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REVIEW

Post cataract-intraocular lens (IOL) surgery opacification

RH Trivedi[1], L Werner[1], DJ Apple[1], SK Pandey[1] and AM Izak[1]

Abstract

Intraocular lens (IOL) implantation has no doubt been one of the most satisfying advances of medicine. Millions of individuals with visual disability or frank blindness from cataracts had and continue to have benefit from this procedure. It has been reported by ophthalmologists that the modern cataract-intraocular lens (IOL) surgery is safe and complication-free most of the time. This makes the watchword for any cataract surgeon to be 'implantation,' 'implantation,' 'implantation.' In the mid-1980s, as IOLs were evolving rapidly, the watchword of the implant surgeon was 'fixation,' 'fixation,' 'fixation.' Most techniques, lenses and surgical adjuncts now allow us to achieve the basic requirement for successful IOL implantation, namely long-term stable IOL fixation in the capsular bag.

However despite this advancement some items 'slipped through cracks.' In this article, we would like to alert the reader to a new watchword, namely 'opacification,' 'opacification,' 'opacification.' Here we will be talking about the good, the bad, and the ugly. Examples of the 'good' include the recent successes now being achieved in reducing the incidence of posterior capsule opacification. Examples of the 'bad' include various proliferations of anterior capsule cells, problems caused by silicone oil adherence to IOLs and problems with piggyback IOLs. The 'ugly' include the sometimes striking and often visually disabling opacifications occurring on and within IOL optics, both on some modern foldable IOLs as well as a poly(methyl methacrylate) (PMMA) optic degradation occurring with some models a decade or more after implantation.
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Keywords: intraocular lens; complication; opacification; anterior capsule opacification; silicone; calcification; glistening; snowflake; interlenticular opacification; piggyback; posterior capsule opacification

Introduction

Implanting an intraocular lens (IOL) into an adult eye after cataract surgery is an extremely successful procedure since its invention by Sir Harold Ridley.[1] It is often difficult to imagine another medical specialty implanting foreign material with such a high success rate. Decreased incidence of postoperative complications of cataract-IOL surgery led us to become complacent and less vigilant regarding assessment and careful testing of new ocular prosthesis and surgical procedures. However, despite the positive evolution of cataract-IOL surgery, but concurrent with this era of probably decreased vigilance, we are now unfortunately identifying some serious problems. Table 1 describes some entities related to post cataract-IOL surgery related opacification. Ophthalmic surgeons have responded to these challenges and continued research is now ongoing that will even further improve the outcome of the cataract-IOL operation in order to help surgeons to provide better care to our patients.

Our research center was founded in 1983 by David J Apple, MD and Randall J Olson, MD, in Salt Lake City, UT, USA. The research and specimens analyses during this early period were almost totally focused on cataract-IOL surgery, hence the center was named the Center for IOL Research. Following David J Apple's move to Charleston, SC in 1989, the scope of the work expanded and we therefore changed the name to a more inclusive one, the Center for Research on Ocular Therapeutics and Biodevices.[2] As of December 2000 we had accessioned more than 16500 IOL-related specimens including more than 7800 pseudophakic human globes. From January

[1]Center for Research on Ocular Therapeutics and Biodevices
Storm Eye Institute
Medical University of South Carolina
Charleston, SC, USA

Correspondence:
DJ Apple
Storm Eye Institute
Department of Ophthalmology
Medical University of South Carolina
167 Ashley Avenue
PO Box 250676
Charleston
SC 29425–5536, USA
Tel: (843) 792 2760
Fax: (843) 792 7920
E-mail: appledj@musc.edu

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Table 1 Post cataract IOL surgery related opacifications described in this review article

(1)	Front (anterior) (A) Anterior capsule opacification (ACO) (B) Silicone oil adherence to IOLs
(2)	On (surface changes on the optical component of IOLs) Calcification on the surface of the Bausch & Lomb Hydroview™ IOL
(3)	Within (alteration inside the IOL optic) (A) Degeneration of ultraviolet absorber material and calcium deposits within the optic of a hydrophilic IOL (manufactured by Medical Developmental Research) (B) Glistening of the AcrySof™ IOL (C) 'Snowflake' or 'crystalline' alteration of poly(methyl methacrylate) (PMMA) IOL optic: a syndrome caused by an unexpected late biodegradation of PMMA
(4)	Between (opacification between 'piggyback' IOLs) Interlenticular opacification (ILO) of 'piggyback' IOLs
(5)	Behind (posterior) Posterior capsule opacification (PCO)

1988 through December 2000, 6425 eyes with posterior chamber (PC) IOLs were analyzed including 1109 eyes implanted with foldable IOLs.

Anterior capsule opacification

Introduction

Like posterior capsule opacification (PCO), anterior capsule opacification (ACO) is also actually a misnomer since it is not the capsule which opacifies, but rather the cells lining the capsule[3] (Figure 1). A more accurate term is anterior subcapsular opacification. However, the former term is firmly established in the literature and in clinical usage. ACO generally occurs much earlier in comparison to PCO, sometimes within one month postoperatively.[4,5] It has been demonstrated that the area of the anterior capsule opening seems to gradually decrease for up to 6 months postoperatively.[4,6–9]

The process of opacification of the anterior capsule may progress in four stages: (1) fibrosis/opacification of the capsulorhexis margin at some places; (2) the entire anterior capsular edge in contact with the IOL optic's biomaterial then becomes progressively opacified; (3) formation of capsular folds; and (4) advanced/excessive and/or asymmetric fibrosis and shrinkage may result in some complications such as eccentric displacement of the CCC opening, IOL decentration, and capsulorhexis phimosis.

An excessive anterior capsule fibrosis/opacification may lead to major clinical problems and sequelae such as difficulty in examining the retinal periphery, which leads to difficulty in diagnosing and treating retinal problems. It can also lead to fibrous contraction of the capsule, capsulorhexis phimosis, and IOL decentration.

Pathogenesis

When the anterior surface of the IOL optic biomaterial is in contact with the adjacent posterior aspect of the anterior capsule, the remaining anterior lens epithelial cells (A cells) may undergo fibrous metaplasia leading to anterior or posterior capsule opacification.[10] The cuboidal cells lining the anterior capsule (A cells) are the cells of origin of ACO. Some authors[3] demonstrated two phases in the formation of ACO: an early phase consisting of proliferation of lens epithelial cells and a late phase involving degeneration or disappearance of lens epithelial cells and the presence of extracellular matrix.

Factors that may contribute to ACO

Three major factors have been postulated to affect the degree of ACO: (1) the initial size of the continuous curvilinear capsulorhexis (CCC); (2) the IOL material and design; and (3) pre-existing conditions, eg the quality of the zonular support.

(1) Capsulorhexis size: With a CCC smaller than the diameter of the IOL optic, the contact of the optics' biomaterial with the anterior capsule will induce fibrosis/opacification. It is postulated that the more epithelium that is left, the greater the potential for opacification. The magnitude of the postoperative changes appears to be related to the initial CCC size, although some authors did not find any correlation between these parameters.[11] Tsuboi *et al*[12] have studied the influence of the CCC and IOL fixation on the blood-aqueous barrier. Their results indicate an unfavorable effect of in-the-bag fixation with a small CCC, and thus a broad contact of the IOL optic with the anterior capsule. The important

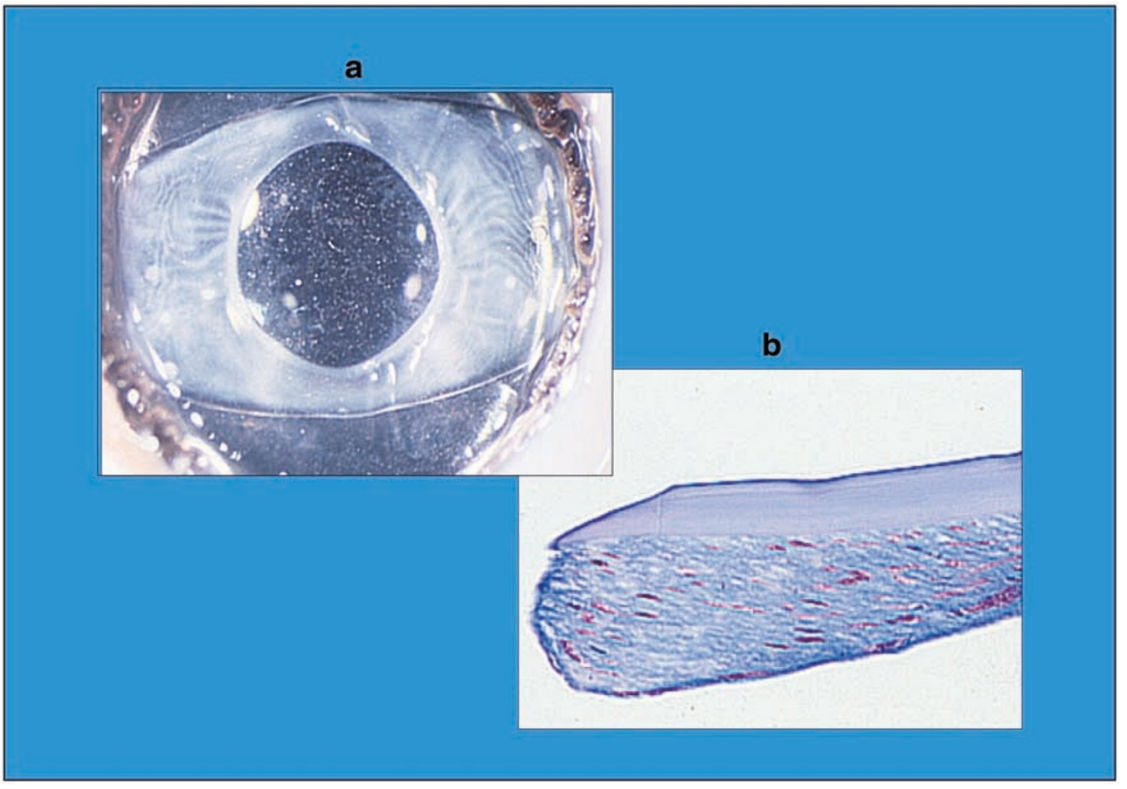

Figure 1 Anterior capsule opacification (ACO). (a) Gross photographs of pseudophakic human eyes obtained post-mortem (anterior or surgeon's view) showing ACO with silicone-plate intraocular lens (IOL). (b) Photomicrograph taken at the CCC margin of pseudophakic human globes obtained post-mortem (Masson's trichrome stain, original magnification ×400) showing anterior capsule fibrosis.

subset of ACO, capsular phimosis, relates to the CCC size. Although no correlation between the initial CCC size and the postoperative CCC constriction has been found by Gonvers *et al*,[11] some authors have postulated that performing small, intact CCCs strongly increases the risk for capsule fibrosis and shrinkage.[7,9]

(2) IOL material and design: Werner and associates from our laboratory performed extensive research work on the subject.[13–16] They compared at the microscopic level the influence of different IOL biomaterials and IOL designs on the development of anterior capsule fibrosis.[13] Results of this histopathological study confirm the observations of others[17,18] that the rate of ACO is higher with silicone IOLs. Results of a macroscopic study performed by Werner *et al*[14] also concur with histological findings that the ACO score was highest with silicone IOLs.

Among the four silicone IOL groups studied, plate-haptic silicone IOLs had significantly higher scores than the 3-piece designs. Histopathological findings concur with clinical findings in that the excessive CCC constriction observed with plate-haptic IOLs is probably due to the relatively large area of contact of the plate haptic silicone material with the anterior capsule, in sharp contrast to 3-piece IOLs where the contact is limited to the surface of the optic. Thus, the plate IOL has a large surface exposure that may stimulate cell proliferation and fibrosis.

(3) Pre-existing conditions: In conditions such as pseudoexfoliation, the zonules can become markedly weakened. Weak or absent zonular fibers may be unable to oppose the relatively increased strength of the centrally directed contractile forces generated by capsular fibrosis. Capsular contraction has also been associated with other conditions such as diabetes, uveitis, myotonic muscular dystrophy, or retinitis pigmentosa.[19–22]

Clinical significance

Studies from our laboratory[13,14] and also other literature have reported the lowest mean decentration and ACO scores were found with AcrySof™ IOLs. These findings may be of clinical significance in that, when using this IOL type: (1) anterior capsule

polishing should not be necessary in most cases; (2) the incidence of decentration and capsulorhexis phimosis should be minimized; and (3) one might expect a better view of the peripheral retina through a clear anterior capsule during indirect ophthalmoscopy. Severe ACO may represent a significant clinical problem for the retinal surgeon due to difficulty in examining the retinal periphery. The large size of the capsulorhexis and/or implantation of hydrophobic acrylic IOL (AcrySof™) are useful surgical pearls to overcome this problem.

Prevention

Several methods have been proposed to prevent CCC contraction and the resultant IOL decentration.[23] In routine cataract surgery thorough polishing of the anterior capsule can be a useful procedure.[24] It is time consuming, somewhat impractical, and generally not necessary to achieve excellent results in most cases. It is clear, however, that anterior capsule polishing will make the onset of ACO less likely. Some authors recommend a careful anterior capsular polishing and removing of the anterior subcapsular epithelial cells. Nishi[25] proposed the use of a modified irrigating-aspirating tip with an abrasive surface. An effective hydrodissection helps to make lens substance removal easier, assuring a more complete removal of masses of cortex and cells. Large CCC (>5.5 mm in diameter) was also found to be correlated with less capsule contraction. However, it is not technically easy to perform large capsulorhexis and it also hampers endocapsular phacoemulsification. Recently, the 'Initiative and Definitive' (I and D) concept of capsulorhexis has also been reported to take the advantage of the best of both words, endocapsular phacoemulsification and less ACO.[26]

Treatment

When capsular phimosis develops, radial anterior Nd:YAG capsulotomies can be performed to create four equally spaced radial cuts about 1.0 mm in length using an average power of 1.5 mJ.[27] It might be prudent to initiate linear cuts in all four quadrants, removing traction symmetrically, before completing the cuts. This technique may avoid extension of a radial tear from the first cut. Some authors recommend relaxing anterior capsulotomies immediately when capsule contraction is observed.[23] They postulate that active capsular fibrosis can be influenced with early YAG laser, whereas later intervention may not help.[27] Although early Nd:YAG laser anterior capsulotomy will presumably prevent further lens decentration eventually associated with capsular phimosis, and improve symptoms in most patients, it is not without risks. The IOL may dislocate posteriorly if a rupture in the posterior capsule is created.

Summary

The size of the CCC has major influence on the development of ACO as well as the IOL material and design. According to recent studies, ACO was found to be lowest with hydrophobic acrylic lenses and highest with plate-haptic silicone IOLs. The IOL design and material also influence the clinical presentation/sequelae of capsular shrinkage.

Silicone oil adherence to IOLs

Introduction

The use of silicone oil in vitreoretinal microsurgery has been reported in the literature.[28,29] However, intraocular use of silicone oil can lead to various complications. The very important issue that needs to be considered in vitrectomized, silicone oil-filled eyes undergoing cataract surgery with IOL implantation is the adhesion of silicone oil to the IOL surface, especially to silicone optic IOL designs.[30] Although the incidence of clinically significant silicone oil-IOL complication is reported to be relatively low, it is probably higher than what is generally assumed clinically because affected patients or potentially affected patients are usually seen later by a vitreo-retinal surgeon rather than by the anterior segment surgeon. Also, this complication may be more common in countries outside of the United States because silicone oil is used more commonly.

Irreversible adherence of silicone oil to the IOL optic may lead to devastating sequelae, including visual disturbances and visual loss for the patient, as well as obstruction of the vitreoretinal surgeon's view into the eye. Therefore use of standard silicone optic IOL is not recommended in patients with either present or potential vitreoretinal disease that may require use of silicone oil as a tamponade.[30,31]

Silicone oil interaction with different IOL materials

Literature has reported that significant silicone oil coverage may occur on the surface of an IOL optic, especially one made from a hydrophobic material, as opposed to more hydrophilic materials.[30–35] Apple and associates[30,31,34,35] in three different studies have compared the degree of silicone oil adherence occurring with several IOLs fabricated from various

biomaterials. These studies from our laboratory have demonstrated that the more hydrophobic materials with higher dispersive energy and relatively higher contact angles had more silicone oil adherence.[30,31] Hydrophilic biomaterial with relatively low contact angles and low dispersive surface energy demonstrated less silicone oil adherence. Silicone oil coverage of poly (methyl methacrylate) (PMMA) IOLs was found to be significantly decreased once the latter were heparin-surface-modified (HSM).[33] This phenomenon might be explained by the fact that coating of PMMA IOLs with heparin converts their hydrophobic surface into a hydrophilic one. Studies from our laboratory[34,35] have reported that the interaction of silicone oil with a silicone IOL is dramatically decreased if the latter is surface modified with heparin (Figure 2a and b). Its hydrophilic chains bound to the surface of the IOL extend into the aqueous media and form a highly hydrated layer around the lens by trapping water molecules. This leads to reduction of silicone oil adherence to this kind of IOL as has also been described with PMMA IOLs.

Mechanism of action

Dick and associates[36] summarized the three main factors that influence silicone oil–IOL biomaterial interaction, *in vitro* and *in vivo*, being: (1) contact angle of the polymer—hydrophobic materials having higher contact angle than hydrophilic materials; (2) free energy of the polymer—a sum of polar and dispersive components; and (3) surrounding biological factors such as body temperature, eye movements, and characteristics of the aqueous humor.

Treatment

In addition to appropriate IOL choice when addressing silicone oil–IOL interaction, investigators are finding new means to remove silicone oil from IOL surfaces in cases where the condition has become manifested. For example, Langefeld and associates,[37] and Zeana and associates[38] demonstrated the effectiveness of perfluorhexyl-octan [($C_{14}F_{13}H_{17}$ (F6H8)] in removing silicone oil from silicone IOL surfaces. Furthermore, Dick and Augustin[39] demonstrated that this solvent is more effective in removing silicone oil from an IOL with hydrophilic surfaces than from hydrophobic IOLs. This solvent appears to be tolerated by surrounding intraocular tissues. Hoerauf and associates[40] have reported on the effectiveness of using the solvent O44 for removal of silicone oil from the IOL surface. Kageyama and Yaguchi[41] have demonstrated a mechanical method of removing silicone oil from the

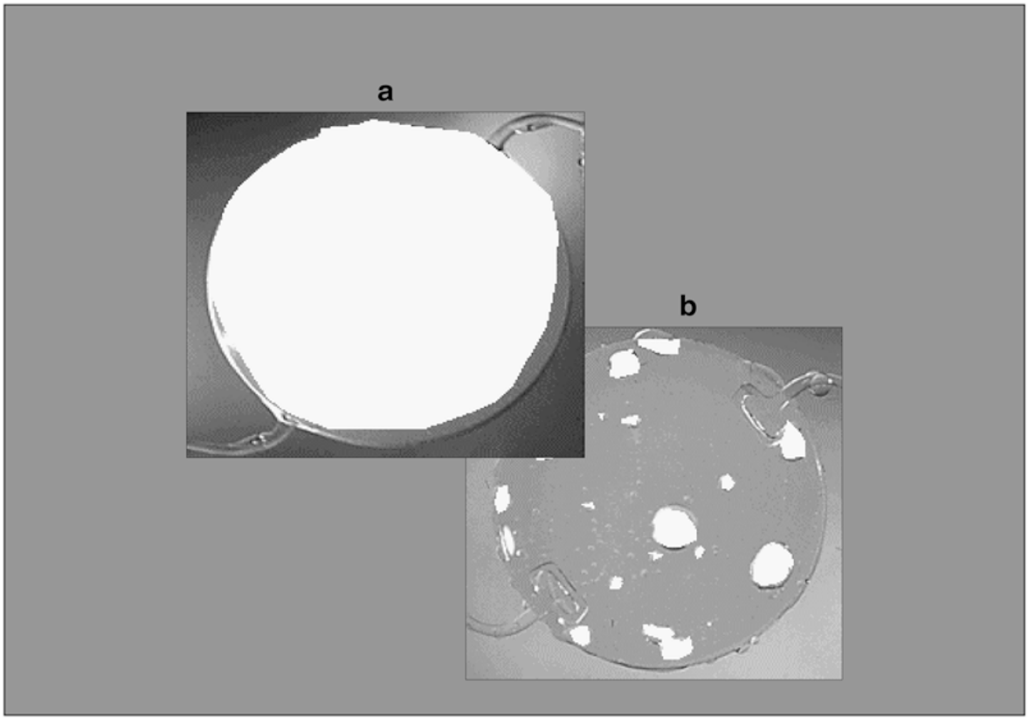

Figure 2 Gross photographs showing image analysis of silicone IOLs (Pharmacia Corporation, Peapack, New Jersey, USA) after submersion in silicone oil. The white area indicates the silicone oil adherence to the IOL. (a) Standard silicone IOL. (b) HSM silicone IOL.

IOL surfaces. Although effective, these procedures are invasive and require secondary surgical intervention.

Summary

Special care should be taken when selecting IOLs for patients who may be deemed to have a high propensity or potential for severe vitreoretinal disease that may require silicone oil treatment later. An awareness of clinically significant IOL-silicone oil interaction should be useful in lowering the incidence of such complications.

Calcification on the surface of the Bausch & Lomb Hydroview™ IOL

Introduction

The Bausch and Lomb Surgical (Rochester, NY, USA) Hydroview™ IOL is a foldable hydrogel that has been implanted for several years in international markets; over 400000 have been implanted worldwide. Relatively late postoperative Ca deposition on the optic of Hydroview™ lenses (model H60M) has been reported in the literature.[42–47] At the time of writing, the number of all reported cases with complications is relatively small; 309 of approximately 400000 lenses implanted worldwide. In 96 cases, the IOL changes were clinically significant, decreasing patient vision enough to result in lens explantation. The clinical reports have not been randomly distributed. Although this IOL model has been implanted in 3500 centers worldwide, reports have appeared in clusters. The vast majority has come from 31 ophthalmic practices in 11 countries. We have analyzed explanted opacified IOLs from several of these centers.[42–47]

Analyses of explanted IOLs

We have recently reported analyses of the first six explanted Hydroview™ lenses we received in our Center. In each case, the lens has been explanted due to deposition of crystalline material on its optical surfaces (Figure 3a) associated with a decrease in visual acuity (VA) and glare in the late postoperative period. One of the lenses was explanted in Australia (Dr BB Crayford), four in Sweden (Dr A Öhrström) and one in Canada (Dr JP Gravel).

At the time of explantation, the age of the patients (two female and four male patients) ranged from 70 to 85 years. Two patients were in treatment for cardiovascular diseases, two were diabetics and the other two were otherwise healthy. All lenses were explanted at least one year after the primary procedure due to opacification observed at the level of the optics, associated with a decrease in VA and significant glare. The surgeons described the findings as a 'brown granularity' or 'small red corpuscles' present on both external optical surfaces of the lenses. In some cases, the optic of the lenses was almost completely covered by those structures giving them a 'frosty' and very reflective appearance. Nd:YAG laser was performed in all cases in an attempt to clean the optical surfaces, without success.

After initial primary gross and microscopic examination, lenses were stained with Alizarin red. Full thickness sections were performed through the optic of two explanted Hydroview™ lenses and a control Hydroview™ lens. The resultant cylindrical blocks were dehydrated and embedded in paraffin. Sagittal sections were performed and stained using the von Kossa method for calcium (Ca).[48–50] One lens was analyzed under scanning electron microscope (SEM).

Gross and microscopic evaluations of all of the explanted Hydroview™ lenses had almost identical findings. By gross evaluation the presence of the deposits on their optical surfaces was noted to cause different degrees of IOL haze/opacification (Figure 3b), directly proportional to the amount of deposits on the IOL. A layer of irregular granular deposits, composed of multiple, fine, translucent spherical-ovoid granules covered the surfaces of the unstained IOLs. The deposits occurred on both anterior and posterior IOL optic surfaces, but not the haptics. In some cases, both surfaces were almost completely covered by a confluent granular layer, whereas in other cases some intervening clear areas were observed. Multiple pits related to Nd:YAG laser treatment were observed on the posterior surface of the IOLs in all cases. Also, the deposits on the surfaces of the IOLs stained positive with alizarin red in all cases (Figure 3c). In some areas presenting scattered, small granules, it was observed that only the deposits themselves stained red while the IOL surface itself was not stained.

Sagittal histological sections through the optic of two Hydroview™ lenses, stained using von Kossa's method showed a continuous layer of dark brown, irregular granules on the anterior and posterior optical surfaces, and the edges of the lenses. SEM also helps us to understand the aspect of deposits in a better way. Energy dispersive X-ray analyses (EDS) performed on the deposits demonstrated the presence of peaks of Ca and phosphate.

After completion of these analyses, we received eight other explanted Hydroview™ lenses in our Center, three from Dr JP Gravel (Canada), two from Dr Sher (Canada), two from Dr A Öhrström (Sweden), and one from Dr A Apel (Australia). The surgical, clinical and

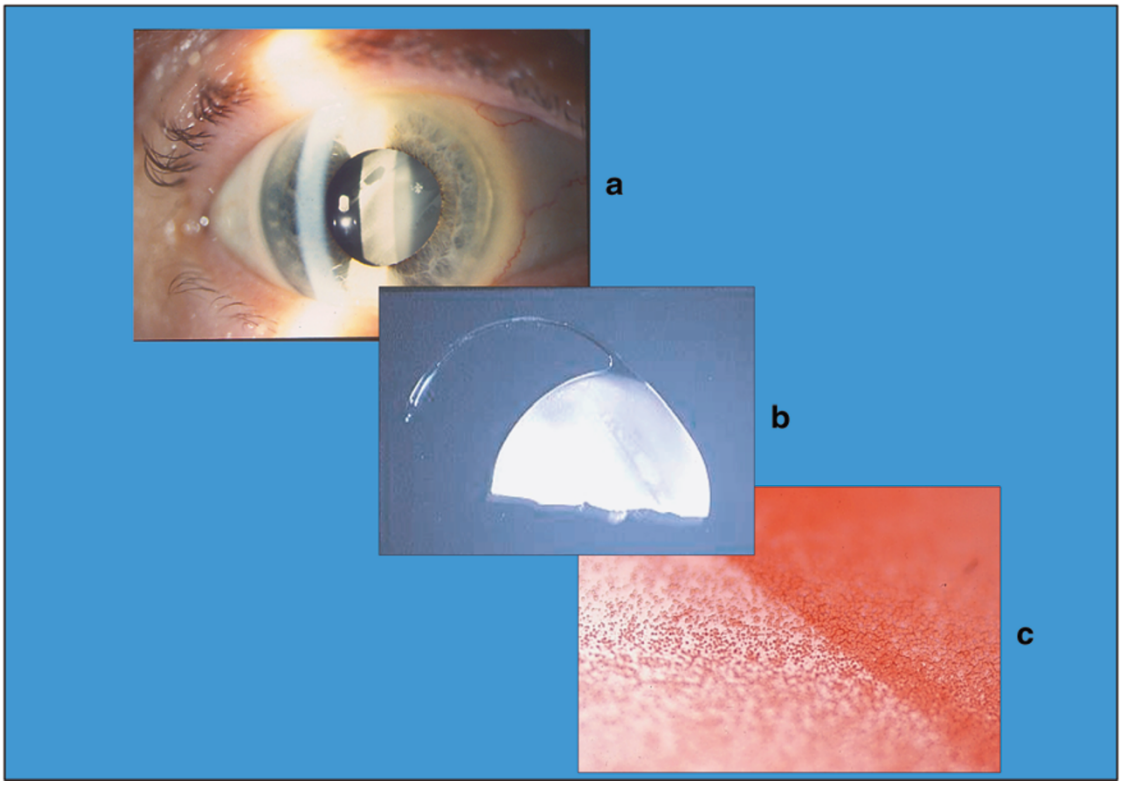

Figure 3 Calcification on the surface of Hydroview™ IOLs. (a) Slit-lamp photograph of a patient implanted with a Hydroview™ IOL showing the granularity present on the anterior surface of the lens (courtesy Dr Arne Öhrström, Vasteras, Sweden). (b) Gross photograph showing an example of Hydroview™ IOL explanted due to optical opacification. (c) Photomicrographs from the surface of an explanted Hydroview™ lens showing the granular deposits (Alizarin red; original magnification × 200).

pathological features of these cases were similar to those described above.

According to Dr Crayford, infrared spectroscopic analyses performed on the surface of two other explanted lenses of the same model (not available to us) also revealed the presence of the same components (Basil B Crayford, FRACO, personal communication, February 2000). Ca and phosphates were also found on the surfaces of three other Hydroview™ lenses explanted by Yu *et al*,[51] using Raman spectra analysis and EDS.

Possible factors involved in the pathogenesis

The mechanism of this complication is not fully understood, but it does not seem to be directly related to substances used during the surgery as it occurred in the late postoperative period. Also, the substances used during the surgery were not the same in all cases. The majority of the patients involved had an associated systemic disease; therefore, the possibility of a patient-related factor, such as a metabolic imbalance cannot be ruled out.

Ca deposition observed in the cases described here occurred in the late postoperative period. In the case of Hydroview™ IOLs, chemical removal of Ca phosphate revealed the presence of a few small pits and fissures with the SEM, that were found to be artifactual, rather than permanent damage caused by the deposits on the IOL surfaces (George Green, PhD at Bausch and Lomb, personal communication, February 2000). Yu *et al*[51] also confirmed that the deposits on their lenses were mainly localized on the external surfaces, but the polymer structure was not affected.

Lot history, component history, process changes, surgical setting and techniques, environmental factors, pre-existing patient conditions, and packaging have been examined. According to Bausch and Lomb studies, part of the components of this packaging contain silicone, which may come off the packaging onto the optic of the lens. It then appears to be a catalyst for Ca precipitation. Fatty acids and silicone, perhaps in association with a metabolic disease in the affected patient, could result in the calcification. In a February 2001 letter to surgeons who have implanted the Hydroview™ IOL, Bausch and Lomb described their investigation into the phenomenon. Surface chemistry studies identified the lens deposits as a

layered mixture of octa Ca phosphate, fatty acids, salts, and small amounts of silicone (Guttman C, 'Hydroview calcification resolved'. *Ophthalmology Times*, 2001; 26: No. 4). An *in vitro* model was then constructed to find out how the material deposited onto the lens. This model, according to the manufacturer, revealed a migration of silicone from a gasket in the lens packaging onto the surface of the IOL. The manufacturer has correlated a change in packaging with the appearance of the opacification. In lenses placed into the current IOL packaging, trace amounts of low-molecular-weight silicone have been detected on some IOL surfaces. Although this substance was not present with the original packaging, the possible role of silicone in the causation of the complication remains unclear. The models also showed that in addition to silicone, fatty acids had to be present to attract Ca ions to the lens surface. A separate retrospective clinical case/control study was also conducted by the manufacturer at the sites where the highest incidences of calcification were reported. The manufacturer now believes that this problem is resolved. However, final verification will require a careful 1- to 2-year clinical study. It is important to carefully follow patients with these lenses in order to determine the exact extent of this phenomenon.

Prevention and treatment

It is important for the surgeons who implanted Hydroview™ lenses to recognize this condition. Excessive Nd:YAG laser treatment, in an attempt to clean the optical surfaces of the lenses may jeopardize implantation of a new lens in the capsular bag after explantation of the Hydroview™. Nd:YAG laser treatment was proven to be ineffective in the cleaning of the lenses' surfaces. The cause of this condition seems to be multifactorial, and until the pathogenic mechanism is fully clarified, explantation and exchange of the IOL is the only available option. Methods for the prevention of this condition are also not completely defined to date. The manufacturer will make changes in the SureFold™ packaging, which will be produced with a gasket made from a nonsilicone material. Long-term clinical studies will determine the efficacy of this modification in the prevention of lens calcification.

Summary

The opacification of Hydroview™ lenses appears most commonly between 12 and 25 months postoperatively. Attempts to remove the opacity with a Nd:YAG laser has been unsuccessful. Analyses of opacified Hydroview™ lenses demonstrated that the deposit formation on their surfaces contains Ca.

Opacification within the optic of a hydrophilic IOL

Introduction

Foldable hydrogel (hydrophilic acrylic) IOLs are not yet available in the United States but have been marketed by several firms for several years in international markets. Late postoperative opacification within the optic substance of some IOLs manufactured from at least one source of a hydrophilic acrylic biomaterial has recently been reported[52–55] (Werner L, Apple DJ, Pandey SK. 'Late postoperative opacification of 2 hydrophilic acrylic intraocular lenses'—Best Paper of the Session—presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, April/May 2001, San Diego, CA, USA). The source of the polymer of this IOL, the SC60B-OUV design was Vista Optics, UK; the manufacturer and distributor is Medical Developmental Research (MDR Inc, Clearwater, FL, USA). As of May 2000, MDR had announced 56 cases of late postoperative lens opacification out of over 75 000 SC60B-OUV lenses implanted worldwide. At the time of this writing we are currently in the process of analyzing 24 more IOLs of the same model that we have recently received in our Center from different countries. In addition to the cases which will be described here the manufacturers were aware of at least 20 other cases that required explantation because of significant visual loss. The manufacturer has withdrawn all SC60B-OUV IOLs that have been fabricated from materials obtained from Vista Optics, UK and has sent in June of 2000 an informational letter to all lens users. All of these IOLs are now being manufactured from polymer material obtained from a new source, Benz Research, Sarasota, FL, USA. We analyzed the clinicopathological, histochemical, ultrastructural and spectrographic features of these cases and tried to ascertain the nature of the intralenticular deposits in our Center.[52–55]

Analysis of explanted IOLs

All of the IOLs were explanted because of late postoperative opacification of the lens optic associated with decreased VA.[52] Dr Mahmut Kaskaloglu has implanted 361 of these lenses between November 1997 and October 1999. He observed 18 cases of late postoperative opacification of the SC60B-OUV lens, nine of which had associated visual symptoms sufficient to justify explantation and submit for

pathological analysis. Although some patients are diabetics, until now there has not been enough information to establish a correlation between diabetics and postoperative opacification.

In general, the patients returned at around 24 months after the surgery complaining of a significant decrease in visual acuity. The clinical characteristics of these lenses were different from the previously described 'granularity' covering the optical surfaces of the Hydroview™ design. The clinical appearance was that of a clouding similar to a 'nuclear cataract' (Figure 4a). The lenses were explanted around 24 months postoperatively. In rare cases, the opacification was observed as early as 3 months postoperatively.

After initial gross and microscopic examination following tests were performed, details of which are described elsewhere: alizarin red staining, von Kossa method for Ca and SEM. Gross and microscopic evaluations demonstrated that the optical surfaces and the haptics of some of the lenses were free of any deposits. However, there were multiple small structures initially noted to resemble 'glistenings' within the central 5 mm of the IOL optical component. These were found to be the cause of each lens opacification. The haptics appeared clear (Figure 4b). However, In some cases the opacification extended towards the haptics, which were completely opacified in one case.

Alizarin red staining of the surfaces of all lenses was negative. Analysis of the cut sections (sagittal view) of the lens optics revealed multiple granules of variable sizes in a region beneath the external anterior and posterior surfaces of the IOLs. The granules were distributed in a line parallel to the anterior and posterior curvatures of the optics. They stained positive with alizarin red (Figure 4c). In contrast to the findings of what morphologically resembled 'glistenings' of AcrySof™ IOL, light microscopic analyses revealed that the structures causing the opacification with these IOLs are not fluid-filled vacuoles, but rather are granules of variable sizes. Sagittal histological sections stained with the von Kossa method also confirmed the presence of multiple dark brown/black granules mostly concentrated in a

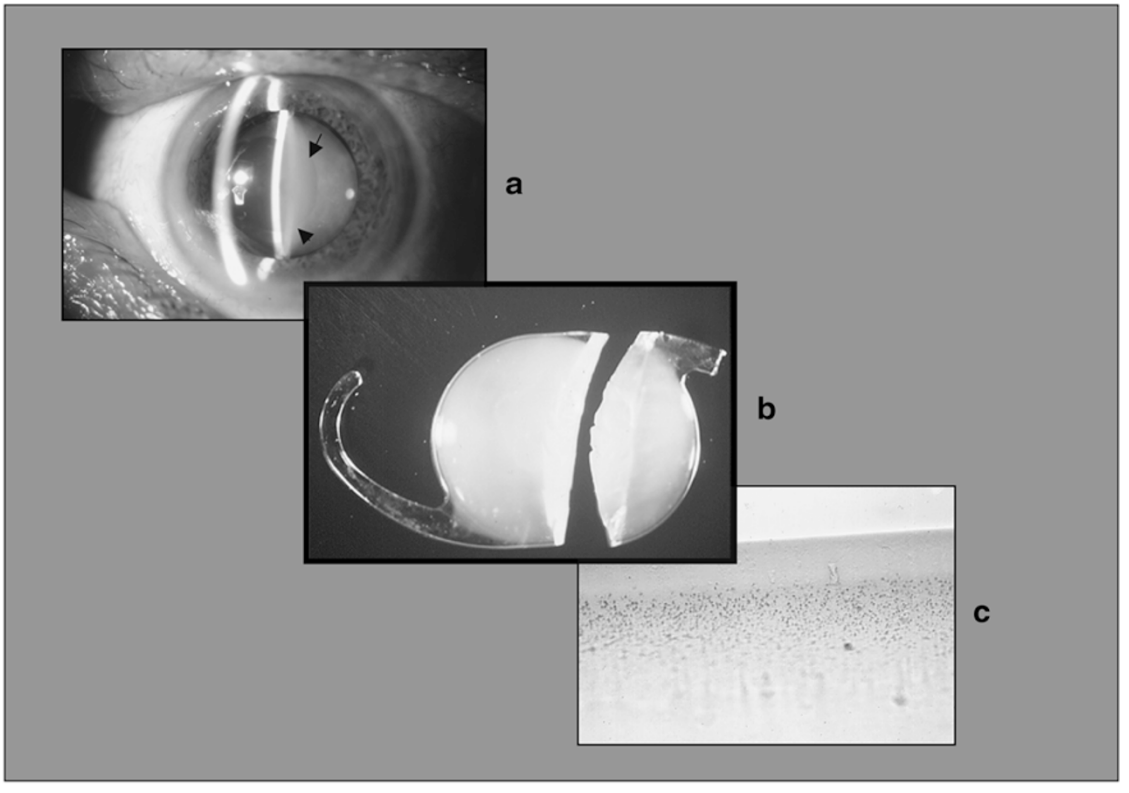

Figure 4 Opacification of SC60B-OUV IOLs. (a) Clinical photograph from a patient implanted with the SC60B-OUV lens. The surgeon noted that the optic of the lens actually resembled a cataract (courtesy Dr Mahmoud Soliman, Cairo, Egypt). Arrows indicate the edge of capsulorhexis. (b) Gross photograph of an explanted SC60B-OUV lens, showing dense opacification of the central opacified optic area. The IOL haptics are clear. (c) Photomicrograph of a cut section of the lens optic (sagittal view) of an explanted SC60B-OUV lens, showing the distribution of the deposits within its substance. The deposits stain positive with alizarin red (Alizarin red; original magnification $\times 200$).

region immediately beneath the anterior and posterior optical surfaces.

SEM analysis of a cut section (sagittal view) of the IOL optic confirmed that the region immediately subjacent to the IOLs' outer surfaces as well as the central area of the optical cut section were free of deposits. This also revealed the presence of the granules in the intermediate region beneath the anterior and posterior surfaces. EDS performed precisely on the deposits in the same section revealed the presence of Ca peaks. The central area of the optical cut section where no granules were present served as a control, showing only peaks of carbon and oxygen. EDS analysis of the deposits from the specimen obtained from one case, coated with aluminum, also demonstrated the presence of peaks of Ca and phosphate.

Three separate tests—the alizarin red stain, the von Kossa stain and SEM analyses with EDS, strongly suggest that the granules are at least in part composed of Ca. Coating a specimen with aluminum instead of gold/palladium enhanced identification of the substances by EDS. The EDS analysis of the latter demonstrated the presence of Ca and phosphate peaks. This suggests that the deposits within the IOL optics are composed of hydroxyapatite—a thermodynamically stable phase of Ca phosphate. EDS demonstrated the presence of Ca peaks only at the level of the deposits, not in the center of the optic and not in the region immediately subjacent to the surface.

Frohn, Dick, and associates from the University of Mainz, Germany, have studied explants of this IOL model and noted that the opacification within the optics may be related to the presence of unbound ultraviolet-absorbers (monomers).[56] According to these researchers, spectroscopic findings indicated premature aging of the UV blocking agent incorporated in the lens biomaterial. Their findings and the calcification process demonstrated by us may be correlated, although our data do not allow us to make definitive conclusions.

Summary

Analysis of explanted SC60B-OUV lenses because of opacification has demonstrated the cause to be the presence of granular deposits within the optics. The mechanism is not fully understood. The opacification does not seem to be directly related to substances used during the surgery since it always occurred in the late postoperative period. The possibility of a patient-related factor, such as a metabolic imbalance cannot be ruled in or out. We have noted material positive for Ca in the deposits and Dick and associates have noted unbound ultraviolet-absorber monomers. Further biochemical studies are necessary to reveal the complete biochemical profile of these alterations. It is now important to carefully follow clinical outcomes of this lens in order to assure if this phenomenon will disappear following this change in polymer source.

Glistening of the AcrySof™ IOL

Introduction

Glistening[57–62] related to the AcrySof™ IOL is well described in the literature as an acute onset of intralenticular small refractile fluid-filled vacuoles present inside the optic of the Alcon AcrySof™ (Figure 5). Glistenings have been reported to occur as soon as 1 week after surgery. The occurrence of some degree of glistening formation has been reported in all eyes implanted with an AcrySof™ lens for at least 6 months postoperatively. Some authors could not find a statistically significant relationship between the time and severity of glistenings. However, 93% of the IOLs that had more than trace glistenings had been in the eye for more than 1 year postoperatively.[60] Mitooka and associates reported a prevalence of nearly 60% glistening formation, 4–22 months postoperatively in 144 patients with AcrySof™ IOLs (K Mitooka, MD *et al*, poster presented at the Symposium on Cataract, IOL and Refractive Surgery, Seattle, Washington, USA, April 1999).

Pathogenesis

In vitro studies have suggested that the occurrence of glistenings (microvacuoles) in AcrySof™ IOLs may be related to variations in the temperature (Δt). The formation of vacuoles within the submersed acrylic

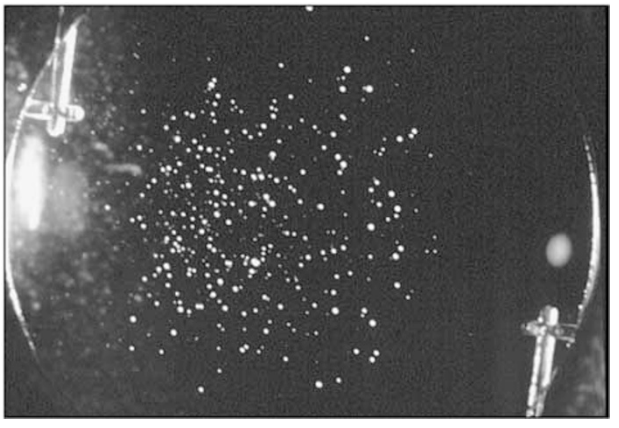

Figure 5 Gross photograph showing the glistenings within an AcrySof™ IOL.

polymer is observed when there is a transient increase in temperature above the glass transition temperature, which is approximately 18.5°C for AcrySof™ (Apple DJ, 'Clinicopathological correlation of vacuoles in an acrylic IOL'—Best Paper of Session—presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, April 1998, San Diego, CA, USA). 'Glistenings' may then subsequently form from anterior chamber fluid. The vacuoles have the characteristics of fluid rather than air bubbles.

Another *in vitro* study has demonstrated that when maintained at a constant temperature, Wagon Wheel (WW) packaged IOLs showed no glistening formation and the AcryPak™(AP) packaged IOLs showed significant glistening formation.[58] Glistenings were noted with WW packaged IOLs only under fluctuating temperature conditions. It has been reported that the IOL packaging, the AcryPak™, and the sterilization technique used with that system may have made the IOL susceptible to the microvacuole formation. *In vitro* studies have also demonstrated that the temperature at which the IOLs were stored and shipped in the dry state had no influence on the 'glistenings' and was thus unrelated to this phenomenon. In another *in vitro* study, glistenings initially progressed in size and density, gradually stabilizing in size with increasing density throughout the study period.[58]

The voluntary withdrawal of the AP packaged IOLs seems to have cured the glistening problem for this lens. However, in a recent retrospective study, Christiansen *et al*[60] have reported the appearance of glistenings in many patients with the AcrySof™ IOL even after the change to the WW packaged IOLs.

Impact on visual function

Clinical studies on the AcrySof™ IOL have demonstrated that contrast sensitivity has been decreased in some patients, but a clinically significant decrease in VA in association with glistenings has been rare. However, a recent study has demonstrated a statistically significant difference in VA between eyes with mild and severe glistening,[60] but for glare and contrast sensitivity no significant difference was found.

Summary

Glistening or vacuoles is described in the literature as acute onset of intralenticular small refractile fluid-filled vacuoles, inside the optic of the Alcon AcrySof™ IOL. It has been reported to occur as early as 1 week postoperatively. Although, initially reported to occur only with the AP packaging system, recent literature has reported it with WW packaging also.

'Snowflake' or crystalline opacification of PMMA IOL optic biomaterial

Introduction

PMMA was used as an optic biomaterial in Sir Harold Ridley's original IOL, manufactured by Rayner Intraocular Lenses Ltd, London, UK, and first implanted in 1949–1950.[63] Although surgeons in the industrialized world and in selected areas in the developing world have largely transitioned to foldable IOL biomaterials, PMMA does remain in widespread use in many regions. Over the past 50 years PMMA has been rightly considered a safe, tried and true material for IOL manufacturing with good and high quality control. Biomaterial studies on PMMA IOL optics were rarely required. Until now, any untoward complications such as PMMA-optic material alteration/breakdown have not been seen with this material and its fabrication. However, we have recently reported gradual but progressive late postoperative alteration/destruction of PMMA optic biomaterial causing significant decrease in VA, sometimes to a severity that requires IOL explantation.

Jean Champbell, MD, sent the first explant with this phenomenon to us in 1991. Subsequently and at an increased rate over the past 4 years, 25 cases including nine explanted IOLs were submitted to our laboratory.[64,65]

All of the explanted IOLs were 3-piece posterior chamber (PC)-IOLs with rigid PMMA optical components and blue polypropylene or extruded PMMA haptics. These had been implanted in the early 1980s to early 1990s in most cases and the clinical symptoms appeared late postoperatively, *ca* 8–15 years after the implantation. The clinical, gross, light and electron microscopic profiles of all the cases showed almost identical findings, differing only in the degree of intensity of the 'snowflake' lesions that in turn reflected the severity and probably the duration of the opacification. In the early stages of many of the cases, the lesions were first noted clinically by a routine slit lamp examination, in the absence of visual disturbances. Most examiners described the white-brown opacities within the IOL optics as 'crystalline deposits' (Figure 6a). They appeared to progress gradually in most cases. Clinically, the slowly progressive opacities of the IOL optics usually start as scattered white-brown spots within the substance of the IOL optic. These usually do not have an impact on the patients' VA. They gradually increase in intensity and number, eventually reaching a point where the VA loss necessitates removal or exchange of the IOL. In addition to visual loss the symptoms included decrease

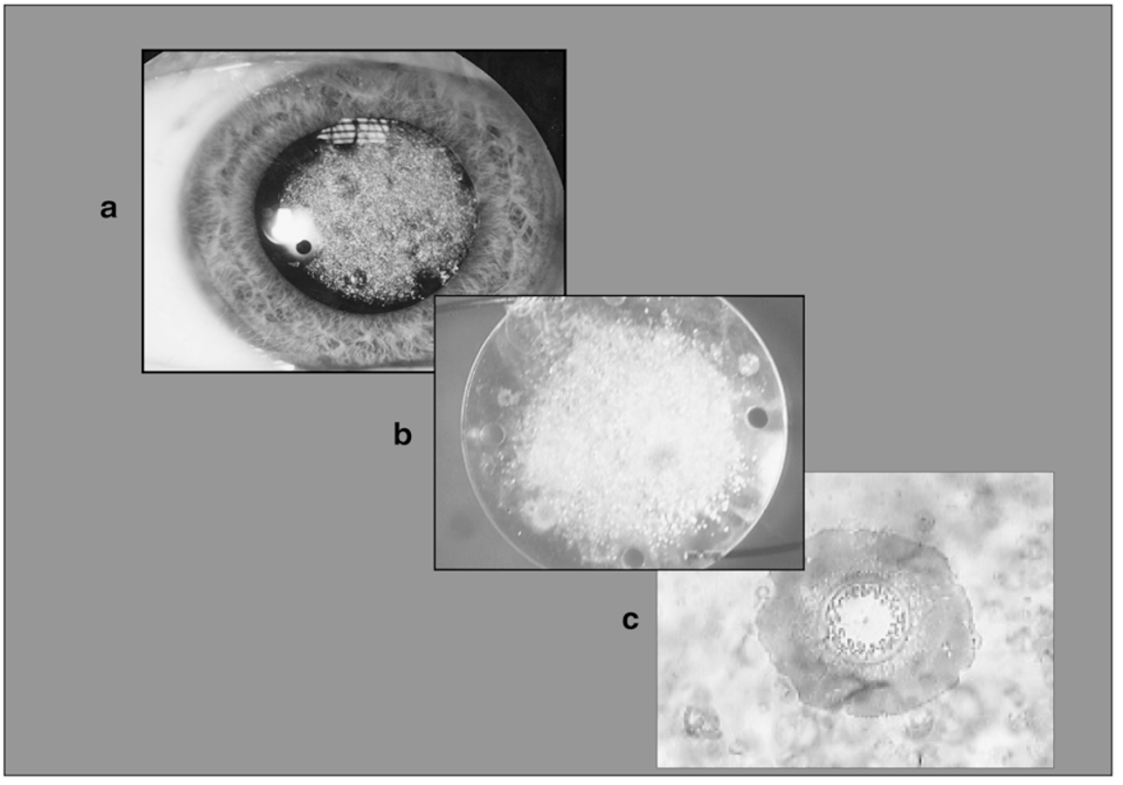

Figure 6 'Snowflake' or crystalline opacification of PMMA IOLs. (a) Clinical picture of an eye implanted with a PMMA IOL. Note the dense lesions covering the central part of the IOL optic. The peripheral optic protected by the iris is clear of the lesions. (b) Gross photograph of a rigid 3-piece PMMA lens affected with snowflake degradation, demonstrating that most of the involvement is within the central core of the lens optic, with sparing of the outer periphery of the optic. (c) High power 3-dimensional light photomicrograph of a rigid 3-piece PMMA lens affected with snowflake degradation showing an individual snowflake lesion. There is an empty central space containing few particles of PMMA convoluted material (fragmented PMMA) surrounded by a dense outer pseudocapsule.

in contrast sensitivity and various visual disturbances and aberrations, including glare.

Analysis of explanted IOLs

The 'snowflake' lesions were most commonly observed in the central and mid-peripheral portion of the IOL optics. The peripheral 0.5–1 mm rim of the lens optics appeared to be free of opacification (Figure 6b). Views of the cut edges of the bisected optic specimens prepared for SEM confirmed that the 'snowflake' lesions were all within the substance of the IOL. Many were focal and discrete, with intervening clear areas, but some appeared coalescent. In at least some cases there was an uninvolved space between the front IOL surface and the actual lesions, which involved the anterior 1/3 of the optic's substance. The opacifications showed no birefringence in polarized light. All histochemical and EDS analyses were negative, indicating no infiltration of exogenous material. SEM revealed that, although various miscellaneous changes, such as surface protein depositions were noted in some cases, no other surface changes correlated with the opacification could be identified. Confocal microscopy of one IOL confirmed the spherical (circular) nature of the lesions as observed under light microscopy and SEM. Under higher magnification, the individual opacities revealed a distinct pattern consisting of a pseudocapsule surrounding the core of the lesion, which appeared to be 'empty' except for the fragments of convoluted material. The examinations performed to identify the nature of the deposits, including EDS did not document any exogenous chemicals apart from the lens optic's PMMA itself. High power three-dimensional light microscopy (Figure 6c) and SEM of bisected IOL optics were the most informative examinations with regard to illustrating the structural nature of the opacifications.

Mechanism of action

The manufacturing variations in some lenses fabricated in the 1980s-early 1990s, especially those made with molding processes (injection, compression, cast) may be

responsible for the 'snowflake' lesions. PMMA is a polymer of methyl methacrylate (MMA). It is manufactured by additional polymerization using the MMA monomer, the process being started by an initiator substance.[66–68] A frequently used initiator is azo-bis-isobutyryl nitrile (ABIN). It can be postulated that PMMA disruption might be related to a specific manufacturing problem such as, leaving the residual initiator substance (ABIN) embedded in the substance of the PMMA optic. This can occur during a molding process. The two double-bonded units of the ABIN initiator may be broken by gradual ultraviolet stimulation, with a release of Nitrogen gas (N_2). Either heat or UV light exposure can cause such gas formation. Indeed the normal polymerization process for PMMA synthesis in part consists of a heat-induced N_2 formation. During this normal process the N_2 escapes from the mixture. However, with a poor manufacturing process, for example using excessive initiator more than the fractional amount required, unwanted initiator might be entrapped in the PMMA substance. Therefore, the double bonds of the initiator might leave to a continuous UV radiation, thereby releasing gaseous N_2 within the PMMA substance. This would explain the formation of loculated cavitations in the lesions, in which the outer 'pseudocapsule' consists of PMMA material compressed outwardly from the cavity, the central spaces containing the N_2 gas and the convoluted material within the spaces consisting of disrupted PMMA. Since there is no route for aqueous ingress into the optic, eg pores, a permeation of aqueous into the parenchyma forming the cavities is unlikely. The molding procedure, in which each mold is made one at a time, would be more likely to be prone to manufacturing problems within the individual molds.

Two pathologic observations of the 'snowflake' phenomenon suggest that the lesions may be sensitive to long-term solar (ultraviolet) exposure. First, opacities are often situated in the center of the optic, extending to the mid-peripheral portion but often leaving the distal peripheral rim free of the opacities. Furthermore, the opacities are present most commonly and intensely on the anterior one-third IOL's thickness, the stratum that might be expected to have more interaction with ultraviolet radiation.

Although, it is possible that UV radiation is a contributing factor, the exact pathogenesis can as of now only be hypothesized. Potential causes of the development of a snowflake lesion include: poor filtrations of the pre-cured monomeric components (MMA, UV blocker, thermal initiator); non-homogeneous dispersement of the UV chromophore and/or thermal initiator into the polymer chain; excessive thermal energy during the curing process leaving voids in the polymer matrix; insufficient post-annealing of the cured PMMA polymer.

These hypothetical mechanisms have the potential to form micro-heterogeneity within the PMMA polymer that, over time and potentially with exposure to UV radiation, could result in a lesion within the polymer. Additional experimentation is necessary to determine if any of these proposed mechanisms for the formation of a snowflake lesion are realized.

Summary

As a footnote to the description of this condition, these late-occurring lesions may be looked upon as representing a 'time bomb' effect, indeed so designated by some authorities in the 1990s. This syndrome referred to as 'snowflake' opacification, occurs unexpectedly long after the implantation and in some ways provides a partial vindication of those who spoke with concern about this possibility. This necessitates that today's ophthalmologists be aware of, diagnose, and know when to explant and exchange these lenses. It is important to know the nature of this syndrome in order to spare patients and their doctors unwarranted worries about the cause of his or her visual problems/loss and also to obviate for unwarranted diagnostic testing. Awareness of this delayed complication may also be warranted in developing countries, where PMMA IOLs are still used in the majority of cases. Virtually all IOLs manufactured today seem to be satisfactory. However, one should always be aware that many such early designs from American manufacturers as described in this report, have been delivered to the developing world over the years, sometimes implanted without regard to expiration dates on the packaging. It would be very unfortunate to see this complication showing up in underprivileged areas where patients have little resources for managing this type of visual loss/blindness.

Interlenticular opacification of 'piggyback' IOLS

Introduction

One of the most important complications related to the implantation of multiple PC IOLs (piggyback IOL or polypseudophakia) is 'Interlenticular Opacification' (ILO), also named 'Interpseudophakos Elschnig Pearls' or 'Red Rock Syndrome' (Stasiuk R, 'Red rock syndrome: Interlenticular opacification with piggyback IOL implantation', presented at the ESCRS Symposium on Cataract, IOL and Refractive Surgery, September

1999, Vienna, Austria).[69–72] Together with surgeons performing piggyback implantation, our laboratory has been devoting constant efforts to determine the pathogenesis and management of this complication (Figures 7–9).[72–75] We have recently proposed clinical and pathological lessons for prevention and management of this entity (Pandey SK, Snyder ME, Werner L, Apple DJ, Trivedi RH, Macky TA, Izak AM, 'Interlenticular opacification (ILO): Clinical and pathological lessons for prevention and management', prize winning video; Pandey SK, Werner L, Apple DJ, Solomon KD, Snyder ME, Brint SF, Gayton JL, Shugar JK. Interlenticular opacification after piggyback intraocular lens implantation, Best cataract poster, presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, April–May 2001, San Diego, CA, USA). The technique of piggyback IOLs is used relatively frequently now and it will increase in use during the next decades. Therefore, an awareness of this new condition, as well as of the surgical methods to prevent its development is warranted.

Analysis of explanted IOLs

With the first two specimens we received in our laboratory, surgeons had exhaustively tried to clean the interface between the lenses before explantation.[72,73] However, we have recently received in our Center four new pairs of acrylic piggyback lenses explanted because of ILO. Three of these new cases shared the common aspect that exhaustive attempts to clean the interface between the lenses were not performed by the surgeons before explantation, probably because ILO is now a well-known entity. This fact allowed us to analyze new explanted piggyback lenses with all the original components of ILO *in situ*, which helped us better understand the pathogenesis of this complication.[74]

After macroscopic and microscopic analysis, lenses from some cases had their surfaces directly stained with hematoxylin and eosin (H & E) and were re-examined under the light microscope. The posterior lens of one case was processed for histopathological examination (dehydration in ethanol; embedding in

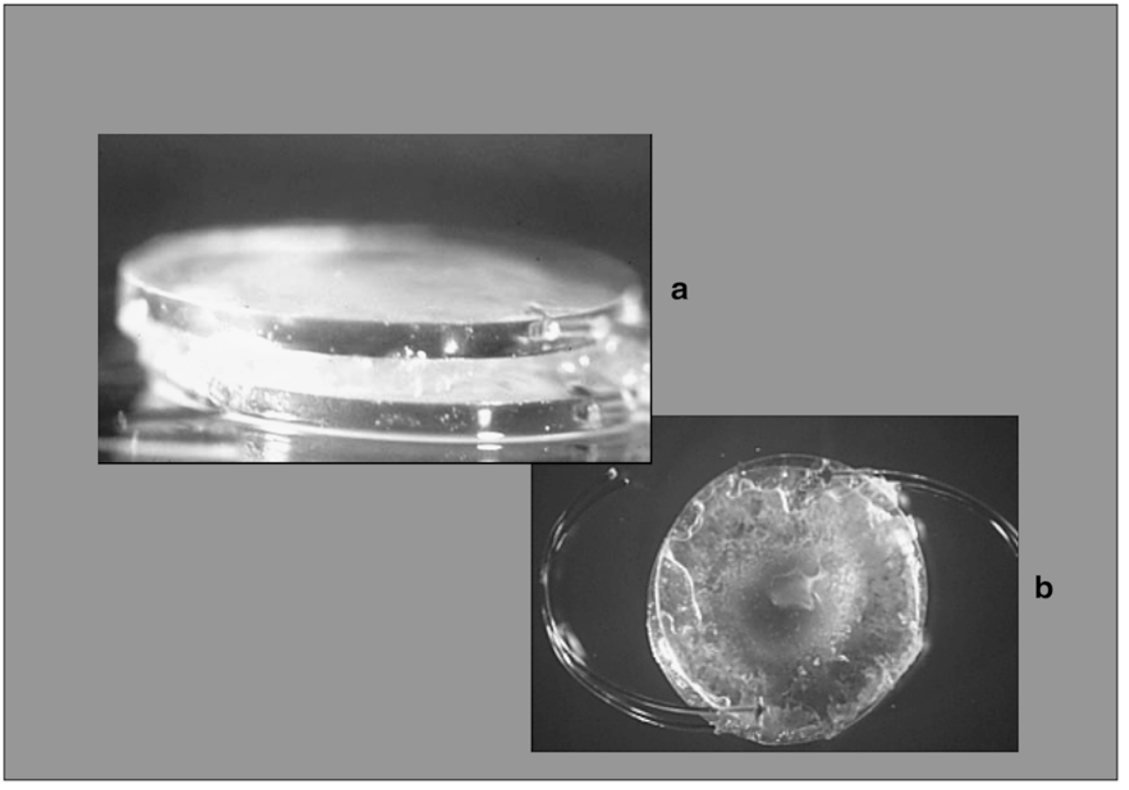

Figure 7 Interlenticular opacification between piggyback IOLs. (a) Gross photograph from a pair of explanted piggyback lenses (sagittal view) showing the membrane-like formation sandwiched between the lenses. (b) Frontal view of the same pair of lenses. Note the white opacification between the two implants. There are some clear areas, including the central zone, where a depression on the anterior surface of the anterior lens can be observed.

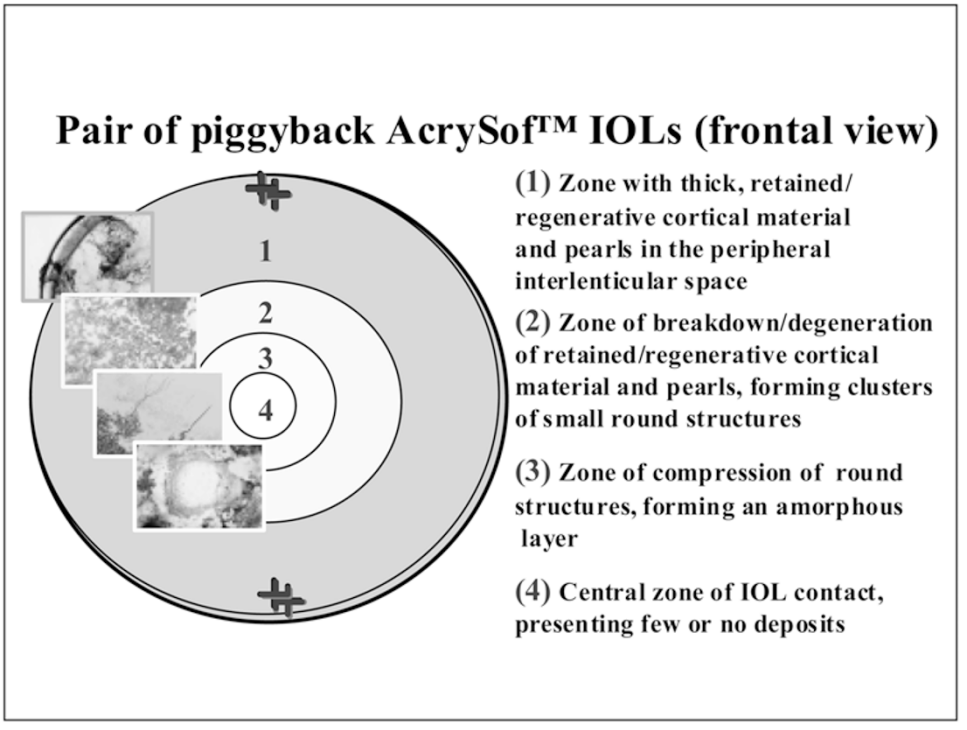

Figure 8 Schematic drawing representing a frontal view of a pair of AcrySof™ piggyback lenses. The interlenticular space was divided into four zones, according to its thickness and the aspect of the material attached to the IOLs' opposing surfaces. Schematic drawing by Liliana Werner, MD, PhD, Charleston, SC, USA.

paraffin; section) and the resultant tissue sections were stained with H & E, Periodic acid-Schiff (PAS), and Masson's trichrome. The anterior lens of another specimen was prepared for SEM.

In our first clinicopathologic report (Dr Gayton's cases), the opaque, membrane-like material localized between the piggyback lenses was histopathologically demonstrated to be composed of retained/regenerative cortex and proliferating lens epithelial cells, including bladder (Wedl) cells. This profile is virtually identical to the pathologic process seen in posterior subcapsular cataracts and in the typical 'pearl' form of PCO.[72]

In our second report (Dr Shugar's case), the surgeon could not aspirate the paracentral material attached mostly to the anterior surface of the posterior IOL, which was amorphous, compact and completely acellular. He could only aspirate the pearls and retained/regenerative cortex in the peripheral interface. The cases described in the two above-mentioned reports were considered as different forms of ILO at that time.[73]

However, further analysis of the lenses explanted without previous attempts to clean their opposing surfaces and thus with the ILO components *in situ* helped us to understand its pathogenesis.[74] It shows that the classification of ILO in different forms may be artificial. The material opacifying the interlenticular space was composed mostly of retained/regenerative cortical material in all cases. From the peripheral interface towards the central interface, the aspect of the opacifying material changed as the interlenticular space was progressively narrower. Figure 8 is a schematic drawing showing a frontal view of a pair of AcrySof™ piggyback lenses separated in the periphery and almost fused together in the center. The material attached to the peripheral interface (zone 1), where the interlenticular space is wider was very thick. At the midperipheral interface (zone 2), it could be observed that the thick cortical material was broken into multiple small, round structures. At the paracentral zone (zone 3) the round structures were progressively compressed until only a flat, compact layer of an amorphous material could be observed. SEM photographs clearly demonstrated this fact. At the central interface (zone 4) where the lenses were in close opposition, almost no material could be found.[76]

Histological sections obtained from the posterior lens in one case and stained with H & E, PAS, and Masson's trichrome demonstrated the breakdown of residual/regenerative cortical material into multiple, small globules. Compression of the globules in the paracentral area because of the narrower interlenticular space was demonstrated by SEM analysis of the posterior surface of the anterior lens in another case.

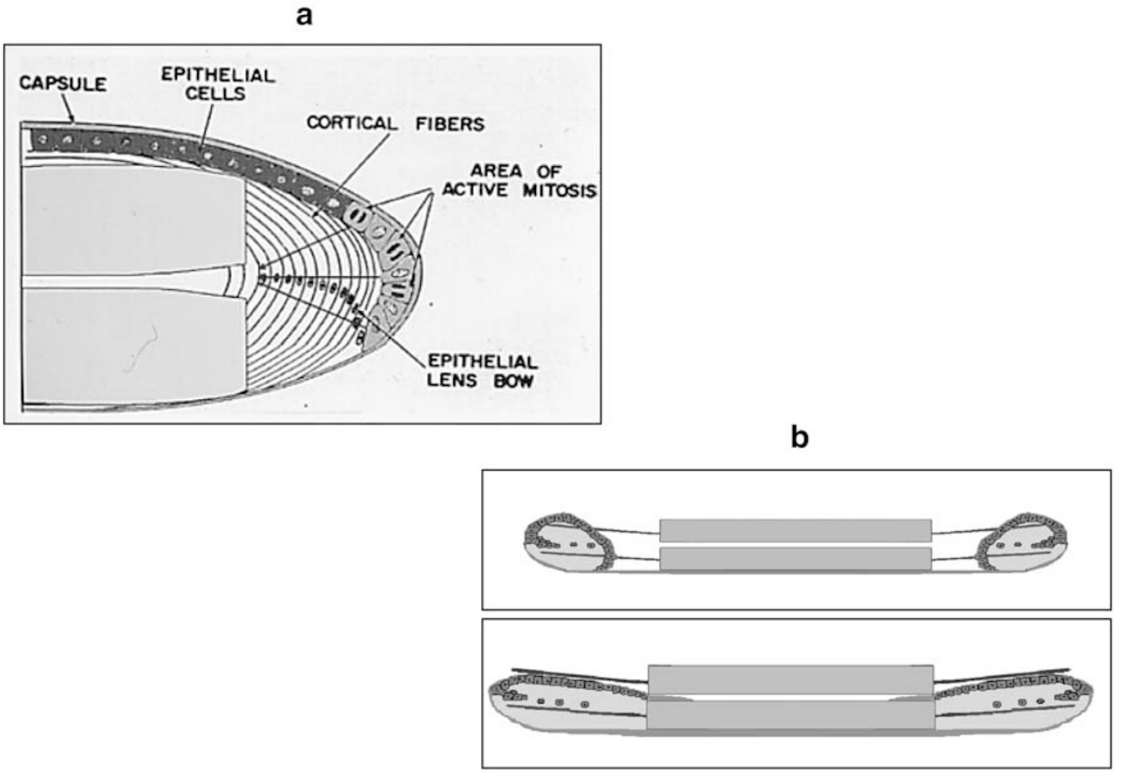

Figure 9 (a) Schematic illustration showing two intraocular lenses placed in the capsular bag. Note the potential ingrowth of lens epithelial cells from the equatorial lens bow in the interlenticular space. Schematic drawing by Nithi Visessook, MD, Charleston, SC, USA. (b) Schematic illustration of various scenarios of piggyback IOL implantation (suggested by the authors and other surgeons in consultation, including Johnny L Gayton, MD, Paul Ernest, MD and Ron Stasiuk, MD). With the Alcon AcrySof™ IOL the anterior lens epithelial cells usually atrophy and the capsule adheres to the anterior capsule. Schematic drawing by Beau B Evans, BS, Charleston, SC, USA. (i) Piggyback IOLs: both IOLs implanted are in the capsular bag but with a relatively larger diameter CCC. In this scenario, there is a possibility that the cut edge of the CCC may fuse with the posterior capsule as shown here. This fusion process should help sequester the retained/proliferative equatorial lens epithelial cells within the equatorial fornix and prohibit growth towards the ILS. This should thus lessen the likelihood of migration of cells into this space. (ii) Piggyback IOLs: the posterior (rear) IOL is implanted in the capsular bag with the cut edge of the relatively small diameter CCC resting on its anterior optical surface. The anterior (front) IOL is placed in the ciliary sulcus, anterior to the CCC. Retained/proliferative lens epithelial cells are confined to the compartment of the capsular bag around the rear IOL, but the ILS in front of the CCC is sequestered with this scenario.

EDS analysis performed on the deposits demonstrated the presence of peaks of sodium.

Pathogenesis

To date, all cases of ILO we analyzed in our laboratory seemed to be related to two PC-IOLs being implanted in the capsular bag through a small capsulorhexis, with its margins overlapping the optic edge of the anterior IOL for 360°. There may also be a specific interaction with the AcrySof™ material itself as it has been found to present adhesive properties *in vitro*. When two AcrySof™ lenses are implanted in the capsular bag, there is a bioadhesion 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 (Figure 9a). In this scenario, the two IOLs are sequestered together with aqueous and lens epithelial cells in a hermetically closed microenvironment. The migration of the cells from the equatorial bow is then directed towards the interlenticular space. Changes in pH and oxygen content may promote liquefactive degeneration of the retained/regenerative cortical material, with the formation of clusters of small, round structures. Cortical liquefactive degeneration with the formation of 'globules', similar to the round structures observed in our last few ILO cases is an important histopathologic indication of cataractous changes.

Findl *et al*[76,77] studied the morphological appearance and size of contact zones of piggyback IOLs. Changes in the morphology and the size of the contact zone of the piggyback IOLs of different materials and optic designs were analyzed prospectively. The contact zone between the anterior and posterior IOLs was photodocumented from day 1 to 1 year after surgery using specular microscopy. A contact zone was present

with all IOL materials studied. The area of contact, however, differed significantly. With PMMA IOLs, the contact zone was small and surrounded by Newton rings, indicating the tiny gap between the IOLs. With IOLs of soft material, such as silicone and hydrogel, it was larger than with PMMA IOLs and had a slightly irregular shape. With foldable acrylic IOLs, it was regular, round, and slightly larger than with the other soft materials. The contact area enlarged primarily during the first 3 months after surgery. After 1 year, two eyes with acrylic piggyback IOLs had a membrane formation around the contact zone and two eyes developed Elschnig pearls between the IOLs. Contact area enlargement appears to be induced by capsular shrinkage.

Surgical prevention

Based on the common features of ILO cases, some surgical methods were proposed for its prevention (Figure 9b). The first option would be to implant both IOLs in the capsular bag but with a relatively large diameter capsulorhexis. In this scenario, there is a possibility that the cut edge of the rhexis may fuse with the posterior capsule. This should help sequester the retained/proliferated equatorial lens epithelial cells within the equatorial fornix. The other possibility is to implant the anterior IOL in the sulcus and the posterior IOL in the bag with a small rhexis. The rhexis margin will adhere to the anterior surface of the posterior IOL and the cells within the equatorial fornix will also be sequestered. Careful follow up of the cases implanted using these techniques will indicate their effectiveness in the prevention of ILO. We have recently been able to evaluate the efficacy of the second surgical option. Dr M Edward Wilson from Charleston, South Carolina, USA implanted piggyback AcrySof™ lenses in infantile eyes to manage the changing refractive status of these patients. This procedure, called 'temporary polypseudophakia', may help in the prevention and treatment of amblyopia by avoiding residual hyperopia. The posterior lens is implanted in the capsular bag, through a capsulorhexis that is smaller than the IOL optic, and the anterior lens is implanted in the ciliary sulcus. Within 12–24 months after the primary surgical procedure, the lens implanted in the ciliary sulcus is explanted/exchanged. To date, 15 infantile eyes have had this procedure performed successfully, without significant clinical complications. Seven AcrySof™ lenses have already been explanted. After almost 2 years of follow up, no significant ILO was observed in any of these cases.[78]

Summary

Analyses of new ILO cases where all the components of the opacifying material were *in situ* allowed us to confirm that the pathogenesis of this complication is similar to that of PCO. The aspect of this material varies according to the space available in the interlenticular interface. One should be aware that careful cortical clean up is mandatory in piggyback IOL implantation.

Posterior capsule opacification

Introduction

PCO has been well known since extra capsular cataract extraction (ECCE) was introduced in cataract surgery. It occurred at an incidence of between 30% to 50% through the 1980s and early 1990s, when the surgical importance of cortical and cell clean up was less understood than it is now.[79] In a 1998 meta-analysis, PCO rates of 11.8% after 1 year, 20.7% after 3 years, and 28.4% after 5 years have been reported.[80] Our current data show that with modern surgical techniques, IOL designs and materials the Nd:YAG laser treatment rate for PCO is decreasing[81–89] (Figures 10–12). The validity of this observation can be at least partially verified and documented by tying the information and conclusions gained from clinical studies with the PCO/Nd:YAG laser data.

Pathogenesis

Although all of the lens epithelial cells are a continuous single cell line, in terms of function and pathologic processes, it is useful to divide these into two different functional groups, the A cells and the E cells. The primary type of response of the A cells to any stimulus is to proliferate and form fibrous tissue by undergoing fibrous metaplasia, sometimes termed 'pseudofibrous metaplasia' by Font and Brownstein.[10] The E cells comprise the germinal cells, which are the primary cells in the origin of PCO. They normally migrate centrally from the lens equator and contribute to the formation of the nucleus, epinucleus, and cortex throughout life. E cells are the primary source of the pearl form of PCO. In contrast to the A cells which, when disturbed, tend to remain in place and not migrate, the E cells of the equatorial lens bow tend to migrate posteriorly along the posterior capsule. Therefore, the term PCO is a misnomer. It is not the capsule which opacifies. The opaque membrane ensues as retained cells proliferate and migrate onto the posterior capsule. The resulting opacity usually takes

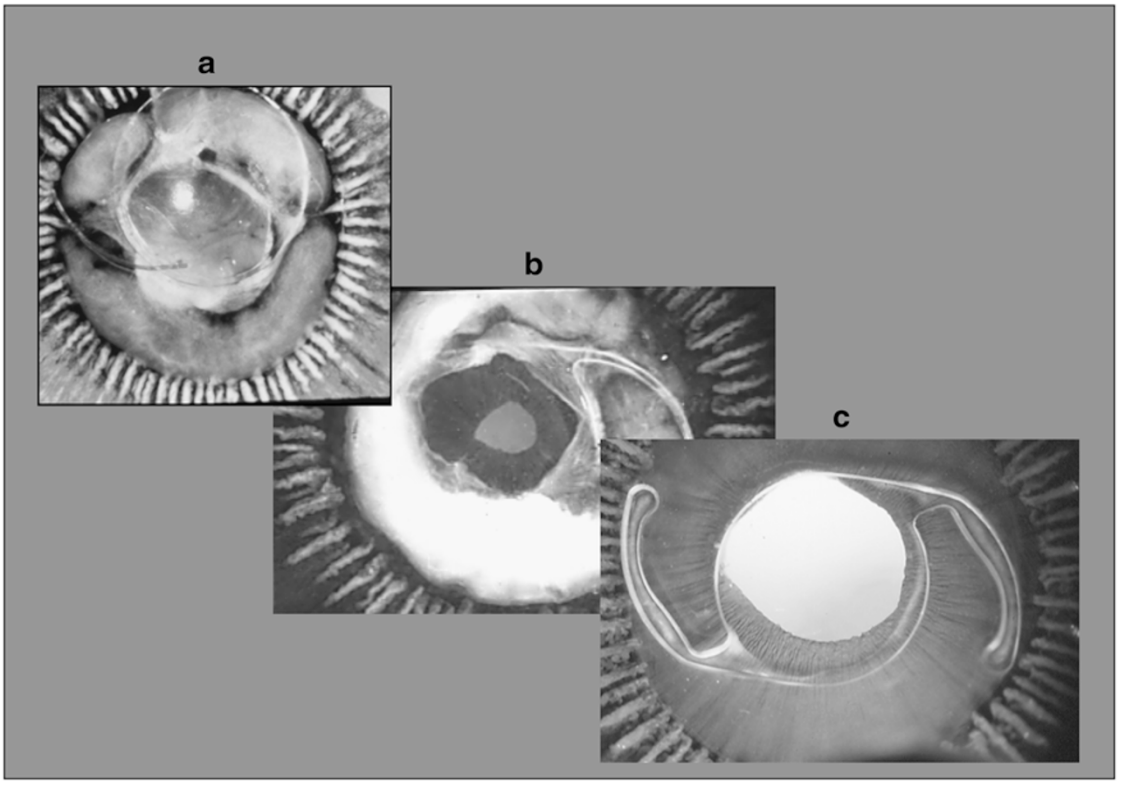

Figure 10 Posterior capsule opacification (PCO). (a) Miyake-Apple view showing dense PCO. (b) Miyake-Apple view of a rigid one-piece PMMA IOL in situ, following Nd:YAG capsulotomy. Note the polygonal rim of the capsulotomy and the dense aspect of the PCO. (c) Miyake-Apple view of a foldable one-piece Alcon AcrySof™ lens showing excellent centration and clarity of the media with perfect symmetric in-the-bag fixation. There is slight contact of the iris at the upper left edge of the IOL optic, but otherwise this represents an excellent result. This is the first pseudophakic human eye obtained post-mortem implanted with this design we received in our Center, as a single piece AcrySof™ IOL has only recently been introduced in the market.

one or two morphologic forms or a mixture of the two: (1) clusters of swollen, opacified epithelial 'pearls' or clusters of proliferated and posterior migrated E cells (bladder or Wedl cells). It is probable that both the A and the E cells have the capability to contribute to the 'pearl' form of PCO as well as the second form; (2) the fibrous form. A cells probably are more implicated in the pathogenesis of the fibrotic form of PCO, since the primary type of response of these cells is fibrous metaplasia. Although the preferred type of growth of the E cells is in the direction of bullous-like bladder (Wedl) cells, they may also contribute to the formation of the fibrous form of PCO by undergoing a fibrous metaplasia. The E cells within the Soemmering's ring are the source of PCO in most cases. Therefore, it is important to note that Soemmering's ring is a direct precursor to PCO. If surgeons were able to prevent Soemmering's ring formation by any means, then a decrease in PCO rates would follow.

Analysis of Nd:YAG posterior capsulotomy rates in rigid and foldable IOL designs

Table 2 shows the ranking of the Nd:YAG laser posterior capsulotomy rates (%) for eight lens designs as of December 2000, starting with the lens showing the lowest percentage at the top and the highest rate at the bottom. Note that the four lenses with the lowest rates ranging between 3.3% and 20.7% are modern designs, mostly implanted after 1992 in contrast to the four lenses with the higher rates ranging between 23.3% and 33.7%. These were all older designs, already in the database prior to 1992. The difference in the Nd:YAG laser rates between the acrylic IOLs and the other IOL types was found to be statistically significant ($P < 0.05$, for all comparisons, Chi-square test). The Nd:YAG laser rate of all six foldable IOLs collectively, 15.3% (170/1109), was significantly lower than the rate of the rigid IOLs (32.3%; 1722/5316; $P < 0.05$, Chi-square test). If one removes the AcrySof™ IOL from the

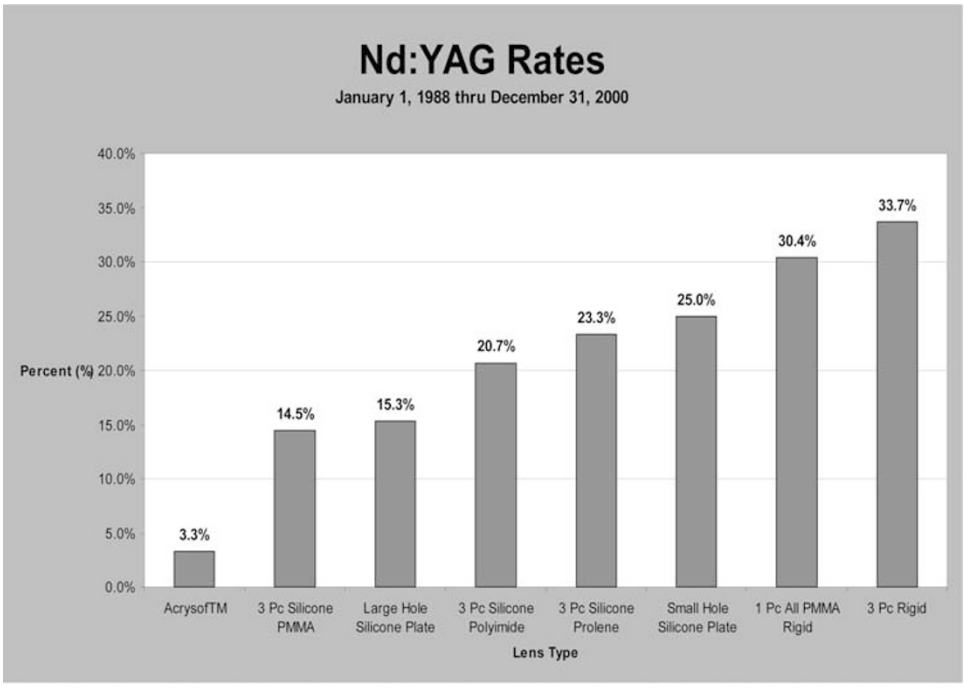

Figure 11 Bar graph showing relative Nd:YAG laser posterior capsulotomy rates of the eight IOLs described in this article. Note the low rate (3.3%) of the acrylic-PMMA (Alcon AcrySof™) lens. The four lenses with the lowest rates were all relatively new, as compared to the four lenses with the highest rates. This suggests that the differences in Nd:YAG laser rates between the two groups at least in part relate to variations in surgical technique, with obvious information on small incision surgery helping create the efficient results of the newer lenses.

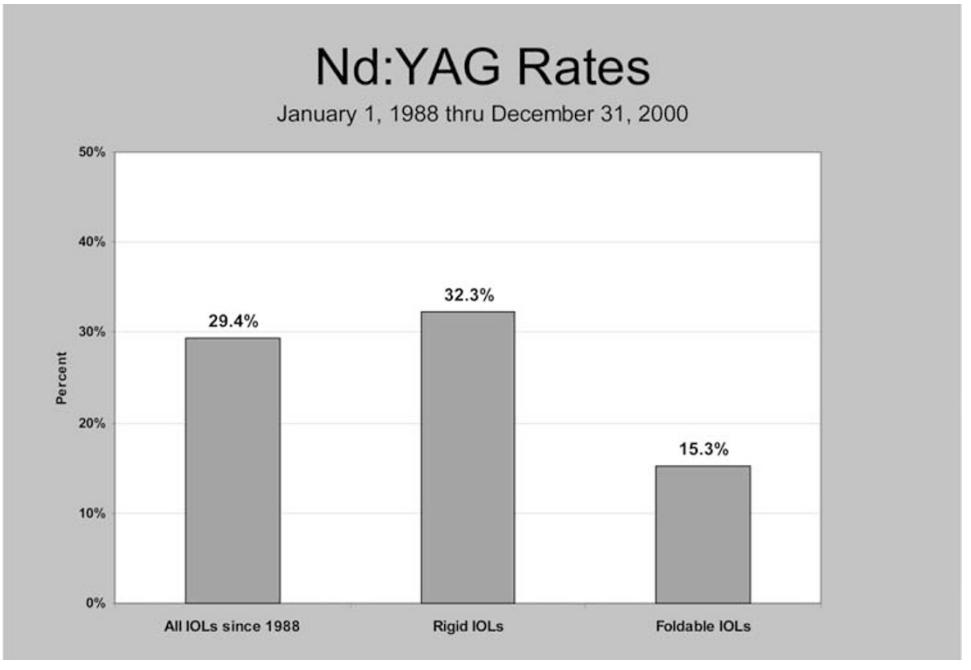

Figure 12 The Nd:YAG posterior capsulotomy rate of all lenses in this study was 29.4%. The rate of the rigid lenses was 32.3%. Note, in sharp contrast, that the rate for the foldable lenses taken together was only 15.3%. This efficacious result is based on the combination of high quality modern 'capsular' surgery associated with high quality modern foldable IOLs.

Table 2 Nd:YAG rate (%) Jan 1 1988–Dec 31 2000

IOL	*Total*	*Nd:YAG*	*YAG %*
3 PC Acrylic-PMMA (Acrysof)	361	12	3.3%
3 PC Silicone-PMMA	110	16	14.5%
1 PC Silicone plate, large hole	85	13	15.3%
3 PC Silicone-polyimide	82	17	20.7%
3 PC Silicone-prolene	347	81	23.3%
1 PC Silicone plate, small hole	124	31	25.0%
1 PC All-PMMA (rigid)	2128	647	30.4%
3 PC PMMA (rigid)	3188	1075	33.7%
All lenses since 1/88	6425	1892	29.4%
Foldable lenses	1109	170	15.3%
Rigid lenses	5316	1722	32.3%

group, the rate noted amongst the other foldable IOLs studied increases to 158/748 (21.1%).

In order to evaluate the influence of lens quality *vs* the influence of the surgical technique on the PCO/Nd:YAG laser posterior capsulotomy rates, it is useful to follow a trend-line over a long-term period. Under optimal conditions, but not possible in this analysis, the information should be viewed considering the age and the duration of each implant. However, the dates of implantation or the time between implantation and death were difficult to determine, due to ethical considerations. These variables are going to factor out over time as larger numbers are obtained and the trend 'time line' is extended.

Tracking the trend 'time lines' for each lens design will be necessary to help rule out other factors in addition to the duration of each implant in the eye (for example, the quality of surgery) in order to properly assess the differences among the IOLs. Various surgeons' criteria for Nd:YAG laser capsulotomy (eg aggressive, conservative) also play a role in the rate. Nevertheless surgeons' criteria, surgical technique, and implant duration will become equalized as the number of accessions and the duration of the study increases.

Two principles of PCO prevention

The principles of PCO prevention can be subdivided into two categories:

(1) Primary line of defense: To minimize the number of retained/regenerated cells and cortex in the capsular bag.
(2) Secondary line of defense: If some cells do remain, the barrier effect works as a second line of defense and helps to prevent PCO by blocking the growth of the cells from the equatorial region toward the center of the visual axis.

After several experimental studies on the pathogenesis and treatment of PCO in our laboratory, and after compiling information derived from other laboratories and clinical studies from several centers worldwide, we have ascertained various factors that help bring about the very positive conclusion that surgeons now have the sufficient tools and appropriate IOLs to help reduce the incidence of PCO.[81–89]

Although all steps of the cataract operation are, of course, important in reducing any complication, we have identified three surgery-related factors and three IOL-related factors that stand out as particularly important in relation to preventing or at least delaying this complication. It is our goal to show that all of these factors as a unit are key to achieving PCO reduction.

Three surgery-related factors to reduce PCO

(1) Hydrodissection-enhanced cortical clean up: With careful, meticulous hydrodissection, the operation is much easier and faster, cortex and cell removal is more thorough and formation of an unwanted Soemmering's ring is minimized. Recently, we have shown this important additional long-term advantage of hydrodissection namely, a means of more efficient removal of cortex and cells that in turn is essential in reducing PCO.[86]
(2) In-the-bag (capsular) fixation: The hallmark of modern cataract surgery is the achievement of consistent and secure in-the-bag (capsular) fixation. The most obvious advantage of in-the-bag fixation is the sequestration of the IOL from adjacent uveal tissues. It is not often appreciated that this is also extremely important in reducing the amount of PCO. The primary function of in-the-bag fixation is enhancing the IOL-optic barrier effect, which is functional and maximal when the lens optic is fully in-the-bag with direct contact with the posterior capsule. In case one or both haptics are not placed in the bag, a potential space is created, allowing an avenue for cells to grow posteriorly toward the visual axis.
(3) Capsulorhexis edge on IOL surface: A less obvious, but significant addition to precise in-the-bag fixation is creating a CCC diameter slightly smaller than that of the IOL optic. For example, if the IOL optic was 6.0 mm, the capsulorhexis diameter would ideally be slightly smaller, perhaps 5.0–5.5 mm. This places the cut anterior capsule edge on the anterior surface of the optic, providing a tight fit (analogous to a 'shrink wrap') therefore helping to sequester the optic in the capsular bag from the surrounding aqueous humor. This mechanism may support protecting the milieu within the capsule

from at least some potentially deleterious factors within the aqueous, especially some macromolecules, and some inflammatory mediators. The concept of capsular sequestration based on the CCC size and shape is subtle, but more and more surgeons appear to be applying this principle and seeing its advantages.

Three IOL-related factors to reduce PCO

In addition to the three above-mentioned surgery-related factors we will briefly describe the three IOL-related factors, which in our opinion play an important role in the eradication of PCO.

(1) Biocompatibility: Lens material biocompatibility is an often-misunderstood term. It may be defined by many criteria such as the ability to inhibit stimulation of epithelial cellular proliferation: the less the cell proliferation the less the chance for secondary cataract formation. The Alcon AcrySof™ IOL scored well with these criteria, with respect to Soemmering's ring formation, PCO and with respect to ACO. In addition, the amount of cell proliferation is greatly influenced by surgical factors, such as copious cortical clean up. Furthermore, the time factor plays a role, such as the duration of the implant in the eye. Additional long-term studies are required to assess the overall role of 'biocompatibility' in the pathogenesis of PCO.
(2) Maximal IOL optic-posterior capsule contact: Other contributing factors in reducing PCO are posterior angulation of the IOL haptic and posterior convexity of the optic. This is due to the creation of a 'shrink wrap', a tight fit of the posterior capsule against the back of the IOL optic. The relative 'stickiness' of the IOL optic biomaterial probably helps to produce an adhesion between the capsule and IOL optic. There is preliminary evidence that the Alcon AcrySof™ IOL biomaterial provides such enhanced adhesion, or 'bioadhesion'.[90,91] This will require further study.
(3) Barrier effect of the IOL optic: The IOL optic barrier effect plays an important role as a second line of defense against PCO, especially in cases where retained cortex and cells remain following ECCE ('no space, no cells'). A lens with one or both haptics 'out-of-the-bag' has much less of a chance to produce a barrier effect. Indeed, the IOL optic's barrier function has been one of the main reasons that PC IOLs implanted after ECCE throughout the decades did not produce an unacceptably high incidence of florid PCO. Actually, the barrier effect has enabled the success of IOL implantation after ECCE during the past decades.

A subtle difference between classic optics with a round tapered edge and optics with a square truncated edge became evident recently. The effect of a square-edge optic design as a barrier was first reported by Nishi *et al* in the rabbit model (O Nishi, MD, presented at the XVth Congress of the European Society of Cataract and Refractive Surgeons, Prague, Czech Republic, September 1997). In a clinicopathological study, our laboratory was the first to confirm this phenomenon in human eyes (DJ Apple, MD, 'Optic geometry in relation to posterior capsule opacification', presented at the Chicago Ophthalmology Society, Chicago, Illinois, USA, November 1997). We reported our results of a large histopathological analysis covering the IOL barrier effect, with special reference to the efficacy of the truncated edge.[87] A truncated, square-edged optic rim appears to cause a complete blockade of cells at the optic edge, preventing epithelial ingrowth over the posterior capsule. The enhanced barrier effect provided by this optic geometry probably functions as an 'icing on the cake'. It seems to provide another reserve factor, in addition to the five above-mentioned factors, contributing in diminishing the overall incidence of visually significant PCO.

Our studies up to date have shown that the Alcon AcrySof™ IOL best achieves the goals of these three IOL-related factors. Recently Nishi *et al*[92] have reported that the AcrySof™ lens lost its preventive effect on PCO when the optic was rounded. According to the same author, the effect of the AcrySof™ lens in preventing PCO is mainly a result of its rectangular, sharp-edged optic design. The acrylic material may play a complementary role by helping to create a sharp capsular bend. Capsular bend formation would be the key to the PCO preventive effect of the IOL. Other IOL designers are rapidly moving to provide comparable features, especially a conversion to sharp edges. A major disadvantage of the truncated edge is the possible formation of clinical visual aberration such as glare, halos, and crescents. Subtle changes in manufacturing are now helping alleviate these complications.

Summary

A major reduction of Nd:YAG laser capsulotomy rates towards single digits is now possible because of application of these surgical factors and modern lenses—at least in the industrialized world. This will obviously be of great benefit to patients in achieving

improved long-term results and avoidance of Nd:YAG laser capsulotomy complications. Eradication of the Nd:YAG laser procedure will help control what has been the second most expensive cost to the US Medicare System.

To date one cannot precisely determine the relative proportion or contribution of IOL design *vs* surgical techniques to the decrease of Nd:YAG laser rates observed here. However, this could be possible with continuing analysis including annual updates and increasing numbers of pseudophakic autopsy eyes. The tools, surgical procedures, skills, and appropriate IOLs are now available to eradicate PCO. Continued motivation to apply the six factors noted in this article, the efficacy of which have been further suggested in a recent study, will help diminish this final major complication of cataract-IOL surgery exactly 50 years after Ridley's first encounter with this complication.

Conclusion

In this review article, we have tried to alert the reader to IOL related opacifications in front of, on, within, between and behind the IOL. Although opacification of the posterior capsule was always a concern after extracapsular cataract extraction, in recent years, efforts towards controlling and indeed eradicating PCO have been explored in more depth. However, in spite of the finer and wondrous achievements of IOL implantation a few items have 'slipped through the cracks.' In this text we tried to discuss several problematic issues regarding the opacification phenomena that we should not be encountering at such a late stage in the evolution of IOL implantation. Many of them are totally unexpected threats to vision and sometimes 'blinding IOL opacifications' that we should not have to concern ourselves with, within our current advanced stage in the evolution of the cataract-IOL procedure.[93]

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