COMPLICATIONS OF CATARACT AND REFRACTIVE SURGERY: A CLINICOPATHOLOGICAL DOCUMENTATION*

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ABSTRACT

Purpose: To present selected complications of keratorefractive and phakic intraocular lens (IOL) surgery and a series of IOLs that required explantation because of various postimplantation opacification of the IOL optic.

Methods: Two specimens obtained after keratorefractive surgery, 2 phakic IOLs, and a total of 23 explanted IOLs from cases in which postimplantation opacification of the IOL optic had occurred were studied. These included 6 Bausch and Lomb (B&L) Hydroview H60M designs, 9 Medical Developmental Research (MDR) SC60B-OUV designs, and 24 IOLs with rigid PMMA optics that had been implanted in the 1980s and early 1990s. Of the latter, 8 required late explantation because of decreased visual acuity. Analyses performed included gross and light microscopic evaluation, histochemical staining, electron microscopy, and energy-dispersive spectroscopy.

Results: We provide examples of 3 postrefractive surgery complications: (1) fungal keratitis after LASIK, (2) post-LASIK corneal decompensation, and (3) cataract formation after implantation of phakic posterior chamber IOLs. Regarding the IOL optic opacities, classifications of 3 types are described: (1) a surface calcification of the B&L Hydroview IOL; (2) diffusion of calcium into the substance of the optic of the hydrophilic "acrylic" SC60B-OUV MDR foldable IOL design, sometimes leading to *total* opacification of the IOL optic and also its haptics; (3) a distinct pattern of intraoptical opacification with rigid PMMA designs that we term a snowflake degeneration. This term is based on the clinical and pathologic appearance of the individual lesions. Each snowflake lesion represents a focal breakdown of PMMA material as opposed to deposition of exogenous material.

Conclusions: Analysis of complications of refractive surgery represents a new field of ocular pathology. The clinicopathological reports presented here provide an overview of selected complications after refractive surgery. We also help define 3 newly recognized, clinically significant conditions based on postoperative IOL optic opacification. The calcification processes noted on the 2 modern foldable designs studied here (B&L and MDR lenses) need further review by the manufacturers in order to reassess production processes, especially in terms of polymer selection, manufacturing techniques, and other factors required to produce a safe and effective lens. Any lens not meeting today's high standards should not be marketed. The important fact in recognizing the snowflake complication of PMMA IOLs as described here is to alert surgeons about the nature of the lesion so that they will not alarm patients or require extensive and unnecessary testing in trying to determine its pathogenesis. There is no reason why successful explantation cannot be performed in cases where severe visual decrease or loss has occurred.

INTRODUCTION

It has been purported by some that the modern cataract–intraocular lens (IOL) operation and various popular kerato-IOL refractive procedures are safe and free of complications in up to 99+% of cases. Some surgeons admit to having had no complications in their practices. It is indeed a fact that the incidence of most postoperative complications of anterior segment surgery has decreased. However, this has led some individuals to become complacent and less vigilant regarding assessment and careful testing of new ocular prosthetics and surgical procedures. Despite the positive evolution of these anterior segment procedures, but concurrent with this era of decreased vigilance, we are unfortunately now identifying some serious problems, in some cases requiring explantation, corneal grafting, or other procedures. In this report, we provide a brief review of selected cases of refractive surgery complications associated with vision-threatening sequelae, and a clinicopathological correlative study of 3 newly recognized cataract-IOL related complications. To accomplish this, a series of explanted IOLs and excised surgical prostheses and corneas were studied by gross, light, and electron microscopic examination as well as energy dispersive spectroscopy.

Our research center was founded in 1983 by the senior author (D.J.A.) and Randall Olson, MD, in Salt Lake City, Utah. The research and specimen analysis during this early period was 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, South Carolina, in 1988, 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.[1] Since its inception, the laboratory has been funded almost entirely by industry and private foundations. In 2000, thanks to a generous grant from the Magill Foundation, we expanded our oversight toward studying refractive surgery procedures and their complications. Therefore, in addition to the already established laboratory, a new center termed the Arthur and Holly Magill Research Center for Vision Correction, led by both of us and Dr Kerry Solomon, reflects this change. The 3 refractive cases briefly noted in this report represent examples of this new specialty of pathology of refractive surgery.

Since late 1982, we have received almost 17,000 specimens (Fig 1 top), both explanted IOLs and human eyes obtained postmortem with IOLs. One of the most important techniques used in the study of autopsy eyes is the Miyake-Apple technique, a modification of Miyake's 1982 postmortem videophotographic technique.[2] The information derived from this specimen database is the basis of the analysis of IOL opacification described in this paper. Especially significant is the recent addition of over 1,000 foldable IOLs (Fig 1 bottom) and refractive specimens to the database. All of these accessions have now provided material support to establish a new classification of postaphakic and phakic IOL opacifications, some of which are discussed in this study (Table I, No. 3, 5, 6, 7 and 8).

Today's cataract-IOL and refractive surgical procedures are not perfect. This is exemplified by the series of complications demonstrated in this study, many for the first time as of the time of this writing. These represent a microcosm of a
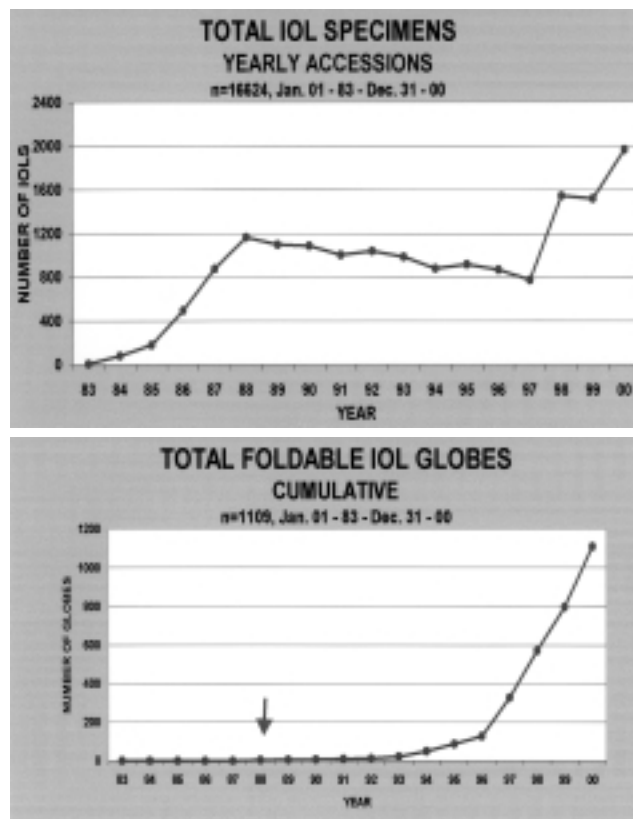

FIGURE 1

Accession of IOL-related specimens in Center for Research on Ocular Therapeutics and Biodevices, January 1983 through December 2000. Top, Total IOL specimens (n = 16,624). Bottom, Foldable IOLs in human globes obtained postmortem (n = 1,109). Arrow indicates transfer of our center to Charleston, SC, in 1988.

much larger clinical picture worldwide. We have correlated over the years that for every dozen or so specimens we receive in the laboratory, there are often thousands of patients suffering from these complications in the real world. Clinicians and governmental organizations should continue to closely scrutinize both established and newly marketed products and techniques so that unsafe products not be launched on the clinical market. This becomes problematic when the complications are only found after the fact, long after a product's introduction or launch, in patients who expected stellar results. We do not intend to be alarmist as we describe these various complications. However, the pathological specimens we present are clear, irrefutable evidence that these conditions exist and thus require our attention.

1. A BRIEF PRESENTATION OF 3 SELECTED COMPLICATIONS OF MODERN KERATOREFRACTIVE AND IOL REFRACTIVE SURGERY

FUNGAL KERATITIS AFTER LASIK AND DLK

Postoperative infection after laser in situ keratomileusis

TABLE I: POSTAPHAKIC AND PHAKIC IOL OPACIFICATIONS

1. Excessive anterior capsule opacificatioin (ACO)
2. Silicone oil adherence to IOLs
3. **Phakic posterior chamber IOL-induced cataract**
4. Interlenticular opacification (ILO) of "piggyback" IOLs
5. **Calcification on surface of optic of Bausch & Lomb Hydroview (B & L H60M)**
6. **Calcium deposits within optic of a hydrophilic "acrylic" IOL (MDR SC60B-OUV)**
7. **Snowflake opacification of PMMA IOL optic material 5 to 15 years postoperatively (an unexpected late degradation of PMMA)**
8. **Posterior capsule opacification (PCO)**

IOL, intraocular lens; MDR, Medical Developmental Research; PMMA, poly(methyl methacrylate).

Complications of Cataract and Refractive Surgery: A Clinicopathological Documentation

(LASIK) is relatively rare, partly because the corneal epithelial layer is kept relatively intact. However, when it occurs, it may be a serious and potentially sight-threatening complication. Post-LASIK infection can resemble or, as we note here, can evolve from diffuse lamellar keratitis (DLK), an idiopathic, presumed sterile inflammatory condition affecting the corneal interface after lamellar surgery. Accurate diagnosis is imperative because DLK and infectious keratitis require different treatment regimens.

We have recently reported cases of 3 patients who developed interface fungal infection following LASIK and DLK.[3] Culture and pathological analysis revealed *Candida albicans* in all 3 cases. Figure 2 shows a clinical photograph (Fig 2 top left), a light photomicrograph (Fig 2 top right), and an electron photomicrograph (Fig 2 middle) from the right eye of one of the patients, who had the corneal flap lifted, removed, and submitted to pathological analyses. Common features in all 3 cases were (1) early onset of DLK followed by intensive corticosteroid and antibiotic treatment and (2) later onset of interface fungal infection. All cases resolved and good vision was restored after medical treatment with antifungal agents. It is difficult to determine whether the fungal infections were the result of original LASIK surgery, or whether they represented secondary superinfections associated with treatment of the nonspecific inflammatory response (DLK) with topical corticosteroid and antibiotic regimen, or both. It is very important that clinicians report their experience with DLK (and other complications) in the hope that definite causes can be detected and that prevention and cures can be attained.

FUCHS' DYSTROPHY AND LASIK

It has been speculated whether excimer laser treatment could lead to endothelial cell damage. Creation of long wavelength fluorescent radiation with absorption of energy by deep tissues, acoustic and shock waves generated by
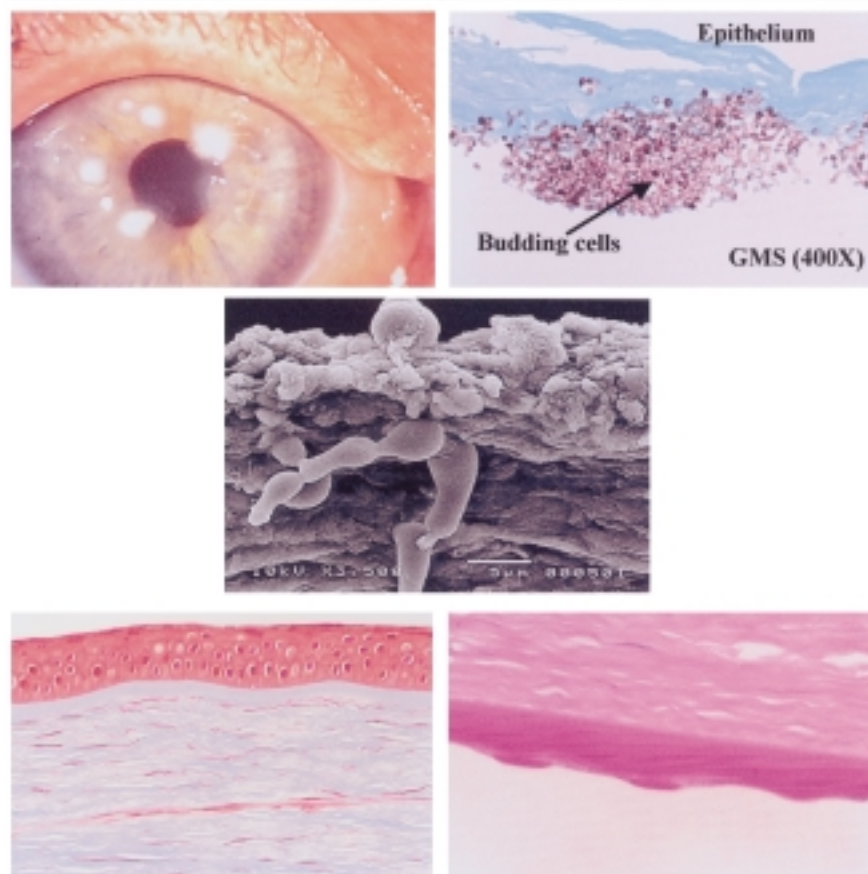

FIGURE 2

Complications after LASIK. Top left, Slit-lamp biomicroscopy 6 weeks post-LASIK, prior to surgical amputation of corneal flap from 1 of 3 patients with fungus keratitis. Dense infiltration with superficial ulceration of corneal flap was noted. Top right, Amputated flap of patient shown at left. Budding yeasts, hyphae, and pseudohyphae were confirmed (Grocott's methenamine–silver nitrate, original magnification x400). Middle, Scanning electron microscopic examination showing posterior surface of flap interface presented at top right reveals multiple budding and hyphae-forming cells (original magnification x75). Bottom left, Cornea of 48-year-old patient after LASIK. Red line shows normal flap interface (Masson's trichrome, original magnification x100). Bottom right, Cornea (same patient as in middle) showing severe endothelial cell loss with guttata formation (Fuchs' dystrophy) (PAS, original magnification x400).

ultra-short energy pulses, and resonance created by pulse repetition have all been implicated. In cases of LASIK, the role of the microkeratome and increased intraocular pressure must also be considered. Other factors that could influence the amount of damage include flap thickness, hyperopic versus myopic treatment, and type of beam or spot size. These factors affect the depth of tissue penetration and the location of energy application.

We recently reported a case of a 58-year-old woman who underwent LASIK in spite of a presurgical observation that she had moderate Fuchs' dystrophy.[4] Fourteen months postoperatively the patient had a corneal transplant because of visual loss in the left eye secondary to severe corneal decompensation. Histopathological evaluation of this corneal button revealed a slightly increased keratocyte population along the interface without significant new collagen formation (Fig 2 bottom left). The photomicrograph of Descemet's layer shows almost total endothelial cell degeneration, with an absolute decrease in number of endothelial cells (Fig 2 bottom right). The focal thickenings or excrescences of Descemet's membrane (guttata) are, of course, indicative of the preexisting Fuchs' dystrophy.

Regardless of the mechanism of injury, this case again elevates the question, still unanswered, about the possibility of endothelial damage after LASIK. A treatment as noted here may bring patients with Fuchs' dystrophy to the requirement for corneal transplantation earlier than otherwise might have been necessary, if at all. This should be considered when operating on eyes with even minimal or trace guttata.

CATARACT FORMATION AFTER PHAKIC POSTERIOR CHAMBER INTRAOCULAR LENS IMPLANTATION

The possibility of crystalline lens damage with subsequent formation of anterior subcapsular opacities probably represents the most controversial issue of phakic posterior chamber (PPC) IOL implantation.[5-11] The anterior subcapsular opacities that have been described with various PPC-IOLs are based on A-cell proliferation. The fibrotic response that may be caused by metaplasia of the anterior lens epithelium is what determines the degree of anterior capsular "thickening" following implantation of a PPC-IOL, which by definition rests in close proximity to (or on) the anterior surface of the crystalline lens.

We have had the opportunity to examine 3 Chiron-Adatomed silicone PPC lenses, all explanted because of late postoperative anterior subcapsular cataracts with visual loss.[7] Although these lenses have been withdrawn from the market, that study allowed us to clearly describe what *not* to do in the manufacture of PPC-IOLs. The lenses were well polished, but too thick, especially at the optic edge. We experimentally reimplanted one of the explanted IOLs in cadaver eyes and reviewed them from the anterior

view (surgeon's perspective), from the posterior aspect (Miyake-Apple technique) as well as a side (sagittal) view. This lens had zonular fixation; it was virtually impossible to achieve true ciliary sulcus fixation as purported for this lens design. It was in contact with both the posterior surface of the iris and the anterior surface of the crystalline lens.

The modern Staar (Monrovia, California) PPC-IOL (the implantable contact lens, or ICL) seems not to be immune to this complication.[9-11] We have recently received a pair of these lenses, explanted by Dr Paul Koch (Warwick, Rhode Island) from a 47-year-old white woman.[10] The patient presented with anterior subcapsular opacities, as well as age-related cataract associated with decreased visual acuity and glare, requiring explantation 13 months after the primary procedure. Clinical and gross photographs of the explanted lenses relative to this case, are presented in Fig 3.

Several cases of cataract formation associated with PPC-IOLs have been well documented in the literature.[5-11] Most investigators have attributed this complication to the lack of enough space between the PPC-IOL and the crystalline lens. Nevertheless, other factors may be involved in the cataractogenesis process, such as surgical trauma and direct or indirect IOL-related factors, including continuous or intermittent contact between the phakic lens and the crystalline lens, and/or subclinical inflammation and metabolic disturbances of the crystalline lens. The incidence of cataract formation after PPC-IOL implantation varies considerably in the various reports available in the literature. Different studies cannot be compared because of many factors. First, great variation is observed regarding the age of the patients at implantation and the follow-up period. In many studies, the patients included were implanted with successive models of the same PPC-IOL design, as the previous models were considered obsolete.

PPC-IOL implantation appears to be an effective method for correcting moderate to high myopia, hyperopia, and also extreme myopia, when compared to methods such as LASIK (bioptic procedure).[12-17] Improvements in power calculation of the lenses are needed in order to increase the predictability of the refractive outcome. A method more accurate than the white-to-white distance is also required for determining the lens overall diameter. Adequate IOL sizing will help reduce the incidence of complications such as cataract and lens decentration. Although new PPC-IOL designs, such as the Staar ICL, seem to perform better in relation to cataract formation than the earlier Fyodorov and Chiron-Adatomed lenses, this still is an important issue with PPC-IOLs.[6,8,9] Long-term, standardized clinical studies will determine the safety of this technique for refractive correction.

We would recommend that surgeons, when explanting these IOLs with associated cataract, save and submit not only the IOL, but also the capsulorhexis and any adjacent tissue from the crystalline lens behind it. There is
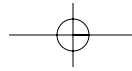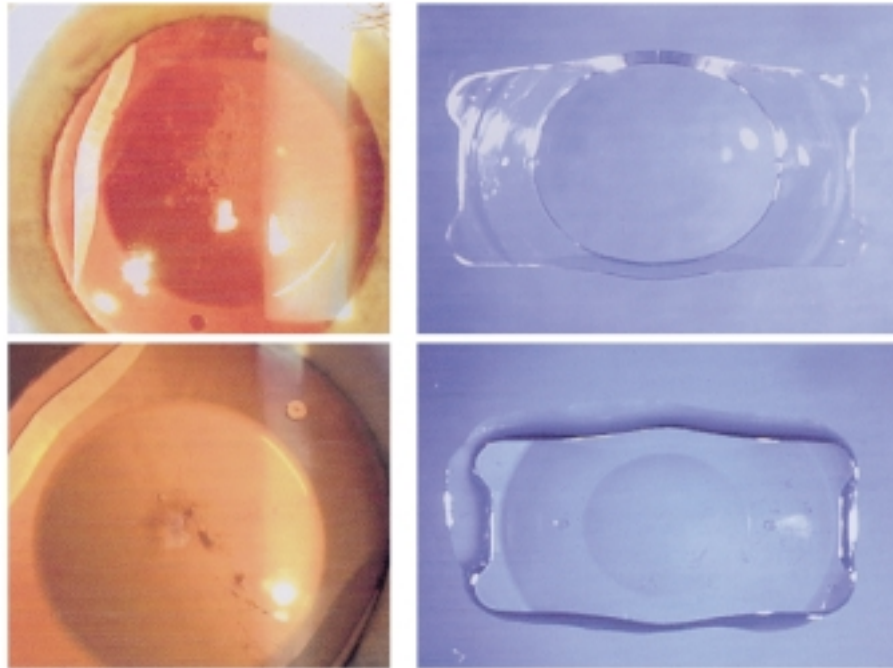
FIGURE 3

Top and bottom left, Retroillumination photographs from a bilateral case of anterior subcapsular cataract taken 13 months after ICL. Top and bottom right, Explanted ICLs currently being analyzed in our laboratory.

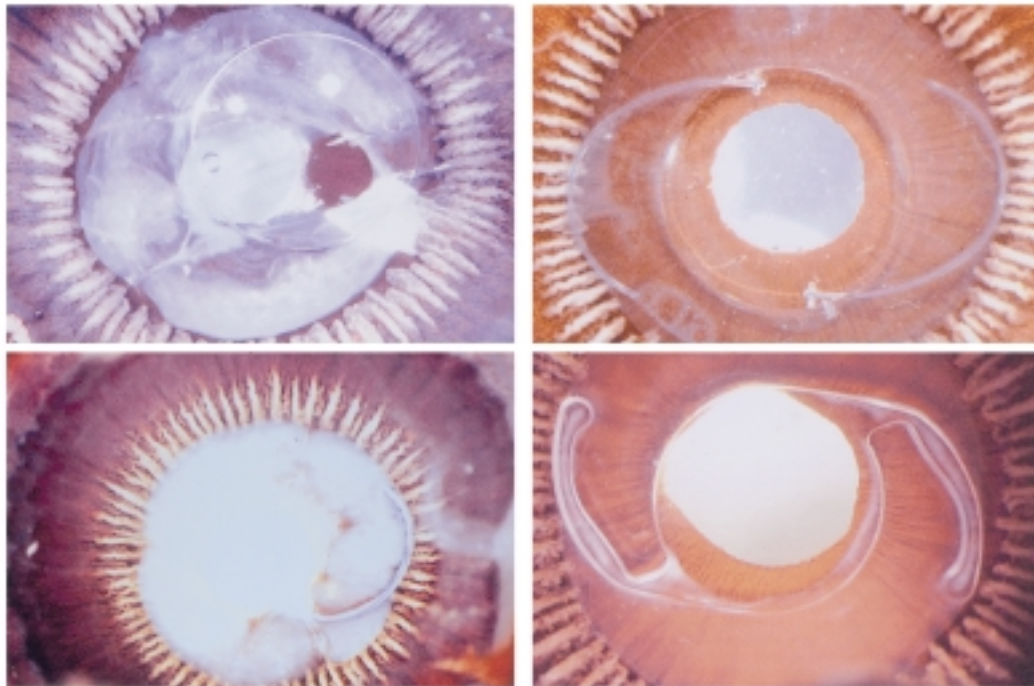*Courtesy Paul Koch, MD, Koch Eye Surgicenter, Inc, Warwick, Rhode Island.*

FIGURE 4

Gross photographs of pseudophakic human globes obtained postmortem, taken from behind (Miyake-Apple posterior view), showing marked variation in posterior chamber IOLs implanted in early 1980s, as compared to present (2001). Top left, Three-piece PMMA posterior chamber IOL implanted in early 1980s. This J-loop IOL is asymmetrically implanted with 1 haptic in capsular bag and other extending back to pars plicata. Note marked decentration with edge of optic and a positioning hole within pupillary aperture. Also note extensive secondary cataract (PCO) that required posterior capsulotomy. Top right, Three-piece Alcon AcrySof IOL with excellent fixation, centration, and total clarity of media, an excellent result (circa year 2000). Bottom left, Three-piece PMMA posterior chamber IOL implanted in mid-1980s, with malfixation, marked decentration, and extensive peripheral and posterior capsule opacification. Bottom right, One-piece acrylic IOL showing excellent centration and clarity of media with perfect symmetric in-the-bag fixation. There is slight contact of iris at upper left edge of IOL optic, but otherwise this represents an excellent result.
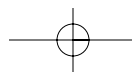
virtually no available pathological information on the nature of the post–PPC–IOL–related anterior subcapsular cataract, and pathological studies would be very helpful, for example, in differentiating surgeon-induced versus IOL-induced secondary cataracts.

2. COMPLICATIONS OF INTRAOCULAR LENSES, WITH SPECIAL REFERENCE TO VARIOUS POSTOPERATIVE OPACIFICATIONS

POSTERIOR CAPSULE OPACIFICATION

We recently reported the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser posterior capsulotomy rate of 8 rigid and foldable IOL designs in a series of 5,416 pseudophakic human eyes obtained postmortem, accessioned in our Center between January 1988 and January 2000.[18] This study helped us identify factors that are instrumental in reducing the incidence of posterior capsule opacification (PCO, secondary cataract) and hence the need for Nd:YAG laser posterior capsulotomy (Table II).

TABLE II: **6** FACTORS TO REDUCE THE INCIDENCE OF PCO

SURGERY-RELATED FACTORS ("CAPSULAR" SURGERY)
1. Hydrodissection-enhanced cortical clean-up
2. In-the-bag fixation
3. Small CCC diameter slightly smaller than that of IOL optic. This places the CCC edge on anterior surface of optic and helps sequester capsular bag. This creates a "shrink wrap" of capsule around IOL optic.

IOL-RELATED FACTORS
1. Biocompatible IOL to reduce stimulation of cellular proliferation
2. Maximal IOL optic–posterior capsule contact, angulated haptic, "bioadhesive" biomaterial to create a "shrink wrap"
3. IOL optic geometry square, truncated edge

CCC, continuous curvilinear capsulorrhexis; IOL, intraocular lens; PCO, posterior capsule opacification.

The Miyake-Apple posterior photographic technique was used to identify the presence or absence of Nd:YAG laser capsulotomy orifice on the posterior capsule of each eye. The Nd:YAG laser posterior capsulotomy rate (%) as of January 2000 was documented.

Relatively high Nd:YAG laser posterior capsulotomy rates, ranging from 20.3% to 33.4%, were noted with 4 relatively older designs (high incidence of implantation between 1988 and the early 1990s). Four modern foldable IOLs manufactured from silicone and acrylic materials had significantly lower Nd:YAG posterior capsulotomy rates, ranging from 0.9% to 17.1%. The difference in Nd:YAG rates among the 8 IOL designs was found to be significant ($P < .0001$, chi-square test). Comparing foldable versus rigid designs, the foldable IOLs were associated with a much lower Nd:YAG laser posterior capsulotomy rate (14.1% versus 31.1%).

We have demonstrated that the noteworthy reduction of Nd:YAG rates toward single digits is possible if one follows basic principles being essential to PCO reduction, namely (1) to improve cellular-cortical removal, decreasing the incidence of Soemmering's ring formation, and (2) to ensure a barrier effect if residual and potentially migratory cells are still present. These principles are embodied in the 6 factors we have identified (Table II), 3 surgical factors and 3 IOL-related factors, the latter present in some modern lens designs (Fig 4). By use of the 6 factors identified in those analyses, we strongly believe that the overall incidence of PCO, and hence the incidence of Nd:YAG laser capsulotomy, is now available to bring these rates down to single digits. Careful application and use of these tools by surgeons can genuinely lead in the direction of virtual eradication of secondary cataract, the second most common cause of visual loss worldwide.[19-26]

OPACIFICATION BASED ON CALCIFICATION ON OR WITHIN THE OPTIC OF **2** MODERN FOLDABLE IOL DESIGNS

Bausch & Lomb Hydroview (H60M)
Significant deposition of crystalline material on the surface of IOLs is uncommon. It has been reported to occur intraoperatively during cataract surgery with implantation of silicone IOLs, or in the early postoperative period after implantation of hydrogel IOLs. The deposits described in those studies were composed of calcium hydroxyapatite, and the hypothesized pathogenic mechanisms involved an oversupply of calcium/phosphate from intraocular solutions used during cataract surgery.[27-31]

We have recently received in our Center 6 explanted Hydroview lenses for pathological analyses.[32-36] The Bausch and Lomb Surgical (Rochester, New York) Hydroview IOL is a foldable hydrogel posterior chamber design that has been implanted for several years in international markets; over 400,000 have been implanted worldwide. However, although it was cleared for marketing in November 1999 by the US Food and Drug Administration (FDA), it has not yet been launched for general implantation in this country.

In each case, the lens has been explanted owing to deposition of crystalline material on its optical surfaces associated with decrease in visual acuity and glare, in the late postoperative period. The explanted lenses were sent to our Center for pathological, histochemical, and ultrastructural evaluation.

At the time of explantation, the age of the patients (2 women and 4 men) ranged from 70 to 85 years. Two patients were being treated for cardiovascular diseases, 2 were diabetic, and the other 2 were otherwise healthy. One of the lenses was explanted in Australia, 4 in Sweden, and 1 in Canada. All lenses were explanted at least 1 year

after the primary procedure owing to opacification observed at the level of the optics, associated with decrease in visual acuity 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.

Once received in our Center, the IOLs were immediately placed in 4% formaldehyde in 0.1 M phosphate buffer, pH 7.4. Care was taken to avoid any manipulation of the IOLs' optics with forceps or other grasping instruments. Some lenses were bisected for explantation, and only half of them were available to us.

Gross (macroscopic) analysis of the explanted IOLs was performed, and gross pictures were taken using a camera (Nikon N905 AF, Nikon Corporation, Tokyo, Japan) fitted to an operating microscope (Leica/Wild MZ-8 Zoom Stereomicroscope, Vashaw Scientific, Inc, Norcross, Georgia). The unstained lenses were then microscopically evaluated and photographed under a light microscope (Olympus Optical Co Ltd, Japan). They were then rinsed in distilled water, immersed in a 1% alizarin red solution (a special stain for calcium) for 2 minutes, rinsed again in distilled water, and reexamined under the light microscope.[37] Staining with alizarin red was also performed in 1 additional Hydroview, explanted owing to IOL malposition, to be used as a control.

We then performed full-thickness sections through the optic of 2 explanted Hydroview lenses and the control Hydroview explanted lens. The resultant cylindrical blocks were dehydrated and embedded in paraffin. Sagittal sections were performed and stained using the von Kossa method for calcium (staining with nitrate solution for 60 minutes; exposure to a 100-W lamp light; rinsing with distilled water; reaction with sodium thiosulfate solution for 2 minutes; rinsing with distilled water; counterstaining in nuclear fast red solution for 5 minutes). Calcium salts stain dark brown with this technique.

One lens was air-dried at room temperature for 7 days, sputter-coated with aluminum, and examined under a JEOL JSM 5410LV scanning electron microscope (SEM). This specimen was further analyzed by Dr. D. G. Dunkelberger (Electron Microscopy Center of the University of South Carolina, Columbia) under a Hitachi 2500 Delta SEM equipped with a Kevex x-ray detector with light element capabilities for energy dispersive x-ray analyses (EDS).

Gross and microscopic evaluations of all of the explanted Hydroview lenses had almost identical findings (Fig 5). By gross evaluation, the presence of the deposits on their optical surfaces was noted to cause different degrees of IOL haze/opacification, directly proportional to the amount of deposits and the surface of the lenses covered by them.

The surfaces of the unstained IOLs were covered by a layer of irregular granular deposits, composed of multiple fine, translucent spherical-ovoid granules. 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. Also, intervening clear areas, probably corresponding to marks caused by forceps during the folding process, were observed in all lenses. These areas were, however, not completely clear, and in high magnification they presented a layer of few, scattered, small round granules. Multiple pits related to Nd:YAG laser treatment were observed on the posterior surface of the IOLs in all cases. The deposits on the surfaces of the IOLs stained positive with alizarin red in all cases. In the areas presenting scattered, small granules, it was observed that only the deposits themselves stained red, while the IOL surface itself was not stained. No positive staining was observed on the haptics of the IOLs. Staining of the control Hydroview lens was also negative.

Sagittal histologic sections through the optic of 2 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. Staining of the control Hydroview lens using the same method was negative. EDS performed on the deposits demonstrated the presence of peaks of calcium and phosphate.

After completion of these analyses, we received 7 other explanted Hydroview lenses in our Center, 3 from Dr. J. P. Gravel (Canada), 2 from Dr. A. Öhrström (Sweden), 1 from Dr. A. Apel (Australia), and 1 from Dr. J. Sher (Canada). The surgical, clinical, and pathological features of these cases were similar to those described above.

Medical Developmental Research SC60B-OUV
The other hydrophilic IOL (termed a hydrophilic acrylic IOL style) to be recently associated with clinically significant postoperative opacification within the optic is a one-piece design. The source of the polymer was Vista Optics, United Kingdom; the manufacturer and distributor is Medical Developmental Research (MDR Inc, Clearwater, Florida). Chang and associates[38] have reported 1 case of clouding and fogging of this IOL design. They noted an opacification associated with significant visual loss that occurred 7 months after uneventful lens implantation. This was a clinical report without explantation. Prior to
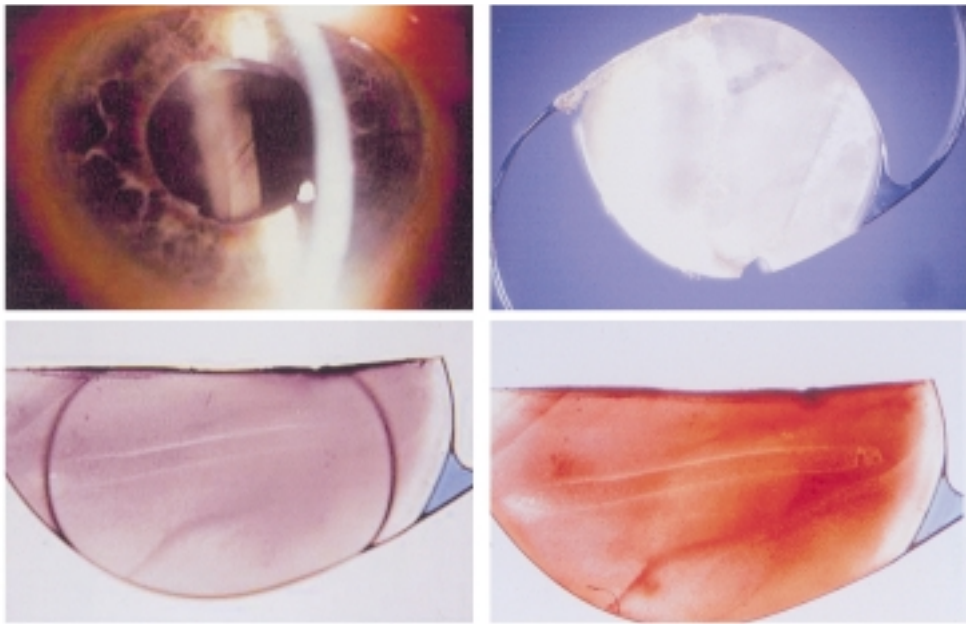
FIGURE 5A

Analyses of opacified Hydroview lenses. Top left, Slit-lamp photograph of patient implanted with Hydroview IOL showing a granularity present on anterior surface of lens. Imprints of folding/holding forceps can be observed (courtesy Arne Öhrström, MD, Vasteras, Sweden). Top right, Gross photograph showing 1 of the Hydroview IOLs explanted owing to optical opacification and accessioned in our Center. Bottom left, Photomicrograph of another Hydroview from our collection. Granular deposits can be observed covering optical surface of lens. Linear, parallel marks correspond to forceps imprints (original magnification x40). Bottom right, Photomicrograph (same case as in bottom left) showing deposits on surface of lens stained positive with alizarin red, indicating presence of calcium salts (alizarin red stain, original magnification x40).
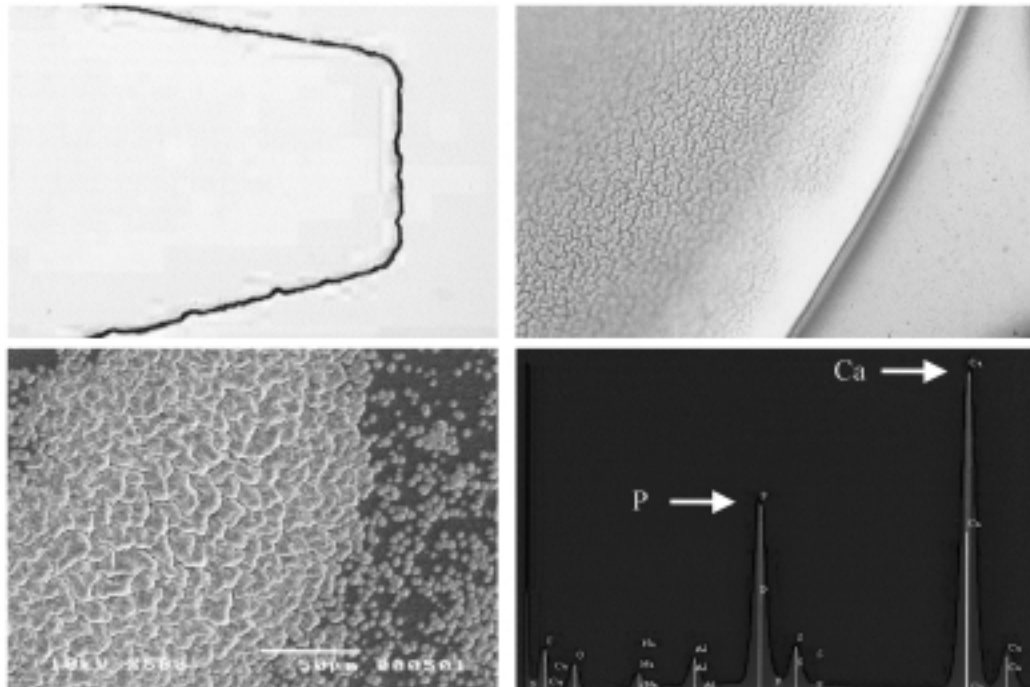

FIGURE 5B

Analyses of opacified Hydroview lenses. Top left, Photomicrograph showing sagittal section of lens optic of opacified Hydroview. Lens material itself was dissolved during preparation for histological examination, but lens optic surface is delineated by a continuous layer of dark brown, irregular granules composed of calcium salts (von Kossa's stain, original magnification x200). Top right, Photomicrograph showing optic surface of another Hydroview lens covered with confluent layer of granules, while haptic (blue PMMA) is clear (original magnification x100). Bottom left, Scanning electron photomicrograph (SEM) from anterior optical surface of another Hydroview lens showing deposits, which are composed of multiple globules of variable sizes (Bar = 50 μm). Bottom right, Energy dispersive x-ray (EDS) spectrum from Hydroview lens showed in bottom left. Note presence of important peaks of calcium and phosphate (arrows) at level of granular deposits.

our study, there have been no detailed clinicopathological analyses other than a brief preliminary report we recently published in a non–peer reviewed journal (Apple DJ, Werner L, Pandey SK. Opacification of hydrophilic acrylic intraocular lenses. *Eye World* 2000;5[9]:57).

We present the analyses of 9 explanted IOLs manufactured by MDR performed in our Center.[39,40] All of the accessioned lenses were model SC60B-OUV, the same model in Chang's report. It is a one-piece foldable design manufactured from a 28% hydrophilic material. All of the lenses were explanted because of late postoperative opacification of the lens optic associated with decreased visual function. We analyzed the clinical, pathological, histochemical, ultrastructural, and spectrographic features of these cases and tried to ascertain the nature of the intralenticular deposits.

All of the 9 lenses analyzed were implanted and explanted by the same surgeon, Mahmut Kaskaloglu, MD, from the Ege University, Alsancak Izmir, Turkey.[39] Two patients had diabetes, but the majority of patients did not have any known associated systemic or ocular conditions. In general, the patients returned around 24 months after the surgery complaining of a significant decrease in visual acuity (from 20/20 after the primary procedure to 20/50). The clinical characteristics of the SC60B-OUV lenses were different from the previously described "granularity" covering the optical surfaces of the Hydroview design. The clinical appearance of the SC60B-OUV lenses was that of a clouding similar to a "nuclear cataract." The lenses were explanted from 14 to 29 months postoperatively (24.42 ± 5.12). At the time of explantation, the ages of the patients ranged from 62 to 77 years (70.28 ± 5.76).

The analyses of the SC60B-OUV lenses followed the same protocol as described for the Hydroview lenses (Fig 6).[32] Gross and microscopic evaluations demonstrated that the optical surfaces and the haptics of the SC60B-OUV 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 edges of the optics and the haptics appeared clear. Alizarin red staining of the surfaces of all lenses was negative. This stain was likewise negative on the optical surfaces and haptics of the control IOLs.

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. Sagittal histological sections stained with the von Kossa method also confirmed the presence of multiple dark brown-black granules mostly concentrated in a 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, was 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 calcium 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.

Burkhard Dick, MD, University of Mainz, Germany, has studied explants of this IOL model and has noted that the opacification within the optics may be related to the presence of unbound ultraviolet absorbers (monomers).[41] We have not yet done studies to verify Dick's findings that unbound UV-absorber monomers or any impurity causes opacification within the IOL optic. These findings and the calcification process demonstrated by us may be correlated, although our data does not allow us to make definitive conclusions.

3. SNOWFLAKE OR LATE DEGENERATION OF POLY(METHYL METHACRYLATE) POSTERIOR CHAMBER IOL OPTIC MATERIAL

By the late 1980s most surgeons and researchers had not only concluded that poly(methyl methacrylate) (PMMA) was a safe biomaterial but also had confidence in the various manufacturing techniques required for lens fabrication.[42,43] Indeed, until recently, after examination of over 17,000 IOL-related specimens in our Center over a 19-year period from 1982 to the present, we had not documented any instances of PMMA-optic material alteration or breakdown. However, beginning with a gradual accumulation of anedoctal reports in the mid-1990s, culminating in a rapid accumulation of cases accessioned in our laboratory, we document in this report a series of cases characterized by a gradual and sometimes progressive late postoperative alteration or destruction of PMMA optic biomaterial.[44]

All of the 24 cases documented here are 3-piece PC-IOLs with rigid PMMA optical components and blue polypropylene or extruded PMMA haptics. The majority were IOPTEX and Surgidev models. Most had been implanted in the 1980s to early 1990s, and the clinical symptoms occurred late postoperatively, sometimes more than a decade after the implantation. Sixteen of the 24 cases were submitted as clinical histories and photographs. In 8 cases IOLs that had to be explanted because of visual aberrations or glare and progressive decrease in visual acuity were submitted with clinical histories and photographs provided by the explanting surgeons. These
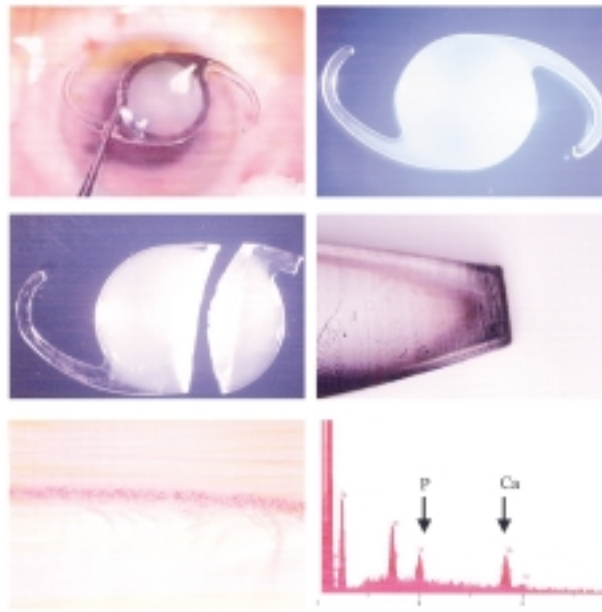
FIGURE 6

Analyses of opacified SC60B-OUV lenses. Top left, Gross photograph taken immediately after lens explantation. Opacification is observed in central 5 mm of optic, while edge and haptics are transparent (courtesy Mahmut Kaskaloglu, MD, Ege University, Alsancak Izmir, Turkey). Top right, Gross photograph from another lens explanted by Dr Kaskaloglu showing total opacification. Middle left, Gross photograph from SC60B-OUV lens explanted by Dr Nitin Anand (Luton, United Kingdom). The opacified optic was bissected for pathological analysis. Middle right, Photomicrograph of 1 cut section of lens optic showing distribution of deposits within its substance (unstained, original magnification x40). Bottom left, Deposits shown in middle right stain positive with alizarin red (alizarin red stain, original magnification x200). Bottom right, Energy dispersive x-ray (EDS) spectrum from another opacified SC60B-OUV lens. Note presence of calcium (Ca) and phosphate (P) peaks (arrows) at level of granular deposits.
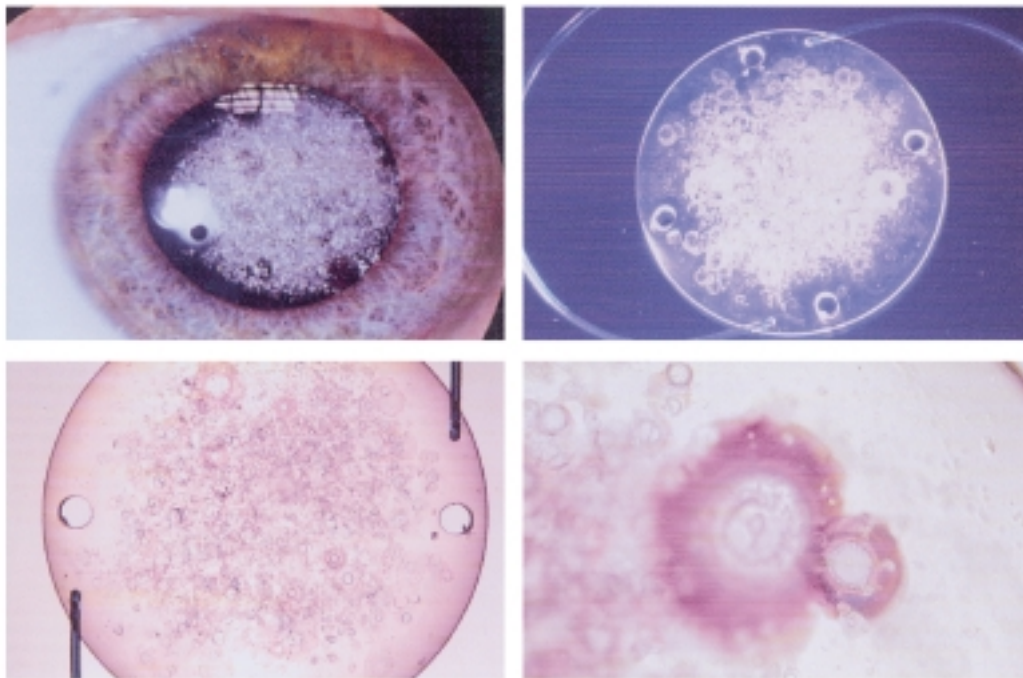

FIGURE 7

Examples of snowflake lesions within PMMA lenses. Top left, Clinical photograph of eye containing early PMMA IOL showing snowflake degradation. Top right, Gross photograph of rigid three-piece PMMA lens affected with snowflake degradation, demonstrating that most of involvement is within central core of lens optic, with sparing of outer periphery of optic. Bottom left, Three-dimensional light photomicrograph of another three-piece PMMA lens showing snowflake opacities. Bottom right, High-power three-dimensional light photomicrograph of same lens as in bottom left, showing individual snowflake lesions. There is an empty central space containing few particles of PMMA convoluted material (fragmented PMMA) surrounded by dense outer pseudocapsule.

lenses were also analyzed in our Center according to the protocol previously described.

The optics of the 8 explanted lenses had almost identical findings except for the degree of involvement (Fig 7). The common finding in all cases was the presence of the roughly spherical snowflake lesion, which we interpreted as foci of degenerated PMMA biomaterial. The amount of opacification corresponded proportionally to the number and density of lesions noted. Views of the cut edges of the bisected optic specimens prepared for scanning electron microscopy confirmed that the snowflake lesions were not surface deposits but rather were all situated within the substance of the optic. The snowflake lesions were clustered most commonly in the central and midperipheral zones of the IOL optics. The outer 0.5 to 1.0 mm peripheral (equatorial) rims of the lens optics were generally less involved or free of opacification. The lesions were usually focal and discrete, with intervening clear areas, but some did appear to coalesce. They generally involved the anterior one third of the optic's substance. Histochemical and spectroscopic analyses were negative, indicating no infiltration of exogenous material.

We suggest that manufacturing variations in some lenses fabricated in the 1980s to early 1990s, especially some made with a molding process (specifically, the cast molding process of the IOPTEX Research IOLs), may be responsible. It is highly likely that the late PMMA destructive process is facilitated by long-term ultraviolet (UV) exposure. This is supported by 2 pathologic observations. First, many opacities have been indeed clustered in the central zone of the optic, extending to the midperipheral portion but often leaving the distal peripheral rim free of opacities. Furthermore, the opacities are present most commonly and intensely within the anterior one third of the optic's substance stratum that is the first to be a recipient of UV radiation as it enters the lens. These observations would support the hypothesis that the slow and sometimes progressive lesion formation noted here might relate to the fact that the IOL's central optic is exposed to UV radiation over an extended period, whereas the peripheral optic may be protected by the iris. Since the anterior strata of the optic are the first to encounter the UV light, this might explain why the opacities are seen more frequently in this zone.

The emergence of this complication could have represented a true disaster, except for the fact that many of the patients implanted with these IOLs are now deceased. However, there are probably still sufficient numbers of patients living with varying stages of this complication. This necessitates that today's ophthalmologists be aware of, diagnose, and know when not to explant and/or exchange these lenses. It is important to know the nature of this syndrome in order to spare now-elderly patients and their doctors of unwarranted anxiety about the cause of visual problems or loss and also to obviate request for unwarranted diagnostic testing.

DISCUSSION/CONCLUSION/SUMMARY

In spite of extensive hype, complications of modern kerato-IOL refractive surgery do exist. We provide examples of a new subdivision of ocular pathology: pathology of refractive surgery. Just as was done with IOL pathology, these studies will benefit patients undergoing these procedures.

In the 1980s, PC-IOLs came into vogue and underwent constant improvement; important research efforts were made to produce an "ideal" IOL to be "married" to the best possible surgical technique. During this period, we found that most IOL complications were in many ways related to problems with *fixation*.[45-49] Lenses and techniques designed to improve haptic fixation resulted from these efforts. Important elements of the surgical operation perfected during these early years were phacoemulsification, continuous curvilinear capsulorrhexis (CCC), and hydrodissection, among others.[50]

By the late 1990s, the cataract-IOL procedure had advanced to the high level that we enjoy today. Early problems caused by malfixation (eg, decentration) were almost eliminated. High-quality rigid and foldable IOLs had become available, the latter including those manufactured from silicone, acrylic, and hydrogel material.[24]

We believe the data related to the Nd:YAG laser posterior capsulotomy rates presented here are helpful in understanding how those 8 groups of lenses are performing in relation to PCO. To date, one cannot precisely determine the relative contribution of IOL design versus surgical techniques to the decrease of Nd:YAG rates, but this will be possible with continuing analysis, including annual updates, increasing number of pseudophakic cadaver eyes, and passage of time. The tools, surgical procedures and skills, and appropriate IOLs are now available to eradicate PCO. Continued motivation to apply the 6 factors we described will help diminish this final major complication of cataract-IOL surgery.

However, we have recently identified in 3 IOL groups new modalities of postoperative opacification after cataract surgery. Clinical details, incidence, epidemiology, and detailed case studies are described elsewhere.[32,39,44] The purpose of this report was to provide a clinicopathological overview of these 3 IOL groups, which represent 3 of the 8 conditions we have recently cited as causes of postaphakic and phakic IOL opacifications (Table I).

Bausch and Lomb has recently suggested that the Hydroview calcification might be attributed to problems with a silicone gasket in the packaging.[35,36] It has been postulated that minute amounts of silicone material may catalyze a reaction that will lead to deposition of calcium. We

have not studied this personally and await further verification and publication by the manufacturer. Because this condition takes at least 1 to 2 years to appear clinically, this amount of time must be allocated for clinical studies to truly verify whether this is the cause and its correction would be curative of this problem.

The MDR lens is manufactured in the United States in Clearwater, Florida, from polymer derived until recently from Vista Optics in the United Kingdom. To our knowledge the lens has been sold only outside of the United States, in Brazil, China, Egypt, France, Germany, Italy, and Turkey, among other countries.[39,40] Because this lens is apparently sold only outside of the United States, there is no possibility of the FDA oversight. However, since many countries depend on the FDA's opinion for introduction and use of such products, we feel it would be useful that changes in policy might be considered.

The third group of lenses, the rigid PMMA designs manufactured mostly in the 1980s and early in the 1990s, all represent a late postoperative complication, to our knowledge occurring mostly from 5 to 15 years after implantation. The lesions may be fairly nonprogressive, as we have noted with much of the Surgidev designs in the study, or are more progressive, leading to visual loss requiring explantation, as has been the case with some of the IOPTEX lenses noted here as well as with other designs of an unknown source.[44] The main reason to publicize the existence of these problems now is to make the surgeon aware of this clinical pattern so that during long-term postoperative examination, one realizes what this process is. This knowledge would therefore save unneeded clinical diagnosis and testing and certainly spare the surgeon and the patient undue fear regarding these visually threatening lesions, which at first glance by clinical examination appear startling, and which in our experience present a unique appearance not described previously.

The snowflake lesions appear to be erupting now. We would suspect, on the basis of the age of these patients and the number of postoperative years, that the number of eruptions will increase and peak within the next 5 years. They will probably only recede as the patients die. It is important to emphasize that these probably represent a problem with IOL manufacture, in particular, specific molding processes used at that time, and should not represent a universal condemnation of PMMA optic biomaterial. It is also probable that some of these IOLs have been or continue to be sold to distributors in developing countries, and a knowledge of this condition will be useful to perhaps avoid this problem in some underprivileged countries.

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DISCUSSION

DR ROBERT C. DREWS.   Problems with low molecular weight PMMA have occurred before. Let me show some old slides.

In order to force PMMA molecules through a small aperture to injection mold IOL's, the chain length must be short, with a low molecular weight. Physical problems with such lenses have included warpage of one brand of injection molded intraocular lenses after they were implanted in the eye. The stress patterns inherent within injection molded lenses are easily revealed by placing the lenses between crossed Polaroid filters. Flashing and other edge finish problems have caused major chafing of the iris and other ocular tissues. Clinically, it was lenses that were injection molded from low molecular weight PMMA that first gave rise to epidemics of the UGH syndrome. Although UGH syndrome can occur with any intraocular lens, it was rare until injection molded intraocular lenses were introduced by American manufacturers

for mass production. Good finishes of this softer material were not achieved until tumble polishing was employed.

John Pearce first called attention to the myriad tiny refractile specks commonly visible by slit lamp in injection molded lenses placed in the posterior chamber. Like the specular corneal endothelial pattern, these are difficult to see at first; but, once seen, they are striking and easy to find. They are so tiny and the lighting requirements so strict to visualize them that I have never been able to photograph them. Like the "snowflakes", they absorb laser energy and make YAG capsulotomy difficult without injury to the IOL, and are one of the reasons I gave up using injection molded posterior chamber lenses, even when well finished.

The polymerization of methyl methacrylate into polymethyl methacrylate can yield chains of varying length and the final, commercial material can vary widely. The length of the PMMA chain turns out to be important. Perspex CQ (Clinical Quality), for example, has a molecular weight over 1.2 million. It is very pure and non-toxic. Its long chains are very stable, but cannot be forced through a small aperture for injection molding. It must be machined or compression molded. It is easily polished to a high finish. High molecular weight PMMA has a superb 50 year track record.

Now Drs Apple and Werner have alerted us to the appearance of "snowflakes" within the optics of IOL's presumably made from low molecular weight PMMA. They can become so dense that they make the lens opaque, another tragic long term complication. Because large numbers were exported, many eyes have been compromised.

I have 3 observations. 1) It used to be illegal to export non-FDA-approved drugs and devices. I assume it still is. 2) Whether all of these lenses were made of low molecular weight PMMA would be easy to verify by placing them between crossed polarized filters. 3) It would be interesting to look carefully in retrospect at some other injection molded PC IOL's to see whether the refractile specks found by John Pearce were early snowflakes.

I thank Drs Apple and Werner for a most interesting paper, and another cautionary lesson. The use of low molecular weight PMMA to make intraocular lenses has led to several, large scale tragedies.

[Editor's note] DR DOUGLAS D. KOCH was not as sanguine as Dr Apple that posterior capsule opacification is no longer a problem. He was involved in studies of some of the modern lenses. He found that capsule opacification may not occur for over 5 years, but it still occurs and is merely delayed. DR WOODFORD S. VANMETER asked whether modern equipment and techniques, such as low-flow, closed-circuit systems and the use of a continuous curvilinear capsulorrhexis, both of which make cortical cleanup easier, might be a factor in the lower incidence of posterior capsule opacification. DR JOHN C. MERRIAM was intrigued by the speculation that snowflake degeneration might be related to ultraviolet light exposure. He asked whether there was a difference in the number of these complications between northern and southern latitudes; he also asked if there was any experimental evidence as to what wavelengths of light were involved.

DR DAVID J. APPLE AND DR LILIANA WERNER. We thank Dr Drews for his remarks regarding our paper. His presentation makes us feel like we are the students lecturing our mentor. With the Society's permission, we would like to turn around our discussion and take this opportunity to thank Dr Drews for his efforts. Many of the achievements we have accomplished in our laboratory are based on the work by Dr Drews, who is one of the pioneers in the study of intraocular lens and cataract surgery complications, including the use of pathologic techniques and scanning electon microscopy. The studies date from as early as the late 1970's and 1980's and several are referenced here.[1-14]

Our work today on explants is based on the classic study of Dr Drews on explanted Barraquer implants. These lenses were implanted between 1954 and 1961 and Dr Drews reported on these in his Binkhorst Lecture of 1982 and published these in the Transactions of the American Academy of Ophthalmology 1982;89:386-393. This is the classic article on explants that we and others have taken as a model. The studies we present in this paper on various opacifications are based on these.

The poorly fabricated lenses using low molecular weight PMMA are largely things of the past, although scrutiny in areas without good oversight is still warranted to be sure that poor lenses are still not distributed. Today there should be absolutely zero tolerance with intraocular lenses, since research over the last several decades has been very thorough. Today's research is mostly one of "fine-tuning the technology;" the era of disastrous complications should be long past.

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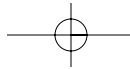
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