Secondary Cataract

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5.16

Definition: Secondary cataract, also known as posterior capsule opacification (PCO), is the most common complication after cataract surgery, resulting from migration and proliferation of residual lens epithelial cells (LECs) onto the central posterior capsule, leading to decrease in visual function, and ultimately in visual acuity. Opacification within the capsular bag may also present as anterior capsule opacification (ACO) or interlenticular opacification (ILO).

Key features

- Caused by migration and proliferation of residual lens epithelial cells
- Treatment is most commonly Nd:YAG laser
- May be exacerbated or ameliorated via surgical technques and specific lens design

INTRODUCTION

Secondary cataract or posterior capsule opacification (PCO) is the most common post-operative complication of cataract surgery. Its incidence has decreased over the past few decades as the understanding of its pathogenesis has evolved. Advances in surgical technique, intraocular lens (IOL) design and materials have all contributed to the gradual decline in PCO incidence. However it remains a major cause of decreased visual acuity after cataract surgery, occurring at a rate of between 3–50% in the first five post-operative years.[1]

PATHOGENESIS

PCO results from migration and proliferation of residual lens epithelial cells (LECs) onto the central posterior capsule. When the cells invade the visual axis as pearls, fibrotic plaques, or wrinkles, the patient experiences a decrease in visual function, and ultimately in visual acuity.[2] The epithelium of the crystalline lens consists of a sheet of anterior epithelial cells ('A' cells) that are in continuity with the cells of the equatorial lens bow ('E' cells). The latter cells comprise the germinal cells that undergo mitosis as they peel off from the equator. They constantly form new lens fibers during normal lens growth. Although both the anterior and equatorial LECs stem from a continuous cell line and remain in continuity, it is useful to divide these into two functional groups. They differ in terms of function, growth patterns, and pathologic processes. The anterior or 'A' cells, when disturbed, tend to remain in place and not migrate. They are prone to a transformation into fibrous-like tissue (pseudo-fibrous metaplasia).

In contrast, in pathologic states, the 'E' cells of the equatorial lens bow tend to migrate posteriorly along the posterior capsule; e.g., in posterior subcapsular cataracts, and the pearl form of PCO. In general, instead of undergoing a fibrotic transformation, they tend to form large, balloon-like bladder cells (the cells of Wedl). These are the cells that are clinically visible as 'pearls' (Elschnig pearls). These equatorial cells are the primary source of classic secondary cataract, especially the pearl form of PCO. In a clinical study by Neumayer and coworkers, significant changes in the morphology of Elschnig pearls were observed within time intervals of only 24 hours. Appearance and disappearance of pearls, as well as progression and regression of pearls within these short intervals illustrate the dynamic behavior of regeneratory PCO.[3]

The 'E' cells are also those responsible for formation of a Soemmerring's ring, which is a doughnut-shaped lesion composed of retained/regenerated cortex and cells that may form following any type of disruption of the anterior lens capsule. This lesion was initially described in connection with ocular trauma. The basic pathogenic factor of the Soemmerring's ring is the anterior capsular break, which may then allow exit of central nuclear and cortical material out of the lens, with subsequent Elschnig pearl formation. A Soemmerring's ring forms every time any form of extracapsular cataract extraction (ECCE) is done, whether manually, automated, or with phacoemulsification (phaco). For practical purposes it is useful to consider this lesion as the basic precursor of classic PCO, especially the 'pearl' form. The LECs have higher proliferative capacity in the young compared with the old, therefore, the incidence of PCO formation is higher in younger patients.

The same cell types mentioned above are also involved in other processes of opacification within the capsular bag (Fig. 5-16-1). These include anterior capsule opacification (ACO),[4,5] and interlenticular opacification (ILO).[6,7] This latter is the opacification of the space between two or more IOLs implanted in the bag (piggyback implantation).

Treatment and Prevention

The treatment of PCO is typically neodymium:YAG (Nd:YAG) laser posterior capsulectomy. This is a simple procedure in most cases, but is not without risks. Complications include IOL damage, IOL subluxation or dislocation, retinal detachment, and secondary glaucoma.[8] Therefore, prevention of this complication is important, not only because of the risks associated with its treatment, but also because of the costs involved in the procedure. Extensive research has been performed on the inhibition of LEC proliferation and migration by pharmacologic agents through various delivery systems, or IOL coatings, in vitro and in vivo animal studies.[9–11] Use of pharmacological and non-pharmacological agents for this purpose in an unsealed system may increase the risk of toxicity to surrounding intraocular structures, especially corneal endothelial cells. The PerfectCapsule™, a silicone device that reseals the capsular bag allowing isolated safe delivery of irrigating solutions into its inner compartment, was therefore developed.[12] Immunotherapy and gene therapy, as well as physical techniques to kill/remove LECs have also been investigated.[13,14] We have evaluated in our laboratory the efficacy of a Nd:YAG laser photolysis system in removing LECs using human cadaver eyes. Light microscopy and immunohistochemistry revealed that the laser photolysis system removed LECs from the anterior lens capsule and capsule fornix. Along with the cells, laminin, fibronectin, and cell debris remained in the untreated areas but were removed by the treatment, which may be useful for PCO prevention.[14]

While basic research on an effective mechanism for PCO eradication evolves, the practical surgeon can already apply some principles to prevent it.[15] Studies done in our laboratory, as well as clinical studies done in other centers, have helped in the definition of three surgery-related factors that help in the prevention of PCO:

- Hydrodissection-enhanced cortical clean-up,
- In-the-bag IOL fixation, and
- Performance of a capsulorrhexis slightly smaller than the diameter of the IOL optic (Fig. 5-16-2).

The same studies helped in the definition of three IOL-related factors for PCO prevention:

- Use of a biocompatible IOL to reduce stimulation of cellular proliferation,
- Enhancement of the contact between the IOL optic and the posterior capsule, and
- An IOL with a square, truncated optic edge.

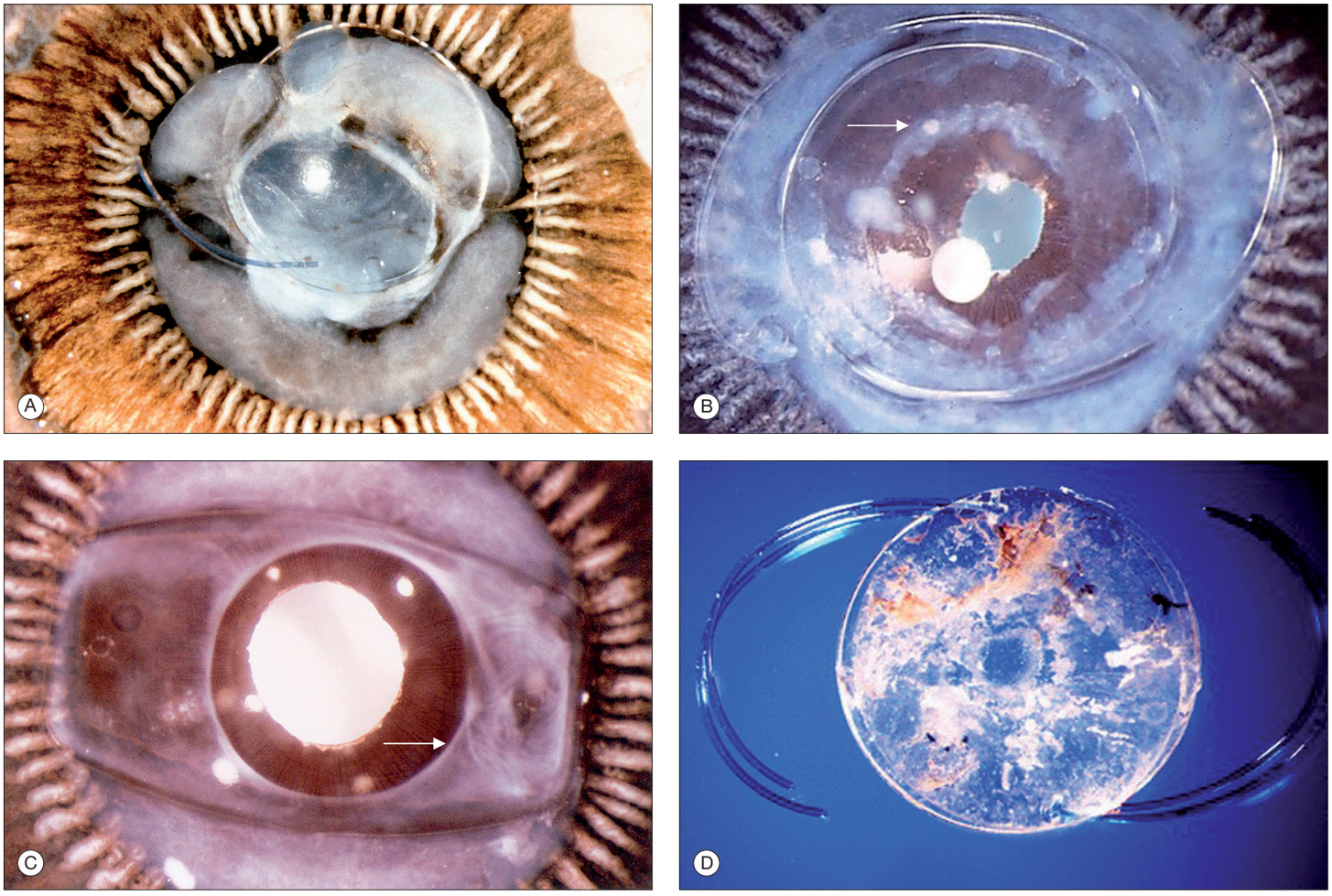

Fig. 5-16-1 Different forms of opacification within the capsular bag. A: Human eye obtained postmortem (posterior or Miyake-Apple view) implanted with a rigid lens, showing asymmetric fixation, and decentration. A doughnut-shaped, white lesion can be seen for 360° in the equatorial region of the capsular bag (Soemmerring's ring), and the posterior capsule is fibrotic. **B**: Human eye obtained postmortem (posterior view) implanted with a rigid lens. Soemmerring's ring is also present. A posterior capsulotomy had been performed for posterior capsule opacification, and proliferation of Elschnig pearls can be seen at the edges of the capsulotomy (arrow). **C**: Human eye obtained postmortem (posterior view) implanted with a foldable, plate silicone lens. The anterior capsule is fibrotic (arrow). Although Soemmerring's ring formation can be seen, the posterior capsule is not opacified. **D**: Pair of foldable, hydrophobic acrylic lenses explanted because of interlenticular opacification. The lenses are fused together through the material within the interlenticular space.

Hydrodissection-enhanced cortical clean-up

Howard Fine introduced this technique and coined the term cortical cleaving hydrodissection. The edge of the anterior capsule is slightly tented up by the tip of the cannula, while injecting the fluid. The technique is used by many surgeons to facilitate cortex and equatorial LEC ('E' cell) removal, also enhancing the safety of the operation. Experimental studies used different solutions during the hydrodissection step of the phacoprocedure, e.g., preservative-free lidocaine 1%, antimitotics, etc.[18] Further studies are necessary to establish the safety and utility of these solutions in terms of PCO prevention.

While a careful cortical clean up and elimination of as many 'E' cells as possible is fundamental in reducing the incidence of PCO, the role of anterior capsule polishing and elimination of 'A' cells remains to be demonstrated. Indeed, Sacu and colleagues have performed a randomized, prospective study to evaluate the effect of anterior capsule polishing on PCO.[16] The anterior capsule was extensively polished in one eye and was left unpolished in the other eye. Digital slit-lamp photographs taken one year post-operatively using a standardized photographic technique showed that anterior capsule polishing caused no significant difference in the outcome of PCO. Some authors actually believe that the post-operative fibrous metaplasia of remaining 'A' cells would push the IOL against the posterior capsule, and that would explain the relatively low PCO rates of eyes implanted with silicone lenses having rounded optic edges.[17]

In-the-bag IOL fixation

The hallmark of modern cataract surgery is the achievement of consistent and secure in-the-bag or endocapsular IOL fixation. The most obvious advantage of in-the-bag fixation is the accomplishment of good lens centration. However, endocapsular fixation functions primarily to enhance the IOL-optic barrier effect, as will be discussed later. In a series of human cadaver eyes implanted with different IOLs and analyzed in our laboratory, central PCO and Nd:YAG rates were both influenced by IOL fixation; i.e., less PCO and Nd:YAG capsulotomies in eyes where the IOLs were in the bag.[15]

Marie-José Tassignon proposed a variation of the in-the-bag IOL fixation concept for PCO prevention, named 'bag-in-the-lens' implantation.[18] This involves the use of a twin-capsulorrhexis IOL design, and performance of anterior and posterior capsulorrhexis of the same size. The biconvex lens has a circular equatorial groove in the surrounding haptic, for placement of both capsules after capsulorrhexis. If the capsules are well stretched around the optic of this lens, the LECs will be captured within the remaining space of the capsular bag and their proliferation will be limited to this space, so the visual axis will remain clear (Fig. 5-16-3). Experimental and clinical studies showed that bag-in-the-lens implantation was highly effective in preventing PCO when the anterior and posterior capsules were properly secured in the IOL groove.

Capsulorrhexis size

There is evidence that PCO is reduced if the capsulorrhexis diameter is slightly smaller than that of the lens optic, so that the anterior edge rests on the optic. This helps provide a tight fit of the capsule around the optic analogous to 'shrink-wrap', which has beneficial effects in maximizing the contact between the lens optic and the posterior capsule. In a retrospective clinical study performed at the John A. Moran Eye Center, University of Utah, on patients implanted with different IOLs, including lenses with round or square optic edges, the degree of post-operative PCO was correlated with the degree of anterior capsule

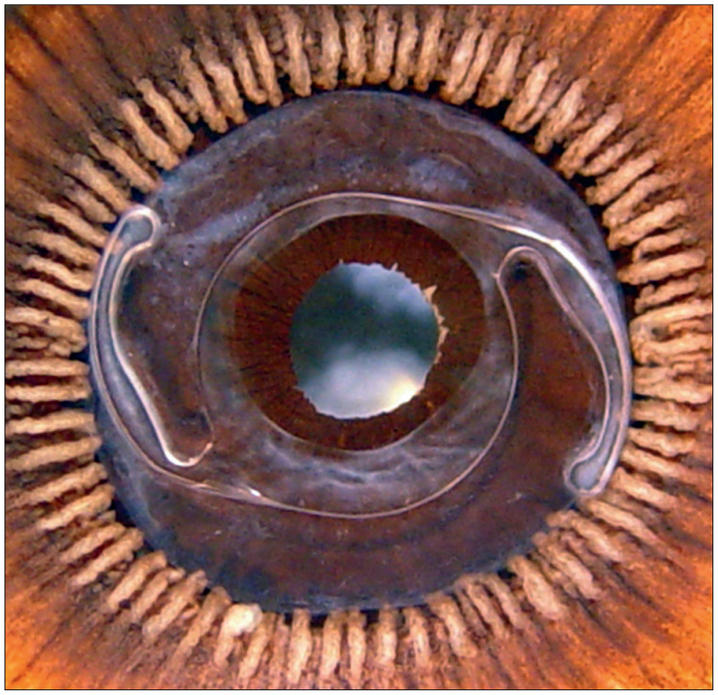

Fig. 5-16-2 Human eye obtained postmortem (posterior view) 19 months after implantation of a single-piece hydrophobic acrylic lens. This is an example of application of the three surgery-related factors for prevention of posterior capsule opacification. The lens was symmetrically implanted in the bag, via capsulorrhexis smaller than the optic diameter of the lenses (ideally, the capsulorrhexis margin should cover the edge of the lens for 360°). No significant Soemmerring's ring formation is present.

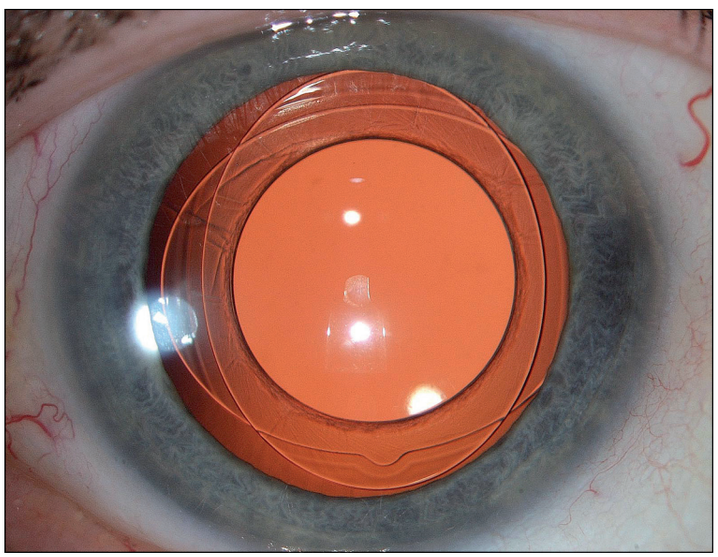

Fig. 5-16-3 Clinical photograph taken 6 months after cataract surgery with 'bag-in-the-lens' implantation in a 64-year-old patient. The area corresponding to the optic of the lens is completely free of opacities. Courtesy of Dr. Marie-José Tassignon, Belgium.

overlap.[19] Considering all patients, but also considering the patients distributed in different IOL groups, there was always a significant negative, linear correlation between the degree of overlap and PCO.

Biocompatible IOL

There are many definitions for the term 'biocompatibility'. With regards to PCO, materials with the ability to inhibit stimulation of cell proliferation are more 'biocompatible'. The 'Sandwich' theory states that a hydrophobic acrylic IOL with bioadhesive surface would allow only a monolayer of LECs to attach to the capsule and the lens, preventing further cell proliferation and capsular bag opacification. We performed two immunohistochemical studies on the adhesion of proteins to different IOLs that had been implanted in human eyes obtained postmortem.[20,21] Analyses of histological sections have demonstrated that fibronectin mediates the adhesion of this hydrophobic acrylic lens to the anterior and posterior capsules. Analyses of explanted lenses have confirmed the presence of greater amounts of fibronectin on the surfaces of the same lens. However, even though differences among materials exist, in terms of PCO prevention it appears that the geometry of the lens, with a square posterior optic edge is the most important factor (see IOL optic geometry below).

The adhesiveness of the material may have a more direct impact on the development of ACO. This generally occurs much earlier in comparison to PCO, sometimes within one month post-operatively. When the continuous curvilinear capsulorrhexis (CCC) is smaller than the IOL optic, the anterior surface of the optic's biomaterial maintains contact with the adjacent posterior aspect of the anterior capsule. Any remaining anterior LECs (A cells) in contact with the IOL have the potential to undergo fibrous proliferation; thus ACO is essentially a fibrotic entity. Studies in our laboratory using pseudophakic human eyes obtained postmortem showed that ACO is more common with silicone IOLs, especially the plate designs, because of the larger area of contact between these lenses and the anterior capsule (Fig. 5-16-1C).[4] However, the same studies showed that the plate design resists contraction forces within the capsular bag better than three-piece silicone lenses with flexible haptics (polypropylene).[5] These latter showed the higher rates of capsulorrhexis phimosis and IOL decentration as a result of excessive capsular bag fibrosis. There is, therefore, a tendency in IOL manufacture favoring haptic materials with higher rigidity, such as poly(methyl methacrylate) (PMMA), polyimide (Elastimide), and poly(vinylidene) fluoride (PVDF). In the same studies, ACO was less significant with hydrophobic acrylic lenses having an adhesive surface.

ACO has been considered a clinical problem when anterior capsular shrinkage associated with constriction of the anterior capsulectomy opening (capsulorrhexis contraction syndrome or capsular phimosis) accompanies excessive anterior capsule fibrosis. This has been especially observed in conditions associated with zonular weakness, e.g., pseudoexfoliation and advanced age, and with chronic intraocular inflammation. Besides phimosis of the CCC opening, excessive zonular traction and its sequelae, IOL dislocation and retinal detachment can also occur because of excessive capsular fibrosis. Excessive opacification of the anterior capsule is problematic in that it hinders visualization of the peripheral fundus during retinal examination. Otherwise, a certain degree of ACO is sometimes considered an advantage, as it can prevent potential dysphotopsia phenomena caused by the square edge of some IOL optic designs. Also, anterior capsule fibrosis with contraction of the capsular bag will push the IOL optic against the posterior capsule, helping in the prevention of PCO according to the 'no space, no cells' theory. This mechanism would explain the relatively low PCO rates with some silicone lenses, in the absence of a square optic edge profile, as noted above (Hydrodissection-enhanced cortical clean-up).[17]

The adhesiveness of the IOL material may also have an influence on ILO formation. To date, all cases of ILO we analyzed in our laboratory seemed to be related to two hydrophobic acrylic IOLs being implanted in the capsular bag through a small capsulorrhexis, with its margins overlapping the optic edge of the anterior IOL for 360°.[6] When these lenses are implanted in the capsular bag through a small capsulorrhexis, the bio-adhesion of the anterior surface of the front lens to the anterior capsule edge and of the posterior surface of the back lens to the posterior capsule prevents the migration of the cells from the equatorial bow onto the posterior capsule. This migration may be directed towards the inter-lenticular space. In this scenario, the two IOLs are sequestered together with aqueous and LECs in a hermetically closed microenvironment. In addition, the adhesive nature of the material seems to render the opacifying material very difficult to remove by any surgical means (Fig. 5-16-1D).

Based on the common features of different cases of ILO, some surgical methods were proposed for its prevention. The first option would be to implant both IOLs in the capsular bag but with a relatively large-diameter capsulorrhexis. The other possibility is to implant the anterior IOL in the sulcus and the posterior IOL in the bag with a small rhexis. These should help sequester the retained/proliferated equatorial LECs within the equatorial fornix. Re-assessment of factors leading to ILO formation is important because of the development of dual-optic accommodating IOLs to be implanted in the capsular bag.[7] Also, piggyback implantation for correction of residual refractive errors appears to be increasing in popularity, including implantation of a multifocal IOL in pseudophakic patients. However, in these cases the second (anterior) IOL is generally fixated in the ciliary sulcus.

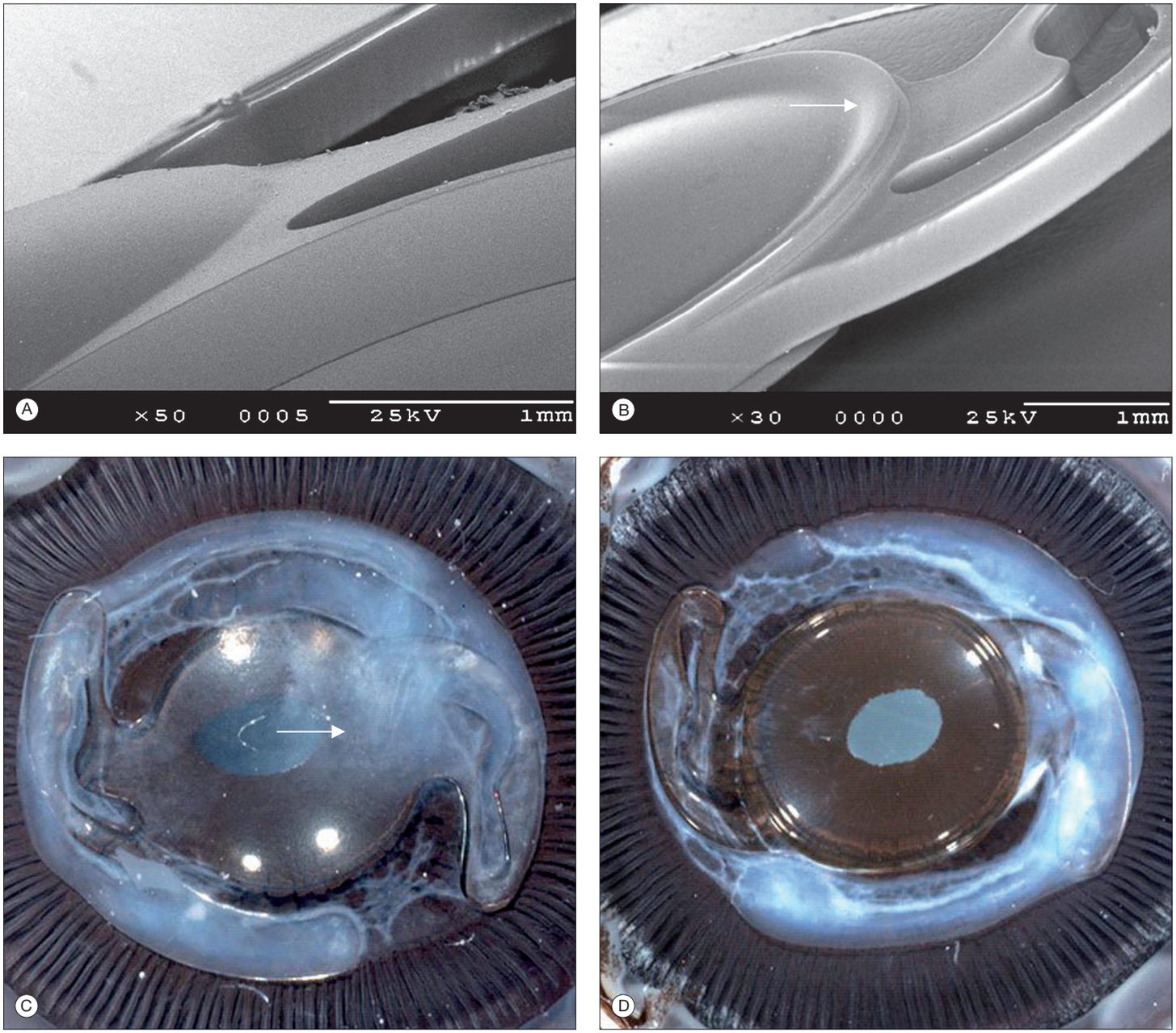

Fig. 5-16-4 Foldable, hydrophilic acrylic lenses with square optic and haptic edges. The lens in B was modified to incorporate an extra ridge all around the optic (enhanced square edge; arrow). C and D are photographs obtained from rabbit eyes (posterior view), experimentally implanted with the lenses in A and B, respectively. Soemmerring's ring formation is observed in both eyes. The arrow in C shows the opacification of the posterior capsule, which started at the level of the optic-haptic junction. From: Werner L, Mamalis N, Pandey SK, et al. Posterior capsule opacification in rabbit eyes implanted with hydrophilic acrylic intraocular lenses with enhanced square edge. J Cataract Refract Surg 2004; 30:2403–2409.

Contact between the IOL optic and the posterior capsule

Different factors can help maximize the contact between the IOL and the posterior capsule, contributing to the so-called 'no space, no cells' concept. Optic/haptic angulation displacing the optic posteriorly, and stickiness of the IOL optic material are the most important lens features for obtaining a tight fit between lens and capsule. Three-piece lenses manufactured from the different haptic materials currently available today have in general a posterior optic/haptic angulation ranging from 5 to 10°. To keep the advantages of the two above-mentioned factors, it is important to achieve endocapsular lens fixation and to create a capsulorrhexis smaller than the diameter of the lens optic.

Capsular tension rings may also have a role in the prevention of PCO. Equatorial capsular tension rings have the ability to maintain the contour of the capsular bag and to stretch the posterior capsule. They have thus primarily been used in cases of zonular rupture or dehiscence, secondary to trauma, or when inherent zonular weakness is present, such as in pseudo-exfoliation syndrome. It has been demonstrated by high-resolution laser interferometric studies that there is a space between the IOL and the posterior capsule with different lens designs. With a capsular tension ring in place, this space was found to be smaller or non-existent. Thus, LECs would not find a space to migrate and proliferate onto the posterior capsule. Capsular tension rings also produce a circumferential stretch on the capsular bag, with the radial distention forces equally distributed. Formation of traction folds in the posterior capsule, which may be used as an avenue for cell ingrowth is thus avoided.

Capsular tension rings may also have a role in the prevention of opacification of the anterior capsule. The presence of a broad, band-shaped, capsular ring would keep the anterior capsule leaf away from the anterior optic surface and the posterior capsule. This would ultimately lead to less metaplasia of LECs on the inner surface of the anterior capsule with less fibrous tissue formation, and thus less opacification and contraction of this structure. IOLs with design features that also help maintaining the anterior capsule away from the anterior surface of the lens have also been evaluated in our laboratory.[7] A capsular tension ring designed to prevent opacification within the capsular bag was evaluated in two centers, one in Japan (Nishi O) and the other in Austria (Menapace R).[22] Both centers reported a significant reduction

in PCO and ACO with the rings, in comparison to the contralateral eyes implanted with the same lens design.[22]

IOL optic geometry

The square, truncated lens optic edge acts as a barrier, preventing migration of proliferative material from the equatorial region onto the posterior capsule.[15] The barrier effect is absent in lenses having rounded edges, and proliferative material from the equatorial region has greater free access to the posterior capsule, opacifying the visual axis. The barrier effect of the square optic edge is functional when the lens optic is fully in the bag, in contact with the posterior capsule. When one or both haptics are out of the bag, a potential space exists that allows an avenue for cellular ingrowth towards the visual axis. Different modern lenses manufactured from different materials currently on the market present this important design feature. Some of them have a square edge on the posterior optic surface, while the anterior optic edge remains round in order to prevent disphotopsia. Findings from experimental studies which demonstrate that the square edges of different lenses on the market are not equally 'sharp', even when the same class of materials is considered, are however noteworthy.[23,24]

The optic–haptic junctions of square-edged single-piece lenses may represent a site for cell ingrowth and PCO formation.[25] At the level of those junctions, the barrier effect of the square edge appears to be less effective. We obtained better results regarding PCO formation with a hydrophilic acrylic single-piece lens having an 'enhanced' square edge, than with the standard model of the same design.[25] The enhanced edge provided the lens with a peripheral ridge around the lens optic for 360°. In the standard model, the square edge profile appeared to be absent at the level of the optic–haptic junctions (Fig. 5-16-4). Therefore, the square optic edge is probably the most important IOL design feature for PCO prevention. It appears however that it should be present for 360° around the IOL optic in order to provide an effective barrier effect.

IOLS MAINTAINING THE CAPSULAR BAG OPEN OR EXPANDED

We have recently evaluated the outcome of capsular bag opacification with a new single-piece, disk-shaped hydrophilic acrylic IOL as compared to a commercially available single-piece, hydrophobic acrylic IOL in the rabbit eye for 5 weeks (Fig. 5-16-5).[26] The peripheral rings of the disk-shaped lens, by expanding the capsular bag and preventing IOL surface contact with the anterior capsule, prevented ACO and PCO. We hypothesized that IOL designs maintaining an open or expanded capsular bag are associated with bag clarity. Mechanical compression of the inner bag surface (and residual LECs) by a relatively bulky device/IOL has been one of the possible mechanisms advanced to explain this finding. Another factor may be mechanical stretch of the bag at the level of the equatorial region (maintaining the overall bag contour), by devices such as the capsular bending ring of Nishi and Menapace,[22] and Hara's equator ring.[27] Constant irrigation of the capsular bag's inner compartment by the aqueous humor may also have an influence on the prevention of proliferation of residual LECs. Equatorial stretch and aqueous humor irrigation would help explain the PCO preventative effect, even in eyes where there was no contact between the IOL optic and the posterior capsule. Previous reports indicated that TGF-β2 in the normal aqueous humor inhibits proliferation of LECs and corneal endothelial cells.[28] According to Nishi, constant irrigation by the aqueous humor may prevent certain cytokines that are involved in stimulating LEC proliferation from reaching a threshold concentration level within the bag compartment; one of these cytokines would be represented by interleukin-1.[29]

In summary, development of PCO is multifactorial, and its eradication depends on the quality of the surgery, as well as on the quality of the IOL implanted. Each factor described here does not act in isolation, and it is their interaction that produces the best results. Research on the prevention of any form of opacification/fibrosis within the capsular bag is increasing in importance, especially with the advent of specialized IOLs such as accommodative lenses, which are designed to enable a forward movement of the optic upon efforts of accommodation. The functionality of such lenses will likely require the long-term transparency and elasticity of the capsular bag. Further research to investigate new proposed mechanisms for capsular bag opacification prevention, such as with IOLs/devices maintaining an open capsular bag is warranted.

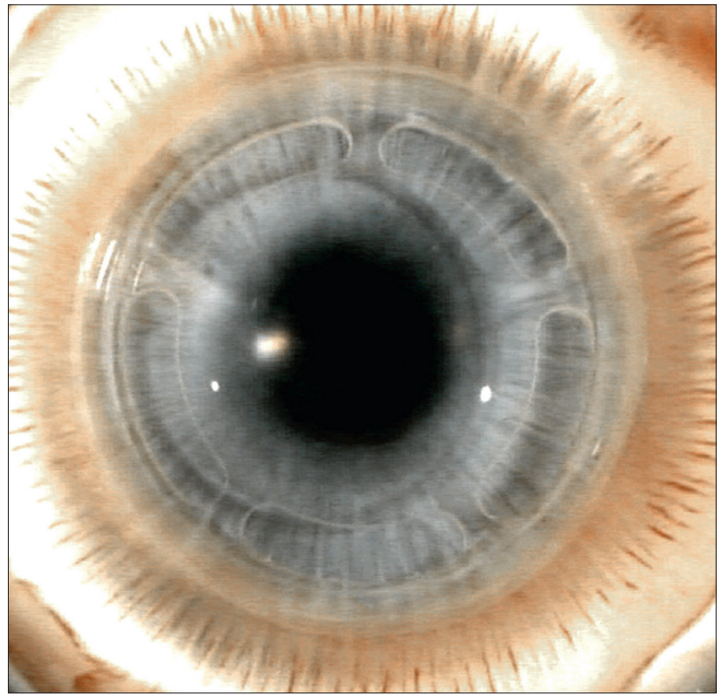

Fig. 5-16-5 Gross photograph (Miyake-Apple view) of the anterior segment of a rabbit eye implanted with a new disk-shaped IOL, taken 5 weeks post-operatively. The lens is a single-piece, hydrophilic acrylic, monofocal lens suspended between two complete haptic rings that are connected by a pillar of the haptic material. This design maintains the capsular bag expanded, with the anterior capsule separated from the anterior optic surface Anterior and posterior capsules are overall clear. Minimal proliferation is limited to the space between the peripheral rings.

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