Objective: To restore accommodation in primate eyes by refilling the lens capsule with injectable silicone compounds.

Materials and Methods: Eight eyes of 8 monkeys (Macaca fascicularis) were treated by the lens refilling procedure. To prevent leakage of the injected liquid silicone before it polymerized in the capsule in vivo, a silicone plug for sealing the capsular opening was developed. After endocapsular phacoemulsification following an upper minicircular capsulorhexis, the plug was introduced into the capsulorhexis opening. A silicone mixture was injected into the capsular bag through the delivery tube of the plug. Automated refractometry was performed 1 week and 3 months after surgery. Accommodation amplitude was determined as the difference between the refractions before and 1 hour after topical application of 4% pilocarpine chloride.

Results: Five of 8 eyes could be refilled. In 4 of 5 eyes, refraction could be measured. Accommodation amplitude ranged from 1.0 to 4.5 diopters, with a mean of 2.3 ± 1.3 diopters (8.0 ± 2.0 preoperative values). At 3-month examination, thick posterior capsule opacification precluded refractometry in all eyes.

Conclusions: The lens refilling procedure with the use of a silicone plug for sealing the capsular opening was feasible in primate eyes. The accommodation amplitude attained was a small fraction of the value before surgery. This may result from the loss of so-called intracapsular accommodation, ie, active participation of lens fiber cells in accommodation. However, since the obtained accommodation may be sufficient for near vision after cataract surgery, this lens refilling procedure warrants further study. Elucidation of the mechanism of intracapsular accommodation may also be necessary.

MATERIALS AND METHODS

PREPARATION BEFORE LENS REFILLING

Eight lenses of 8 young crab-eating monkeys (Macaca fascicularis) were used for the study. Two to 3 months before the lens capsule was refilled, sector iridectomies at the 6- and 12-o’clock positions were performed to facilitate the lens refilling procedure and automated refractometry after surgery. Refraction and accommodation amplitude (see below) were determined at least 1 month after iridectomy. The animals were housed at the Yaotsu Breeding Laboratory (Japan EDM Inc, Gifu, Japan), where the experiments were performed. The monkeys were treated humanely according to the principles of the Primate Society of Japan.10

CAPSULAR PLUG FOR SEALING

THE CAPSULAR OPENING

A capsular plug for sealing the capsular opening to prevent leakage of the injected silicone was made from silicone. The plug consisted of a thin delivery tube (outer diameter, 0.365 mm; inner diameter, 0.305 mm) with a disk-shaped silicone double plate, 0.38 mm thick, fixed to the end of the delivery tube. Between the 2 plates, there was a soft silicone gel that attached the 2 plates. The inner lumen of the delivery tube was filled with a soft, cured silicone gel to prevent reflux of the injected filling material.

LENS REFILLING PROCEDURE

After the monkey was anesthetized with ketamine hydrochloride (5 mg/kg) and xylazine hydrochloride (2 mg/kg), the pupil was maximally dilated. Then, a 3-mm incision was made at the limbus by means of a disposable 3-mm keratome. After the anterior chamber was filled with a viscoelastic substance, a prick was made in the capsule at the 12-o’clock position. After the anterior chamber was refilled, sector iridectomies at the 6- and 12-o’clock positions were performed to facilitate the lens refilling procedure. Refraction was determined as the difference between these 2 refraction values. Accommodation amplitude was determined as the difference between these 2 refraction values. Each measurement was performed 5 times by 1 of 3 masked persons, and the median value for each animal was used to calculate the overall mean value.

However, the CCC opening appeared to have already been damaged during insertion of the capsular bag.

SLITLAMP FINDINGS

At 1-week examination, the whole lens capsule was clear in 3 eyes, and migrating cells and flare in the anterior chamber were few and slight. Refraction could be measured by the automated refractometer. Two of 5 eyes showed fibrinous exudation on the anterior lens capsule (Figure 1). Fibrinous exudation in 1 of these 2 eyes in which refraction could be measured despite the condition had disappeared at 3-month examination. The other eye eventually progressed to phthisis bulbi because of endophthalmitis. These monkeys were the first to undergo surgery. Thereafter, we disinfected the eye more strictly before surgery, as in surgery on humans. As a result, changes in refraction could be measured in 4 eyes 1 week after surgery (Table). However, at 3 months postoperatively, anterior and posterior capsule opacification precluded refractometry in all 4 eyes. The anterior capsule was relatively clear, sporadically showing a fine fibrotic type of opacification (Figure 1).

AMPLITUDE OF ACCOMMODATION

The preoperative refraction before pilocarpine application ranged from 0 to –2.0 D, and those 1 hour after such
Preoperative and Postoperative Refractions and Accommodation Amplitude in Lenses Refilled With Injectable Silicone: Change in Refraction Before and 1 Hour After Topical Application of 4% Pilocarpine

<table>
<thead>
<tr>
<th>Monkey No./Age, y</th>
<th>Preoperative Refractions, Diopters (D)</th>
<th>Postoperative Refractions, D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>1/13</td>
<td>−2.00</td>
<td>−13.25</td>
</tr>
<tr>
<td>2/5</td>
<td>−1.00</td>
<td>−6.75</td>
</tr>
<tr>
<td>3/5</td>
<td>0</td>
<td>−7.50</td>
</tr>
<tr>
<td>4/6</td>
<td>−1.75</td>
<td>−9.25</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>−1.2 ± 0.8</td>
<td>−9.2 ± 2.5</td>
</tr>
</tbody>
</table>

|                  | Before  | After | Change |
|                  | −5.00   | 0.50  | 4.50   |
| 2/5              | −7.25   | 6.25  | 1.00   |
| 3/5              | 5.00    | 3.00  | 2.00   |
| 4/6              | −8.50   | 7.00  | 1.50   |

|                  | +6.4 ± 1.5 | +4.2 ± 0.6 | 2.3 ± 1.3 |

Figure 1. Slitlamp finding of the refilled lens of a primate eye 3 months after surgery. Fibrotic anterior capsule opacification developed and precluded refractometry. The posterior capsule is relatively clear. Note the optically empty silicone within the capsular bag. The arrows indicate the capsular plug.

Figure 2. Histopathological section of a refilled lens capsule from the monkey eye shown in Figure 1, 6 months after surgery. The section was cut horizontally from the middle of the resected specimen. Note the lens epithelial cells that migrated onto the posterior capsule (toluidine blue, original magnification ×8).

We performed refractometry 1 week after surgery, because our previous study showed that posterior capsule opacification occurred rapidly in the refilled lens capsule, precluding refractometry. As a result, changes in refraction in the refilled lenses could be measured in 4 lenses, excluding 1 that developed fibrinous reaction. At 3-month examination, refraction could not be measured in any of the eyes because of increasing posterior capsule opacification, obviously showing that prevention of this opacification is an essential issue to be solved in lens refilling. In this regard, ultrasonographic biometry may provide useful additional data regarding posterior capsule opacification in future studies.

Postoperative refraction will be primarily determined by refractive index of the injected silicone with a fixed certain value and anterior capsule curvature that depends on the degree of filling. The more tautly the capsule is filled, the steeper the anterior capsule curvature, thus the greater the refraction. Filling degree, however, also influences accommodation amplitude. The optimal accommodation amplitude will be obtained by filling the capsule with 60% to 70% of bag volume with silicone compounds, according to our previous study. Thus, postoperative refraction and accommodation amplitude both depend on filling degree, yet they comprise 2 reciprocally counterbalancing variables in lens refilling on the premise that filling material with only 1 specific refractive index is available. In other words, obtaining the optimal accommodation amplitude in lens refilling can be achieved at the price of achieving emmetropia. In this study, we attempted to obtain optimal accommodation by filling the lens capsule to 60% to 70% of bag volume. As a result, a mean accommodation amplitude of 2.3 ± 1.3 D could be obtained at the price of hyperopic shift in postoperative refraction with a mean value of +0.4 D.

Postoperative emmetropia may be achieved by intraoperative or postoperative refractive corneal surgery or phakic intraocular lens. Therefore, refractive surgery may have great implications in lens refilling.

HISTOPATHOLOGICAL EXAMINATION

The lens capsule was well stretched and showed that its integrity was obviously preserved. Thick posterior capsule opacification could be observed (Figure 2).
Although we refilled the lens capsule to obtain apparently optimal accommodation amplitude, we obtained only a small fraction of the amplitude before surgery. Similar results were also obtained in our previous study involving lenses refilled with inflatable endocapsular balloon. We think this may be caused by the loss of intracapsular accommodation, i.e., the active participation of lens fiber cells in accommodation. On the basis of his mathematical calculations, Gullstrand postulated that the change in the shape of the lens during accommodation could be realized only by the shifting of lens fiber cells against each other.

As circumstantial evidence, some findings indicate the existence of intracapsular accommodation. The fiber itself does not shift, but rather the contents of the fibers shift during accommodation. Metabolism in lens fiber cells is similar to that in muscle contraction. Contractile and cytoskeletal filaments such as actin, vimentin, and tubulin have been detected in the intracellular matrix of lens fiber cells. The adenosine triphosphate–adenosine diphosphate ratio falls after fiber shifting, but it is restored rapidly, similar to that in muscle. If there is such intracapsular accommodation, the full accommodation amplitude cannot be restored simply by refilling the lens capsule with an artificial material, although 3D restitution of accommodation might be clinically sufficient for near vision after surgery.

In conclusion, refilling the lens capsule with an artificial material, although 3D restitution of accommodation might be clinically sufficient for near vision after surgery. The rapidly developing posterior capsule opacification is another problem to be solved. The use of YAG laser capsulotomy may annul the accommodation attained. Furthermore, the question of whether a useful degree of accommodation remains unknown. The procedure should be tested in an aged primate eye.

In conclusion, refilling the lens capsule with injectable silicone in monkey eyes was feasible. The obtained accommodation amplitude was a small fraction of the value before surgery. This may have resulted from the loss of so-called intracapsular accommodation. Nevertheless, this lens refilling procedure warrants further investigation, since 3D accommodation might be sufficient for near vision after surgery. Posterior capsule opacification must be prevented, because capsulotomy might annul the accommodation attained.

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REFERENCES


JAMA Telomerase and the Aging Cell: Implications for Human Health

Michael Fossel, MD, PhD

Recent research has shown that inserting a gene for the protein component of telomerase into senescent human cells reextends their telomeres to lengths typical of young cells, and the cells then display all the other identifiable characteristics of young, healthy cells. This advance not only suggests that telomeres are the central timing mechanism for cellular aging, but also demonstrates that such a mechanism can be reset, extending the replicative life span of such cells and resulting in markers of gene expression typical of “younger” (ie, early passage) cells without the hallmarks of malignant transformation. It is now possible to explore the fundamental cellular mechanisms underlying human aging, clarifying the role played by replicative senescence. By implication, we may soon be able to determine the extent to which the major causes of death and disability in aging populations in developed countries—cancer, atherosclerosis, osteoarthritis, macular degeneration, and Alzheimer dementia—are attributable to such fundamental mechanisms. If they are amenable to prevention or treatment by alteration of cellular senescence, the clinical implications have few historic precedents. (1998;279:1732-1735)

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