In Vitro Study on the Closure of Posterior Capsulorrhexis in the Human Eye

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PURPOSE. An unexplained clinical observation is the development of posterior capsular opacification (PCO), even when the central part of the posterior capsule has been removed. The purpose of this study was to investigate in vitro the mechanisms involved in the closure of the posterior capsulorrhexis in a capsular bag model.

METHODS. A sham extracapsular cataract extraction was performed in 71 human donor eyes, followed by a central posterior capsulorrhexis 3 to 4 mm in diameter. Each capsular bag was pinned to a PMMA ring with a central hole of 5 mm and placed in a Petri dish. The capsular bags were cultured and monitored for 3 to 7 weeks by phase-contrast microscopy, after which they were prepared for light, transmission, and scanning electron microscopy.

RESULTS. Proliferation of lens epithelial cells (LECs) within the posterior rhexis area was found in 22 cases (31%) of which 3 had a complete closure. In the absence of the posterior capsule, a monolayer of LECs was observed growing on a basal lamina, consisting of loosely arranged fibers. Further observations on noncultured capsular bags revealed that this basal lamina corresponds to the anterior hyaloid membrane.

CONCLUSIONS. This study corroborates the clinical observation that LECs that remain after cataract extraction have the potential to proliferate, in the absence of their natural substrate, on a basal lamina of vitreous origin and are able to close the posterior capsulorrhexis partially or totally in approximately one third of cases. (*Invest Ophthalmol Vis Sci.* 2003;44: 2076–2083) DOI:10.1167/iovs.02-0525

P osterior capsular opacification (PCO), or after cataract, is the most common cause of reduced visual acuity after extracapsular cataract extraction (ECCE) and intraocular lens (IOL) implantation. The prevalence varies between 4% and 50%, depending on postimplantation follow-up time, the type and material of the IOL used, the surgeon's skill, and the presence of systemic or ocular diseases.[1–5] Factors thought to predispose for PCO include young age, complicated or traumatic surgery,[6] uveitis,[7] and diabetes,[8–11] all of which show an increased risk for postoperative inflammation.

During ECCE, the lens nucleus and cortex are emulsified and aspirated through an anterior circular capsulorrhexis. Lens epithelial cells (LECs) always remain attached to the inner surface of the anterior and equatorial parts of the capsular bag. The posterior capsule is usually free of LECs, but in cases of posterior subcapsular cataracts some additional cleaning of the posterior capsule may be necessary. The LECs on the anterior capsule, seen as small light-scattering areas, can be aspirated. However, it is technically impossible to remove the LECs at the equator of the capsular bag. These remaining germinative LECs will proliferate and migrate across the posterior capsule into the visual axis. They produce cortical material, the Elschnig pearls, or they transform into myofibroblasts and cause a whitish fibrotic opacification and/or contracture (wrinkling) of the posterior capsule in the following years.[12]

For the prevention of PCO, a posterior continuous curvilinear capsulorrhexis (PCCC) has been proposed as an optional step in ECCE.[13,14] It was thought that if the central part of the posterior capsule is removed, the LEC migration stops at the border of the rhexis and the visual axis will remain clear. Although theoretically promising, partial or total closure of the posterior rhexis has been observed in 40% of patients treated, especially in those at risk of postoperative inflammation, such as patients with uveitis, retinitis pigmentosa, and diabetes.[15] Patients have exactly the same symptoms as in normal PCO: increased light-scattering and decreased visual acuity. This is not due to a contraction of the posterior capsule, but to a proliferation of cells in its center. Clinically, three types of secondary proliferation have been observed: a multilayered cellular proliferation corresponding to a classic Elschnig pearl formation, a monolayered cellular proliferation, and a fibrotic proliferation. It is clinically impossible to determine whether these LECs are growing on the anterior hyaloid membrane, on the posterior surface of the IOL, or on a newly formed lamina.[15] The mechanisms for closure of the PCCC are currently not completely understood. We therefore studied the closure of the posterior rhexis zone in an in vitro capsular bag model, described by Wormstone et al.[16]

MATERIALS AND METHODS

A sham cataract extraction was performed on 71 human donor eyes obtained from the Cornea Bank Amsterdam (The Netherlands). The mean age of the donors was 58.3 ± 17.2 years ($\pm$SD; range, 14–80). The postmortem times varied between 12 and 36 hours. The research adhered to the tenets of the Declaration of Helsinki on the use of human tissue in research. After removal of the corneoscleral disc for transplantation purposes, the iris was dissected, an anterior continuous curvilinear anterior capsulorrhexis was performed, followed by hydro-expression of the lens nucleus and aspiration of the remaining cortical lens fibers. The capsular bag was refilled with a saline solution. After a central puncture with a needle, a circular tearing of the posterior capsule with a capsular forceps was initiated. A posterior capsulorrhexis approximately 3 to 4 mm in diameter was performed. To avoid vitreous prolapse, care was taken not to exert pressure on the posterior segment of the eye globe during surgery.

When the capsular bags were prepared under the operating microscope after a PCCC was performed, a shining surface could be identi-
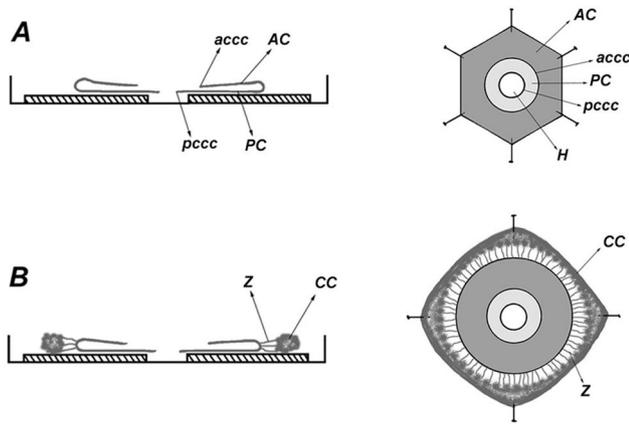
FIGURE 1. Schematic drawings of the in vitro capsular bag models used in this study. Capsular bags are pinned to a PMMA ring placed in a Petri dish in such a way that the posterior capsule does not touch the bottom of the dish. Fixation is performed in two ways: (**A**) pinning of the bag with six needles at the periphery of the capsular bag, through the anterior (AC) and the posterior (PC) capsules, and (**B**) pinning of the ciliary body (CC) attached to the capsular bag by the zonules (Z), on the PMMA ring. H, posterior rhexis area or hole; pccc, posterior continuous circular capsulorrhexis; accc, anterior continuous circular capsulorrhexis.

fied in the posterior rhexis opening in almost all cases. This may be the surface of the hyaloid, which anatomically corresponds to the anterior hyaloid membrane. Because this membrane may have an influence on LEC growth, we carefully grasped and dissected it in the last nine eyes, for further examination. If no interface was visible, we still performed several cuttings in the PCCC opening with surgical scissors, to be sure that even an invisible surface would be disrupted. The bags of these nine eyes were also cultured as described later, to evaluate whether LEC migration would be different compared to the other 62 bags.

The capsular bags were prepared in two ways, with or without corpus ciliare (Fig. 1). The bags were isolated, either by cutting the uvea just behind the ciliary body or by cutting the zonules. The vitreous adhering to the periphery of the capsule, at the level of the ligament of Wieger, was removed. The corpus ciliare or the bag itself was pinned to a sterile polymethyl methacrylate (PMMA) ring by means of four to six needles (Fig. 1). This PMMA ring was then placed in a sterile PMMA Petri dish in such a way that the central 5 mm of the posterior capsule had no contact with the bottom of the Petri dish (Fig. 1) and that the border of the PCCC was free floating in the culture medium.

The capsules were cultured in Eagle's minimal essential medium (EMEM) supplemented with 2% fetal calf serum (FCS) and incubated at 37°C in a 5% CO_2 atmosphere. The culture medium was renewed every 7 days. The growth of the LECs was regularly monitored during the culture period by phase-contrast microscopy.

After 3 to 7 weeks the bags were fixed in 1% paraformaldehyde and 1.25% glutaraldehyde in 0.08 M sodium cacodylate buffer at pH 7.4. The tissue was rinsed in the buffer and dehydrated in a graded series of ethanols. For light microscopy (LM) the tissue was embedded in mounting medium (Technovit 7100; Kulzer, Wehrheim, Germany), cut at 3 μm thickness and stained with toluidine blue. For transmission electron microscopy (TEM) the tissue was postfixed in OsO_4, dehydrated, and embedded in epoxy resin. Ultrathin sections (60–90 nm) were stained with uranyl acetate and lead citrate and inspected by transmission electron microscope (model CM 12; Philips Industries, Eindhoven, The Netherlands). For scanning electron microscopy (SEM) the tissue was immersed in hexamethyldisilazane (Sigma, Poole, UK), dried, and coated with 7 nm platinum. The specimens were evaluated by scanning electron microscope (model XL20; Philips Industries, Eindhoven, The Netherlands). Capsular bags showing signs of infection within the first 7 days were not included in the study ($n = 7$).

To examine the anterior hyaloid specifically, three intact human donor eyes were prepared for SEM, LM, and TEM, after cataract surgery including PCCC. We looked specifically at the anterior hyaloid mem-
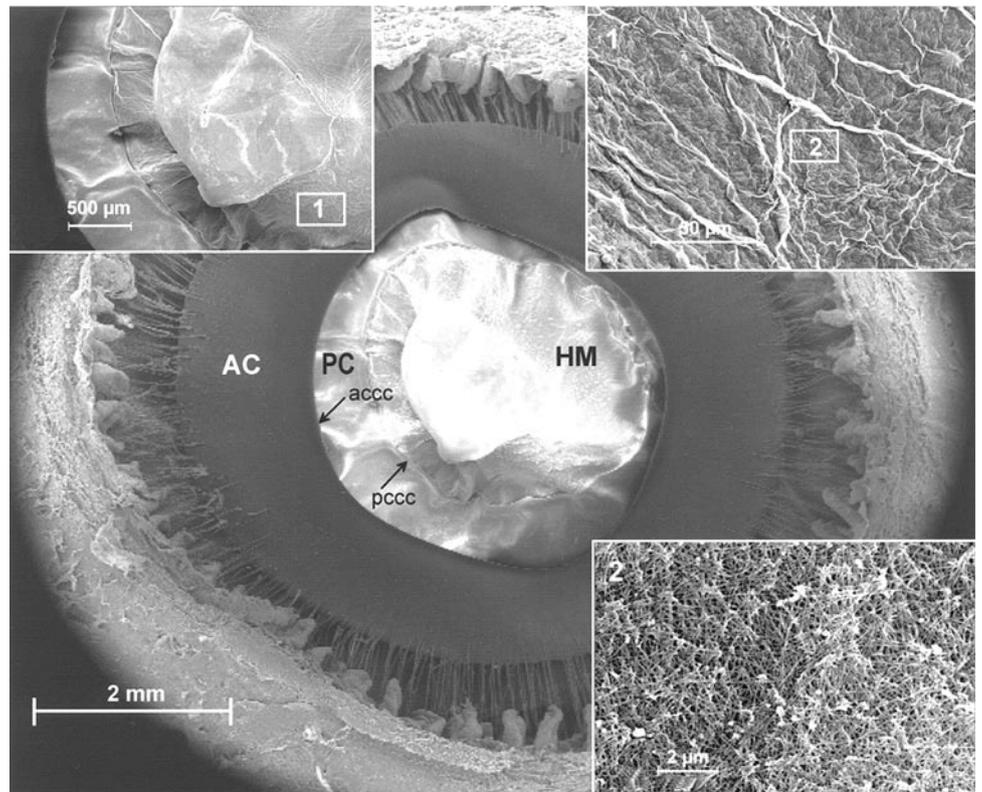
FIGURE 2. SEM micrographs of the surface within the PCCC opening in a noncultured donor eye showing a network of fibers within the PCCC opening. *Top left*: detail of the central part of the hyaloid membrane (HM) viewed at a slightly different angle. *Top right*: medium-power micrograph of the hyaloid membrane in the boxed zone 1; *bottom right*: a high magnification of boxed zone 2, showing the fibrillar network. AC, anterior capsule; accc, anterior continuous circular capsulorrhexis; PC, posterior capsule; pccc, posterior continuous circular capsulorrhexis; HM, hyaloid membrane.
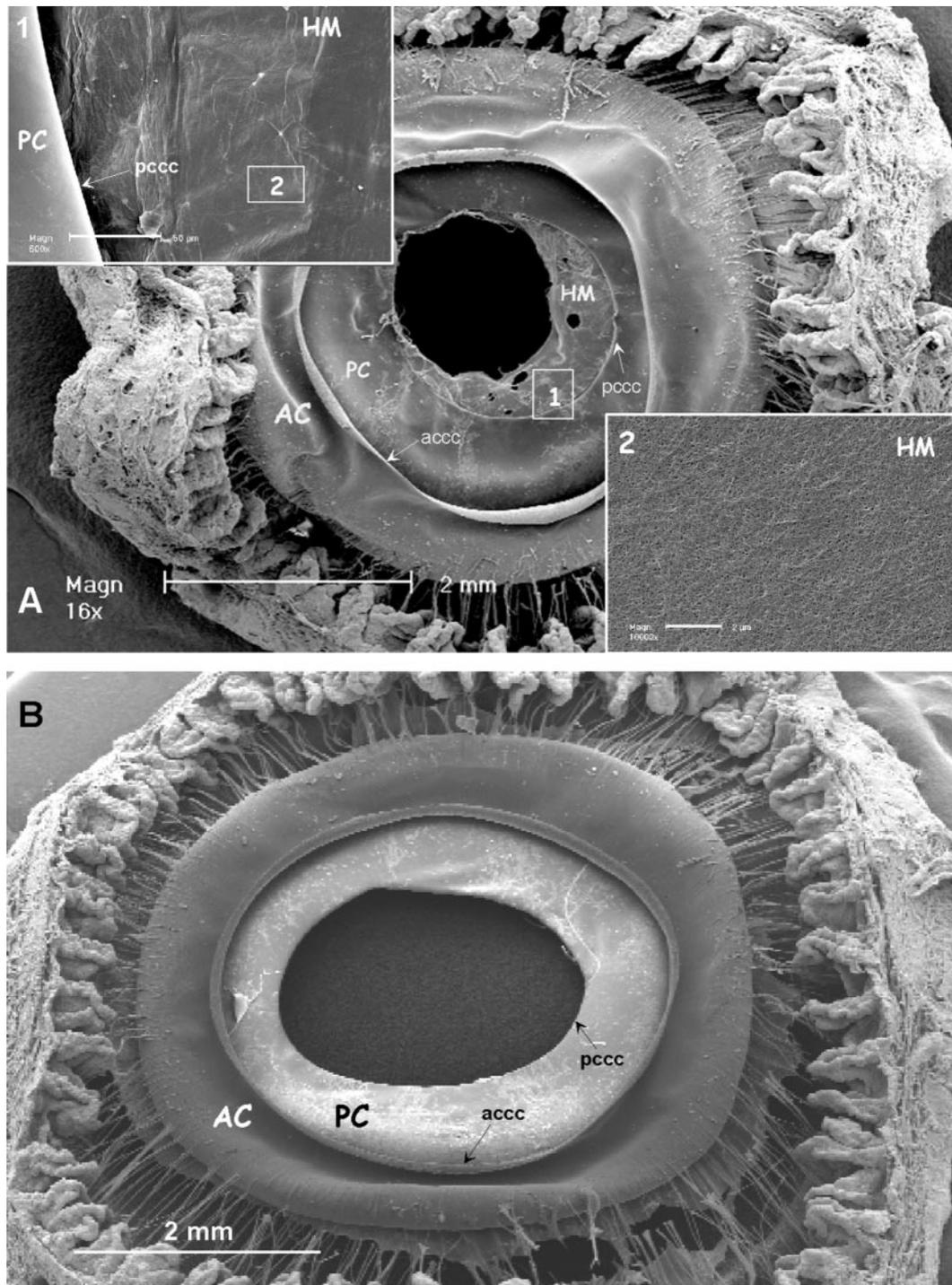
FIGURE 3. SEM micrographs of two capsular bags immediately fixed after being mounted in the Petri dish. (**A**) Bag in which only the peripheral vitreous adhesions were dissected. The anterior hyaloid membrane was still partially present within the PCCC opening. *Top left*: detail of boxed zone 1 with the pccc border and the anterior hyaloid membrane; *bottom right*: high magnification of the anterior hyaloid membrane in boxed zone 2, again showing the fibrillar meshwork. (**B**) Bag in which the central part of the anterior hyaloid membrane (HM) within the PCCC opening was removed or disrupted. No structure was visible in the rhexis opening. The dark material in the hole represents the mounting glue. AC, anterior capsule; accc, anterior continuous circular capsulorrhexis; PC, posterior capsule; pccc, posterior continuous circular capsulorrhexis.

brane facing the PCCC. Two additional capsular bags mounted in the Petri dish were fixed for SEM without culturing: in bag A only the peripheral vitreous adhesions were dissected, as in the first 62 bags; in bag B also the central anterior hyaloid membrane within the PCCC opening was cut, as in the last nine bags.

RESULTS

Microscopic Observations

During the operating procedure, a shiny surface was visible within the PCCC opening in almost all eyes. As shown in the
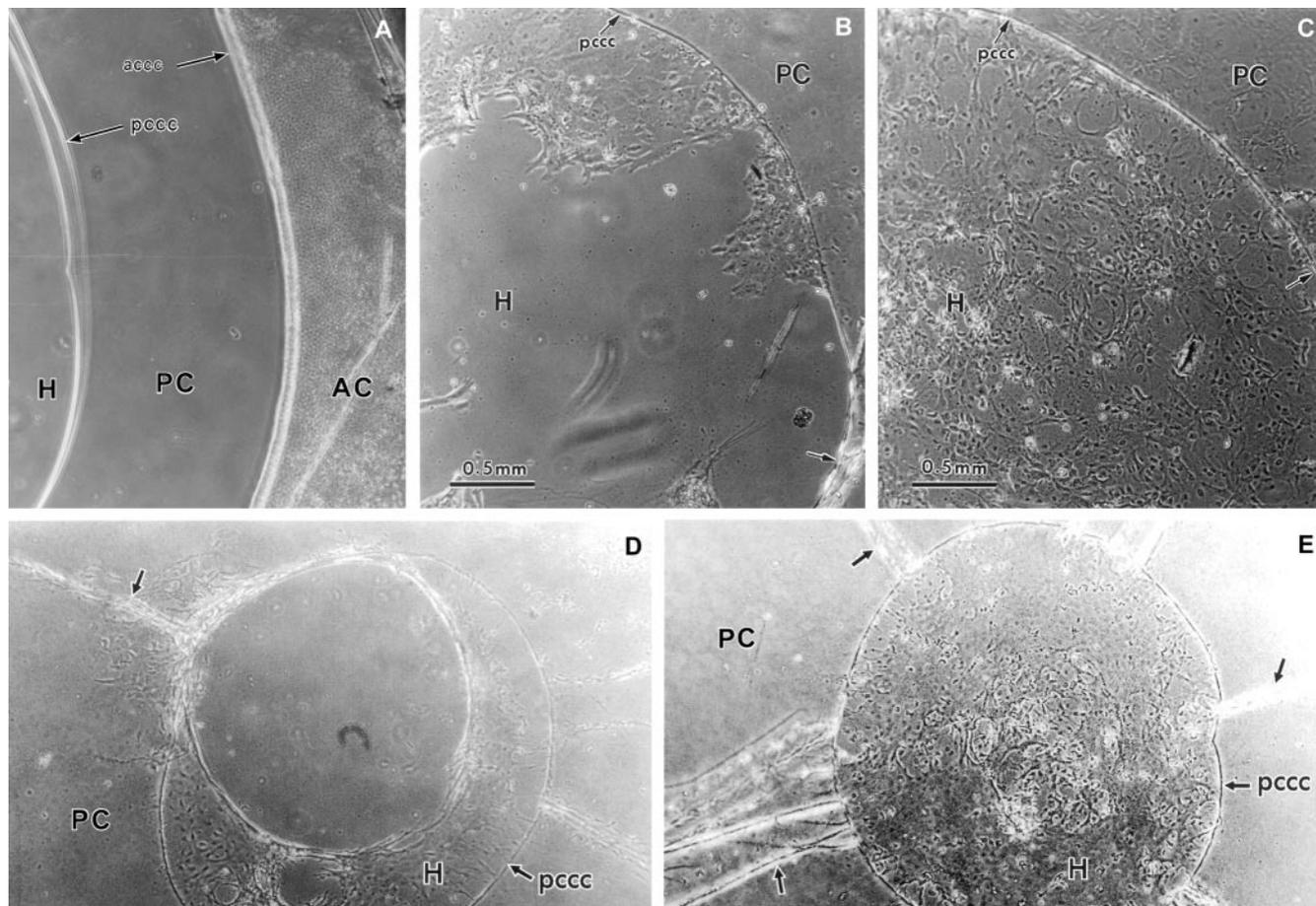
FIGURE 4. Phase-contrast micrographs of an individual capsular bag (**A**) at the start (*t* = 0), (**B**) at 2 weeks, and (**C**) at 4 weeks of culture. Note the LECs on the anterior capsule and the absence of cells on the posterior capsule and in the PCCC at the start; and the progression in closure of the hole (H) up to 4 weeks. Phase-contrast micrographs of two other capsular bags after 4 weeks of culture, showing (**D**) partial and (**E**) full closure. *Arrows*: radial folds in the posterior capsule. accc, anterior continuous circular capsulorrhexis; pccc, posterior continuous circular capsulorrhexis; PC, posterior capsule; AC, anterior capsule.

SEM overview micrographs of the wholemounted donor eyes (Fig. 2), no cells are visible on this surface. After the capsular bag was dissected, all peripheral vitreous adhesions cut, and the bags fixated in the Petri dish, this surface within the PCCC opening was often no longer visible with the operating microscope. It is more difficult and sometimes impossible to see it, because of the absence of the red reflex of the eye fundus. In some cases, the membrane was partially disrupted during the removal of vitreous adhesions, as demonstrated by SEM of a bag immediately fixed in the Petri dish (Fig. 3A). In the bags where the surface was visible, no cells were seen on this surface. In other cases, no membrane was visible (Fig. 3B).

The phase-contrast micrographs of Figure 4, taken from the same bag at the start (*t* = 0; Fig. 4A), and after 2 (Fig. 4B) and 4 (Fig. 4C) weeks in culture, reveal that the posterior capsule and the rhexis area were free of cells at *t* = 0, that the closure of the posterior rhexis started at the posterior rhexis margin, and that the LECs grew centripetally toward the center of the rhexis hole. After 3 to 7 weeks in culture, the posterior rhexis of the bags may exhibit no closure (Fig. 5A), partial closure (Fig. 4D), complete closure (Figs. 4E, 5B), or complete closure with a small hole in the center (Fig. 6).

SEM (Fig. 5B) and TEM (Fig. 7B) micrographs show that the LECs in the hole area formed a layer of cells continuous with those on the posterior capsule. In all bags studied, the anterior and posterior capsule were observed to be sticking closely

together and that the anterior faces of both the anterior and posterior capsules were overgrown by LECs (data not shown). At higher magnification, these cells formed a closed monolayer of polygonal cells. On TEM, we also observed that in some bags, the posterior rhexis margin, or part of it, folded forward (inward) to the anterior face of the posterior capsule (Fig. 7A). The LECs were captured in this fold and did not grow beyond the rhexis margin. Furthermore, high-power micrographs show that the ultrastructure of the LECs growing on the capsule and in the posterior rhexis was rather similar. In the rhexis area, the LECs grew on a lamina of loosely arranged fibers (Fig. 7C). The LECs growing on the posterior capsule and on the lamina both were interdigitating and exhibited endo- and exocytotic vesicles with electron-dense material adherent to it (Fig. 7D). The fine structure of the lamina in the rhexis hole is also illustrated with SEM in Figure 8. It shows that the LECs grew with pseudopodia-like extensions on a meshwork of fibers (Fig. 8A) which can have a tight (Fig. 8B) or a loose (Fig. 8C) aspect.

The origin of the lamina in the posterior rhexis was not evident and could either represent the anterior hyaloid membrane or could be formed de novo by the growing LECs. The SEM observations of the nine carefully dissected anterior hyaloid membranes show a meshwork of tightly or loosely arranged fibers similar to that between LECs growing in the posterior rhexis of the cultured bags. This strongly suggests
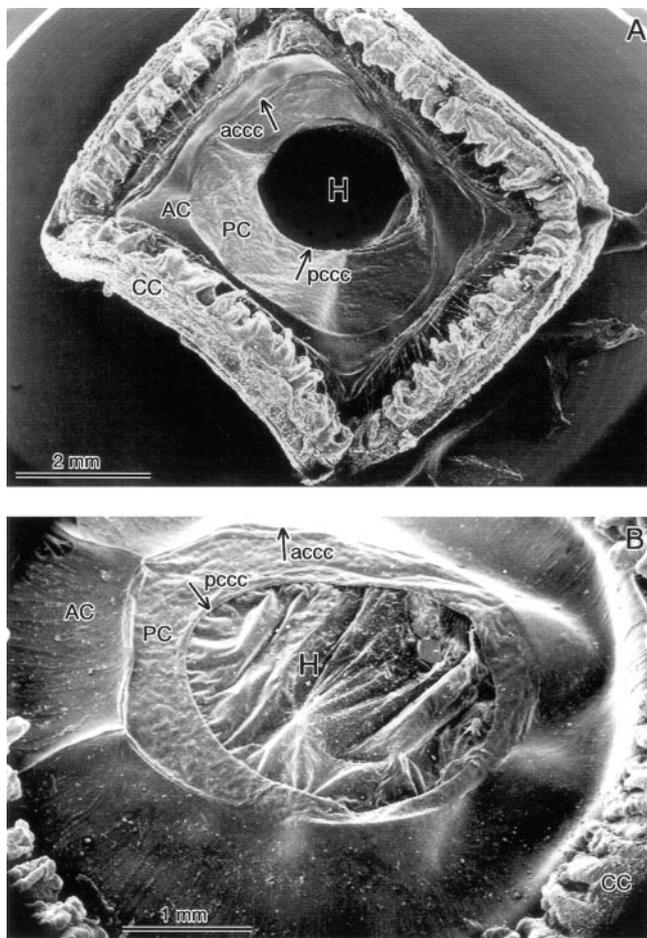
FIGURE 5. SEM overview micrographs of two capsular bags after a 4-week culture period: (**A**) The central posterior rhexis (H) remained open. No structure was visible in this hole. The pins were removed before fixation. (**B**) The posterior rhexis was completely closed, showing a wrinkled aspect of the newly formed tissue. accc, anterior continuous circular capsulorrhexis; pccc, posterior continuous circular capsulorrhexis; CC, ciliary body; AC, anterior face of anterior capsule; PC, posterior capsule.

that the lamina on which the LECs were growing within the rhexis is the anterior hyaloid membrane.

This is further shown by SEM observations of immediately fixed, in situ capsular bags with PCCC, as illustrated in Fig. 2. The structure in the hole area, which certainly is the anterior hyaloid membrane, shows a meshwork of fibers with identical ultrastructural organization and size, as in the lamina within posterior rhexis of the cultured bags (Fig. 8).

SEM of two immediately fixed capsular bags after they were mounted in the Petri dish, showed, in the bag with removal of the peripheral vitreous adhesions, the same structure in the hole area (Fig. 3A). The bag with additional removal of the anterior hyaloid membrane in the PCCC opening, showed no structure in the PCCC opening (Fig. 3B).

Quantitative Results

Closure of the rhexis opening, partial or total, was seen only in the first group of 62 bags without careful surgical removal of the anterior hyaloid within the PCCC opening. In the nine bags with careful removal of the anterior hyaloid membrane, none of the bags showed signs of closure, indicating that the presence of the anterior hyaloid membrane seems to favor the

growth of LECs in the posterior rhexis. The number and percentage of bags with a partially or fully closed posterior rhexis are summarized in Table 1.

If we consider the 62 bags without careful surgical removal of the anterior hyaloid membrane within the PCCC opening and compare the partial or total closure rate between the bags cultured with ciliary body and the bags without ciliary body, no significant difference was obtained. The mean age of the 21 bags showing partial or full closure was 50.7 ± 16.6 years and that of the 50 bags showing no closure at all was 61.5 ± 16.6 years. In the first group, 48% of the donors were younger than 50 years; in the second group, only 17% were younger than 50 years. This difference is significant ($P = 0.021$, nonpaired t-test) and indicates that younger age may be a factor in closure of the posterior rhexis.

DISCUSSION

In a previous clinical study[15] we observed that in vivo closure of the posterior rhexis was caused by proliferation of newly formed tissue within the rhexis area. Closure rate was higher in patients at risk of inflammation—for example, due to diabetes, uveitis, or their youth. However, it was impossible to determine the matrix on which the LECs were growing. The most likely hypothesis is that these cells use the anterior surface of
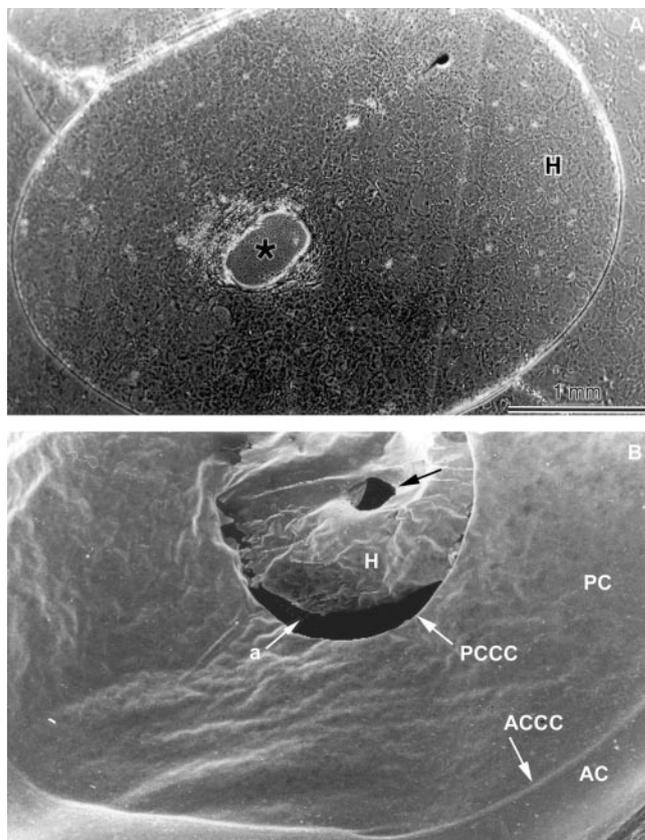

FIGURE 6. Phase-contrast (**A**) and SEM (**B**) micrographs of a posterior rhexis area (H) completely closed by LECs after 4 weeks of culture. Only a very small semicircular area remained open (**A**, ✶). No structure was visible in this hole. The opening (**B**, *arrow*) is probably due to a hole in the anterior hyaloid membrane after puncture of the posterior capsule. pccc, posterior continuous circular capsulorrhexis; accc, anterior continuous circular capsulorrhexis; a, the *dark* area at the pccc in the lower part is an artifact due to rupture of the tissues during the manipulation.
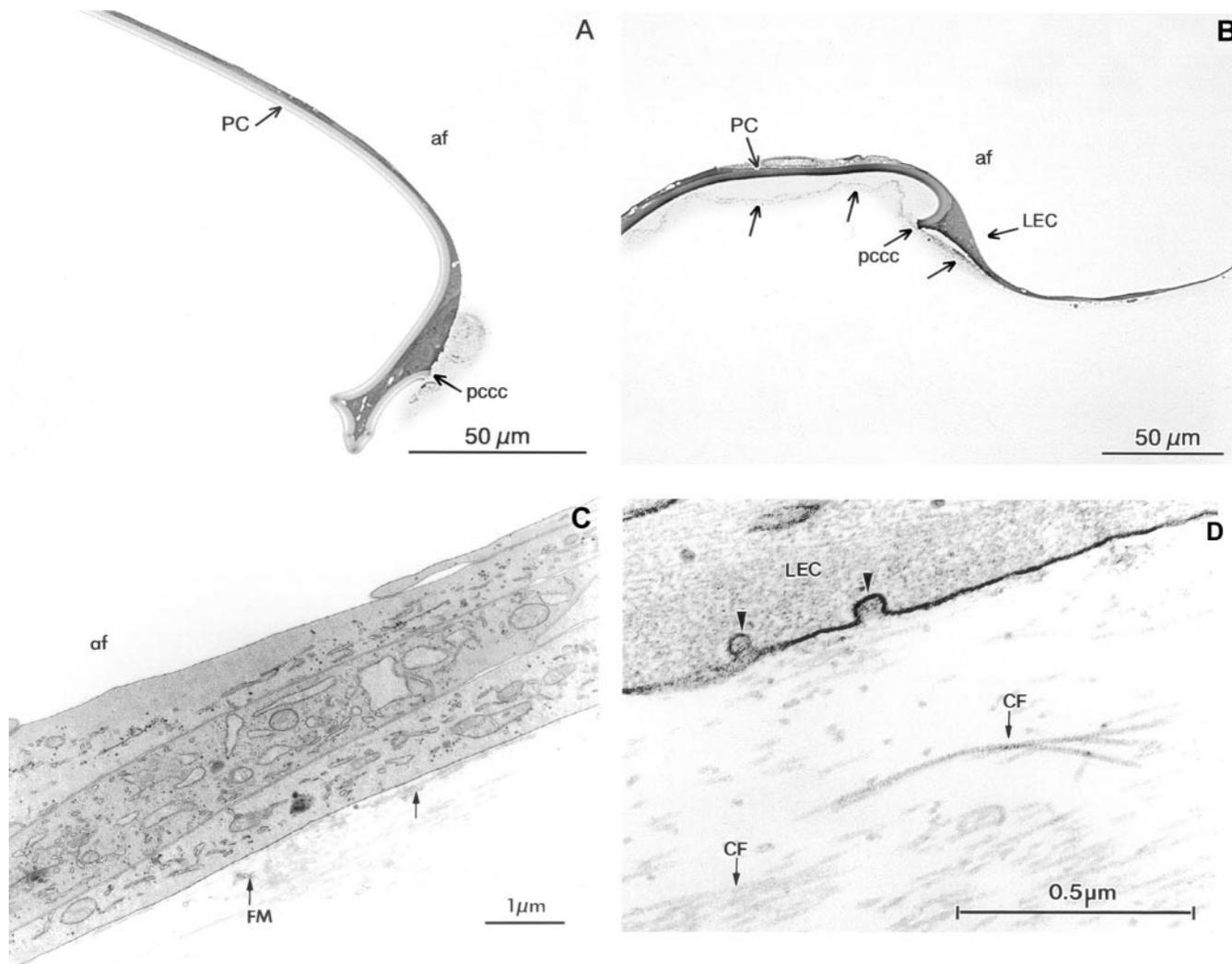
Figure 7. (**A**) LM micrograph of a posterior capsulorrhexis margin (pccc) folding back to its own inner surface. LECs are unable to grow beyond the rhexis margin. (**B**) LM micrograph of the capsulorrhexis margin of a capsular bag with a surface folded slightly backward. The LECs formed a layer beyond the rhexis margin in the hole. The faintly stained material (*arrows*) underneath the posterior capsule, which extends beyond it, seemed to support the growing LECs. (**C**) Medium-power EM micrograph of LECs growing within the central rhexis area. The latter are growing on loosely arranged fibrous material (FM, *arrows*) at the posterior face of the capsule. Note the well-preserved ultrastructure of the cytoplasm indicating that these cells are vital. Further note the interdigitating neighboring LECs. (**D**) High-magnification TEM micrograph showing LECs growing on the loosely arranged basal lamina. Note the endo- or exocytotic vesicles along the cell borders facing the basal lamina (*arrowheads*). af, anterior face; CF, collagen fibers; PC, posterior capsule.

the vitreous or a newly formed lamina they create themselves as a surface on which to grow. The posterior surface of the IOL was also considered, although with low probability. Another question is why closure occurred in a restricted number (40%) of patients.[15]

Our results indicate that LECs in vitro have the potential to grow beyond the margin of a posterior rhexis, and in the present study this occurred in approximately 34% of the cultured capsular bags if the anterior hyaloid membrane was not carefully dissected and therefore remained largely intact. This percentage is rather close to the 40% found in the clinical study mentioned.[15] The reason that roughly one of three capsular bags with PCCC closed and that some showed partial and others total closure is not known. A higher closure rate occurs in eyes of young donors, which is in line with previous clinical observations[15] and with in vitro observations that LECs have a higher growth potential in young donor lenses.[16] Because no IOL was implanted in this in vitro study, the hypothesis that the

IOL is the substrate for LEC growth can be rejected. However, this does not exclude a potential inhibitory or excitatory influence of the IOL biomaterials on LEC proliferation.

When looking at the posterior rhexis margin, a point to be addressed is to which extent the configuration of the rhexis margin affects PCCC closure. In LM and TEM we observed that the PCCC margin can take three configurations: straight, slightly folded backward to the vitreous (Fig. 7B), or fully folded forward to its anterior surface (Fig. 7A). At the sites where the sections were taken, bags showing partial or full closure had either a straight or a slightly backward-folded posterior rhexis border. In the sections were no outgrowth on the posterior lamina was found, the rhexis margin was always fully folded forward. From this latter we can conclude that if the rhexis border is folded inward at some site, the LECs are trapped in these folds, making it impossible for them to migrate onto the lamina. Because of this, it can be postulated that partial closure may occur because the rhexis margin of an
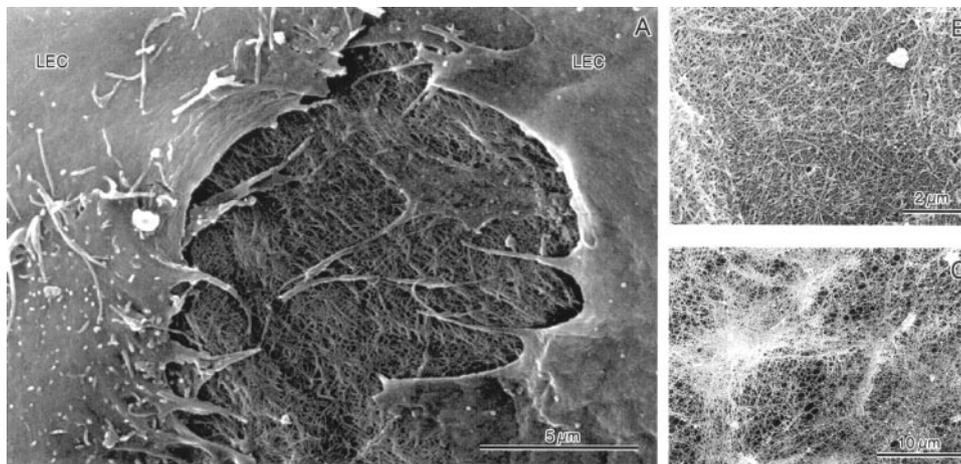
FIGURE 8. (**A**) SEM micrograph showing the posterior rhexis of a partially closed bag. LECs within the hole are growing on a surface of fibers, which can have a tight (**B**) or a loose (**C**) aspect, similar to the anterior hyaloid membrane in Figure 2.

individual bag is not always uniform (it can be straight at one site and folded at the opposite site) and that in fully closed holes, the margin must have been straight along all or most of its outline. This is a mechanical explanation for the inhibition of the outgrowth of LECs in the posterior hole. But because not all capsular bags with a straight rhexis border showed closure, other factors must also be involved in the control of LEC proliferation.

An important point of discussion concerns the origin of the surface on which the LECs are able to grow within the PCCC area. Phase-contrast and SEM observations show that LECs migrated from the margin of the posterior rhexis and across the whole rhexis area on a substrate present within the PCCC area. At higher magnification this substrate looks like a lamina composed of loosely or densely arranged fibers. LM and EM also confirmed the presence of these fibers within the posterior rhexis on top of which the LECs formed a well-aligned, closed monolayer. Looking with phase-contrast microscopy, at bags in early stages of culture and with partial closure, it is evident that the LECs are growing on a preexisting structure. It is very likely that this structure is the anterior hyaloid membrane. From the morphologic observations on carefully dissected anterior hyaloid membranes and from the wholemounted eyes in which the anterior hyaloid membrane was examined through the PCCC opening, it can be concluded that the anterior hyaloid membrane has an ultrastructure identical with that of the lamina within the rhexis area on which the LECs grow in culture. Hogan[17] showed the ultrastructure of the peripheral part of the anterior hyaloid facing the ciliary body, which closely resembles our observations. As far as we know, the ultrastructure of the central part of the anterior hyaloid facing the posterior capsule has never been published. Because the dissected membranes and the structure in the rhexis area of the wholemounts represent, without doubt, the anterior hyaloid membrane, it seems fully justified to conclude that the

substrate on which the LECs grow in culture is the anterior hyaloid membrane. SEM of the immediately fixed bags mounted in the Petri dish confirmed that the anterior hyaloid membrane can still be present in bags where only the peripheral vitreous adhesions were dissected (Fig. 3).

This observation helps explain the presence of a small hole in one bag showing nearly complete closure (Fig. 6). This small hole corresponds to the location where the puncture of the posterior capsule was performed before the posterior rhexis. When the anterior hyaloid membrane and the posterior capsule were strongly adherent, both were punctured simultaneously, creating a hole in the anterior hyaloid membrane on which the LECs were unable to grow.

It is known that LECs produce matrix proteins for the capsule, including procollagens.[18] The presence of small exo- and/or endocytotic vesicles at the base of these cells is in support of this observation. Because the anterior hyaloid is also composed of collagen fibers, one could hypothesize that the LECs continue their role as procollagen producers to support the anterior hyaloid membrane in the absence of their natural basal membrane, the posterior capsule.

Based on the present findings, we postulate that the anterior hyaloid membrane is the structure that guides the growth of LECs in the absence of the posterior capsule. The fact that the anterior capsulorrhexis never shows closure, unless in the presence of special biocompatible IOLs, supports the idea that closure of the PCCC occurs because of the presence of another basal lamina—namely, the anterior hyaloid membrane—taking over the role of the natural substrate.

A point to be addressed in a separate study is to what extent the macromolecular (collagen) composition of the anterior hyaloid membrane is similar to that of the posterior capsule, showing the cross biocompatibility of these structures for LEC growth. Another point of interest is whether the natural anatomic variation in the depth of the space of Berger[19] and the

TABLE 1. Quantitative Results on the Closure of the PCCC Opening in the Different Setups of the Capsular Bag Model

Experimental Set-up	*n*	Partial Closure	Full Closure
Group I: without removal of the anterior hyaloid			
A, without corpus ciliare	29 (100)	9 (31)	2 (7)
B, with corpus ciliare	33 (100)	9 (27)	1 (3)
Total	62 (100)	18 (29)	3 (5)
Group II: with removal of the anterior hyaloid in the PCCC	9	0	0
Total	71 (100)	18 (25)	3 (4)

Data are number of eyes with percentage of the total in parentheses.

adherence of Wieger's ligament[20,21] to the posterior capsule may be responsible for the fact that only approximately one of three capsular bags with PCCC show partial or full closure of the rhexis area in vivo.

CONCLUSION

This in vitro study demonstrates that, after a posterior capsulorrhexis, LECs have the potential to proliferate beyond the margins of the rhexis. It further demonstrates that LECs grow on the anterior hyaloid membrane and excludes the idea that LECs need the posterior surface of the IOL optic to grow on. In one third of the capsular bags studied, partial or full closure of the posterior capsulorrhexis opening was observed.

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