Lens refilling to restore accommodation

Yutaro Nishi, MD, Kamiar Mireskandari, MD, FRCOphth, Peng Khaw, PhD, FRCP, FRCS, FRCOphth, FIBiol, FRCPath, FMedSci, Oliver Findl, MD, MBA

The ultimate goal of cataract surgery, besides the restoration of distance visual acuity, is the restoration of accommodation. Lens refilling with an injectable polymer has the potential of restoring accommodation following cataract surgery. Two main difficulties have hampered the success of lens refilling strategies in the past. First was leakage of the injectable material from the capsular bag and second was after-cataract formation resulting in loss of elasticity and opacification of the lens–bag complex. Recently, simplified and highly reproducible lens refilling procedures have been introduced with a potential for clinical application to restore accommodation. We present a summary of the existing methods of lens refilling for restoration of accommodation and some obstacles to clinical application that remain.

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Modern small incision cataract surgery with intraocular lens (IOL) implantation results in good visual acuity with an acceptably low risk for complications. However, the ultimate goal of modern cataract surgery also entails the elimination of the need for spectacles for near and distance by preserving accommodation in prepresbyopic patients and restoring it in the presbyopic age group. This goal remains elusive. Lens capsular refilling with an injectable material in the presence of capsular and zonular integrity and ciliary muscle function is an exciting and attractive prospect to restore ocular accommodation following lens surgery.

Despite repeated experimental studies and modifications to capsular bag refilling techniques, several issues persistently plague investigators and prevent surgeons from achieving the ultimate clinical goal of restoring accommodation. The first is the leakage of injectable materials from the anterior capsule opening through which the lens matter was removed. The second is after-cataract in the form of fibrotic and regeneratory capsule opacification, which compromises elasticity of the capsule and visual acuity and, therefore, accommodative function and optical clarity. The third is the titration of refractive power to achieve emmetropia as well as effective accommodation without induced optical aberrations and poor visual quality. Last but not least, the question remains if the residual ciliary muscle contractile force in aging eyes is enough to afford sufficient accommodative function with the available polymers.

This review article presents an overview of the current knowledge about lens refilling techniques and their effect on accommodation and capsular bag transparency as well as the issues that remain to be resolved before they can become clinically applicable.

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From the Ocular Repair and Regeneration Biology Research Unit, UCL Institute of Ophthalmology (Nishi, Mireskandari, Khaw), Biomedical Centre for Ophthalmology (Khaw), and Moorfields Eye Hospital NHS Foundation Trust (Nishi, Mireskandari, Khaw, Findl), London, United Kingdom.

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Correspondence address: Oliver Findl, MD, MBA, Moorfields Eye Hospital NHS Foundation Trust, 162 City Road, EC1V 2PD, London, United Kingdom. E-mail: oliver@findl.at.

MECHANISM OF OCULAR ACCOMMODATION AND PRESBYOPIA

Models of Accommodation Mechanism

The lens capsule, the lens substance, the zonular fibers, and the ciliary muscle compose the components needed for human ocular accommodation. Accommodation is achieved via an accurately regulated change in the thickness and shape of the lens in order to adjust the focal point of the eye to the distance of the target viewed.[1,2]

Accommodation has been shown to be associated mainly with changes in curvature of the anterior lens surface.[1–3] According to the theory of Helmholtz,[4]

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the increase of the anterior lens curvature in accommodation is induced by the contraction of the ciliary muscle (Figure 1). When the ciliary muscle contracts, it moves closer to the lens equator, the tension on the zonules is released, and hence the elastic lens assumes a thicker accommodated shape.[1–3,5–7] In disaccommodation, the reverse occurs and the tension on the zonules increases and the lens resumes a thinner, disaccommodated state.

The lens assumes the shape determined by the capsule during accommodation.[8] When the zonules relax, diminished tension on the capsule allows it to overcome the stiffness of the lens contents resulting in the moulding of the substance of the lens to its accommodated form. When the zonules are stretched the lens reverts to its disaccommodated form.

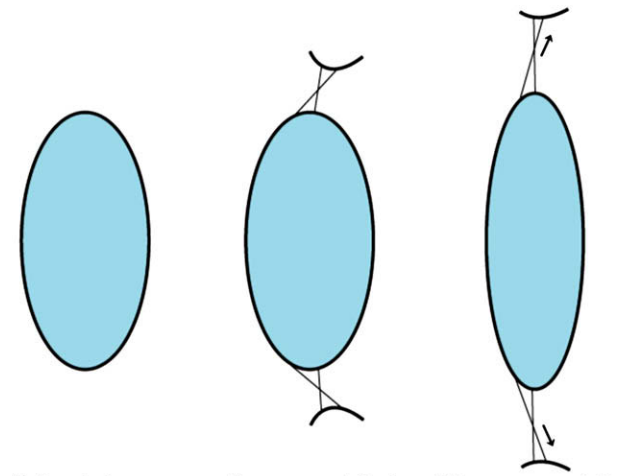

Figure 1. Simple representation of the Helmholtz model of accommodation.

Elasticity of the Lens

Several investigations have been undertaken to measure lens elasticity.[1–3,9,10] Ziebarth et al.[10] measured the elasticity of the whole lens including the capsule by means of atomic force microscopy. The values were found to be similar to those measured with dynamic mechanical analysis on human lenses and further investigations to determine the correlation between age and lens elasticity and to quantify the contribution of the nucleus, cortex, and capsule to the modulus of elasticity are still to be done.[10] The pending results should permit greater understanding of the roles of each component and aid in the development of lens refilling techniques.

Causes of Presbyopia

The anatomic structures involved in accommodation show changes with aging which could explain presbyopia.[1,2] As the lens volume and mass increase with age, the accommodative change in the lens shape becomes less. Also the hardening of the lens cortex and nucleus is expected to be a key factor in presbyopia as it adversely affects the ability of the lens to change shape during accommodation. Schachar and Pierscionek,[11] however, believe that lens sclerosis is not related to the decreased accommodative amplitude seen with aging.

By means of ultrasound biomicroscopy, human ciliary muscle contraction was shown to occur even in elderly subjects, indicating that the age changes in the ciliary muscle do not seem to be mainly responsible for presbyopia.[12] On the other hand, Croft et al.[13] studied age-related changes in accommodation in rhesus monkeys by means of ultrasound real-time video techniques and demonstrated an age-dependent decline in amplitude and velocity of ciliary body movement during accommodation, suggesting that ciliary body dysfunction might play a role in presbyopia, at least in this nonhuman primate model.

Investigations of the anterior segment changes with age and during accommodation by means of partial coherence interferometry indicated a decline in forward lens shift that may play a role for presbyopia.[14]

In summary, the mechanism for human ocular accommodation and presbyopia is still not fully understood and warrants further investigation. However, it appears that there may be enough extralenticular accommodative function to drive an elastic lens in the presbyopic eye.

Currently, some designs of focus-shift accommodative IOLs are available.[15–18] These are IOLs whose overall appearance is quite similar to conventional IOLs, but they should work by forward shift of the optic during ciliary muscle contraction. However, to date there is no evidence that any of the currently available accommodative IOLs have reproducible and clinically relevant optic shifts nor do they outperform monofocal IOLs concerning near vision.[15] Newer lens designs, such as dual-optic accommodating lenses and others, are being developed that attempt to maximally utilize the residual ciliary muscle function to induce either optic shift or change in optic curvature.[19–23]

TECHNIQUES OF LENS REFILLING

Surgical Procedures and Injectable Materials

Kessler[24] and later Agarwal et al.[25] introduced the original concept of lens refilling with a synthetic material after cataract removal. However, at the time, due to the absence of the necessary surgical techniques and instruments, the concept could not be realized. After the introduction of modern cataract surgery,

Table 1. Published in vivo animal lens refilling experiments in chronological order.

Year	Author (citation)	Implant material	Procedure	Animal Model	Main Findings	Problems	After-cataract
1985	Gindi (28)	Silicone polymer, cross-linked in situ	3.0 mm capsulotomy, 21G cannula	Rabbit	Silicone polymer useful for lens refilling	Due to leakage, only incomplete refilling	After 2 months
1987, 1994	Haefliger (26,30)	Pre-cured silicone polymer	1.3 mm peripheral capsule hole with diathermy, 20G cannula	Rabbit, owl monkey, rhesus monkey	Change of ACD and anterior lens curvature after ciliary body stimulation; some cases with 6.0–8.0 D; inflammation and after-cataract	Slight underfill leakage	Early, extensive
1989, 1992, 1993	Nishi (31,32,40)	Balloon filled with silicone polymer	Endocapsular balloons	Rabbit, monkey	No leakage; little accommodation in rabbit eyes; 6.0 D of accommodation in single primate eye	Sometimes balloon undersized; progressive decrease in accomm. amplitude with fibrosis	Long-term: extensive
1994	Hettlich (27)	Acrylate copolymer	Two 1.2 mm capsulotomies; endocapsular polymerization with ultraviolet light	Rabbit	No leakage; light induced polymerization appeared safe	Potential risk; for thermal and photochemical harm	After 3 months, especially in underfilled cases
1998	Nishi (34)	Silicone polymer	Plug for sealing 1.5 mm rhexis; attempt 65% filling	Monkey	No leakage;	2.0 D accommodation shortly after surgery; hyperopic shift of 6.0 D due to underfilling	After 3 months; extensive
2006	Koopmans (5)	Silicone polymer	Plug for sealing 1.5 mm rhexis; intraoperative PCO treatment	Rhesus monkey	6.0 D of accommodation in PCO treated eyes	After-cataract in eyes not treated for PCO	Mild after 37 weeks in PCO treated group; otherwise extensive
2007, 2008	Nishi (38)	Silicone polymer	Foldable silicone optic for sealing 5.0 mm rhexis; +/- optic for posterior rhexis	Rabbit, monkey	Simple procedure without leakage; prevention of central ACO and PCO with posterior optic; 1.0-2.0 D of accommodation and change of ACD	Inflammation	After 3 months, without posterior optic

ACD = anterior chamber depth; ACO = anterior capsule opacification; PCO = posterior capsule opacification

investigators were encouraged to reintroduce the refilling idea for clinical application.[3,5,26–34]

The material for injection in lens refilling should be fluid enough to allow smooth injection and yet be viscous enough to reduce the risk for leakage. Once injected, the viscoelastic properties should ideally imitate those of the young crystalline lens. The injection material should be safe concerning toxicity and stability and be optically transparent.[35]

To prevent leakage of the injected material after lens refilling, several methods have been developed (Table 1). One strategy is injecting the polymer in a fluid state which then transforms to a gel state in the capsule. Pre-cured silicone gel was used by

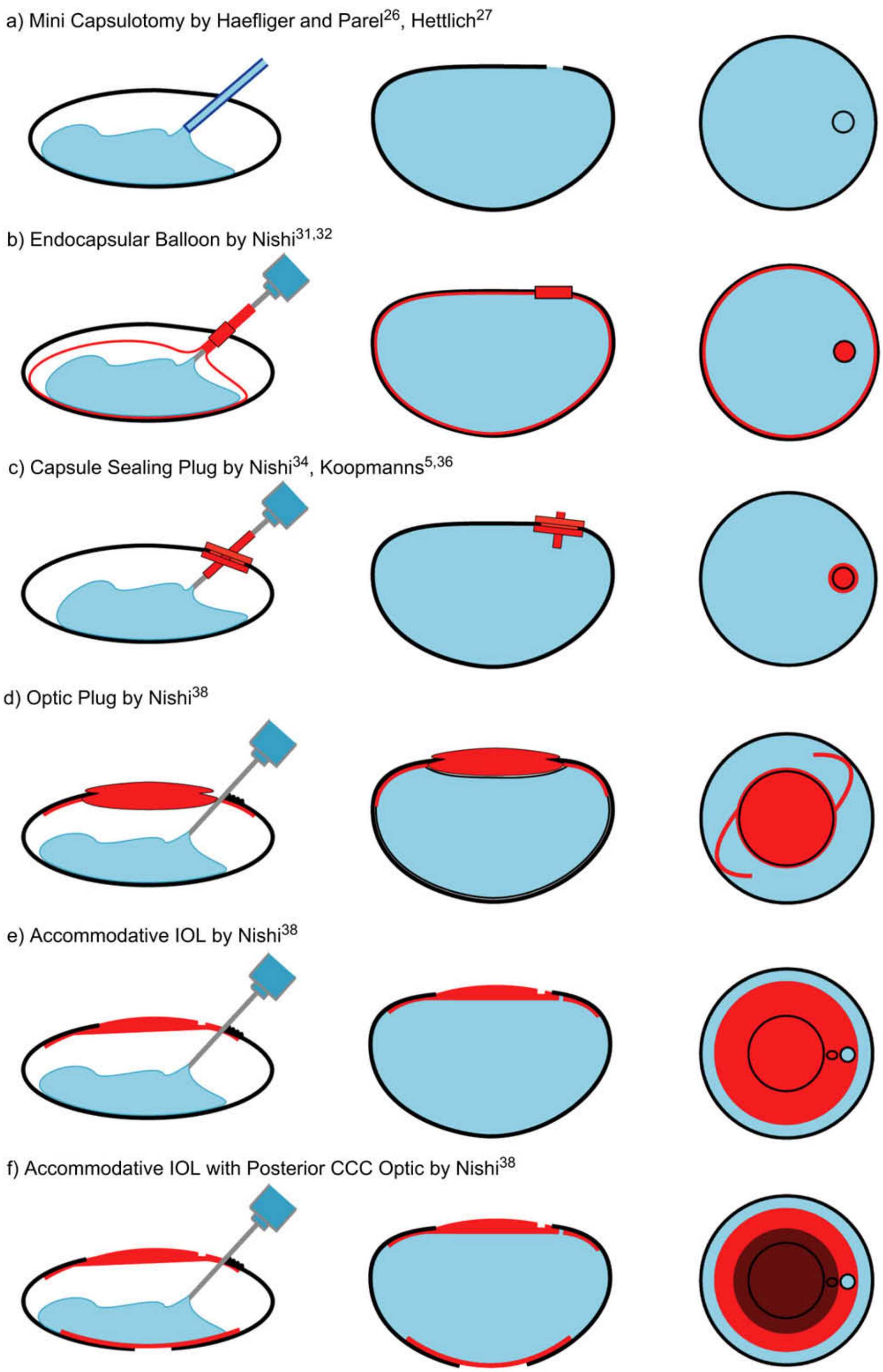

Figure 2. Schematic representation of lens refilling techniques used in animal experiments. Diagrams depict filling technique (*left*) and sagittal (*middle*), and frontal (*right*) views of filled capsular bag with injectable polymers (*blue*) and implanted devices (*red*).

Haefliger et al.[26] (Figure 2, *A*) and Gindi et al.,[28] but the authors mentioned difficulties in attaining complete filling with this strategy. Endocapsular polymerization using ultraviolet light was developed by Hettlich et al.[27] Hettlich et al. used an injectable fluid material which could be polymerized inside the capsule by short light exposure. They demonstrated the safety of this light-induced polymerization, despite the arguments of the potential thermal and photochemical harm of the technique to the eye. In their study, after-cataract development seemed minimal; however, it was not quantified.

Nishi et al.[31,32] (Figure 2, *B*) developed an endocapsular balloon which prevented silicone leakage with reasonable preservation of accommodation. However, this technique sometimes caused a discrepancy between the balloon shape and that of the capsule bag with a resulting compromise in amplitude of accommodation. Also the procedure was considered too complicated for standard clinical application. To improve on the endocapsular balloon technique, a plug to seal a small continuous curvilinear capsulorhexis (CCC) was developed by Nishi and Nishi[34] (Figure 2, *C*) which was also recently used in the study by Koopmans et al.[5,36] Yalon et al.[29] and Assia et al.[37] used an expansible hydroxyethyl methacrylate (HEMA) IOL for refilling the capsular bag in cats and rabbits, respectively. The authors observed excellent centration and a small degree of posterior capsule opacification with this IOL, indicating clinical feasibility of this lens.

Historically, the approaches to prevent leakage of the injected material have not proven to be entirely effective, reproducible, simple, and safe for human application. Recently, Nishi et al.[38] developed a new foldable silicone IOL with a thin plate disk haptic that serves as an optic as well as a plug for sealing the capsular opening (Figure 2, *E*,*F*) (O. Nishi, MD, "Approaches to Future Cataract Surgery; Charles D. Kelman Innovator's Lecture," presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, San Diego, California, USA, April 2007. Abstract available at: http://www.ascrs.org/Meetings/abstract-search-results.cfm?id=16763. Accessed November 4, 2008). A small delivery hole in the haptic and a small, round, cave-like dent at the optic margin served as a positioning pocket. The novelty of this technique is that during the polymer injection, the CCC edge is slightly pulled aside and the silicone injected through the delivery hole into the capsular bag and beneath the IOL. This technique allows the anterior capsule to then cover the injection hole to prevent leakage of the silicone. Also, it may be that due to its buoyancy, the cohesive silicone polymer with its high molecular weight does not leak through the space between the anterior capsule and the IOL. Moreover, the injected liquid silicone polymerized in 2 hours in vitro and, therefore, postoperative leakage may not be expected. However, further studies are required on this design.

Attained Accommodation In Vitro and In Vivo

In a study of primates, Haefliger et al.[26] showed that accommodative changes like those of anterior chamber depth and anterior lens curvature that were similar to those of the natural lens could be attained with silicone filling of the capsular bag when stimulating the ciliary body. The authors stressed the importance and the difficulty of controlling the degree of filling of the capsular bag because of its effect on the amplitude of accommodation and the residual nonaccommodated refractive error. A similar note in terms of the degree of capsular bag filling was described by Nishi et al.[33] They refilled the lens with a silicone volume corresponding to 45%, 55%, 75%, and 95% of the mean normal lens volume. They found that moderate refilling with a volume corresponding to around 60% to 70% yielded a greater amplitude of accommodation than a more complete refill. In that study, zonular tension was created using a simple ciliary stretching ring sutured to the ciliary body. Also, they investigated the effect of volume of silicone injected on capsular shape and its relationship to refraction and amplitude of accommodation. Koopmans et al.[39] also demonstrated a similar relationship between refilled material volume and accommodation amplitude.

Haefliger et al.[26] developed a closed system through which the state of lens inflation could be regulated, thus enabling intraoperative monitoring of the refractive state during the bag refilling procedure.

In the study by Haefliger and Parel,[30] monkeys whose capsules were refilled showed accommodative potential as judged from the changes in anterior chamber depth and anterior lens curvature, but the exact accommodative amplitude was not measured. Lens refilling with an inflatable endocapsular balloon demonstrated 6 diopters (D) of accommodation in one primate eye by measuring the change in refraction after topical pilocarpine with an automated refractometer.[32] Although there was limited after-cataract development shortly after surgery, it progressed to affect vision later. The accommodative amplitude decreased as the capsule fibrosis and opacification developed, suggesting the importance of capsular elasticity in accommodation. Also, the importance of the volume of the injected material for obtaining appropriate postoperative refraction was demonstrated. In the study using 2 types of endocapsular balloons, the one that had the shape of a nonaccommodated lens resulted in a higher amplitude of accommodation than the one that had the shape of a lens in the accommodated state.[40] In this way, the feasibility of lens refilling with an inflatable balloon to achieve some accommodation in monkey eyes was shown.

When refilling the lens using a plug to seal the capsule, only a small fraction of the amplitude of accommodation compared to before surgery was achieved.[34] The authors suggested that it could have been due to the loss of the intracapsular part of accommodation, indicating that full accommodation could not be obtained by refilling the capsule with injectable materials. The rhexis capturing IOL (Figure 2, *D*) that was developed to seal the capsule and prevent anterior capsule opacification often caused iris capture (O. Nishi, MD, "Approaches to Future Cataract Surgery; Charles D. Kelman Innovator's Lecture," presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, San Diego, California, USA, April 2007).

Koopmans et al.[3] applied accommodative forces to refilled and natural lenses by stretching through the zonules and the ciliary body. By means of scanning laser ray tracing, the lens power was calculated. Additionally, the thickness and the diameter of the lens were measured. As expected, the lenses of older eyes showed less ability to change power. In a recent study of rhesus monkeys that had refilling of the lens capsule with a silicone polymer using a plug, a certain level of accommodation was restored.[5] Refraction and accommodation, induced by using carbachol iontophoresis or pilocarpine, were measured using a Hartinger refractometer. In 4 monkeys that did not receive antiinflammatory or after-cataract inhibiting treatment, measurements were successful in only one because of the postoperative inflammation and posterior capsule opacification. In other monkeys, which were intraoperatively treated with a sodium hyaluronate solution containing cycloheximide and actinomycin-D in demineralized water to inhibit after-cataract formation, refraction measurements were successful in all cases. Two of these monkeys achieved stable accommodative amplitudes of 4 D; the other 3 showed almost no accommodation 37 weeks after surgery. As the authors mentioned, the accommodative amplitude achieved in the best cases could be considered to be sufficient for reading purposes in humans.

Young's modulus indicates the stiffness of a given material and is experimentally determined from the slope of a stress strain curve of tensile tests conducted on the sample of the material. Young's modulus can vary depending on the composition of the material. As expected, Koopmans et al.[3] found that the Young's modulus of the silicone polymers used influenced the lens power change.

Further investigations with measurements of accommodative amplitude after lens refilling in aged monkeys that display characteristics similar to those of the human presbyopic eye would be desirable.

CAPSULE TRANSPARENCY, STABILITY, AND AFTER-CATARACT PREVENTION

Capsule elasticity and transparency are mandatory for a successful outcome after lens refilling. After-cataract has been one of the main obstacles to lens refilling as a procedure to treat presbyopia. Following cataract surgery, lens epithelial cells (LECs) proliferate and cause after-cataract in 2 ways: fibrotic and regeneratory after-cataract. The former results mainly in the loss of elasticity of the capsule due to lay down of collagen by myofibroblasts and the latter in compromised visual function due to inhomogeneities caused by Elschnig pearls. Both components of after-cataract play a critical role with lens refilling. We are using the term after-cataract instead of posterior capsule opacification (PCO), as the latter term, even though often used synonymously, actually describes only changes on the posterior capsule.

In modern cataract surgery, fibrotic after-cataract rarely causes clinical problems and regeneratory after-cataract can be treated using neodymium:YAG capsulotomy. However, in the case of lens-refilling, fibrotic after-cataract can severely compromise accommodative function due to a decrease in capsule elasticity and regeneratory after-cataract may be difficult or impossible to treat due to the risk for leakage of refilling material into the posterior segment. This has made after-cataract the main hurdle to be tackled to achieve successful lens refilling. Therefore, the eradication or modulation of LECs is important for after-cataract prevention or control for lens refilling.

In standard cataract surgery, the introduction of IOLs with a sharp optic edge has resulted in a significant decrease in PCO rates,[41] probably due to contact inhibition at the capsule bend created by the optic edge.[42] However, other factors such as IOL optic material and overall design of the IOL also influence PCO development.[41,43] Also, the regeneratory component of PCO with Elschnig pearls has been shown to undergo changes over relatively short periods of time, with an average life-span of pearls ranging from only a few weeks to several months.[44,45]

Cytokines play a role as autocrine and paracrine agents in immunological, reparative and inflammatory reactions. Human LECs produce prostaglandin E^2 (PGE^2) and many kinds of cytokines, some of which have been detected not only in cell culture, but also in the aqueous humor.[46–48] These agents seem to influence the proliferation of LECs after intraocular surgery. Regulation of cytokine activity has been reported to reduce the amount of postoperative PCO.[49] In some cases, good results may be expected; however, probably due to the wide spectrum of cytokines involved, it seems unlikely that PCO prevention can be achieved in all cases.

Mechanical removal of LECs has been attempted using extensive polishing of the capsule with the use of curettes, but these were found to be insufficient for the complete removal of LECs for the prevention of PCO.[50–54]

Several pharmacological means of LEC inhibition have been found to be effective in vitro or in vivo.[55–61] However, when these agents were applied at a sufficient concentration to kill LECs effectively, increased inflammation and collateral toxicity of these agents on corneal endothelial and retinal cells precluded their clinical use.

A special device allowing intraoperative sealed capsule irrigation may turn out to be useful for safely applying pharmaceutical agents to kill LECs.[62–64] Distilled water was reported to be ineffective[63,64] and substances like 5-fluorouracil were shown to reduce PCO development without harm to other tissues, but total LECs eradication was not attained.[65,66]

Gene therapy using virus-mediated vectors for LECs targeting to induce therapeutic apoptosis and after-cataract prevention has been attempted. Malecaze et al.[67,68] has indicated that gene therapy is somewhat effective both in vitro and in vivo but marked inflammation was induced and collateral tissue damage still occurred. Further improvements using the above approaches may allow total and selective LEC eradication.

AFTER-CATARACT AND LENS REFILLING

In the in vivo animal lens refilling experiments, after-cataract was seen to be a major obstacle (Table 1). Only a few studies analyzed opacification of the capsule quantitatively. The endocapsular balloon showed a high rate of PCO long term, just as other lens-refilling procedures without intraoperative attempts to eradicate LECs. In the most recent attempts, Koopmans et al.[5] could show that intraoperative application of cyclohexamide and actinomycin D in demineralized water was effective in delaying PCO formation. Even though refraction measurements were still possible 37 weeks after surgery, they reported reduced optical quality due to opacification of the posterior capsule as well as fibrotic changes in the midperiphery of the posterior capsule.

To ensure long-term efficacy of the lens refilling procedure, probably complete eradication of LECs during surgery will be necessary, whether by pharmacological, gene therapy, or mechanical means. However, it is not entirely clear whether the lens capsule is viable without resident LECs, which are thought to support the capsule.[1] The LECs might be essential for the long-term integrity of the capsule bag after surgery and their total eradication might lead to as yet unrecognized complications such as a delayed onset of zonular disinsertion, leading to subluxation or dislocation of the refilled bag into the vitreous cavity. Furthermore, it is also unknown whether the capsular bag can maintain its biomechanical integrity long term to permit accommodation to occur. In vitro and in vivo models to investigate the capsule bag under conditions of LEC eradication over a long period need to be established. An alternative approach is to attempt to control LEC behavior, both in growth and in morphological appearance. Attempts of controlling regrowth of a crystalline lens in the animal eye indicate that this may be a promising route to pursue.[69]

Currently, we may need to accept that lens refilling will be achievable only with some degree of concomitant after-cataract. The 2 models recently suggested by Nishi et al. might lead to a future clinical application, although some important issues remain to be solved (O. Nishi, MD, "Approaches to Future Cataract Surgery; Charles D. Kelman Innovator's Lecture," presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, San Diego, California, USA, April 2007).[38] One of the suggested models is the implantation of thin anterior and posterior IOLs with sharp edge design, between which the silicone will be injected. The other model uses the posterior IOL to seal a primary posterior CCC made surgically in order to maintain a visual axis free from LEC proliferation (Figure 2, *F*). However, with this design, the necessary changes of curvature of the anterior lens surface now replaced with an IOL optic, may not be achievable. As a possible solution for this problem, the authors suggested using a very thin and soft membranous anterior IOL to allow a forward movement and steepening of the anterior curvature.

Those techniques need further investigation of the attainable accommodative amplitudes, the elasticity and the integrity of the entire capsule, the calculation of the lens power of both the posterior and anterior IOLs, and a long-term follow-up of potential in vivo complications. Postoperative clinical emmetropia may necessitate the need for intraoperative or postoperative refractive corneal surgery or a phakic IOL. Additionally, the development of an intraoperative monitoring device to measure refraction during lens refilling must be developed.

In conclusion, even though the accommodative process is not yet fully understood, animal experiments with lens refilling from the last 3 decades have shown lens shape changes to be attainable in the early postoperative period. Thereafter, after-cataract remains the main obstacle, resulting in both a decrease in lens elasticity and a loss of optical clarity of the capsule. Attempts to eradicate LECs during surgery have not yet been fully successful and a depletion of all LECs may also result in long-term decay in lens capsule integrity.

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First author

Yutaro Nishi, MD

Ocular Repair and Regeneration Biology Department of Pathology, Institute of Ophthalmology, University College London, and Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom.