Latanoprost and cystoid macular edema: is there a causal relation?

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Published reports of the occurrence of cystoid macular edema (CME) in eyes being treated with latanoprost have led to concern regarding a possible causal relation between the two. Review of all published cases (28 eyes in 25 patients), plus another case reported here for the first time, indicates that all eyes had independent risk for development of CME, so that definitive conclusions about a causal relation cannot be established. In addition, controlled clinical trials and experimental studies with latanoprost have given no indication that latanoprost causes clinical CME. Pharmacokinetic considerations indicate that the concentration of latanoprost expected in the posterior segment of the eye is too low to have a pharmacologic effect, and latanoprost is not known to exhibit vasoactive or inflammatory properties. Nevertheless, reports of a possible association between CME and latanoprost use must be given serious consideration, and in eyes that are at risk for CME, an increased level of surveillance for its development is recommended. Curr Opin Ophthalmol 2000, 11:94–100

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Case reports of cystoid macular edema with latanoprost

During the course of a compassionate-use program prior to commercial availability, an isolated case of CME arose during the course of treatment with latanoprost. This case, observed by one of the authors (R.A.S.), was reported to the manufacturer in June 1995 and is described here in the accompanying case history report. Beginning shortly after market release in September 1996, the manufacturer received a series of spontaneous reports of the apparent occurrence of CME in association with latanoprost use. Beginning in early 1998, a series of case reports were published, each involving relatively small
numbers of eyes. Currently, 12 such publications [12–23] have appeared, describing 28 eyes in 25 patients, as summarized in Table 1.

Of interest, all 28 eyes described in prior publications, and also the eye described here, had widely accepted risk factors (RFs) for the occurrence of CME. Table 1 lists the clinical history of these eyes. Twenty-seven of the 29 eyes had undergone prior cataract surgery. Twenty-one had an open posterior capsule. There were no reports of CME occurring in eyes that were phakic and without risk for development of CME.

The occurrence of CME in an eye at risk is not unusual. For example, a recent meta-analysis of complications of cataract surgery concluded that clinically apparent CME occurs in 0.6% to 6.0% of eyes after phacoemulsification (median duration of follow-up: 228 days) and 0% to 7.6% of eyes after extracapsular cataract extraction (median duration of follow-up: 421 days) [24]. The incidence of

**Case history**

A 65-year-old caucasian male with primary open-angle glaucoma in both eyes, without history of diabetes mellitus or systemic hypertension, had retinal detachment in the left eye (OS) treated by cryotherapy and scleral buckle in 1989. He then underwent argon laser trabeculoplasty in both eyes (OU). He had a combined planned extracapsular cataract extraction and trabeculectomy OS in 1989, at which time inadvertent rupture of the posterior capsule occurred. Anterior vitrectomy was performed, and an anterior chamber intraocular lens (Cooper Cilco MT5U00 lens) was inserted without complication. Vision improved to 20/15 OS. Six months postoperatively, using timolol maleate 0.5% OS, he spontaneously noted a reduction in vision OS to 20/25. Yellowish pigmentary macular changes in a petaloid distribution were noted, and FA confirmed vascular macular leakage. Treatment with topical prednisoloneacetate 1% twice daily was undertaken for several weeks; vision returned to 20/15 and the macular petaloid pattern resolved fully soon after its initial appearance. The patient was closely followed by a retinologist after the episode of CME and was stable for 5½ years until enrollment in the latanoprost compassionate-use program in May 1995.

The patient had long-standing paracentral arcuate scotomas OU related to glaucoma. In the right eye, the scotoma ultimately involved fixation with loss of most of the superior hemifield and resultant acuity of 20/70. The patient was intolerant of oral carbonic anhydrase inhibitors and had developed an allergic reaction to topical apraclonidine. Pilocarpine was avoided because of the history of retinal detachment. Dipivefrin and other epi-
nephrine compounds were avoided because of the disrupted posterior capsule and the risk of CME. Using timolol maleate 0.5% OU twice daily, IOPs had averaged 20 mmHg OD and 17 mmHg OS; these IOPs were deemed inadequate for glaucoma control.

After informed consent had been obtained (as approved by the Institutional Review Board of the Mt. Sinai School of Medicine in New York City, NY, USA), the patient was provided with latanoprost through a manu-

facturer-sponsored compassionate use protocol. Dilated stereobiomicroscopy of the optic nerve head and macular region and visual field testing were performed. The discs showed advanced cupping, and the maculae were normal. The patient was begun on latanoprost 0.005% OU, used once daily between the hours of 6–8 pm.

Beginning several days after initial use of latanoprost, the patient noticed haziness of vision in the left eye. About two weeks later, this progressed to a distinct blur that was present each morning but which resolved by afternoon. Four weeks after beginning latanoprost treatment, the blur became more profound, so that the patient could no longer read, and the blur did not resolve as the day proceeded. He contacted his ophthalmologist (R.A.S.), was instructed to discontinue use of latanoprost, and was examined the following morning. He was found to have best-corrected acuity of 20/70 OD and 20/50- OS, with unchanged refractive error and stable anterior segment exam result. In particular, there was neither corneal haze, epitheliopathy, or irregularity, nor were there media opacities or signs of anterior segment inflammation. IOPs were 18.5 mmHg OD and 19 mmHg OS. Distinct yellowish petaloid macular changes were noted, which had not been seen previously. FA was obtained the same day and demonstrated vascular leakage OS. Latanoprost was discontinued OU, and the patient was told to begin use of diclofenac 0.1% OS four times daily and prednisolone acetate 1% OS four times daily, but the patient elected not to use the prednisolone acetate. He was seen one day later. The petaloid pattern was still present, and vision had improved to 20/20- OS. Subjectively, the blur was largely resolved. On the following day, vision was 20/25 OS. IOPs were 18 mmHg OD and 18.5 mmHg OS. The petaloid macular pattern was undetectable. He was seen again one week and two weeks afterward, and on both days vision was 20/15-1 OS, and IOPs on these occasions were 20 mmHg and 18 mmHg, respectively. At the time of most recent examination, over four years following the events described above, visual acuity OS has remained 20/15-1, and there have been no further episodes of blurred vision.
CME was reported to be 8% for anterior chamber intraocular lens implantation and 3.5% for posterior chamber intraocular lens implantation within one year of surgery [25]. After neodymium:YAG laser capsulotomy, the incidence of reported CME ranges from 0.5% to 4.9% [26]. Importantly, the number of eyes developing CME described in published reports is small in comparison with the number of eyes that have been treated with latanoprost worldwide. The manufacturer estimates this number to be over 1,700,000 eyes treated as of June 1999. In addition to the 28 already published cases of CME, less than 120 other cases were known to the manufacturer (almost entirely through spontaneous reports) as of June 1999. In such a large group of treated eyes, many of which are at risk for the development of CME, it would be expected that a far greater number of cases of CME should have developed. Under-reporting of putative cases of CME may have occurred because of physicians’ possible assumption that CME was caused by other risk factors and not by latanoprost. Over-reporting, on the other hand, may actually have occurred because of a widespread belief among ophthalmologists that PGs are pro-inflammatory and can cause CME [27]. It nevertheless appears that CME rarely occurs.

In three cases, the affected eye was rechallenged with latanoprost after the initial episode of CME [12,14,19]. Latanoprost was discontinued in all three eyes, and visual acuity returned to within one line of the baseline of 20/20 to 20/25 in all eyes. In two eyes that had a fluorescein angiogram (FA) repeated just prior to rechallenge, persisting angiographic CME was demonstrated in one [12], whereas no CME was seen in the other [19]. In one rechallenged eye, there was no evidence of recurrence of CME after three separate one-month-long rechallenges [19]. Two other rechallenged eyes [12,14] had decreased visual acuity of three and eight lines occurring two weeks and two months, respectively, after restarting latanoprost.

### Prior preclinical and clinical studies

Latanoprost is a poor substrate for those PG receptors that mediate vasoactive responses. In addition, clinical

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**Table 1. Published reports of the occurrence of cystoid macular edema in association with latanoprost use**

<table>
<thead>
<tr>
<th>Publication</th>
<th>Eyes, #</th>
<th>Patients, #</th>
<th>Clinical history*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avakian et al. 1998 [12]</td>
<td>2</td>
<td>2</td>
<td>1. ACIOL, DPC, AV</td>
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<td></td>
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<td>2. PCIOL, endo-CPC</td>
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<td>2. CE, DPC</td>
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<td>3. ICCE, aphakia, DPC</td>
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<td>4. ICCE, aphakia, DPC</td>
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<td>5. PCIOL, DPC</td>
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<td>6. PCIOL, uveitis (concurrent), prior CME</td>
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<td>Callanan et al. 1998 [14]</td>
<td>2</td>
<td>2</td>
<td>1. PCIOL, DPC</td>
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<td>2. sutured PCIOL, DPC, AV, trab x 2</td>
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<tr>
<td>Gaddie &amp; Bennett 1998 [15]</td>
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<td>2</td>
<td>1. PCIOL, DPC</td>
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<td></td>
<td></td>
<td></td>
<td>2. ACIOL, DPC, uveitis</td>
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<tr>
<td>Heier et al. 1998 [16]</td>
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<td>1. ACIOL, lens exchange, AV, DPC, PK</td>
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<td>Reis et al. 1998 [17]</td>
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<td>PCIOL</td>
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<td>Rowe et al. 1997 [18]</td>
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<td>PCIOL, prior CME</td>
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<td>Thorne et al. 1998 [19]</td>
<td>2</td>
<td>1</td>
<td>ACIOL each eye</td>
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<td>Wardrop &amp; Wishart 1998 [20]</td>
<td>1</td>
<td>1</td>
<td>RDR (3 times), vitrectomy, PCIOL, CryoTx</td>
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<tr>
<td>Warwar et al. 1998 [21]</td>
<td>2</td>
<td>2</td>
<td>1. ACIOL, DPC, prior CME</td>
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<td></td>
<td></td>
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<td>2. PCIOL, recent uveitis</td>
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<tr>
<td>Morii et al. 1999 [22]</td>
<td>7</td>
<td>7</td>
<td>1. BRVO, ERF, prior CME</td>
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<td>2. ERF, uveitis, PCIOL, trab, Ahmed</td>
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<td>3. HLA B27 + uveitis, subluxated lens, TS, AV</td>
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<td>4. PCIOL, DPC, PLS, PPV, MP</td>
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<td>5. PCIOL, DPC, prior CME</td>
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<td>1</td>
<td>PCIOL, DPC, vitreous to wound</td>
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<tr>
<td>This article</td>
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<td>1</td>
<td>ACIOL, DPC, AV, RDR, prior CME</td>
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<tr>
<td>Totals</td>
<td>26</td>
<td>29</td>
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*As derived from publication.

ACIOL, anterior chamber intraocular lens implant; Ahmed, Ahmed glaucoma valve implant; AV, anterior vitrectomy; BRVO, branch retinal vein occlusion; CE, cataract extraction; CME, cystoid macular edema; CPC, cyclophotocoagulation; CryoTx, cryotherapy; DPC, disrupted posterior capsule; ERF, epiretinal fibrosis; HLA, human leukocyte antigen; ICCE, intracapsular cataract surgery; MP, membrane peeling; PCIOL, posterior chamber intraocular lens implant; PK, penetrating keratoplasty; PLS, posterior lip sclerectomy; PPV, pars plana vitrectomy; RDR, retinal detachment repair; trab, trabeculectomy; TS, thermal sclerostomy.
investigations reviewed elsewhere [6,28,29] have lent little credence to an action of latanoprost on the blood-aqueous barrier of humans. Whereas topical application of certain PGs produces marked anterior chamber flare reaction in rabbits [4,30–32], highly significant species-specific responses to PGs are well documented. Results concerning the blood-aqueous barrier obtained in the rabbit cannot be applied to the human [32]. In controlled clinical trials, slit-lamp biomicroscopic assessment after treatment with either PhXA34 (a compound consisting of the epimeric mixture of latanoprost and its considerably less active 15 S-epimer) or with latanoprost has consistently failed to show the development of flare. In addition, sensitive laser-flare meter and fluorophotometric measurements of anterior chamber flare and/or protein concentration also have failed to demonstrate alterations in blood-aqueous barrier integrity after treatment with either PhXA34, PGF2α-IE, or latanoprost in clinical studies [6]. Also, chemotaxis, a hallmark of inflammation, has not occurred in response to latanoprost or any PG analogue in clinical trials or, in fact, in controlled experiments involving any animal species. Indeed, the chemotaxis induced by leukotriene LTb4 was inhibited by PGs, including PGF2α [33].

Efforts to detect an effect of latanoprost on the blood-retina barrier have not yielded positive results either. Studies with monkeys failed to find angiographic or histopathologic evidence for CME following two weeks to six months of treatment with latanoprost or the related compound PGF2α-tromethamine salt [7,34,35]. In one study of latanoprost and CME [7], cynomolgus monkeys were subjected to unilateral extracapsular cataract extraction (without lens implant) and, beginning 14 weeks after surgery, were then treated bilaterally with latanoprost 0.035% (seven times the concentration used in human glaucoma therapy) once daily for six months. FAs, performed at one, three, and six months after the beginning of treatment, failed to show vascular leakage; also, there were no ophthalmoscopically-detected macular changes in any eye. However, none of the monkey eyes had posterior capsule disruption or underwent anterior vitrectomy. In another study, it should be noted, complicated and uncomplicated cataract surgery without latanoprost treatment produced histologically-proven disruption of the blood-retina barrier without angiographic CME in seven eyes of four monkeys [36]. However, the power of this study prevented definitive conclusions because only a single monkey eye was evaluated at each of seven time intervals following surgery.

In a study specifically designed to investigate the potential of latanoprost to induce CME in human pseudophakic eyes, 24 patients with posterior chamber lenses and with intact posterior capsules were treated unilaterally for four weeks [7]. Sixteen received latanoprost 0.006% twice daily (twice the clinical dose), and eight received placebo. They were examined with macular biomicroscopy and FA before and after treatment. There was no indication of macular edema nor was there a reduction in visual acuity in the latanoprost-treated eyes. One of the placebo-treated eyes had mild angiographic CME. None of the eyes had suffered a prior episode of CME, and all had intact posterior capsules.

Corticosteroids have been claimed to ameliorate uveitis-associated CME, though no randomized prospective trials have shown this. Nonsteroidal anti-inflammatory drugs (NSAIDs) are believed to reduce the likelihood and/or severity of postcataract surgery CME [37–40]. Either corticosteroids or NSAIDs can inhibit the production of PGs and other prostanoids from arachidonic acid. Based on these and other observations, a causal role for PGs in the pathogenesis of aphakic CME has been proposed [41,42]. However, corticosteroids and NSAIDs are nonspecific, having many effects independent of their ability to inhibit PG synthesis [43]. As cyclooxygenase (COX) inhibitors, NSAIDs also inhibit the formation of thromboxanes, prostacyclin, and other prostanoids. In addition, they may inhibit the activity of phosphodies- terases [44] and protein kinases [45], and they may reduce transmembrane calcium flux [46]. Corticosteroids inhibit phospholipase A2 and therefore inhibit PG synthesis, but they also have an even broader spectrum of activity than NSAIDs. They inhibit migration of macrophages and neutrophils; induce lymphocytopenia, eosinopenia, monocytopenia, and neutrophilic leukocytosis; reduce capillary permeability and suppress vasodilatation; inhibit neutrophil and mast cell degranulation; stabilize lysosomes and suppress action of lymphokines; and decrease leukotriene formation [47]. Surgical trauma stimulates not only the production of PGs but also many other eicosanoids and inflammatory mediators [5,48,49]. Therefore, the apparent palliative role of corticosteroids or NSAIDs in CME, and the increased levels of PGs during inflammation, in and of themselves do not prove a causal role for PGs in producing CME.

To further explore this issue, Miyake et al. [50] performed a randomized double-masked comparison of the effect of latanoprost therapy versus placebo on FA following cataract surgery in eyes with ocular hypertension, normal pressure glaucoma, or primary open-angle glaucoma. They also compared postoperative treatment of these same eyes with either diclofenac sodium or fluoro- metholone (FML), though this part of the study was open-label. All eyes underwent clear-corneal temporal phacoemulsification with implantation of an acrylic, foldable posterior chamber intraocular lens implant through a 3-mm incision. Thirty-five to 37 eyes were treated in each of four groups, receiving either latanoprost and diclofenac, latanoprost and FML, placebo and diclofenac, or placebo and FML. Latanoprost or placebo was used once every morning from two days before until five
weeks following surgery. Diclofenac or FML was used three times daily until five weeks following surgery. FA was performed five weeks postoperatively. No patient in any group experienced CME, as there was no difference in acuity between any of the four groups. Each group had average best-corrected visual acuity greater than 20/25 by five weeks. All groups had similar presurgical IOP, but latanoprost-treated eyes had significantly lower postoperative IOPs, regardless of concomitant therapy with either FML or diclofenac. The incidence of angiographic leakage was higher in latanoprost-treated than in placebo-treated eyes when FML was used postoperatively, but not when diclofenac was used. The authors conclude that latanoprost increases the likelihood of angiographic leakage and that diclofenac, but not FML, effectively protects against the development of leakage. However, the relevance of this study to clinical CME is unclear because no group demonstrated impairment of visual acuity [51].

Because diclofenac, a NSAID and COX-inhibitor, protects against the development of angiographic CME, latanoprost cannot be the direct cause of angiographic CME. The protective effect of the COX-inhibitor has no antagonistic action on the exogenously applied PG analogue, as demonstrated by the inability of diclofenac to inhibit the latanoprost-induced decrease in IOP. It could, though, inhibit the synthesis of a secondary COX-derived inflammatory mediator whose production was stimulated by latanoprost [50,51].

Pharmacologic and pharmacokinetic considerations
Latanoprost is a PG analogue modified from its parent compound, the naturally occurring PGF\(_{2\alpha}\). Latanoprost differs from PGF\(_{2\alpha}\) by addition of an isopropyl ester group on C\(_1\), by 17-phenyl substitution, and by reduction of a double bond at C\(_{13-14}\). It is a lipophilic prodrug, hydrolyzed to the active free acid in the cornea. PGF\(_{2\alpha}\) is one of a large class of related 20-carbon biologic molecules known as eicosanoids, many of which have potent vasoactive effects. For example, thromboxanes cause vasoconstriction, whereas prostacyclin is a potent vasodilator. Of the eight different prostanoid receptors and their subtypes—including DP, EP\(_1\), EP\(_2\), EP\(_3\), EP\(_4\), FP, IP, and TP receptors—vasodilation is known to be mediated by EP\(_2\), DP, and IP receptors and vasoconstriction by TP receptors [52,53]. PGF\(_{2\alpha}\), by acting on the “vasoactive” receptors, has either vasoconstrictive or vasodilatory properties, depending on its concentration and the vascular tissue under investigation [1–3].

Earlier PGF\(_{2\alpha}\)-related compounds tested for their IOP-lowering effect, such as PGF\(_{2\alpha}\)-IE, caused conjunctival hyperemia secondary to vasodilation [54,55]. In the rabbit eye, the hyperemic effect of PGF\(_{2\alpha}\)-IE was abolished by trigeminal nerve ablation or by nitric oxide synthase inhibitors, indicating that the vascular response is mediated by the trigeminal nerve and is dependent on nitric oxide synthesis [1,2]. Therefore, the hyperemia does not appear to be a direct vascular response to the PG [1,2]. In contrast, latanoprost had a minimal effect on conjunctival hyperemia in rabbits [2] and humans [56–58]. The high selective affinity of latanoprost for the FP receptor makes vascular actions for latanoprost extremely unlikely even at high concentrations [59]. Indeed, in a study of bovine ciliary artery and episcleral vein, latanoprost had no vasoactive effect, whereas PGF\(_{2\alpha}\) caused vasoconstriction, which was abolished by TP receptor antagonists [3].

Latanoprost acid should not be able to reach the posterior part of the human eye, as latanoprost, similar to other PGs, is rapidly removed from the anterior segment by an organic anion transport system in the ciliary processes [60–63]. One drop of commercially supplied latanoprost 0.005% solution contains 1.5 µgm of latanoprost. About 1% (ie, 0.015 µgm) is expected to enter the anterior chamber [59]. Peak concentration of the free acid of latanoprost appears in the human anterior chamber 2–3 hrs after topical application and is about 10\(^{-7}\) mol/L [64]. The half-life for elimination of latanoprost from the human anterior chamber is 3–4 hours [64]. Pharmacokinetic studies in phakic cynomolgus monkeys indicate that topically administered latanoprost reaches the anterior but not the posterior segment in detectable amounts [65,66]. Although some diffusion of the administered latanoprost acid might occur in an eye with a disrupted posterior lens capsule, it would then be diluted from its anterior chamber concentration because of volumetric considerations, aqueous humor production, and active transport processes to concentrations less than 10\(^{-9}\) mol/L [67]. At this concentration, there is no known vascular action of latanoprost [1,3]. Indeed, intravitreal injection of more than 500 µgm of PGF\(_{2\alpha}\) was required to produce leakage detected by FA in rabbits [68].

In addition to evidence failing to demonstrate a route through direct intraocular penetration, latanoprost cannot reach the posterior segment through systemic circulation. In humans, the peak plasma concentration of latanoprost acid is about 50 pgm/ml or 10\(^{-10}\) mol/L, with a half-life of 17 minutes [59,67,69]. Latanoprost acid is rapidly metabolized in the liver and excreted primarily in the urine [59,70].

Conclusions
Although a number of cases of CME in association with latanoprost use have been described, the numbers of implicated eyes are small in comparison with the number of eyes that have been treated with latanoprost. Also, all eyes described to date have had other RFs for the development of CME. Indeed, there is no evidence, so far, for CME developing in a phakic eye without RFs for
CME. Repeated rechallenges with placebo controls have not been performed in eyes developing CME. It therefore is impossible to conclude that latanoprost caused CME in any of the cases so far reported because, by definition, these eyes all might have developed CME regardless of whether latanoprost had or had not been used.

All 29 eyes described in previously published case reports and herein arose from uncontrolled clinical observations. Controlled and closely monitored clinical trials and experimental studies with latanoprost have given no indication that latanoprost causes clinical CME. Pharmacologic considerations indicate that the concentration of latanoprost expected in the posterior segment of the eye is far too low to have any effect on those PG receptors that mediate vascular actions. Further, the systemic metabolism and clearance of latanoprost is too rapid to allow latanoprost to reach the posterior segment in a pharmacologically meaningful concentration from a systemic route. In addition, latanoprost is not known to exhibit vasoactive or inflammatory properties.

Nevertheless, reports of a possible association between CME and latanoprost use must be given serious consideration. Latanoprost should be used with caution in eyes with multiple RFs for CME. In these eyes, an increased level of surveillance for the development of CME is recommended. Long-term, randomized, placebo-controlled studies are required to determine whether a causal relation between latanoprost and CME exists in eyes with multiple RFs. Unfortunately, such studies would be very difficult to undertake in view of the large numbers of patients required to provide adequate power to evaluate this rare potential side effect.

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Dr. Camras is a consultant to, and Dr. Mandah is an employee of, the Pharmacia & Upjohn Company, Stockholm, Sweden.

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