Capsule opacification after refilling the capsule with an inflatable endocapsular balloon

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ABSTRACT

Purpose: To describe the features of capsule opacification in rabbits and cynomolgus monkeys after the capsules were refilled with an inflatable endocapsular balloon.

Setting: Nishi Eye Hospital, Jinshikai Medical Foundation, Osaka, Japan.

Method: Capsule opacification was evaluated by slitlamp examination, Miyake view, and histopathological examination in 15 eyes of 15 rabbits and 16 eyes of 13 primates from 4 to 32 months after the lens capsule had been refilled.

Results: The incidence of capsule opacification was 94%. In the eyes that did not have lens epithelial cell (LEC) removal, a monolayer of LECs was seen on the posterior capsule when the lens capsule was tautly refilled, whereas a thick layer was seen when the lens capsule was moderately or poorly refilled. In the eyes that had LEC removal, the opacification was generally less marked regardless of the amount of refilling. In two rabbit capsules that were refilled moderately or tautly and had LEC removal, the capsule remained clear. Neodymium:YAG capsulotomy in two eyes did not cause herniation of the injected silicone.

Conclusions: Filling the capsule tautly and removing the LECs effectively reduced capsule opacification but could not completely inhibit LEC migration. This suggests the need for more efficient and thorough LEC removal or even a pharmaceutical approach to prevent capsule opacification after lens refilling. *J Cataract Refract Surg 1997; 23:1548–1555*

Refilling the empty lens capsule while preserving the zonules and ciliary muscles offers the possibility of restoring ocular accommodation.[1–6] We developed an inflatable endocapsular balloon to prevent leakage of the injected biomaterial and to facilitate its injection into the capsular bag.[3–5] We previously confirmed a mean accommodation amplitude of 4.6 diopters in young primate eyes 2 weeks postsurgery,[5] showing the feasibility of using an endocapsular balloon. The obtained accommodation amplitude, however, was a small fraction of the preoperative accommodation, and it decreased over time. The decrease may have been caused by the loss of capsular pliability because of capsular fibrosis. Capsule opacification may

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therefore be an important issue in lens refilling. In this study, we looked at opacification after lens refilling and considered ways to prevent posterior capsule opacification in cataract surgery and intraocular lens (IOL) implantation.

Materials and Methods

Fifteen eyes of 15 rabbits weighing 1.5 to 3.0 kg and 16 eyes of 13 cynomolgus monkeys were involved in this study. The rabbits were treated according to the Association for Research in Vision and Ophthalmology's Statement for Use of Animals in Ophthalmic and Vision Research. The primates were housed at the Yaotsu Breeding Laboratory (Japan EDM, Inc.) where the experiments were performed. The monkeys were treated according to the principles of the Primate Society of Japan.

The lens capsules of the rabbits and monkeys were refilled by a procedure comprising endocapsular phacoemulsification, lens epithelial cell (LEC) removal, insertion of an inflatable endocapsular balloon into the capsular bag, and injection of liquid silicone into the balloon.[4] The walls of the disc-shaped inflatable endocapsular balloon are approximately 20 µm thick and consist of silicone polymer. The balloon is composed of an inflatable optic and a delivery tube (Figure 1).

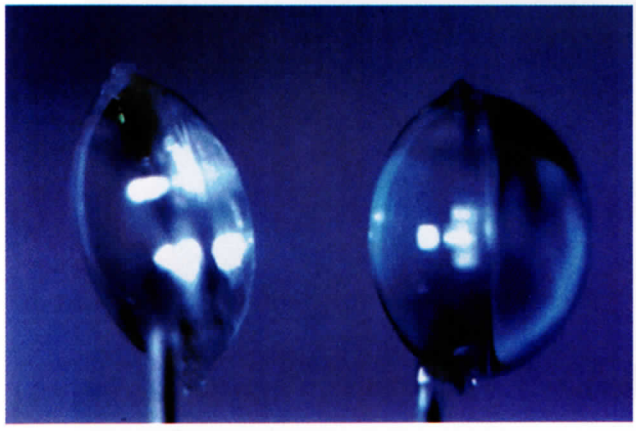

Figure 1. (Nishi) Inflatable endocapsular balloon refilled with the silicone polymer. The delivery tube is filled with a soft, cured silicone that prevents leakage of the injected material. *Left:* Balloon approximating the nonaccommodated state of the crystalline lens (equatorial diameter 8.5 mm). *Right:* Balloon approximating the accommodated state (equatorial diameter 7.5 mm) (reprinted by permission of Archives of Ophthalmology[5]).

The animals were anesthetized with an intramuscular injection of ketamine hydrochloride (5 mg/kg) and xylazine hydrochloride (2 mg/kg). After maximal mydriasis was obtained with topical application of tropicamide and phenylephrine hydrochloride, hyaluronate sodium was injected into the anterior chamber, and a buttonhole capsulotomy or small, circular capsulorhexis (1.2 to 1.5 mm in diameter) was made with a capsulorhexis forceps.

The lens nucleus was emulsified within the capsular bag using a 0.8 mm endocapsular tip (sleeve diameter 1.2 mm) (Cooper Vision). The residual cortex was aspirated using an irrigation/aspiration tip 0.8 mm in diameter. Heparin sodium, 1000 U, and epinephrine, 0.5 mg, were added to 500 mL of balanced salt solution (Alcon Surgical, Inc.) and used for irrigation during the procedures.

Ethylenediaminetetraacetic acid (EDTA), 10 µmol/L, dissolved in hyaluronate sodium (Healon®) was injected into the capsular bag after pure hyaluronate had been injected into the anterior chamber to protect the corneal endothelium. The EDTA chelates calcium and loosens the junctional complexes of the LECs. After 2 minutes, EDTA–hyaluronate and the loosened LECs in the capsular bag were removed with low-level aspiration. Lens epithelial cells at the 12 o'clock position were removed with a Simcoe cannula (American Surgical Instrument Corp.) designed to remove cortex at that position.

After the capsular bag and anterior chamber were filled with sodium hyaluronate, the equator opposite the delivery tube of an endocapsular balloon was grasped with Miyake–Simcoe lens forceps (Inami and Company), and the balloon was introduced into the capsular bag through the 3.0 mm corneal incision and the small upper capsule opening.

The two liquid silicone polymers of polymethyldisiloxane (the main component) and hydrogenpolysiloxane (a cross-linking agent) were mixed at a 2:1 (vol/vol) ratio. The liquid silicone mixture (Menicon Company), which polymerizes in 2 hours in vitro, was injected through the delivery tube with an odontologic syringe injector (Citoject, Bayer Dental Nippon) equipped with a 27 gauge needle. The balloons were filled with 0.15 to 0.25 mL and 0.25 to 0.40 mL of the silicone mixture for primate and rabbit eyes, respectively. After the balloon was filled, the residual air in the

balloon was aspirated through the delivery tube using a 32 gauge needle. The delivery tube was then cut at its root. The tube stump containing the cured silicone was left in place within the wall of the balloon to prevent leakage of the liquid silicone mixture.

Atropine sulfate ointment 1% was applied to the conjunctival sac at the end of the procedure to maintain zonular relaxation. In seven rabbit eyes, the LECs were intentionally not removed.

Slitlamp examination and Miyake view preparations were performed in all animals between 4 and 32 months after surgery. Histopathological examinations were performed in 11 rabbits and all primates. Miyake view and/or histopathological section was prepared after the animal was killed by succinylcholine chloride after the anesthesia described was administered.

The animals were killed in appropriate chronological order to obtain the findings at 6 months and 1, 2, and 3 years after surgery, unless some died spontaneously.

Posterior capsule opacification (PCO) was evaluated by whether LECs were removed and by the quantity of silicone filling.

Two rabbits had a neodymium:YAG (Nd:YAG) capsulotomy (rabbit 2, LECs not removed; rabbit 3, LECs removed, Table 1) before being killed.

Results

The results for rabbits and primates are summarized in Tables 1 and 2, respectively. Primates generally showed less marked PCO than rabbits. The amount of injected silicone varied and was not standardized. This was due to intraoperative technical difficulty and the original bag volume of each rabbit, which could not be measured preoperatively. As a result, the capsular bags were refilled with varying amounts. The amount was eventually expressed as "poor," "moderate," or "taut," according to the thickness of the refilled lenses upon histopathological examination.

Table 1. The results in rabbit eyes that had lens refilling using an inflatable balloon.

Eyes	Follow-up (months)	Silicone Leakage	Amount of Filling	Capsule Opacification	
				Anterior Capsule	Posterior Capsule
Without LEC Removal					
1	5	—	Poor	+++	+++
2	5	—	Moderate	+++	+++
3	6	Minimal	Moderate	++++	++++
4	6	Minimal	Moderate	++	++
5	6	—	Moderate	+	+
6	4	—	Taut	+	−
7	7	Minimal	Taut	−	−
With LEC Removal					
1	10	—	Poor	++	++
2	21	—	Poor	+	+
3	10	—	Moderate	+	+
4	14	—	Moderate	−	−
5	21	—	Moderate	+	+
6	24	—	Moderate	+	++
7	24	—	Moderate	+	+
8	20	—	Taut	−	±

Degree of capsule opacification: + = slight; ++ = moderate; +++ = strong; ++++ = excessive. The amount of filling was determined by the lens thickness at histopathological examination.

Table 2. The results in primate eyes that had lens refilling using an inflatable balloon.

Eyes	Follow-up (months)	Silicone Leakage	Amount of Filling	Capsule Opacification	
				Anterior Capsule	Posterior Capsule
1	7	–	Poor	++	++
2	7	–	Poor	++	++
3	4	+	Moderate	±	±
4	5	–	Moderate	+	+
5	5	–	Moderate	+	+
6	7	–	Moderate	+	++
7	7	–	Moderate	+	±
8	28	–	Moderate	+	+
9	29	–	Moderate	+	++
10	32	–	Moderate	+	+
11	32	–	Moderate	+	+
12	13	–	Moderate	+	+
13	16	–	Taut	+	+
14	28	+	Taut	±	±
15	60	Alive –	Moderate	+	+
16	60	Alive –	Taut	+	+

LEC removal in all animals

Capsule opacification: + = slight; ++ = moderate; +++ = strong; ++++ = excessive. The amount of filling was determined by the lens thickness at histopathological examination.

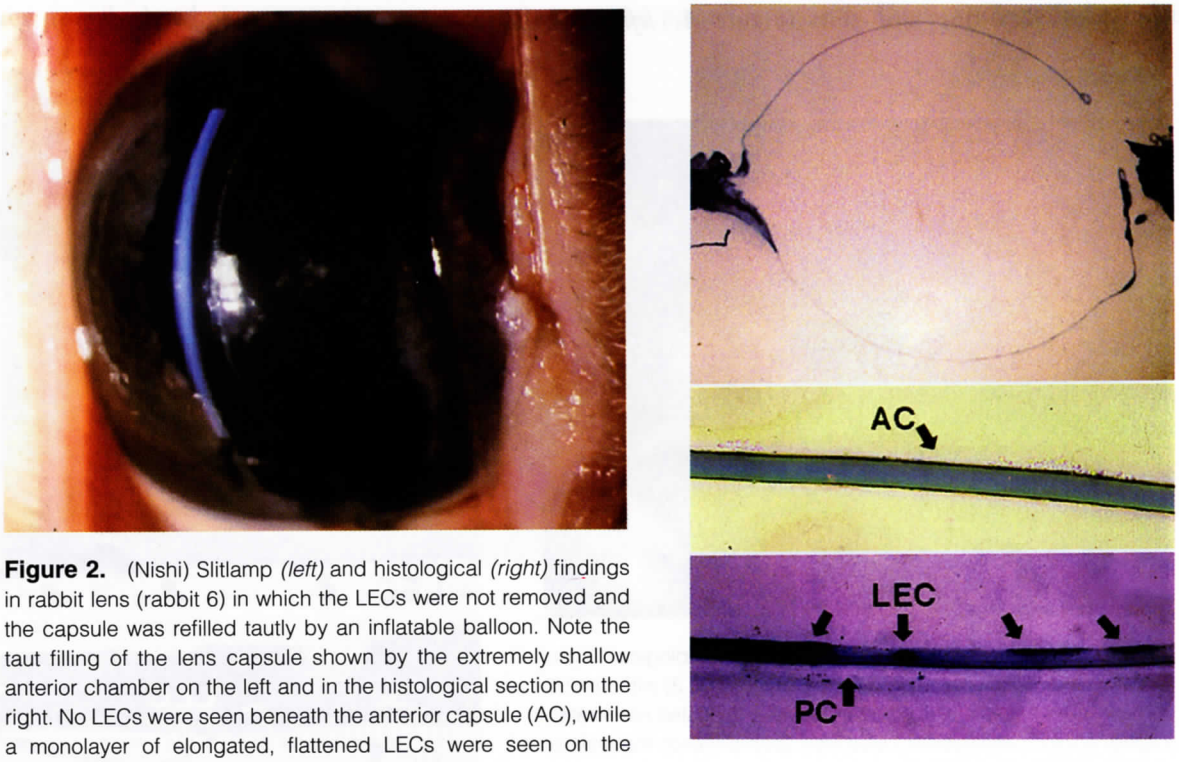

Figure 2. (Nishi) Slitlamp *(left)* and histological *(right)* findings in rabbit lens (rabbit 6) in which the LECs were not removed and the capsule was refilled tautly by an inflatable balloon. Note the taut filling of the lens capsule shown by the extremely shallow anterior chamber on the left and in the histological section on the right. No LECs were seen beneath the anterior capsule (AC), while a monolayer of elongated, flattened LECs were seen on the posterior capsule (PC) *(right, below)*.

Lens Capsules Without LEC Removal

In seven rabbit eyes, the LECs were not removed (Table 1). In two eyes in which the lens capsule was tautly refilled, PCO was apparently not observed by slitlamp examination 1 to 2 months postoperatively (rabbits 6 and 7). Anterior capsule fibrosis was later observed, but it was very thin and fine (Figure 2, *left*). Histopathologically, the LECs formed a monolayer on the posterior capsule. Under the anterior capsule, some cell debris was found, but cells with nuclei and protoplasm were not observed (Figure 2, *right*).

When the lens capsule was moderately or poorly refilled, PCO was observed even 1 week postoperatively and became very thick after several months (rabbits 1 to 5) (Figure 3, *left*). Histopathologically, the LECs formed a thick layer on the posterior capsule (Figure 3, *right*). Beneath the anterior capsule, a few elongated and thin LECs were observed sporadically.

Lens Capsules With LEC Removal

The LECs were removed in 8 rabbit (Table 1) and all primate eyes (Table 2). When the LECs were removed and the lens capsule was tautly or moderately refilled, PCO was initially observed 1 to 2 months postoperatively by slitlamp examination and was thin and weak. Anterior capsule fibrosis was observed much later and was very fine and thin (Figure 4, *left*). Histopathologically, a monolayer of LECs that were thin and elongated or a thin layer that accumulated only near the equatorial region was observed on the posterior capsule (Figure 4, *right*). However, in both rabbit and primate eyes, few cells were found underneath the anterior capsule regardless of the amount of filling, unlike in eyes in which the LECs were not removed. In two rabbit capsules that were tautly or moderately refilled and had LEC removal, slitlamp examination and Miyake view showed a clear capsule even after 1 to 2 years (rabbits 4 and 8) (Figure 5).

When the capsule was poorly filled, PCO was usually observed after 2 to 4 weeks; at the earliest, after 1 week. Anterior capsule opacification was observed later as in the tautly refilled capsule. The LECs formed a multilayer on the posterior capsule (Figure 6). Capsule opacification and LEC proliferation were generally weaker in primate than in rabbit capsules.

Neodymium:YAG Laser Capsulotomy

In the two rabbit eyes in which Nd:YAG capsulotomy was performed, the PCO was so thick it required more than 7.0 mJ of energy and 30 shots to open the central area. The central anterior capsule could be dissected by 3.0 mJ with up to 15 shots. There was no apparent herniation or leakage of the inserted balloon or injected silicone.

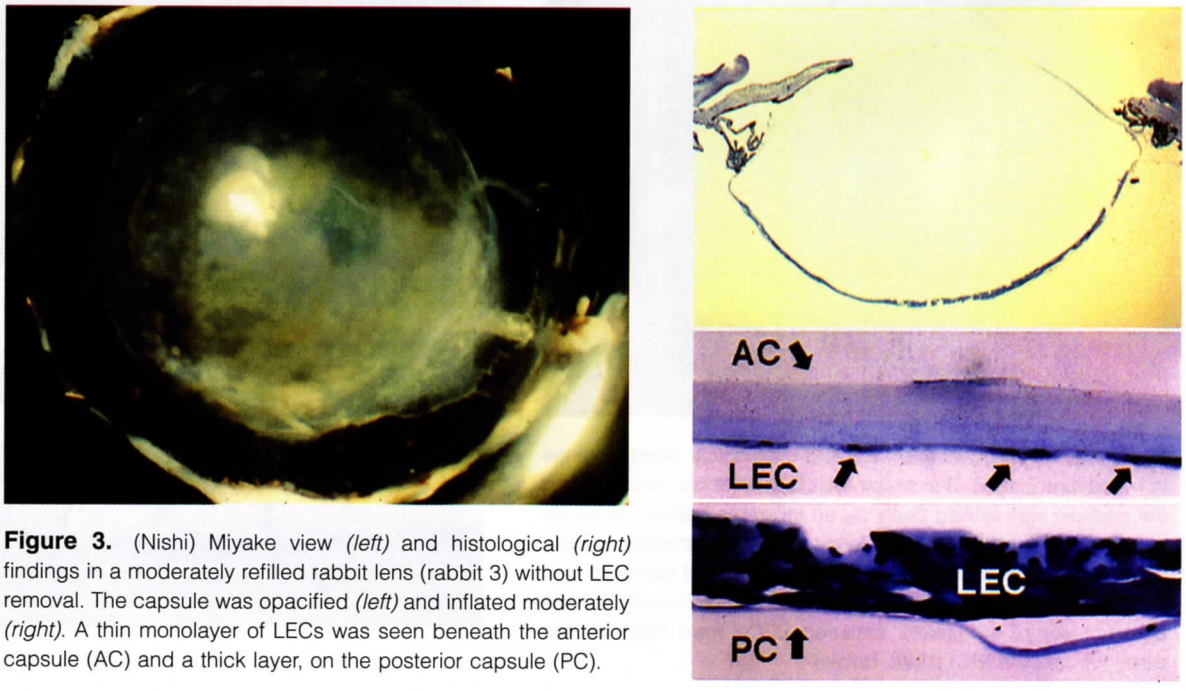

Figure 3. (Nishi) Miyake view *(left)* and histological *(right)* findings in a moderately refilled rabbit lens (rabbit 3) without LEC removal. The capsule was opacified *(left)* and inflated moderately *(right)*. A thin monolayer of LECs was seen beneath the anterior capsule (AC) and a thick layer, on the posterior capsule (PC).

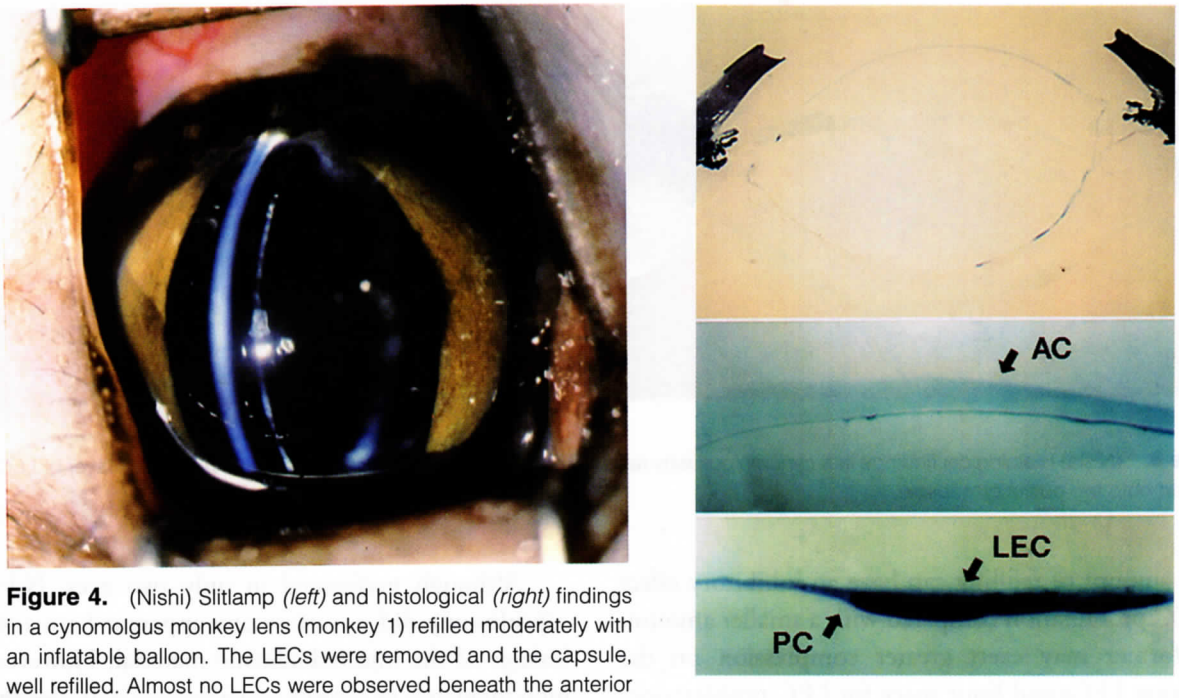

Figure 4. (Nishi) Slitlamp *(left)* and histological *(right)* findings in a cynomolgus monkey lens (monkey 1) refilled moderately with an inflatable balloon. The LECs were removed and the capsule, well refilled. Almost no LECs were observed beneath the anterior capsule. A few LECs accumulated on the posterior capsule near the equatorial region only *(right, below)*.

Discussion

In this study, the incidence of capsule opacification was 94.0% (29 of 31 eyes). Hara et al.[7] also noted a high incidence—all six rabbit eyes that were refilled with the described technique.

When the capsule in the rabbit eyes was tautly refilled, the LECs that migrated onto the posterior capsule usually formed only a monolayer despite their being no LEC removal. When the capsule was refilled moderately or poorly, a thick layer of LECs formed on the posterior capsule. These findings indicated that a

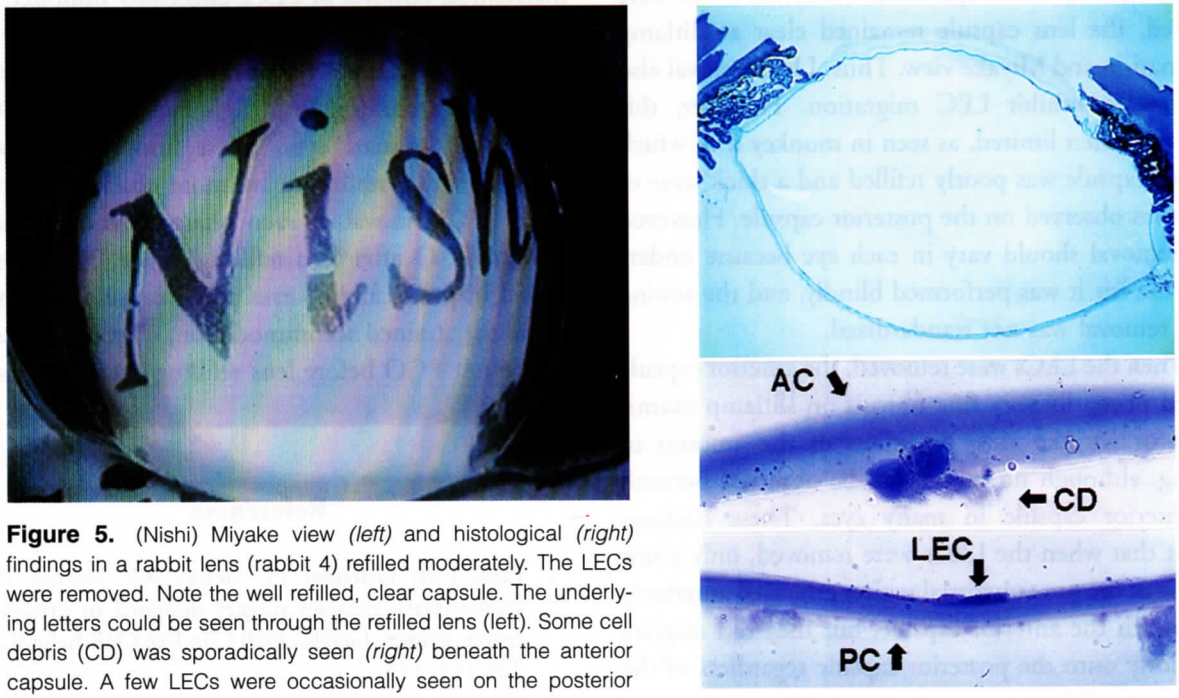

Figure 5. (Nishi) Miyake view *(left)* and histological *(right)* findings in a rabbit lens (rabbit 4) refilled moderately. The LECs were removed. Note the well refilled, clear capsule. The underlying letters could be seen through the refilled lens (left). Some cell debris (CD) was sporadically seen *(right)* beneath the anterior capsule. A few LECs were occasionally seen on the posterior capsule (PC).

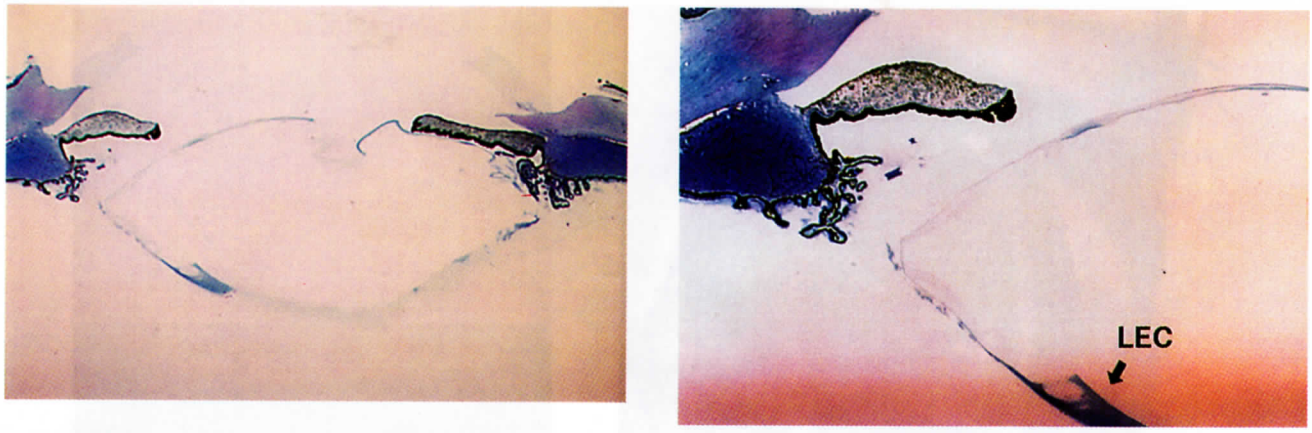

Figure 6. (Nishi) Histological findings in a cynomolgus lens refilled poorly (monkey 2). Despite LEC removal, a thick layer of LECs had migrated onto the posterior capsule.

larger amount of refilling can have an inhibitory effect on LEC proliferation compared with a smaller amount. The former may exert greater compression on the migrating LECs and limit space for LEC proliferation. However, moderate or even taut refilling alone could not completely inhibit LEC migration onto the posterior capsule. This seems to be consistent, because LECs also migrate posteriorly in vivo as a physiological process.

In the eyes from which LECs were removed, there was generally much less PCO and LEC proliferation, and they occurred later than in eyes without LEC removal. In two rabbit eyes from which the LECs were removed, the lens capsule remained clear at slitlamp examination and Miyake view. Thus, LEC removal also appeared to inhibit LEC migration. However, this effect was often limited, as seen in monkey 2 in which the lens capsule was poorly refilled and a thick layer of LECs was observed on the posterior capsule. However, LEC removal should vary in each eye because underneath the iris it was performed blindly, and the timing of the removal was not standardized.

When the LECs were removed, the anterior capsule showed primarily very fine fibrosis on slitlamp examination or Miyake view regardless of the amount of refilling, although no cells could be observed beneath the anterior capsule in many eyes. These findings suggest that when the LECs were removed, only a few of those at the pre-equatorial region migrated anteriorly underneath the anterior capsule, but they did migrate posteriorly onto the posterior capsule regardless of the amount of refilling.

Although performed in only two eyes, Nd:YAG capsulotomy did not cause any apparent herniation or leakage of the injected silicone material. However, the high incidence of capsule opacification indicates that its prevention may be an essential issue in lens refilling, since Nd:YAG laser capsulotomy could annul the accommodation achieved. The results also indicate that PCO might not be completely prevented by "compression" or "no space, no cells" with a conventional IOL, since it cannot fill the capsular bag as tautly as an injectable IOL.

In conclusion, we found that compression and mechanical removal of LECs effectively inhibited LEC migration onto the posterior capsule after the lens capsule was refilled but could not inhibit migration completely, resulting in a high incidence of PCO in rabbit and primate eyes. These findings suggest the need for LEC inhibition by more efficient and thorough LEC removal or even pharmaceutical means to prevent PCO after lens refilling. Since PCO was observed in practically all eyes and a capsulotomy might annul the attained accommodation, we must find a way to prevent PCO before lens refilling can be applied to humans.

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