value was used for each subject for each measurement, the mean of the values for both eyes in 45 subjects and the value for the normal eye in the seven subjects with unilateral abnormalities, as described.

To characterize the change in endothelial cell density over time, we computed its annual rate of decrease. Because first-order processes predominate in nature, we calculated the exponential rate of cell loss per year, and \( t \) = time between examinations in years.

\[
ECD_2 = ECD_1 e^{-rt}
\]

where \( ECD \) = endothelial cell density in cells/mm² in 1985 (ECD₁) and 1995 (ECD₂), \( r \) = exponential rate of cell loss per year, and \( t \) = time between examinations in years. Because human endothelial cell density appears...
to decrease more rapidly during the first decade or two of life,1,2,4 we elected to segregate the 10 subjects (five males, five females; age range, 5 to 15 years) who were younger than 18 years of age at the 1985 examination. This procedure provides a more accurate estimation of the average rate of endothelial cell loss in normal adults.

RESULTS. For the 42 subjects (22 women, 20 men) at least 18 years of age at the initial examination, the time between examinations averaged 10.6 ± 0.2 years (mean ± SD; range, 10.1 to 11 years). These subjects' ages averaged 59.5 ± 16.8 years (range, 30 to 84 years) at the recent examination. None of the subjects had diabetes or wore contact lenses. Scattered guttae (1+ or less) were noted on the second examination in six of the older subjects; we considered this finding to be within normal limits. Guttae were not noted in these subjects on the original examination. During the 10.6-year period, there were statistically significant decreases in the endothelial cell density and the percentage of hexagonal cells and an increase in coefficient of variation of cell area (Table 1). Corneal thickness was unchanged. The exponential rate of cell loss was 0.6% ± 0.5% per year (range, —0.9% to 1.7%) for the 42 adult subjects and 1.1% ± 0.8% per year (range, —0.2% to 2.7%) for the 10 younger subjects (P = 0.03).

The correlation between age in 1995 and the exponential rate of cell loss over the previous 10.6 years in the 42 adult subjects was not statistically significant (r = 0.14, P = 0.43; Fig. 1). Mean and annualized differences and their standard deviations (Sd) between the paired examinations in these 42 subjects are given in Table 2. These data can be used to estimate the number of subjects required to detect a difference between two groups with a given power.

DISCUSSION. In cross-sectional studies, the average annual endothelial cell loss rate in normal eyes appears to be approximately 0.3% to 0.5%.1,2 In longitudinal studies, however, in which the same subjects are examined again at a later date, the annual loss has been higher. Longitudinal data have been published in only four articles, all with follow up of 2 to 5 years. Cheng et al5 examined 103 unoperated fellow eyes sequentially over 2 years and found an average endothelial cell loss of 1% per year. Ambrose et al6 reviewed the data of McGill and Liakos7 and reported a median loss of 0.6% per year in 48 normal unoperated eyes examined sequentially over 2 years. Werblin8 repeated the endothelial examinations after 5 years in five unoperated fellow eyes and found an average cell loss of 0.8% per year. On the other hand, Numa et al9 examined nine normal unoperated eyes over a 5-year period and found a decrease in cell density of only approximately 0.3% per year. Our current finding of a mean cell loss of 0.6% ± 0.5% per year over 10 years is within the range of values found in these previous studies conducted over shorter periods. Higher rates of chronic endothelial cell loss occur after anterior segment intraocular surgery, for example, after cataract extraction (2.5% per year from 1 to 10 years after surgery10) and after penetrating keratoplasty (7.8% per year from 3 to 5 years after surgery11).

In addition, our data provide information about the variability among adults of the morpho-

### TABLE 1. Examination Results

<table>
<thead>
<tr>
<th></th>
<th>1985 Examination</th>
<th>1995 Examination</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial cell density (cells/mm²)</td>
<td>2715 ± 301</td>
<td>2539 ± 284</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coefficient of variation of cell area</td>
<td>0.26 ± 0.05</td>
<td>0.29 ± 0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hexagonal endothelial cells (%)</td>
<td>67 ± 8</td>
<td>64 ± 6</td>
<td>0.003</td>
</tr>
<tr>
<td>Corneal thickness (mm)</td>
<td>0.55 ± 0.02</td>
<td>0.55 ± 0.03</td>
<td>0.54†</td>
</tr>
</tbody>
</table>

Values are mean ± SD; n = 42.
* Two-tailed paired t-test.
† Two-tailed signed-rank test.

FIGURE 1. Exponential endothelial cell loss rate versus age at the 1995 examination. Open circles represent the ten subjects younger than 18 years of age at the initial (1985) examination. The correlation between cell loss rate and age for the 42 adult subjects (filled circles) was not significant (r = −0.14, P = 0.43).
logic changes over time (SD; Table 2). These values can be used to predict the sample sizes needed in future studies of corneal endothelial cell depletion in normal subjects. Larger sample sizes than those predicted from these data may be needed in studies of eyes that have an increased variance of the rate of cell loss, such as those in which cataract extraction or penetrating keratoplasty have been performed. 11

All subjects in our study were white, reflecting the local population at the time. These results, therefore, give us no information about racial differences. No racial differences have been reported except for a higher endothelial cell density in Japan. 12

We limited our conclusions to adults because corneal endothelial cell density is known to be elevated during childhood. 1,2,4 The rate of decrease in cell density is accelerated until at least 10 years of age, 4 and our data are confirmatory, finding a significantly higher rate of cell loss in the 10 subjects 5 to 15 years of age at the 1985 examination. Because it is unknown at what age the rate of cell loss stabilizes, we chose to limit our analysis to subjects who were at least 18 at the initial examination. This is the minimum age for adult research studies with which our data will be compared. We found no change in the rate of cell loss after age 18 (Fig. 1), confirming that the rate is stable in adults.

Key Words
cell loss rate, corneal aging, corneal endothelial cell loss, corneal endothelial morphology, sample size calculation

References
1. Yee RW, Matsuda M, Schultz RO, Edelhauser HF.


<p>| TABLE 2. Changes Over Time in 42 Subjects |</p>
<table>
<thead>
<tr>
<th>Change Over 10.6 Years*</th>
<th>Change Per Year†</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Endothelial cell density (cells/mm²)</td>
<td>-176</td>
</tr>
<tr>
<td>Coefficient of variation of cell area</td>
<td>0.03</td>
</tr>
<tr>
<td>Hexagonal endothelial cells (%)</td>
<td>-4</td>
</tr>
<tr>
<td>Endothelial cell loss (%)</td>
<td>6.4</td>
</tr>
</tbody>
</table>

† (1995–1985 examinations)/time in years between examinations.
‡ Exponential cell loss rate, r, X 100 (see text).