THE INCIDENCE, PATHOGENESIS AND TREATMENT OF CYSTOID MACULAR EDEMA FOLLOWING CATARACT SURGERY*

BY *Allan J. Flach,* MD (BY INVITATION)

INTRODUCTION

Cystoid macular edema (CME) following cataract surgery was first recognized over 4 decades ago by Irvine.[1] Macular edema was mentioned in the 20th century, and CME was identified and studied earlier in the 20th century.[2-6] However, the report of Irvine represents the first clinical description of CME following cataract surgery as a distinct entity.[1] Following this initial description, the syndrome was further studied and described with new methods including fluorescein angiograms.[7,8] Today, this postoperative complication is frequently referred to as the Irvine-Gass syndrome. It is recognized as the most common cause of decreased vision in patients following cataract surgery with or without the implantation of an intraocular lens.[9-17] This syndrome is responsible for a greater and a more frequent loss of vision than many of the more commonly discussed postoperative complications, including retinal detachment and endophthalmitis.[10,11] Despite over 40 years of clinical and laboratory investigative effort, the incidence and pathogenesis of this syndrome remain obscure, and its treatment continues to be controversial.

The purpose of this thesis is to provide a current and comprehensive review of the literature on the Irvine-Gass syndrome and to describe previously unpublished investigations that extend our knowledge about the incidence, pathogenesis, and treatment of this syndrome. The literature review supports the hypothesis that the incidence, pathogenesis, and treatment of CME following cataract surgery are poorly understood. The overall goal of the 7 laboratory and clinical studies described within this thesis is to provide new information concerning the incidence, pathogenesis, and treatment of CME following cataract surgery.

*From the Department of Ophthalmology and the Department of Veterans Affairs, University of California, San Francisco, Medical Center. Supported by a Merit Review grant from the Department of Veterans Affairs; a grant from That Man May See, Inc; a departmental core grant from the National Institutes of Health—University of California, San Francisco, Department of Ophthalmology; a research grant from Syntex, Palo Alto, California; an unrestricted research grant from Allergan; and a grant from Research to Prevent Blindness.

More specifically, the original results and data that are reported within the new investigations section following the literature review include:

I. Incidence of CME Following Cataract Surgery

II. Correlation of Anterior Ocular Inflammation with CME Following Cataract Surgery

III. Topical NSAID Treatment of CME Following Cataract Surgery With Topical NSAIDs

- A. Comparison of Topical NSAIDs and Their Ability to Stabilize the Blood-Aqueous Barrier (BAB) of Rabbits Following Paracentesis
- B. Comparison of Ketorolac Tromethamine 0.5% and Diclofenac Sodium 0.1% Ophthalmic Solutions in Reducing Postoperative Inflammation After Cataract Extraction and Intraocular Lens Implantation
- C. The Effect of Patient Characteristics on Response to Topical NSAID Treatment of Chronic Clinical CME Following Cataract Surgery
- D. Treatment of Acute-Onset Clinical Cystoid Macular Edema Following Cataract Surgery With Topical NSAIDs

IV. Oral Acetazolamide and the Treatment of Chronic Clinical CME Following Cataract Surgery

These original laboratory and clinical efforts consist of 5 studies (I, IIIA, IIIB, IIID, IV) that have not been previously published. In addition, two studies (II, IIIC) are included that have been previously published in part. However, they are reported here in more detail and with a different emphasis in support of this thesis.

A summary and conclusions section derived from both the literature review and the new investigations is placed at the end of this thesis. This section attempts to place the findings of the new investigations and their relationship to the literature review into perspective in a concise manner.

REVIEW OF LITERATURE

INCIDENCE

Although CME following cataract surgery is recognized as the most common cause of decreased vision in the postoperative period, the reported incidence of this postoperative complication has been and continues to be quite variable. Many review articles mention factors that may contribute to the difference in the reported incidence of CME.[15,17-31] These comments are derived from more than 60 published papers, each of which mentions or discusses the incidence of this syndrome. These publications are summarized in the Appendix of this paper.[9-11,14,24,25,28-90] In spite of the extensive effort reflected in these reports and reviews, the incidence of this syndrome remains uncertain. Furthermore, frequently the reasons for the differences

in reported incidence continue to remain a mystery. For example, 2 well-designed studies performed in the same city, including patients with similar characteristics who were operated on by the same surgeon using the same technique and medications, report an incidence of 5.6% and 18.8%, respectively, for angiographic CME in eyes with intact posterior capsules and intraocular lenses lacking UV filters.[14,91] The explanation for this difference in incidence is unclear.[92] Therefore, some of the coexistent variables that can affect the incidence of CME have not been identified.

However, in spite of this uncertainty, it is important to recognize as many of the known variables as is possible for at least 2 reasons. First, it seems prudent to identify factors tending to increase the incidence of CME and to omit them in an attempt to minimize the incidence of this postoperative complication.[92] Second, it is important to identify these variables and recognize their potential impact on the interpretation of results from therapeutic trials that evaluate potential treatments for CME. The presence of these variables and their potential influence on the observed incidence of CME make it unwise to use retrospective controls when evaluating the potential merits of a new therapeutic approach, because the observed difference may reflect the presence of the coexistent variable and not a therapeutic effect. Furthermore, when evaluating the results of a prospective, randomized, double-masked therapeutic trial, one must confirm that these variables are present in both the treatment and control groups in similar numbers at the conclusion of the study to prevent misinterpretation of the results.

Insofar as the factors that influence the incidence of CME are relevant to therapeutic trials concerning this syndrome, a review of these variables is of great practical value. Factors that investigators have considered *potentially* capable of influencing the incidence of CME following cataract surgery include:

1. The thoroughness of the search for this syndrome, including the performance and examination of multiple angiograms[20]
2. Whether the investigators report a retrospective study designed to assess patients with poor vision or a prospective study including fluorescein angiograms[30]
3. The introduction of new instrumentation or technology permitting more careful or complete diagnostic examinations[20]
4. A changing definition of CME following cataract surgery[23]
5. Whether the investigators are reporting clinical CME (angiographic CME associated with a decrease in visual acuity) or only angiographic CME[15,17,19,20,22,28]
6. How long after surgery the patient is examined[20,39,40,45,137,138]
7. Patient characteristics, including age,[20,34,68,73,77,93,94] presence of vascular disease,[7,20,29,34,39,45,50,86,89,90,95,96] race and eye color,[83,97] and a history of

alcoholsim[95]

8. A history of CME following surgery in the contralateral eye[8,20,28,56,99]
9. Comparisons of results following intracapsular cataract extraction (ICCE) and extracapsular cataract extraction (ECCE) with or without the presence of an intraocular lens[17,24,25,28,29,42,47,49,53,55,57,59,62,65,72,81,87,100]
10. The administration of retrobulbar hyaluronidase[101,102]
11. The presence of intraoperative complications, including vitreous loss[9,11,52,54,63,64,72,84,87,103,104]
12. The presence of vitreous to the wound[1,20,104-110]
13. The presence of a peaked pupil in the postoperative period[19,27,93,111-113]
14. The influence of coexistent drug use or other ocular irritants[17,26,51,58,75,83,101,102,114-119]
15. The presence or absence of an intact posterior capsule[31,52,54,59,60,65,69,70,78,98,120-123]
16. The presence of specific intraocular lens qualities such as a polyvinlypyrrolidone coating,[124] metal loops,[125] and UV blockers,[91,98] lens defects,[126] iris clip and rigid anterior chamber (AC) lens[27,30,94]
17. Exposure to excessive intraoperative or postoperative light[79,91,98,122,127-131]
18. The performance of a postoperative yttrium-aluminum-garnet (YAG) capsulotomy[120,132]
19. The lapse of time between cataract extraction and secondary intraocular lens implant[133]
20. Secondary lens implantation compared with primary lens implantation[133]

There is agreement that the incidence of CME is greatest in *prospective* studies reporting *angiographic* CME including *multiple* angiograms performed *1 to 3 months* following an *ICCE* with implantation of an *iris clip* lens in an *older* population of patients with systemic *vascular disease*. Furthermore, the incidence can vary with how, when, and why an investigator looks for this syndrome. However, investigators have not been in agreement concerning the importance of several of the potential variables listed previously. Therefore, the evidence suggesting that these factors may or may not influence the development of angiographic or clinical CME following cataract surgery is summarized in Table I.

CLINICAL CHARACTERISTICS

CME following cataract surgery consists of a maldistribution of the retinal intravascular fluid within the macula. The leakage of the intravascular contents from dilated perifoveal capillaries initially causes thickening of the macula, which may progress to cystoid expansions within the outer plexiform (Henle's) layer and inner nuclear layer of the retina. These cystoid

TABLE I: FACTORS INFLUENCING THE INCIDENCE OF CME FOLLOWING CATARACT SURGERY

VARIABLE	RESULTS OF COMPARISON	ANGIOGRAPHIC CME	CLINICAL CME	REFERENCES
Type of surgery	ICCE>ECCE	Increased	Increased	35,50,51,53,56, 57,59,60,62,65, 69,71,72
Placement of IOL	Iris clip>AC>PC*	Increased	Increased	27,28,30,56,94, 125,134
Integrity of posterior capsule	Absent > present†	Increased	Same	78
Hyaluronidase in retrobulbar	Absent = Present ‡	Same	Same	102
Operating microscope light	UV filter = no filter§	Same	Same	79
Environmental light	IOL without UV filter > IOL with UV filter	Increased	Same	91,98
Contralateral CME	Present>absent	Increased	Increased	8,20,56, 98,99
When examined	1-3 mo greatest incidence	Increased	Increased	20,39,40,45
Age	Older > younger‖	Increased	Increased	20,68,73,77, 93,94
Systemic vascular disease (diabetes, hypertension)	Present > absent¶	Increased	Increased	7,20,29,34, 39, 45,50, 95,96
Vitreous loss	Present > absent#	Increased	Increased	9,11,52,54, 63,64,72,84, 87,103,135
Vitreous to wound	Present > absent	Increased	Increased	1,20,104,105, 106,107,109, 110
Abnormal pupil shape	Present > absent	Increased	Increased	19,27,112,113
Iris incarceration in wound	Present > absent	Increased	Increased	113
Race	White > black	Increased	Increased	83,97
Epinephrine	Present > absent**	Increased	Increased	114,115,116, 117,118,119

AC, anterior chamber; CME, cystoid macular edema; angiographic CME, visual acuity normal; clinical CME, visual acuity abnormal; ECCE, extracapsular cataract extraction; ICCE, intracapsular cataract extraction; IOL, intraocular lens; PC, posterior chamber; UV, ultraviolet.

* Initially investigators observed no difference.[52,57,62,72,136] Subsequently good evidence for AC > PC,[28,134] iris-supported lenses poorer prognosis,[30] iris clip lenses particularly

TABLE I (CONTINUED): FACTORS INFLUENCING THE INCIDENCE OF CME FOLLOWING CATARACT SURGERY

Copeland and metal loop and rigid AC lenses.[27,30,94,125] In addition, defects in IOL[126] and polyvinylpyrrolidone-coated lenses[124] all increased angiographic and clinical CME.

† Many investigators observed disrupting posterior capsule increases CME.[52,54,59,65,69,96,122,123] In addition, a secondary capsulotomy increased CME,[52,54,59,63] including YAG capsulotomy.[120] However, a well-controlled, prospective, randomized study shows an increase in angiographic CME, but no signifiant difference in vision.[78] In addition, a YAG capsulotomy does not appear to increase clinical CME.[132]

‡ Initially, small study suggested presence of hyaluronidase increases CME,[101] but these investigators agreed that a larger study was needed. Subsequently, a larger well-controlled study showed no difference.[102]

§ Although microscopic light can cause retinal damage[131] and investigators wondered if this light might predispose to CME,[127-129] there is no evidence of a relationship. Furthermore, a well-designed study shows no effect on CME.[79]

‖ Most agree that increased age is associated with increased CME, but an increased incidence has been reported in younger adults.[94] Furthermore, a limbal approach to cataract surgery in pediatric patients appears to be associated with more CME[73] as compared with a pars plana approach using vitrectomy instrumentation.[77]

¶ The reported association of systemic disease (systemic hypertension, diabetes mellitus) and increased CME has prompted some to recommend treatment prior to surgery to reduce CME.[96] This is a good idea, but no evidence exists that will decrease CME.[17]

Although most CME occurs without surgical complications, vitreous loss increases CME and vitreous to the wound prolongs CME and can be associated with a poorer prognosis.[27,30,38]

** Topically applied epinephrine and dipivalyl epinephrine can induce CME in eyes following cataract surgery. This is reversible if treatment is discontinued in a timely fashion.

spaces tend to be smaller peripherally and larger centrally and often culminate in a typical petaloid or stellate appearance. This accumulation of transudate may or may not be associated with a measureable decrease in visual acuity.[20,141]

A patient with CME may be asymptomatic or may complain of decreased vision, a positive central scotoma, and metamorphopsia.[96] Direct or indirect ophthalmoscopy may reveal only the absence of the foveal light reflex or a vague irregularity within the macular region. During ophthalmoscopy, red-free light can be used to help demonstrate cystoid spaces.[5,15] However, most of the time, CME is best detected with slit-lamp biomicroscopy using a Goldmann fundus contact lens or a Hruby lens.[139] Initially, there is a loss of the foveal light reflex, which is associated with the loss of the foveal depression and the appearance of a yellowish spot deep in the foveal area. The thickened, yellowish macular changes can progress to the formation of cystoid spaces that are best appreciated using retroillumination and red-free light, which makes the inner walls of the cystic cavities more visible. These can appear in a rosette pattern. Splinter hemorrhages can layer blood in the cystoid spaces.[1,142] Coalescence of the

cystoid spaces can form a foveal cyst or even inner lamellar holes as the surface of the cyst elevates and peels away.[141] A shallow sensory retinal detachment can develop owing to diffusion of excess transudate beneath the photoreceptors.[8] The subretinal fluid can stimulate the retinal pigment epithelium with hypotrophic or hyperpigmentary changes and, less commonly, disciform scar formation.[15] A grayish membrane with glinting reflexes from the inner surface of the retina can indicate the presence of an epiretinal membrane. This has been described in up to 10% of the eyes that have developed CME.[113,141,143,144] In addition to these retinal findings, many eyes with CME have a coexistent circumcorneal flush, mild iritis, vitritis, and a low-grade papillitis sometimes associated with peripapillary hemorrhages.

Most of the time, CME follows an uncomplicated cataract surgery, and it is diagnosed in an eye with a relatively normal gross anatomy. However, patients may demonstrate an associated ocular anatomic derangement such as vitreous and/or iris incarceration in the surgical incision, vitreous adherence to the iris, poor pupillary dilation, an abnormally shaped or updrawn pupil, secondary glaucoma, or corneal decompensation. A clinical examination will not confirm the diagnosis of CME in 5% to 10% of the eyes with CME.[15] Even a retinal detachment can mimic CME.[145] Fluorescein angiography is the diagnostic procedure of choice for patients with a questionable diagnosis of CME.[8,15,139]

Following the systemic administration of sodium fluorescein to a patient with CME, the involved eye demonstrates early perifoveal capillary dilation and leakage with pooling of fluorescein in the macular cystoid spaces and late staining of the optic nerve associated with leaking of capillaries of the optic nerve head.[7] A highly resolved, stereoscopic analysis of negatives from eyes with CME is the best way to identify characteristic angiographic features of this syndrome.[15,139] During the early stages of the angiogram, the macula appears dark as the dye perfuses choroidal and retinal vascular systems. Early in the retinal venous filling phase, the presence of CME becomes apparent as dilated perifoveal vessels that become prominent and leak the dye-stained transudate. In later stages of the angiogram, leakage from the deep retinal capillary circulation fills the larger cystic spaces in a stellate, or rosette, perifoveal pattern. This dye-stained fluid accumulates in the outer plexiform and inner nuclear layers of the retina. Photographs are best taken at 10 minutes postinjection to enhance the appearance of macular cyst or hole formation, which provides a complete and sensitive angiographic analysis.[146] Dye leakage from the retinal vessels, optic nerve, and anterior uvea into the anterior and posterior chambers and into the vitreous cavity during the very late stages of the angiogram create an anterior and posterior haze that reduces the resolution of the macular changes. The dye leakage from the iris and optic disc

may persist even after the CME has resolved.

Fluorescein angiograms are of great diagnostic value. However, even experienced clinicians are unable to read up to 15% of these angiograms owing to factors associated with the postoperative eye. These factors include the presence of an intraocular lens and/or an intact posterior capsule, which create bothersome reflections; anterior synechiae or poorly dilated pupils, which limit sufficient light from entering the eye; vitreous haze, which obscures detail; and inadequate patient cooperation.[140]

Fluorescein angiographic grading systems have been developed to monitor patients with CME.[146,147] However, highly skilled investigators have reported an improvement in vision without change in the degree of edema, a reduction in edema without a corresponding improvement in vision, and a deterioration in vision associated with gradual disappearance of CME on angiogram.[146] Published photographs of 4 angiograms, each taken from a patient with 20/50 visual acuity, depict severity of grade 1 through grade 4.[146] Therefore, there is agreement that angiograms are of great value to confirm the presence or absence of CME, but the degree of leakage does not always correlate with the visual acuity.[15,19,27,52,87,113,146,148-150]

There are several reasons why the correlation between visual acuity and angiogram grade may be poor in patients with CME following cataract surgery. An angiogram documents fluid in cystoid spaces in the outer plexiform layer, but decreased vision may be associated with edema in the photoreceptor area or elsewhere. A coexistent anatomic change such as a preretinal membrane, a macular cyst or hole, the presence of perifoveal retinal pigment epithelium atrophy, disciform scarring, or a papillitis may limit an increase in visual acuity.[15,149] Finally, the presence of ocular diseases other than CME, such as glaucoma and corneal edema, may be responsible for the reduced vision.

The potentially poor correlation between a fluorescein angiogram grade and visual acuity has important clinical implications for the use of angiograms during studies designed to evaluate the effectiveness of a treatment for CME following cataract surgery. A fluorescien angiogram is useful for confirming the diagnosis of CME during clinical studies, but the visual acuity should be the primary efficacy parameter in therapeutic trials. Furthermore, clinical data collected from patients with angiographically proven CME should not be excluded from analysis simply because the corresponding angiogram is unreadable or unavailable. Although the measurement of visual acuity in patients with CME is somewhat subjective, its determination yields the most clinically relevant information at our disposal at present, provided it is obtained using proper technique and precautions.[149,151] However, it must be recognized that the improvement in vision may reflect an ameliorating effect of treatment, which is not synonymous with the elimination of the edema.[146] Investigators may develop

methods to measure retinal thickening that are inexpensive and easy to incorporate into ophthalmic practice in the future. New methods may provide a more objective method for following changes in the retinal edema present in eyes with CME that is more consistent with changes in visual acuity.[148,150,152,153]

HISTOPATHOLOGY

Histopathologic specimens from patients with CME following cataract surgery show retinal capillary dilation and serous fluid in the outer plexiform and inner nuclear layers and inflammatory cells in the iris, ciliary body, and around blood vessels.[135,154-157] Sometimes there are associated iridovitreous adhesions. The eosinophilic transudate displaces rod and cone nuclei and receptor cell axons. Severe CME involves most of the retinal layers. Perifoveal cysts can become confluent, forming larger cysts or lamellar holes. Shallow serous detachments occur in some eyes with CME.[8] In addition to retinal changes, swollen mitochondria are present in ganglion cell axons in the prelaminar area, and degeneration of fibrous astrocytes between axons and occlusion of laminar blood vessels by edematous endothelial cells and pericytes can be present.

The intraretinal cysts can develop from the accumulation of fluid either intracellularly or extracellulary. Initially, extracellular serous fluid was thought to compress Müller cells and receptor cell axons to form the walls of the cysts.[7] Subsequently, histologic evidence of intracytoplasmic edema of Müller cells suggested intracellular fluid accumulation as the origin and location of the cystic changes.[158,159] However, evidence exists that the cysts can arise from expansion of extracellular spaces.[160] It is possible that the observed histologic differences relate to tissue fixation technique.[19,160]

Histologic evidence shows vitreous traction producing macular holes with surrounding cystoid changes.[161] This histopathologic observation suggests that vitreous traction may relate to the development of CME following cataract surgery. However, cystic macular degeneration and associated hole formation linked to with vitreoretinal traction occurs in both aphakic and phakic eyes. Therefore, these findings are believed to be related to a different entity.[20] In addition, the cystic spaces in these eyes are filled with a mucopolysaccharide, and these eyes lack the characteristic increased vascular permeability as seen in fluorescein angiograms that support this distinction.[20,162,163]

DYNAMICS OF EDEMA FORMATION

CME is a nonspecific retinal sign of ocular disease that consists of an abnormal accumulation of intracellular and extracellular eosinophilic transudate associated with thickening of the retina and the formation of cystic

changes within the outer plexiform layer and inner nuclear layer of the macula. The blood-retinal barrier (BRB) is a condition of restricted permeability between blood and retina dependent on the integrity of intercellular junctional complexes (tight, nonleaky junctions) existing in both an epithelial (retinal pigment epithelium) and an endothelial (endothelium of retinal capillaries) cell layer within the retina.[164,165]

Our understanding of the dynamics underlying the development of the maldistribution of fluid in eyes with CME following cataract surgery is based on a recognition of Starling's hypothesis and its relationship to the blood-brain barrier and the BRB.[166-168] Edema occurs in any tissue when the rate of capillary filtration exceeds the rate of fluid removal from perivascular interstitium.[166] The abnormal accumulation of transudate within the macula is determined by an increased permeability state of the BRB and an imbalance between tissue forces determined by osmotic pressures in the plasma and retina (largely dependent on protein concentration), hydrostatic pressures within the retinal capillaries and surrounding retinal tissue, and tissue compliance of the corresponding retina.[15,164-168]

Macula edema develops when the rate of capillary filtration exceeds the rate of fluid outflow from the retina in spite of autoregulation of blood flow pressure attempting to prevent increased hydrostatic pressures and increased permeability of retinal capillaries and in spite of the resistance offered by the low retinal tissue compliance. Retinal tissue compliance is low because the cellular elements supported by Müller cells combined with minimal extracellular space resists fluid accumulation. CME will develop when the BRB permits intravascular fluid entry to exceed its exit to the point of overcoming retinal tissue compliance. Disruptions of tight junctions in both inner (capillary endothelial cells) and outer (retinal pigment epithelium) portions of the BRB may be involved in this process.[169,170]

As excessive transudate accumulates within the retina, the macular region is presidposed to the collection of this fluid by virtue of its anatomic structure. The horizontal course of the outer plexiform layer extends transversely from cone nuclei to bipolar cells, and the resultant laxity of this layer predisposes to the formation of a reservoir for the accumulation of transudate.[171] Furthermore, the avascularity of the foveolar area restricts absorption.[163] As a result of this predilection for the accumulation of fluid, the macula has been said by some experienced investigators to "act as a sponge" or to have an "inherent turgesability."[7,172] In addition to these anatomic considerations, the foveal region has large concentrations of cells with a high metabolic activity. Inflammatory, metabolic, or vascular disturbances can lead to increased concentrations of tissue metabolites with loss of biochemical activity.[139]

Although there is agreement about the contribution of these anatomic and biochemical factors to the development of CME following cataract

surgery, a complete understanding of the dynamics of this fluid accumulation is not within our grasp. Investigators have emphasized that the preferential leakage from perifoveal capillaries in eyes with CME observed during angiograms remains unexplained and may reflect an important, unrecognized capillary vitreous interaction.[20]

CME ASSOCIATED WITH OTHER DISORDERS

CME represents the accumulation of fluid within cells or spaces in the outer plexiform layer and the inner nuclear layer of the retina.[7,158-160] This nonspecific intraretinal macular manifestation can be associated with many ocular and systemic disorders in addition to cataract surgery.[139,141] It is important to recognize these potential associations for at least two reasons. First, these associated conditions provide us with clues to the pathogenesis of this syndrome as discussed in the following section of this paper. Second, recognition of these associations is important during the evaluation of a potential therapeutic response. If the associated condition is present, treatment of this disorder can affect the presence or the severity of the associated CME. Furthermore, CME related to this condition may or may not be influenced by the treatment being evaluated. Therefore, the presence of an associated condition must be identified, and patients with the disorder must either be omitted from the study or, if included, some assurance that the condition is present in both treatment and control groups in comparable numbers must be provided.

Therefore, it is important to remember that the following disorders and systemic conditions have been reported in association with CME in the absence of cataract surgery:

1. Choroidal tumors[173-176]
2. Topical epinephrine and dipivalyl epinephrine treatment[75,114-118,177-179]
3. Dominant and X-linked retinitis pigmentosa[5,148,150,180-186] and probably even in the recessive form[187] (characteristic fluorescein angiographic leakage variable even in the same patient)
4. Favre-Goldmann syndrome[188,189]
5. Retinal detachment surgery[6,190-202]
6. Penetrating keratoplasty[203-205]
7. Ocular inflammatory diseases, including bird-shot chorioretinitis, chronic cyclitis, and idiopathic vitritis[45,141, 206-210]
8. Diabetes mellitis[50,89,90,211-213]
9. Arteriosclerotic vascular disease[50,105]
10. Systemic hypertension[45,50,105]
11. Vascular occlusive disease[29,139,159,214-218]
12. Infants without hereditary eye disease at birth[219,220]
13. Vitreous surgery[221]
14. Laser surgery[222]

15. Fundus flavimaculatus[223]
16. Cryotherapy and segmental buckling of retinal tears without detachments[198]
17. Ring choroidal atrophy[224]
18. Gyrate atrophy of choroid and retina[225]
19. Idiopathic epiretinal membranes[226]
20. Serpiginous choroidopathy[227]
21. Dominantly inherited cystoid changes of the retina[228-231]

In addition to these conditions, several disorders have been described as associated with macular edema. However, they do not manifest the characteristic fluorescein angiographic findings of CME. These disorders include nicotinic acid treatment,[232-235] parafoveal retinal telangiectasia,[139-215] juvenille X-chromosome-linked retinoschisis,[236] adult-onset cystic macular degeneration and "hole" formation with or without vitreomacular traction,[20] and possibly ocular trauma.[139,201,237] However, the presence of retinal edema following ocular trauma in clinical cases lacks solid evidence. Even within laboratory studies it is variable, leading some investigators to question if "Berlin edema" is still valid.[238,239]

PATHOGENESIS

The pathogenesis of CME following cataract surgery remains obscure.[15,20,22,26,96,146] Clinical observations and experimental studies suggest that the pathophysiology of this postoperative problem may be multifactorial. Among the factors of potential clinical importance are vitreous traction,[1,33,107,161-163,240-244] vascular instability,[1,18,38,50,155,156,159,210,245-248] a relative ocular hypotony,[37,248-252] a lack of stability inside an aphakic eye called endophthalmodonesis,[253] inflammation[1,7,8,13,6,20-22,28,37-39,45,51,98,112,124,126,135,154-156,207,210,248,254-265] including endogenous chemical mediators such as prostaglandins[26,51,99,196,254,258-262,265-274] and other autacoids,[26,146,267,272] a functional disturbance of the blood-ocular barriers,[122,164,169,275-277] and ultraviolet radiation.[79,91,98,127-130,278] Each of these potential etiologic factors has been considered as a rationale for the consideration of a corresponding treatment as discussed in the following section of this paper.

Most investigators agree that inflammation is the major etiologic factor in the development of CME following cataract surgery.[14,20,22,26,27,146,267,279] There is clinical, histopathologic, experimental, and pharmacologic evidence to support this conclusion. Clinicians have noted that CME is a nonspecific, intraretinal reaction that is often associated with ocular inflammatory diseases, including chronic cyclitis, retinal vasculitis, syphilis, toxoplasmosis, and sarcoidosis.[209,210,264] Clinical descriptions of patients with CME following cataract surgery suggest that inflammation is an important factor. Clinical signs such as circumcorneal flush, trace anterior chamber cells and flare, and anterior vitreal cells are present in these eyes. Patients

Table II: Correlation of Inflammation with CME[286]

Patient*	Eye (treatment)	Day 40 Angiogram grade†	Day 20 Fluorophotometry‡	Average inflammation grade§ (Postoperative days 5, 12, 19) AC cells	Ciliary flush	Conjunctival hyperemia	Vision Day 19
1	OD (K)	0	+0.58	0	0	0	20/25
+2	OS	+2	+1.07	0.33	0.66	1.00	20/25
2	OD (P)	+3	+1.69	0.66	1.66	2.00	20/40
	OS (K)	+2	+1.14	0.66	1.66	1.66	20/60
3	OD (P)	+2	+3.89	1.00	1.33	1.66	20/40
	OS (K)	0	-0.14	0.66	1.00	1.00	20/40
4	OD (K)	0	-0.50	0.33	0.66	1.00	20/40
	OS (P)	+3	+3.05	1.00	2.33	2.33	20/40
5	OD (K)	+3	+1.10	0.33	1.00	1.00	20/60
	OS (P)	+3	+3.59	0.66	2.00	2.00	20/50
6	OD (P)	+1	+1.35	1.33	2.66	2.66	20/40
	OS (K)	0	+0.21	0.66	2.00	2.00	20/40
7	OD (P)	+2	+3.36	0	1.33	1.66	20/25
	OS (K)	0	+1.08	0	0.33	1.00	20/30
8	OD (P)	+1	+1.85	0.33	2.00	2.00	20/20
	OS (K)	0	+0.19	0.33	0.33	1.33	20/25
9	OD (K)	+1	+2.80	0.66	1.66	3.00	20/30
	OS (P)	0	+1.77	0.66	2.66	2.66	20/30
10	OD (K)	0	-0.47	0.33	0	1.00	20/30
	OS (P)	+1	+4.63	1.00	2.00	2.00	20/50

Table II (continued): Correlation of Inflammation with CME

		Average inflammation grade§ (Postoperative days 5, 12, 19)					
Patient*	Eye (treatment)	Day 40 Angiogram grade†	Day 20 Fluorophotometry‡	AC cells	Ciliary flush	Conjunctival hyperemia	Vision Day 19
11	OD (K)	0	+0.25	1.00	1.33	2.00	20/20
	OS (P)	+1	+2.23	0	1.00	1.66	20/60

* Eyes operated on at least 1 month apart.

† Angiogram grade: 0 = none; +1 = partial circle; +2 = full circle (≤ disk); +3 = full circle (> disk).

‡ Fluorophotometry: median percent difference = $\frac{\text{operated eye - unoperated eye}}{\text{unoperated eye}} \times 100$

§ Using system of Hogan et al.[287]

K = treated with topical ketorolac 0.5%

P = treated with placebo

with CME describe a mild photophobia and ocular irritation that is characteristic of ocular inflammation.[1,7] Fluorescein angiogram changes include vasodilation and increased vascular permeability, which are suggestive of an inflammatory process.[7,8,38]

Histopathologic investigations provide evidence that inflammation is an important component of the pathophysiology of CME following cataract surgery. Vitreous aspirates taken from patients with this syndrome demonstrate inflammatory cells.[257] Ocular histologic specimens taken from patients with CME at the time of their death reveal retinal phlebitis, which is consistent with an inflammatory process.[135]

Clinical and laboratory investigations have suggested that inflammation is a prominent feature of CME following cataract surgery. Investigators have shown a disturbance of the BRB by using vitreous fluorophotometry in aphakic and pseudophakic eyes associated with persistent CME.[106,267,277,280] Iris angiography has been found useful in the study of inflammatory ocular disease.[106,281,282] This technique has been used to demonstrate increased leakage from iris and possibly ciliary vessels in patients with CME.[18,106,246] Finally, there is abundant laboratory and clinical evidence that anti-inflammatory drug therapy is of benefit in some patients for the prevention and treatment of CME following cataract surgery as reviewed and discussed in the following section of this paper.[17,26,27,146,267,279,283-285,286]

However, while there is agreement that inflammation is an integral part of the pathogenesis of CME, a clear correlation between the development of CME and inflammation remains to be established. In fact, investigators have studied the time course of perifoveal leakage after cataract surgery and have delineated factors associated with this leakage, noting that no detectable inflammation was present at the time of the 6-week angiograms that showed leakage in 10 of their patients.[50] A potential approach to providing a more direct correlation between CME and postoperative inflammation was expressed during a recent symposium entitled "Quantitative studies utilizing anterior chamber fluorophotometry may prove useful in documenting an association between breakdown of the blood-ocular barriers and subsequent development of CME."[17] This has proven to be true.[286]

TREATMENT

Although the pathogenesis of CME following cataract surgery is unclear, each potential etiologic factor has been considered as a rationale for the application of a corresponding therapy. For example, each of the following has been considered as a potential treatment for improving vision in these patients: laser vitreolysis[104,120,288,289] and surgical vitrectomies,[19,103,107,109,110,207,243,56,257,290-303] anti-inflammatory treatment with corticosteroids[7,37,38,4,121,51,304-306] or NSAIDs,[14,16,17,51,58,75,83,98,99,146,147,149,151,196,259,267,268,270,273,274,281,284,286,307-317] over-

coming potential relative hypotony,[251] and attempts to influence the functional integrity of BRBs with carbonic anhydrase inhibitors[318-321] or hyperbaric oxygen.[322,323]

Several reviews have summarized potential pharmacologic and/or surgical treatments for CME following cataract surgery.[15,17,19,21,22,26,27,146,267,279,283,290,293,296,324,325] These reviews stress the importance of placebo-controlled, double-masked, randomized trials to evaluate therapeutic efficacy because the natural history of CME includes spontaneous resolution.[13,38,43,98,111,140,326] Furthermore, an emphasis is placed on the need to consider prophylactic therapy of CME separately from treatment of chronic CME and the importance of distinguishing angiographic CME from clinical CME. (Clinical CME coexists with a reduction in vision.)

The following review will emphasize the studies that recognize the importance of these basic considerations. In addition to this review, 4 studies relating to the medical treatment of CME following cataract surgery completed in our research facilities are described for the first time. These studies include (1) treatment of acute clinical CME (present 4 months or less) with topical NSAIDs and (2) anatomic factors potentially associated with a poor response to topical NSAID treatment of chronic clinical CME. In addition, (3) a laboratory investigation comparing the relative postoperative anti-inflammatory activity of topical NSAIDs will report the relative effectiveness of the 4 commercially available topical NSAIDs as determined in a double-masked, randomized, placebo-controlled study. Finally, (4) a double-masked, randomized, placebo-controlled study of the treatment of chronic clinical CME following cataract surgery with oral acetazolamide is described for the first time.

Surgical Treatment

Etiologic theories related to vitreous abnormalities and their potential contribution to the development or persistence of CME following cataract surgery have predisposed to surgical approaches designed to improve vision in appropriate patients.[19,33,38,107,109,110,243,244,289,290,295,300,303,327] The goals of these surgical procedures include the lysis of vitreous strands extending to the cataract incision, the disruption of potential posterior vitreoretinal adherence, the alteration of detrimental retinal capillary permeability, and the achievement of a more normal anterior ocular anatomy.[19,107,243,289] The surgical approaches used to achieve these goals have included laser treatments and conventional vitreous surgical techniques.

Laser Surgery. Although an attempt to alter retinal capillary permeability in a beneficial manner by photocoagulation has been considered in the treatment of CME following cataract surgery, its effectiveness and safety have never been proved with appropriately designed clinical studies.[289] The diffuse leakage from the retinal vasculature does not lend itself

to focal photocoagulation.[17,96] Therefore, laser treatment of the retina is not a generally accepted approach for the treatment of this syndrome.[15, 20, 73]

The neodymium YAG laser has been used to transect elevated vitreous strands with good results in some patients with CME as reported in nonrandomized, uncontrolled studies.[104,120,288] However, many patients in these studies have had CME for relatively brief periods, making it difficult to distinguish visual improvement related to spontaneous resolution from a therapeutic effect. In addition, anti-inflammatory drugs are often used following the laser surgery during these studies. This makes it difficult to identify whether it is the surgery, the medical treatment, or a combination of the two treatments that is responsible for the observed visual improvement. Although there are inherent advantages to avoiding an invasive surgical procedure, YAG laser vitreolysis appears to be applicable to a relatively select subgroup of patients with CME.[19] Furthermore, this procedure is not completely innocuous. Postoperative intraocular pressure increases are reported in 50% of patients following YAG laser treatments, and retinal detachments have occurred.[146] Therefore, it remains to be determined whether properly designed studies will establish the safety and efficacy of this treatment.[15]

Surgical Vitrectomy. Following the reports of good results with limbal or pars plana vitrectomy in some patients with CME following cataract surgery, all agreed that the clinical value of this treatment required a prospective, controlled clinical trial.[292,294,299] The results of a 5-year prospective, randomized, controlled, collaborative study (27 experienced vitrectomy surgeons in 15 medical centers) of patients with chronic (present 6 months to 4 years) CME associated with vitreous incarceration to the wound and pupillary distortion following cataract surgery without intraocular lenses indicate that the clinical course of patients receiving vitrectomy is better than that of the control patients.[293,296] The investigators of this study concluded that the CME in these eyes without intraocular lenses appears related to chronic inflammation and that restoring the pupil to as normal as possible reduces uveal inflammation. However, patients within the vitrectomy group received corticosteroids, and the control group did not. Therefore, it is not possible to determine to what extent the corticosteroid treatment contributed to the improvement in vision. Although it was not proved, the investigators have the impression that the pars plana surgical approach is superior to the limbal approach. Furthermore, they feel that a preoperative response to topical steroids may predict improvement following surgery. Therefore, a trial treatment with steroids may provide the potential for a prognostic test for the effectiveness of surgery.[293,296]

A properly designed study of the potential benefit for vision following vitreous surgery for pseudophakic CME does not exist. One small, retrospective, unmasked, uncontrolled study of 24 consecutive patients with

chronic pseudophakic CME associated with vitreous adhesions to anterior ocular structures and visual loss unresponsive to medical therapy suggests that patients may benefit from pars plana vitrectomy with removal of vitreous adhesions.[297] However, the investigators admit that the subconjunctival corticosteroid injections that they administered after vitrectomy may have contributed to the observed visual improvements. Therefore, the role of vitrectomy for the management of CME in pseudophakic eyes remains uncertain.[15,19,328]

While the effectiveness of surgical approaches in apparently anatomically normal eyes is unproved, some investigators postulate the presence of a vitreous "sump," or sponge, that may retain inflammatory agents which encourage the development or persistence of pseudophakic CME.[207] The existence of this supposition has not been proved.[19] Although uncontrolled studies describing pars plana vitrectomy for intraocular inflammation–related CME unresponsive to corticosteroids report good results in some patients, the subgroup of patients that may benefit from this surgery remains to be identified.

In conclusion, most cases of chronic, pseudophakic CME with vitreous strands to the cataract wound and iris have a high incidence of spontaneous remission. Vision can return to 20/20 even after the CME has persisted for more than a year.[96] In addition, many patients respond to medical treatment with anti-inflammatory drugs. Highly skilled retinal surgeons recommend medical treatment prior to surgery because significant surgical complications may occur with anterior vitrectomy through either the limbal or pars plana approach.[96,328] If no improvement occurs after conservative treatment for at least 1 year or something less than 2 years, vitrectomy can be considered.[7,96,290,293,297] The potential specific indications for surgery and the related surgical approaches have been previously outlined.[19]

Other Surgical Procedures. Intraocular lenses have been removed from inflamed eyes with CME following cataract surgery with an improvement in vision.[329] The incidence of CME was reduced from 14.3% to 4.8% by waiting 1 year before implanting a secondary intraocular lens.[133] This study also provides evidence that secondary intraocular lenses, particularly following an intracapsular cataract extraction, have an increased risk of CME. Abnormalities of the anterior segment can occur following cataract surgery, such as distorted pupils and pupillary capture of an intraocular lens with or without coexistent abnormalities of the vitreous, which may increase inflammation. A comprehensive review of the potential surgical approaches for these postoperative problems has been published.[19]

Medical Treatment: NSAIDs

Prophylaxis of CME With NSAIDs. Many studies report that topical

TABLE III: PROPHYLAXIS OF CME WITH NSAIDS

YEAR	SURGERY	INVESTIGATORS	NSAID (ADMINISTRATION)	ANGIOGRAPHIC RESULTS
1976	ICCE	Tennant[270]	Indomethacin (oral)	Effective
1976	ICCE	Yannuzzi,Wallyn[274]	Indomethacin (oral)	Effective
1977	ICCE	Miyake[51]	Indomethacin (topical)	Effective
1978	ICCE	Miyake[99]	Indomethacin (topical)	Effective
1978	ICCE	Miyake et al[259]	Indomethacin (topical)	Effective
1979	ICCE-IOL	Sholiton[313]	Indomethacin (oral)	Negative
1979	ICCE	Klein[58]	Indomethacin (oral)	Effective
1980	ICCE	Miyake[147]	Indomethacin (topical)	Effective
1980	ICCE	Fechner[308]	Indomethacin (topical)	Effective
1981	ICCE	Yannuzzi et al[317]	Indomethacin (topical)	Effective
1982	ECCE-IOL	Kraff et al[14]	Indomethacin (topical)	Effective
1983	ICCE	Tanabe et al[75]	Indomethacin (topical)	Effective
1983	ICCE	Hollwich et al[310]	Indomethacin (topical)	Effective
1983	RD	Miyake et al[196]	Indomethacin (topical)	Effective
1989	ECCE-IOL	Stark et al[315]	Suprofen (topical)	Effective
1989	ICCE-IOL	Quentin et al[311]	Diclofenac (topical)	Effective
1990	ECCE	Flach et al[83]	Ketorolac (topical)	Effective
1995	ECCE-IOL	Solomon, Flurprofen CME Study Group I[314]	Flurbiprofen, indomethacin (topical)	Effective
1995	ECCE-IOL	Ginsburg[309]	Flurbiprofen, indomethacin (topical)	Effective

ECCE, extracapsular cataract extraction, ICCE, intracapsular cataract extraction; IOL, intraocular lens; RD, retinal detachment.

NSAIDs are effective in the prophylaxis of angiographic CME.[14,51,58,75,83,99,147,196,259,270,274,308,310,313,317,330] These studies are summarized in Table III. No study of prophylactic treatment of CME has documented a statistically significant angiographic effect of more than 1 year. Furthermore, only 2 studies show a subtle, transient effect on visual acuity.[147,314] Therefore, the long-term visual benefit from prophylactic treatment remains uncertain.[15,17,21,22,26,27,146,267,279,283,324,325] Commonly cited studies supporting this conclusion are summarized in greater detail in Table IV. One study compares l% indomethacin in sesame seed oil (a preparation that is not commercially available) with a placebo control solution in a randomized, double-masked fashion. This long-term study describes a loss of statistical significance for an early improvement in visual acuity between 7 and l2 months

TABLE IV: PROPHYLAXIS OF CME WITH TOPICAL NSAIDs TREATMENT: DOUBLE-MASKED, RANDOMIZED, PLACEBO-CONTROLLED STUDIES

YEAR	INVESTIGATORS	NSAID DOSAGE	CONCURRENT STEROIDS?	EXAMINATION TIME	ANGIOGRAPHIC ACME*	IMPROVED VISION?*	NSAID
1980	Miyake et al[147]	1 gt tid for 2 wk following surgery	Yes	1-2 mo 4-7 mo 12-18 mo	Decreased Decreased Same	Yes NO No	1% indomethacin (sesame seed oil)
1981	Yannuzzi et al[317]	1 gt qid for 4-6 wk following surgery	Yes	5 wk 10 wk 52 wk	Decreased Same Same	No No No	1% indomethacin (suspension)
1982	Kraff et al[14]	1 gt qid for 9 mo following surgery	Yes	2-12 mo	Decreased	No	1% indomethacin (suspension)
1990	Flach et al[83]	1 gt tid for 19 days following surgery	No	6 wk	Decreased	No	0.5% ketorolac (solution)
1995	Solomon, Flurbiprofen CME Study Group I[314]	1 gt qid 2 days before and 3 mo following surgery	Yes	1-2 mo 4-8 mo	Decreased Same	Yes No	1% indomethacin (suspension) or 0.03% flurbiprofen (solution)

NSAID, nonstroidal anti-inflammatory drug
*NSAID compared with placebo.

following cessation of treatment.[147]

More recently, a study of CME prophylaxis evaluated Snellen and non-Snellen parameters of visual function using glare and contrast sensitivity measurements in the postoperative period.[314] This randomized, double-masked, vehicle-controlled, parallel-group, clinical trial compares 0.03% flurbiprofen, 1% indomethacin, and placebo for their ability to prevent CME following cataract surgery during a 6-month period. Eye drops are instilled 4 times daily beginning 2 days preoperatively and continuing for 3 months following surgery. At the fifth visit (3 weeks to 2 months following surgery), the 2 NSAID treatment groups demonstrate significantly less angiographic CME than the vehicle treatment group (17% flurbiprofen, 12% indomethacin, 32% vehicle). However, there is not a statistically significant difference between the NSAIDs. In addition, the incidence of clinical CME as determined by contrast sensitivity scores is significantly lower for the drug-treated groups (11% flurbiprofen, 10% indomethacin, 22% vehicle). Although Snellen visual acuity differences of 2 lines or more are not significantly different, the drug-treated patients seem to achieve better Snellen vision sooner. Furthermore, there were transient, statistically significant differences between drug treatment and placebo treatment in contrast sensitivity measurements.

Investigators used corticosteroids in 4 of the 5 studies summarized in Table IV. Concurrent corticosteroid treatment introduces the possibility of a synergistic (additive or potentiative) effect when these 2 classes of anti-inflammatory drugs are used together within these studies.[279,283,325,331,332] There is clinical evidence for this pharmacologic interaction. Patients undergoing ECCE with an intraocular lens implantation demonstrated increased aqueous fluorescein concentrations at 3 months following surgery, despite sub-Tenon's steroid injections at the time of surgery and topical steroids in the postoperative period. However, when topical indomethacin was used in addition to the steroids, the blood-aqueous barrier (BAB) was reestablished within 5 weeks.[333] This potential for a synergistic effect between indomethacin and corticosteroids was confirmed in a second study.[334] The effects of topical 0.5% ketorolac and 0.1% dexamethasone ophthalmic solutions on the reestablishment of the BAB following cataract surgery were compared in two studies.[335,336] Only 1 of the studies showed ketorolac 0.5% to be more effective than dexamethasone in reestabilizing the postoperative BAB in pseudophakic eyes.[336] The only difference between these studies was the use of intraoperative sub-Tenon's steroids in the study showing ketorolac to be more effective. Therefore, potential synergism prevents a conclusion about the usefulness of NSAID treatment alone in these 4 studies.[14,147,314,317]

The only study that evaluates the potential benefit of prophylactic treatment of CME without concurrent corticosteroid administration is a

double-masked, placebo-controlled investigation of topically applied 0.5% ketorolac tromethamine ophthalmic solution.[83] Within this study, the topical NSAID is given as 1 drop 4 times daily begining preoperatively and continued for 1 month following completion of the cataract surgery. Patients with bilateral cataracts were enrolled in this paired-comparison study, and each eye was operated on 1 month apart. Eleven patients had evidence of angiographic CME on postoperative day 40. Two of these patients had bilateral CME, 1 patient had CME in the NSAID-treated eye, and 8 patients demonstrated CME in the placebo-treated eye. Ketorolac treatment produced a statistically significant ($P<.05$) reduction in postoperative angiographic CME. Therefore, this study provides support for topical NSAID treatment given alone prior to and following cataract surgery as an effective approach to reduce postoperative angiographic CME. This study reports no significant improvement in visual acuity, as compared with placebo, when measured 3 weeks following surgery.

Treatment of CME With NSAIDs. Several studies report the results of the treatment of chronic clinical CME with NSAIDs as summarized in Table V. Two of these investigations report negative results. One of these studies compares 25 mg of oral indomethacin given 3 times daily for 3 weeks with placebo treatment.[316] However, the results were discouraging. It is now recognized that topical treatment with indomethacin eye drops achieves higher aqueous drug levels than orally administered indomethacin in laboratory animals and humans.[337,338] The second negative study reports results from 14 patients following topical 1% fenoprofen treatment for 8 weeks compared with placebo.[281] Although this small study fails to report statistically significant results, the variations in vision that correspond with drug treatment in an on-off fashion are suggestive of a potential therapeutic effect. Therefore, these results encouraged investigators to study the treatment of larger populations of patients.

Two double-masked, placebo-controlled studies demonstrate a statistically significant, beneficial effect on visual acuity (2 Snellen lines or more improvement) following topical NSAID treatment of chronic (present 6 months or longer) clinical CME.[149,151] The first study included 30 patients treated with either 0.5% ketorolac tromethamine ophthalmic solution or placebo eye drops in a randomized, double-masked fashion for 2 months.[149] Twenty-six patients completed the study, with an improvement in vision described in 8 of the 13 drug-treated patients as compared with only 1 of 13 placebo-treated patients after 2 months of treatment ($P=.005$).

The second double-masked, randomized study is a 4- to 5-month, multicenter investigation including 120 patients (contributed by 12 ophthalmologists) with chronic clinical CME who are treated with either 0.5% ketorolac tromethamine ophthalmic solution or an identically packaged placebo solution for 90 days.[151] A statistically significant improvement in

Table V: Treatment of Chronic CME with NSAIDs

Year	Investigators	NSAID (dosage)	Masked?	Control	Result	Comments
1977	Yannuzzi et al[316] (20 pts)	Oral indomethacin (25 mg tid for 3 wk)	Yes	Placebo	No effect	Enrolled cases 4 mo after surgery
1983	Burnett et al[281] (14 pts)	1% topical fenoprofen (1 gt tid for 8 wk)	Yes	Placebo	No effect	On-off effect impressive
1987	Flach et al[149] (30 pts)	0.5% topical ketorolac (1 gt tid for 2 mo)	Yes	Placebo	Improved vision (2 Snellen lines or more)	On-off effect impressive
1991	Flach et al[151] (120 pts)	0.5% ketorolac (1 gt tid for 3 mo)	Yes	Placebo	Improved vision (2 Snellen lines or more)	On-off effect impressive
1992	Peterson et al[16] (30 pts)	1% indomethacin (1 gt qid for 4 mo)	No	None	Improved vision	On-off effect impressive

distance visual acuity of 2 lines or more as measured by Snellen charts is reported in the drug-treated group as compared with the placebo-treated group at all time periods: 30 days (P=.038), 60 days (P=.017), and 90 days (P=.008). The improvement in visual acuity remained statistically significant 1 month after treatment cessation (P=.001).

In summary, 2 double-masked, randomized, placebo-controlled studies provide evidence that 0.5% ketorolac tromethamine ophthalmic solution given 4 times daily may improve vision in patients with chronic clinical CME following cataract surgery.[149,151] However, not all patients with chronic CME respond with an improvement in vision to topical treatment with this NSAID. Furthermore, many patients require treatment for 2 to 3 months before an improvement in vision is observed.

Medical Treatment: Corticosteroids

Properly controlled studies of the use of corticosteroids for the prevention or treatment of CME following cataract surgery do not exist.[1,15,19,21,22,30,279,382,283] However, there is a strong clinical bias that corticosteroid therapy provides clinical benefit for some patients with this syndrome. This impression began to form at the time the syndrome was first fully described.[38] Investigators believed that many patients showed improvement in visual acuity after intensive corticosteroid treatment, but recurrences were often noted after cessation of treatment. Furthermore, they recognized that the natural history of this syndrome included spontaneous resolution.

In one uncontrolled, retrospective study of patients following ICCEs with full iridectomies, 13 of 17 patients responded with improved vision to 20/30 after treatment with 20 to 40 mg of oral prednisone per day. The average duration of treatment of the CME was 6 weeks.[37] A larger, retrospective, uncontrolled study of 821 consecutive patients following ICCEs with iris fixated intraocular lenses reports that 40 of 49 patients with CME responded with improved vision following oral, topical, and retrobulbar corticosteroid treatment.[94] The investigators recommend 60 mg of prednisone orally for 4 days followed by 40 mg orally for 6 days and then tapering this dose over 4 weeks. If resolution is incomplete, they consider administering 40 mg of triamcinolone given by sub-Tenon's injection. In addition, corticosteroid eye drops are believed to help prevent recurrences. It is not possible to know whether improved vision in these retrospective, uncontrolled studies reflects spontanteous resolution or the effects of corticosteroid treatment.

Many skilled clinicians believe that topical corticosteroids are not always adequate and that orally administered corticosteroids can be too toxic. Therefore, they recommend that 40 to 80 mg of methylprednisolone be injected in the sub-Tenon's space of the superotemporal quadrant just

posterior to the equator after anesthetizing the area with 4% lidocaine on a cotton-tipped applicator.[96] An alternative corticosteroid treatment regimen is the injection of 40 mg of triamcinolone acetonide using a 3-mL syringe and a ⅝-inch needle on a 25-gauge needle.[27] It is well recognized that corticosteroid treatment can be accompanied by both local and systemic side effects.[283,306,359] Therefore, it would seem only prudent to withhold potentially dangerous medical therapy until spontaneous resolution is unlikely.

Overcoming Relative Ocular Hypotony Using Corticosteroids. Several clinical observations suggest that a relative ocular hypotony may relate to the development of CME following cataract surgery. Edema of the posterior pole of the eye associated with decreased intraocular pressure has been described.[248-250] The abrupt loss of residual vision following glaucoma filtering procedures may be related to the development of CME.[198] Finally, epinephrine's ability to induce CME in aphakic patients may be related to its capacity to lower intraocular pressure.[251]

However, there are clinical observations that oppose each of these potential correlations. It is likely that epinephrine's ability to increase capillary permeability relates to the development of CME in aphakic eyes.[20] This belief is supported by the ability of acetazolamide to lower intraocular pressure without an associated development of CME in aphakic eyes.[318,321] Prospective studies of filtering procedures have not described CME in association with ocular hypotony.[34,45] It is likely that the decreased vision associated with ocular hypotony following filtering procedures reflects the presence of choroidal folds.[20] It can be difficult to distinguish the stellate patterns associated with choroidal folds from the pelatoid patterns of CME clinically with an ophthalmoscope. A fluorescein angiogram can confirm the diagnosis.[141] Finally, investigators simply have not linked ocular hypotony with the development of CME following cataract surgery.[37,39,45]

One study links an improvement in vision in patients with this syndrome with an increase in intraocular pressure achieved following treatment with corticosteroids.[251] This study of 16 patients reports an improvement in vision and the resolution of edema in all 28 episodes of CME following the elevation of intraocular pressures with prednisolone acetate 1% given 4 times daily. This is an uncontrolled, unmasked, and nonrandomized study. There is no explanation given for why all these patients happened to respond to corticosteroid. Insofar as this study has not been confirmed in almost 2 decades, few clinicians modulate intraocular pressure in an attempt to improve vision in patients with postoperative CME.

Medical Treatment: Hyperbaric Oxygen and Acetazolamide

These therapeutic efforts are directed at removing edema fluid from with-

in the retina or repairing abnormal microanatomy in patients with CME following cataract surgery rather than preventing or treating factors related to the pathogenesis of the syndrome. Investigators have attempted to enhance the integrity of injured capillary endothelial cell junctional complexes with hyperbaric oxygen or improve the pumping function of the pigmented retinal epithelium with acetazolamide in an attempt to decrease intraretinal fluid and improve vision in patients with CME.[318,321-323]

Treatment of CME With Hyperbaric Oxygen. A randomized, controlled study of 8 patients reports improvement in all patients with CME following cataract surgery who received 2.2 atm of oxygen for 1.5 hours twice daily for 1 week, followed by treatment for 2 hours daily for 2 weeks.[323] The investigators hypothesize that the administration of oxygen induces vascular constriction, which may assist the endothelial cell junctional complexes to heal. In addition, this treatment may stimulate collagen formation, which helps seal the spaces responsible for excess fluid leak. A different group of investigators report improvement in vision in 2 patients with CME following a branch vein occlusion that failed laser treatment.[322] They recommend 2 atm of oxygen for 1 hour twice daily for 4 to 14 days.

The administration of hyperbaric oxygen requires special facilities, an expert staff, and considerable time and inconvenience for the average patient.[360] Furthermore, this treatment is not without dangers.[361-363] Patients with pulmonary problems, ear disease, sinus conditions, and claustrophobic tendencies are at particular risk. Therefore, it is unlikely that this medical approach will gain widespread acceptance until a properly controlled study verifies its efficacy and safety.

A laboratory study demonstrates that aqueous humor oxygen levels can be increased following the transcorneal administration of high concentrations of oxygen by way of specially adapted goggles applied to rabbits and monkeys.[364] This study was designed to explore new potential therapies for various hypoxic ocular diseases, such as rubeosis iridis, retinal vascular occlusions, and anterior segment ischemia. Whether this approach has potential benefit for the treatment of CME following cataract surgery remains to be proved.

Treatment of CME With Acetazolamide. A properly controlled clinical study of oral acetazolamide treatment of clinical CME following cataract surgery has not been published. However, patients are described that have experienced improved vision following 500 mg of acetazolamide given orally once or twice daily for 2 weeks.[318,321] Enthusiasm for this treatment is strengthened by results of a study suggesting that acetazolamide may be of benefit in the treatment of reduced vision associated with CME complicating uveitis.[319]

The rationale supporting this therapeutic effort remains unclear.

However, this treatment may improve the ability of the retinal pigment epithelium to pump fluid from the retina and thereby improve vision in some patients.[365-367] This treatment regimen is potentially complicated by side effects, including paresthesias, diuresis, gastrointestinal upset, and psychological disturbances.[368] In rare instances, serious and potentially lethal reactions may occur.[369] Therefore, investigators have suggested that a properly designed study to determine whether oral acetazolamide benefits vision in patients with chronic clinical CME following cataract surgery is indicated.[21,22,146]

NEW STUDIES OF CME FOLLOWING CATARACT SURGERY

I. INCIDENCE OF CME FOLLOWING CATARACT SURGERY

As summarized in the Incidence section of the Literature Review and in Table I, despite the recognition of different variables and their potential influence on the incidence of CME following cataract surgery, the incidence of clinical CME following cataract surgery remains significant.[9,84,85,87,90] We determined the incidence of clinical CME associated with 350 consecutive planned ECCEs with implantation of an intraocular lens performed during approximately an 18-month period extending from middle of 1988 to early 1989. Intraoperative corticosteroids were not routinely used. Postoperative treatment consisted of a topical cycloplegic-mydriatic given 3 times daily (1% tropicamide) and topical corticosteroid (1% prednisolone acetate) given 4 times daily for 2 to 3 weeks. Patients were examined at monthly intervals with careful refractions during the first 4 months following surgery. Fluorescein angiograms were performed on all patients with Snellen visual acuities less than 20/40. The incidence of clinical CME was 24/350, or 6.9%. This is most certainly an underestimate, because this study only includes patients who developed CME during the first 1 to 4 months following surgery. Although this interval includes the peak incidence for onset of CME, investigators have described the onset of CME more than a decade following cataract surgery.[137,138] However, the results of this prospective study are in agreement with recent reviews stating that the incidence of symptomatic CME is higher than is commonly recognized.[27]

Fortunately, most of these patients underwent spontaneous resolution of their CME with the ultimate achievement of good final visual acuity. This well-recognized potential for spontaneous resolution[38,43,139,140] makes placebo-controlled studies essential for the evaluation of a therapeutic response during studies of the treatment of CME following cataract surgery. The 24 patients identified within this prospective study of the incidence of CME following cataract surgery are included and described in further detail in the study of the medical treatment of acute clinical CME reported and discussed within the subsequent Treatment section of

this discussion of new studies of CME following cataract surgery.

II. PATHOGENSIS OF CME FOLLOWING CATARACT SURGERY

As concluded in the Pathogenesis section of the literature review, there is general agreement that inflammation is an integral part of the pathogenesis of CME following cataract surgery. However, a clear correlation between CME and inflammation remains to be established. A potential approach to providing a more direct correlation between CME and postoperative inflammation was expressed during a symposium entitled "Quantitative studies utilizing anterior chamber fluorophotometry may prove useful in documenting an association between breakdown of the blood-ocular barriers and subsequent development of CME."[17]

In response to this suggestion, the following study was designed and completed. The goal of the investigation is to compare slit-lamp observations of postoperative inflammation following cataract surgery with anterior ocular fluorophometric measurements and the subsequent development of angiographic CME. This investigation relating to the pathophysiologic basis for CME following cataract surgery represents an addendum to a previously reported study that assessed the effects of topical NSAID treatment on the postoperative breakdown of the BAB.[286]

Correlation of Anterior Ocular Inflammation With CME Following Cataract Surgery

The goal of this study is to compare the postoperative signs of anterior ocular inflammation in eyes with and without angiographic CME 6 weeks after cataract surgery in an attempt to more clearly establish any existing relationship between anterior ocular inflammation and CME following cataract surgery.

Materials and Methods. This report includes results taken from the study of 50 patients with bilateral, symmetric cataracts who were operated on by one surgeon and enrolled in a double-masked, randomized, paired-comparison, crossover study comparing 0.5% ketorolac ophthalmic solution with placebo.[286] Complete eye examinations were performed with special attention given to the presence of ocular inflammation, including the presence of anterior chamber cells, ciliary flush, and conjunctival vasodilation. These examinations were performed at baseline and on days 1, 5, 12, and 19 following each surgery. In addition, anterior ocular fluorophotometry was performed on day 20 following surgery.

Although not an official part of the original study, fluorescein angiograms were performed 40 days after each surgery. All 50 patients received angiograms in both eyes. CME was present in 11 patients in this study. These 11 patients are the focus of this report.

Results. All 50 patients received bilateral cataract extractions at least 1

month apart, and each received a fluorescein angiogram 40 days following each surgery. The presence of inflammation and its relationship to subsequent development of CME within these patients are presented in Table II. In each instance, inflammation following cataract surgery within a patient's right eye is compared with inflammation following surgery in the left eye. The parameters of anterior ocular inflammation used in this study include anterior ocular fluorophotometry and graded slit-lamp observations.[287] Bilateral CME was present in patients 2 and 5. The remaining 9 patients had CME in only 1 eye. In all patients, the more severe grades of ocular inflammation noted during the slit-lamp examination were recorded in the eye with the greater anterior segment fluorophotometry value. Therefore, both estimations of anterior ocular inflammation indicate that CME occurred in the most inflamed eye with the exception of patient 9. Furthermore, the slit-lamp observations of inflammation appear to correlate well with the anterior ocular fluorophotometry results.

Conclusion. This study reports the first quantitative correlation of anterior ocular inflammation with the subsequent development of CME following cataract surgery. There appears to be an association between breakdown of the BAB and the subsequent development of CME following cataract surgery. Therefore, the results of this study provide further evidence that the pathogenesis of CME following cataract surgery relates, at least in part, to excessive ocular inflammation.

III. TREATMENT OF CME FOLLOWING CATARACT SURGERY WITH TOPICAL NSAIDS

As summarized in the Treatment section of the Literature Review, topical NSAIDs have been used in an attempt to prevent and treat CME following cataract surgery. It is clear from this review that the most effective topical NSAID has not been identified. Is one agent more effective than the others? Furthermore, not all patients appear to respond to NSAID treatment. Can specific patient groups be identified that do not respond to this treatment? Finally, topical NSAID treatment often must be continued for several months before a beneficial effect is observed during the treatment of chronic clinical CME. Might the initiation of CME treatment at an earlier point following surgery shorten the course of topical NSAID treatment needed to improve vision in patients with CME following cataract surgery?

In an attempt to shed some light on these questions, 3 new studies were completed. The first is a laboratory investigation that compares the effects of the 4 commercially available topically effective NSAIDs following a minor surgical procedure in an attempt to identify a potentially more effective topical NSAID. The use of a topically effective NSAID with the greatest anti-inflammatory activity could increase the success rate of med-

ical treatment of chronic clinical CME. The second study is a clinical investigation that attempts to identify the patients with chronic clinical CME who are less likely to respond with an improvement in visual acuity following topical NSAID treatment. The identification of a subgroup of patients unresponsive to the effects of topical NSAIDs could save time, effort, and expense. The third investigation explores whether earlier treatment of clinical CME following cataract surgery might reduce the treatment time required to improve vision in these patients. The demonstration of an improvement in vision following a shorter duration of treatment would suggest that it may be unwise to wait too long for spontaneous resolution of CME following cataract surgery.

A. Comparison of Topical NSAIDs and Their Ability to Stabilize the BAB of Rabbits Following Paracentesis

Four NSAIDs formulated as ophthalmic preparations are commercially available for use in the United States: 0.1% diclofenac, 0.03% flurbiprofen, 0.5% ketorolac, and 1% suprofen. These topically applied drugs have been used in an attempt to treat and/or prevent CME following cataract surgery.[279,283] Their effectiveness is thought to be related to their anti-inflammatory activity.[20,22,26,146,279] However, there are no studies comparing the anti-inflammatory activity of these agents.[279,283,339]

The purpose of this study is to compare the ability of these ophthalmic NSAID formulations to reduce the BAB disruption induced by anterior chamber paracentesis in rabbits in a double-masked, randomized study. The identification of a topical NSAID with greater anti-inflammatory activity may help improve the results of our treatment of chronic clinical CME following cataract surgery.

Materials and Methods. One hundred and fifty healthy rabbits with normal ocular examinations were randomly divided into the 5 treatment groups and used for this study. All surgical procedures and ocular measurements were performed with rabbits under light sedation using 125 mg of ketamine and 20 mg of xylazine. The rabbits were housed and treated in accordance with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research.

All topical NSAIDs used in this study are commercially available within the United States. They included 0.5% ketorolac tromethamine ophthalmic solution (Acular, Allergan, California), 0.03% flurbiprofen ophthalmic solution (Ocufen, Allergan, California), 1% suprofen ophthalmic solution (Profenal, Alcon, Texas), and 0.1% diclofenac ophthalmic solution (Voltaren, Ciba Vision Ophthalmics, Georgia). The control solution was Balanced Salt Solution (Alcon, Texas). One drop of treatment solution was applied to the left or right eye of each subject every 10 minutes for a total of 4 applications. Approximately 10 minutes following the last drop, the

rabbits were anesthesized with an intravenous bolus of 125 mg of ketamine and 20 mg of xylazine. A rapid, nonleaking paracentesis with removal of 0.1 mL of aqueous was performed on the treated eye of each rabbit. Fluorophotometry was repeated 40 minutes and 24 hours following paracentesis to assess the BAB integrity.

Anterior ocular fluorophotometry was performed by using a fluorophotometer with an anterior chamber adapter (Fluorotron Master, Coherent Radiation, California). Prior to paracentesis, anterior ocular fluorophotometry was performed on each rabbit to ensure that the amount of fluorescein entering the right and left anterior chambers of each animal did not vary by more than 25%.[336,340] Animals showing more than a 25% variation were not used for the study. Fluorescein concentrations within the anterior chambers were measured following the intravenous administration of 0.4 mL of 25% fluorescein sodium for injection (Ak-Fluor, Akorn, Louisiana) with no more than 2 minutes elapsing between right and left eye measurements. Fluorescein concentrations from the central anterior chamber were used in all calculations.

BAB breakdown was quantitated by expressing the percentage increase in fluorescein (Fl) concentration in the paracentesed (op) eye versus the nonparacentesed (unop) eye according to the following formula:

$$\%\text{Increase[Fl]}=([\text{Fl}]\text{op}-[\text{Fl}]\text{unop})/([\text{Fl}]\text{unop})\text{x}100\%$$

Comparing the fluorescein concentration in 1 eye with the contralateral eye minimizes the interanimal variability in BAB permeability. This method of comparing fluorophotometric data is justified because both eyes equilibrate with the same serum concentration of fluorescein.[336,341-343]

Each treatment group's mean %Inc[Fl] value corresponding to 40-minute and 24-hour measurements was compared with the same group's preparacentesis value using a paired *t* test, or Wilcoxon's signed rank test if *t* test assumptions were not valid. Comparisons among the groups at each time point were made using a Kruskall-Wallis test, with the Student-Newman-Kuels test being applied where indicated. These statistical analyses were performed by using a statistical software program. (Sigma Stat, Jandel Scientific, California)

Results. Twenty rabbits were lost from the study. Reasons for the loss of these animals included unexplained deaths in the animal care facility (4), respiratory distress after anesthesia (2), anesthetic deaths (6), and excessive surgical trauma (8). The excessive surgical trauma occurred during the initial surgeries and included damage to the lens (3), inability to aspirate 0.1 mL aqueous without overmanipulation, and excessive leakage or damage to iris (5). The remaining 130 rabbits are subjects in this study.

The paracentesis created an increase in aqueous humor fluorescein

concentration, which indicates a breakdown of the BAB. All treatment groups demonstrated an increase in fluorescein concentration in the paracentesed eye at 40 minutes. However, 24 hours following paracentesis, there was no difference between preparacentesis values and 24-hour values. These data are illustrated in Fig 1.

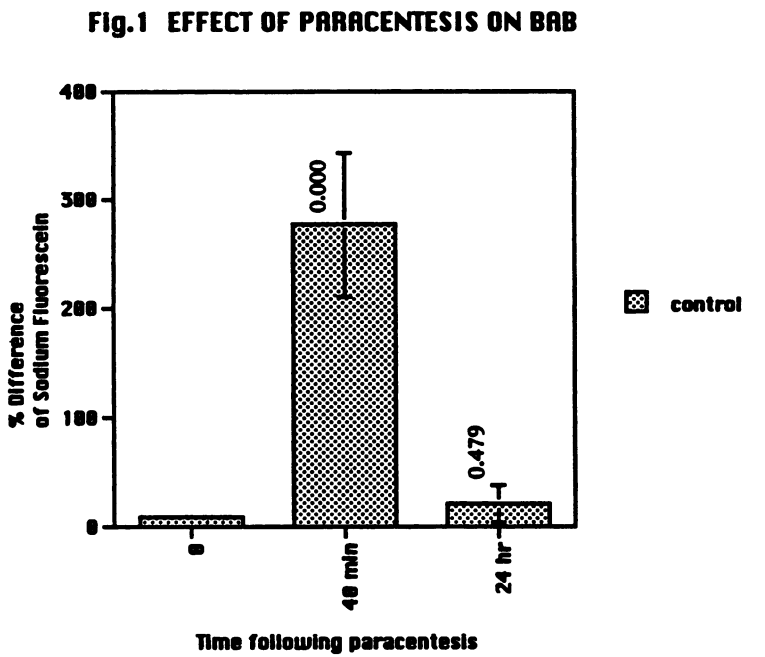

FIGURE 1
Effect of paracentesis on blood-aqueous barrier.

The results of topical pretreatment on BAB breakdown following paracentesis are summarized in Fig 2. There is no difference among treatment groups prior to paracentesis at time zero. ($P>.05$) At 40 minutes following paracentesis, all NSAID-treated groups showed less fluorescein leakage than the placebo-treated group. ($P<.05$) However, there were no significant differences between the NSAID-treated groups. In addition, there were no differences between treatment groups at 24 hours following paracentesis. These data are summarized in Table VI, which includes specific values for the calculated % difference in sodium fluorescein.

Discussion. The present study shows that all 4 commercially available topical NSAIDs are superior to placebo in their ability to stabilize the BAB following paracentesis of the anterior chamber in the rabbit. However,

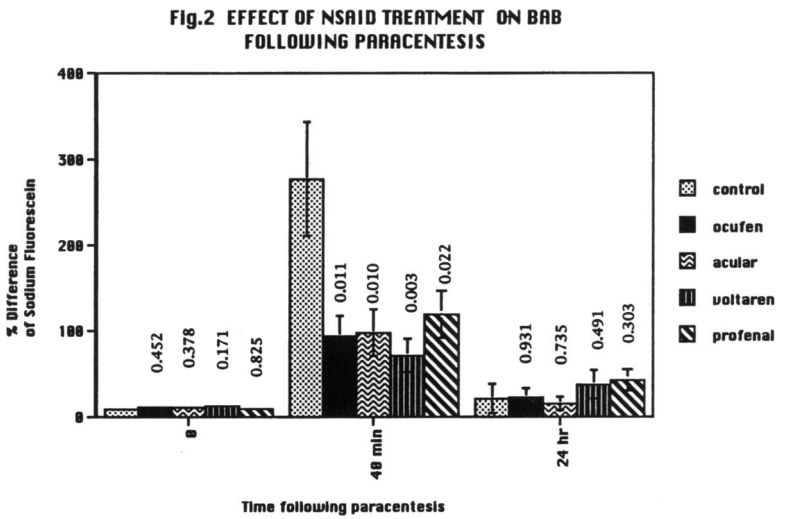

FIGURE 2
Effect of NSAID treatment on blood-aqueous barrier following paracentesis.

there was no statistical difference between these NSAIDs. Therefore, it was not possible to identify from this laboratory study which of these commercially available topically effective NSAIDs is most effective as an anti-inflammatory agent.

Breakdown of the BAB in an animal eye following paracentesis of the anterior chamber has been used as an animal model for studying inhibitors of prostaglandin synthesis.[271,344-346] Several NSAIDs were studied for their comparative BAB stabilizing effect in a dog model using paracentesis of the anterior chamber as an inflammatory stimulus.[32] This investigation reports that topically applied diclofenac, flurbiprofen, and suprofen (each prepared in a 1% solution) are equally effective in stabilizing the BAB 40 minutes following a paracentesis. Unfortunately, the investigation compares each NSAID as a 1% formulation. This is less than optimum, because the bioavailability of each of these drugs depends on the penetration of the molecule through the lipid membranes of the cellular layers of the cornea. This passage is influenced by the acidity of the compound and its relationship to the pH of the ophthalmic preparation.[346] Therefore, each manufacturer has prepared its formulation at a different pH and in different concentrations in an attempt to maximize bioavailability and minimize ocular discomfort.[279,283] In addition, this study did not include all of the commercially available ophthalmic NSAIDs.

The present study used anterior ocular fluorophotometry to follow the breakdown of the BAB following a standardized, minor surgical procedure

TABLE VI: EFFECT OF NSAID TREATMENT ON BLOOD AQUEOUS BARRIER FOLLOWING PARACENTESIS

NSAID TREATMENT (NO. OF RABBITS)	% DIFFERENCE OF SODIUM FLUORESCEIN ± SEM PRIOR TO PARACENTESIS*	40 MIN FOLLOWING PARACENTESIS†	(*P* VALUE)‡ 24 HR FOLLOWING PARACENTESIS§
0.1% Diclofenac (26)	13.00 ± 1.92 (0.171)	71.43 ± 19.42 (0.003)	37.63 ± 16.39 (0.491)
0.03% Flurbiprofen (24)	11.54 ± 2.53 (0.452)	94.22 ± 23.30 (0.011)	22.94 ± 10.48 (0.931)
0.5% Ketorolac (28)	11.15 ± 1.28 (0.378)	97.91 ± 27.03 (0.010)	15.21 ± 7.89 (0.735)
1% Suprofen (29)	9.60 ± 1.63 (0.825)	119.19 ± 27.58 (0.022)	42.54 ± 12.33 (0.303)
Placebo (23)	9.01 ± 2.01	277.18 ± 66.43	21.22 ± 16.96

*No significant difference between treatment groups.[375-377]

†NSAID treatments all significantly less than placebo. No significant differences between NSAID treatment groups.[375-377]

‡Compared with placebo.[375-377]

§No significant differences between treatment groups. No significant difference from prior to paracentesis.[375-377]

performed in rabbits.[347] It is possible that differences in anti-inflammatory activity associated with topical NSAID treatment may be demonstrated by using a different animal, following a different surgical procedure, and using different postoperative methods. Ketorolac and diclofenac ophthalmic solutions are the only topical NSAIDs commercially available in a 5-mL bottle. Therefore, we are evaluating the postoperative effects of topically applied 0.5% ketorolac ophthalmic solution and 0.1% diclofenac ophthalmic solution following cataract surgery and implantation of an intraocular lens in a double-masked, randomized study employing the laser flare-cell meter in an effort to determine their relative activities.[348-357]

Conclusion. All 4 commercially available topically applied NSAIDs were significantly more effective than placebo in their ability to stabilize the BAB following rabbit paracentesis. However, the effects of these topical NSAIDs were not statistically different from each other. Therefore, if

one of these NSAIDs is more effective as an anti-inflammatory agent following surgery, this laboratory surgical model was not sensitive enough to identify this increased activity.

B. Comparison of Ketorolac Tromethamine 0.5% and Diclofenac Sodium 0.1% Ophthalmic Solutions in Reducing Postoperative Inflammation After Cataract Extraction and Intraocular Lens Implantation

Cataract surgery and implantation of an intraocular lens are commonly followed by postoperative inflammation. Excessive postoperative inflammation following cataract surgery may reduce vision related to glaucoma, CME, and opacification of the posterior capsule.[285] Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic, CIBA Vision Ophthalmics, Atlanta, Georgia) is a topical NSAID approved by the Food and Drug Administration for use (1 drop four times daily) in the treatment of postoperative inflammation following cataract surgery.[279] Several double-masked, randomized, controlled studies suggest that ketorolac tromethamine 0.5% ophthalmic solution (Acular, Allergan Pharmaceuticals, Irvine, California) is a safe and effective topically adminsitered NSAID for use following cataract surgery with or without implantation of an intraocular lens.[286,335,341] The purpose of the present study is to compare the relative effectiveness and safety of ketorolac tromethamine 0.5% and diclofenac sodium 0.1% ophthalmic solutions in reducing postoperative inflammation following cataract surgery and implantation of an intraocular lens.

Materials and Methods. Healthy patients admitted for elective, unilateral cataract surgery were recruited for this study from the Department of Veterans Affairs in San Francisco, California. Institutional Review Board Approval was obtained before the study began. Written and signed informed consent was secured from each patient by the primary investigator before enrollment in the study.

Within 1 month prior to surgery and initiation of treatment, an ocular examination was performed on each patient scheduled for cataract surgery to establish the suitability of the patient for participation in this study. Exclusion criteria included the following:

1. Patients allergic to fluorescein
2. Pregnant women or women trying to become pregnant
3. Patients who used systemic corticosteroids or NSAIDs during the prior month
4. Patients who used topical anti-inflammatory drugs during the prior month.
5. Patients participating in another clinical study of an investigational drug
6. Patients under legal age

7. Patients with severe gastrointestinal disease
8. Patients with serious renal, hepatic, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral dysfunction
9. Patients with diabetes mellitus or other metabolic diseases uncontrolled by medical therapy
10. Patients with corneal diseases or ocular infections that prevent adequate visualization of the anterior chamber of their eye
11. Patients with a history of uncontrolled uveitis prior to the cataract surgery
12. Patients with systemic hypertension uncontrolled by medical treatment
13. Patients with a history of serious coexistent ocular disease such as uncontrolled glaucoma, optic atrophy, or ocular tumors
14. Patients with current uncontrolled alcohol or drug abuse problems
15. Patient allergic to NSAIDs

The entry examination consisted of a distance Snellen visual acuity test and external slit-lamp examination performed to assess the health of the external portions of the eye and periocular areas. Following slit-lamp examination, measurements were taken by a different investigator using the laser cell and flare meter (Kowa FC-1000) to objectively determine baseline anterior chamber inflammation. Anterior chamber inflammation was expressed by the laser cell and flare meter with separate numbers in photons for cell and flare. Examiners did not know in which treatment group the patient was to be enrolled, nor did the examiners know the results of the others' examinations. Intraocular pressures were measured by applanation tonometry. A dilated retinal examination was performed using direct and indirect ophthalmoscopy. Topical mydriatic agents (tropicamide 0.5% and phenylephrine 2.5%) were used for retinal diagnostic examinations. This identical and complete ocular evaluation was performed at 3 postoperative visits: visit I (3 to 5 days), visit II (9 to 12 days), and visit III (25 to 30 days) following surgery. All examinations were performed at the Department of Veterans Affairs in San Francisco.

All surgeries were performed by 2 senior resident ophthalmic surgeons under the supervision of a board-certified attending ophthalmologist using the same surgical approach. In each case an extracapsular cataract extraction using phacoemulsification was performed followed by the implantation of a foldable posterior chamber intraocular lens inserted through a 4 mm tunneled scleral incision. The surgical wound was closed with a single 10-0 nylon suture. Patients were excluded from the study if there were any intraoperative complications.

Patients were treated within 1 hour prior to the operation with mydriatic drops (tropicamide 0.5% and phenylephrine 2.5%); each was given 1 drop for three doses 15 minutes apart. In addition, each patient received

1 drop of flurbiprofen sodium 0.03% (Ocufen, Allergan Pharmaceuticals, Irvine, California) for 3 doses 15 minutes apart within the 1 hour prior to surgery. Immediately following surgery, each patient received 50 mg of cefazolin (Ancef, Bristol Myers Squibb, Princeton, NJ) and 50 mg of cefizoxime (Cefizox, Fujisawa, Dearfield, Illinois) injected subconjunctivally under direct visualization using the microscope.

Beginning on the day following surgery, all patients received either ketorolac tromethamine 0.5% or diclofenac sodium 0.1% ophthalmic solutions packaged in identical containers in a double-masked fashion as part of a predetermined randomization schedule. The patients were instructed to instill 1 drop of the treatment solution 4 times daily for 30 days. In addition, each patient received tropicamide 0.5% solution, 1 drop 3 times daily for 2 weeks, and ofloxacin 0.3% solution (Ocuflox, Allergan, Irvine, California), 1 drop 4 times daily for 7 days following surgery.

All patients returned for follow-up examinations and measurements of laser cell and flare meter at 3 postoperative visits: visit I (3 to 5 days), visit II (9 to 12 days), and visit III (25 to 30 days) following surgery. During these visits, each patient's anterior chamber inflammation was evaluated using 2 separate techniques. Initially, patients were subjectively examined at the slit lamp by one investigator, and the observed inflammation was scored.[287] Thereafter, a different examiner, who was unaware of the slit-lamp observations, objectively determined the number of cells and the amount of flare using the laser cell and flare meter.

Throughout the study, patients were instructed to inform the primary investigator of all complaints, systemic and local, at each postoperative visit. If a patient experienced an unusual or significantly discomforting symptom at any time, the patient was instructed to promptly telephone the primary investigator, who determined whether the complaint warranted the patient's returning for examination before the next scheduled visit. Furthermore, at each scheduled postoperative visit, patients were asked whether the topical treatment solution caused discomfort following instillation. Patients were provided with the following descriptive options: none, mild, moderate, or severe discomfort.

The primary efficacy parameter during this study was the comparison of postoperative inflammation as determined by the measurement of cell and flare using the laser cell and flare meter. To assess whether there was a difference between the 2 treatment groups with respect to the laser cell and flare meter measurement of cells and flare, we focused on the change in these 2 parameters of inflammation from baseline. In other words, we used for flare and cell, respectively:

$$\text{flare}(t)\text{-flare}(\text{baseline}) \text{ or } \text{cell}(t)\text{-cell}(\text{baseline})$$

as the measure of change from baseline at time (t). We examined how this measure of change from baseline varied as a function of time from baseline, drug group, and baseline flare or cell measurement. To carry out this analysis, we used a linear spline regression analysis, where the effect of time from baseline on the change in cell or flare was assumed to be piecewise continuous function of the time and where we examined whether this time function varies by drug group or baseline cell or flare measurement . For parameters measured on an ordinal scale, such as slit-lamp measurement of cells and flare, the Wilcoxon rank sum test was used to compare the treatments.

Results. A total of 120 patients were enrolled in this study (7 women and 113 men), and median age was 71 years (range, 47 to 89 years). The characteristics of the treatment groups (58 patients in the ketorolac solution group and 62 in the diclofenac solution group) are shown in Table VII. There are no discernable differences between the 2 treatment groups for any of these characteristics. Furthermore, the distribution of treatment regimens between surgeons was comparable.

All patients enrolled in the study completed treatment and returned for postoperative examinations as requested. The data pertaining to anterior ocular inflammation are summarized in Table VIII. The 2 treatment groups are not different statistically at any of the postoperative visits in terms of flare or cells as measured with the laser cell and flare meter. Furthermore, the slit-lamp subjective measurements of cells and flare correlate well with the meter's objective measurements as summarized in Table VIII.

No adverse reactions were reported or observed during the study. Patients appeared to tolerate the topically administered treatments equally well. There was no statisftical difference between reports of discomfort following instillation of the 2 treatments as shown in Table IX.

Comment. The results of this study suggest that diclofenac sodium 0.01% and ketorolac tromethamine 0.5% ophthalmic solutions are equally effective for the control of postoperative inflammation after uncomplicated cataract surgery and implantation of an intraocular lens. Furthermore, both treatments were well tolerated by patients. Therefore, both topically applied NSAIDs offer an acceptable alternative to topical corticosteroids following cataract surgery.

Several studies suggest that topically applied NSAIDs are comparable to topical corticosteroids in their ability to control inflammation following cataract surgery.[279,283] Furthermore, topically applied NSAIDs may be more effective in stabilizing the BAB as measured by anterior ocular fluorophotometry following cataract surgery and implantation of an intraocular lens.[336] However, all of these studies focused on uncomplicated cataract surgeries. Therefore, it is not known from these studies whether the treat-

TABLE VII: BASELINE CHARACTERISTICS OF ENROLLED PATIENTS

CHARACTERISTIC	TREATMENT GROUP NO. (%) 0.1% DICLOFENAC SOLUTION (N = 62)		0.5% KETOROLAC SOLUTION (N = 58)		P VALUE*
SEX					
Female	3	(4.84)	4	(6.90)	
Male	59	(95.16)	54	(93.10)	
RACE					0.56
Black	6	(9.68)	5	(8.62)	
White	44	(70.97)	38	(65.52)	
Asian	3	(4.84)	7	(12.07)	
Hispanic	9	(14.52)	8	(13.79)	
AGE (YR)					
Mean (SD)	70.6 ± 8.8		72.9 ± 9.4		0.16
Range	48 - 89		47 - 88		
EYE OPERATED ON					0.21
Right	36	(58.06)	27	(46.55)	
Left	26	(41.94)	31	(53.45)	
IRIS COLOR					0.78
Blue	27	(43.55)	29	(5.00)	
Brown	29	(46.77)	24	(41.38)	
Black	6	(9.68)	5	(8.62)	
PRIOR SURGERY CONTRALATERAL EYE					0.21
No	37	(59.68)	28	(48.28)	
Yes	25	(40.32)	30	(51.72)	
DIABETES					0.55
No	44	(70.97)	44	(75.86)	
Yes	18	(29.03)	14	(24.14)	
SYSTEMIC HYPERTENSION					0.56
No	29	(46.77)	24	(41.38)	
Yes	33	(53.23)	34	(58.62)	
Surgeon 1	29	(53.7)	25	(46.3)	0.72
Surgeon 2	33	(50.0)	33	(50.0)	

*All *P* values reflect chi-square tests except the comparison of age, which was done with a *t* test.

ments studied are equally effective following complicated surgeries. This qualification also applies to the present study.

Flurbiprofen 0.03% ophthalmic solution was administered to patients immediately prior to surgery (1 drop 3 times, beginning 1 hour before surgery) throughout this investigation. The preoperative use of a topical NSAID to maintain intraoperative mydriasis during cataract surgery is widespread. Therefore, this treatment was included within this study in an attempt to reflect common surgical practice. There is evidence that this

TABLE VIII: ANTERIOR OCULAR INFLAMMATION

	0.1% DICLOFENAC 62 PATIENTS - MEAN (SD)	0.5% KETOROLAC 58 PATIENTS - MEAN (SD)	*P* VALUE†
LASER CELL AND FLARE METER* (KOWA FC-1000)			
FLARE (PHOTONS PER MILLISECOND)			
Baseline	11.85 ± 7.89	12.12 ± 10.24	0.88
Visit 1	22.53 ± 15.35	23.89 ± 16.29	0.64
Visit 2	18.07 ± 9.22	18.70 ± 11.96	0.75
Visit 3	19.62 ± 14.19	15.28 ± 9.32	0.10
CELLS (CELLS PER 0.075 MM³)			
Baseline	2.90 ± 4.83	2.20 ± 5.20	0.45
Visit 1	6.65 ± 7.07	7.20 ± 7.69	0.69
Visit 2	2.03 ± 2.40	2.13 ± 2.91	0.84
Visit 3	1.86 ± 3.09	1.46 ± 3.03	0.55
	SLIT-LAMP EXAMINATIONS*		
FLARE			
Baseline	0.32 ± 0.44	0.36 ± 0.49	0.45
Visit 1	1.27 ± 0.45	1.39 ± 0.53	0.22
Visit 2	0.95 ± 0.43	0.90 ± 0.67	0.60
Visit 3	0.42 ± 0.56	0.41 ± 0.53	0.95
CELLS			
Baseline	0.29 ± 0.32	0.39 ± 0.41	0.54
Visit 1	1.74 ± 0.97	1.94 ± 0.97	0.25
Visit 2	1.27 ± 0.61	1.38 ± 0.83	0.46
Visit 3	0.90 ± 0.43	1.03 ± 0.37	0.08

*Kendall Taub correlations between laser cell and flare meter and slit-lamp observations were as follows: Visit 1 = 0.43 (P = .0001); visit 2 = 0.32 (P = .0001); visit 3 = 0.28 (P = .0002).
†References 378 and 379.

TABLE IX: PATIENT TOLERANCE

DISCOMFORT ON INSTILLATION*	TREATMENT GROUP 0.1% DICLOFENAC SOLUTION (N = 62) NO. (%)		0.5% KETOROLAC SOLUTION (N = 58) NO. (%)	
None	57	(91.94)	49	(84.48)
Mild	4	(6.45)	5	(8.62)
Moderate	1	(1.61)	4	(6.90)
Severe	0	(0)	0	(0)

*P = .30.

topically applied NSAID has an anti-inflammatory effect.[279] Therefore, it is possible that this preoperative treatment helped to minimize the postoperative inflammation, particularly in the early postoperative period. However, it is unlikely that this potential synergistic effect influenced all of the observations and measurements at subsequent postoperative visits.

There were no significant toxicities associated with either of the treatment regimens during this study. In addition, both treatments appeared to be comparable in terms of ocular discomfort associated with eye drop instillation. However, the discomfort associated with the instillation of 0.5% tropicamide may have overshadowed the potential discomfort that may have accompanied the topical NSAID use. Not only did the patients frequently describe relief after the mydriatic-cycloplegic was discontinued, but they all emphasized that any discomfort associated with the topical NSAID treatment was minor compared with the discomfort induced by the tropicamide.

Conclusions. Diclofenac 0.1% and ketorolac 0.5% ophthalmic solutions were equally safe and effective in controlling postoperative inflammation following cataract surgery and implantation of an intraocular lens. Slit-lamp observations and measurements with the laser cell and flare meter were unable to identify the most effective anti-inflammatory drug using this model for inducing inflammation.

C. The Effect of Patient Characteristics on Response to Topical NSAID Treatment of Chronic Clinical CME Following Cataract Surgery

There is evidence that topically applied NSAIDs may improve vision in some, but not all, patients demonstrating clinical CME following cataract surgery.[16,149,151] The results of a small pilot study gave the impression that the presence of diabetes mellitis or systemic hypertension may predispose to less therapeutic benefit from this topical NSAID treatment.[358] While this pilot study suggested that coexistent conditions might modify the effectiveness of treatment with topical 0.5% ketorolac ophthalmic solution, it was concluded that an increased sample size was required to detect these associations.

Therefore, the goal of the following analysis is to delineate physical factors related to the improvement in vision (2 lines or more using Snellen testing) following treatment with 0.5% ketorolac ophthalmic solution in a larger series of 47 patients with chronic (present 6 months or longer) clinical (vision less than 20/40) CME following cataract surgery.

The identification of a subpopulation of patients within a group of patients with CME that is refractory to treatment could eliminate time, effort, and expense.

Materials and Methods. Forty-seven patients with chronic clinical CME following cataract surgery received 0.5% ketorolac ophthalmic solu-

tion as part of a double-masked, randomized, placebo-controlled study.[151] The percentage of those patients with a given physical or anatomic condition who showed an improvement in vision was compared to the percentage of those without that condition who showed an improvement in vision. Fisher's exact test was used to calculate the nominal 2-sided *P* values for the percentage differences.

Results. The characteristics of patients with and without an improvement in vision present at the onset of the study are summarized in Tables X and XI. We did not find significant differences for any physical or anatomic conditions to have a statistical basis for suggesting a relationship with improvement in vision following treatment including:

1. Diabetes mellitis (85%) versus no diabetes mellitis (65%) $P = .52$
2. Either diabetes mellitis or systemic hypertension (80%) versus neither (65%) $P = .38\%$
3. Systemic hypertension (81%) versus normotension (64%) $P = .45$
4. Iris clip or anterior chamber lens (73%) versus posterior chamber lens (50%) $P = .32$
5. Updrawn pupil (66%) versus round pupil (41%) $P = .41$
6. Presence of posterior capsule (48%) versus absence of posterior capsule (37%) $P = .85$

Conclusions. This study suggests that the presence of diabetes mellitis and systemic hypertension, if medically controlled, does not predispose to less therapeutic benefit from topical treatment of chronic clinical CME with 0.5% ketorolac ophthalmic solution. Furthermore, the presence or absence of a posterior capsule, the type of intraocular lens, and the shape of pupil did not appear to reduce the potential effectiveness of treatment. Therefore, the presence of these patient characteristics or ocular anatomic variables should not discourage an attempt at topical medical treatment of chronic clinical CME following cataract surgery prior to more aggressive treatment.

D. Treatment of Acute-Onset Clinical Cystoid Macular Edema Following Cataract Surgery With Topical NSAIDs

Controlled studies suggest that many patients with chronic CME require treatment with topical NSAIDs for 2 to 3 months before an improvement in vision is observed.[149,151] As a consequence, investigators have recommended treatment with extemporaneously prepared indomethacin 1% ophthalmic suspension, 1 drop 4 times daily for at least 3 months and continued for 1 to 2 months after improvement of visual acuity for an adequate therapeutic effect.[16] All of these studies evaluate the therapeutic effect of a topically applied NSAID given to patients with clinical CME present 6 months or longer. It is possible that acute CME (present 4 months or less) might respond to treatment with an improvement in vision

TABLE X: CHARACTERISTICS OF PATIENTS IMPROVED FOLLOWING TREATMENT

PATIENT	GRADE AGE(SEX)	UPDRAWN VISION	SYSTEMIC ANGIOGRAM	INTACT PUPIL	IOL	DIABETES	HYPERTENSION	INTACT CAPSULE
1	76 (F)	20/400	1	No	AC	No	No	No
2	65 (F)	20/400	4	No	No	No	No	No
3	75 (F)	20/400	4	No	AC	No	No	No
4	72 (M)	20/400	3	No	AC	No	No	No
5	64 (M)	20/400	4	Yes	AC	Yes	No	No
6	75 (F)	20/200	3	No	AC	No	Yes	No
7	69 (M)	20/200	4	No	AC	No	No	No
8	78 (F)	20/200	2	Yes	AC	No	No	No
9	86 (M)	20/200	3	Yes	AC	No	No	No
10	67 (M)	20/200	4	No	AC	Yes	Yes	No
11	65 (M)	20/200	4	No	AC	No	Yes	No
12	62 (M)	20/200	1	No	None	No	No	No
13	70 (M)	20/200	4	No	AC	No	No	No
14	75 (M)	20/100	2	No	None	No	No	No
15	62 (F)	20/100	3	No	None	No	No	No
16	69 (F)	20/100	2	Yes	PC	No	Yes	No
17	73 (F)	20/100	4	Yes	AC	No	No	No
18	77 (M)	20/100	4	No	None	No	Yes	No
19	80 (M)	20/80	2	No	AC	No	Yes	No
20	77 (M)	20/80	2	No	AC	No	No	No
21	76 (M)	20/80	4	No	AC	No	Yes	No
22	67 (M)	20/80	2	No	AC	Yes	Yes	No
23	78 (M)	20/70	1	No	PC	No	No	Yes
24	62 (M)	20/70	2	No	AC	No	No	No
25	68 (M)	20/70	2	No	PC	Yes	No	Yes

TABLE X (CONTINUED): CHARACTERISTICS OF PATIENTS IMPROVED FOLLOWING TREATMENT

PATIENT	GRADE AGE(SEX)	UPDRAWN VISION	SYSTEMIC ANGIOGRAM	INTACT PUPIL	IOL	DIABETES	HYPERTENSION	INTACT CAPSULE
26	78 (F)	20/70	3	No	AC	No	No	No
27	74 (M)	20/50	1	No	AC	Yes	No	No
28	67 (M)	20/50	3	No	AC	No	No	No
29	64 (M)	20/50	3	No	AC	No	No	No
30	84 (M)	20/50	2	No	AC	Yes	Yes	No
31	71 (F)	20/40	1	No	PC	No	No	Yes
32	64 (F)	20/40	1	No	PC	No	No	Yes

TABLE XI: CHARACTERISTICS OF PATIENTS WITHOUT IMPROVEMENT FOLLOWING TREATMENT

PATIENT	AGE(SEX)	VISION	GRADE ANGIOGRAM	UPDRAWN PUPIL	IOL	DIABETES	SYSTEMIC HYPERTENSION	INTACT CAPSULE
A	78 (F)	20/400	4	Yes	AC	No	No	No
B	70 (F)	20/400	1	No	AC	Yes	No	No
C	80 (F)	20/400	2	No	None	No	No	No
D	73 (F)	20/400	3	No	PC	No	No	Yes
E	75 (F)	20/400	2	No	AC	No	No	No
F	79 (F)	20/400	3	No	AC	No	Yes	No
G	88 (M)	20/400	1	No	PC	No	No	Yes
H	95 (M)	20/200	1	No	PC	No	No	No
I	79 (M)	20/200	4	No	AC	No	No	No
J	83 (F)	20/200	3	No	PC	No	Yes	Yes
K	86 (F)	20/200	2	No	AC	No	No	No
L	65 (F)	20/80	2	No	PC	No	No	Yes
M	63 (M)	20/50	1	No	AC	No	No	No
N	66 (M)	20/50	3	No	AC	No	No	No
O	73 (M)	20/40	4	No	AC	No	No	No

following only 1 month of treatment. A response to a shorter duration of treatment would suggest that there is potential benefit in the earlier treatment of CME following cataract surgery. This could provide a rationale for discouraging clinicians from waiting too long for spontaneous resolution of CME. Therefore, a study of the treatment of acute CME following cataract surgery is of potential clinical importance.

Purpose. The goal of this study is to evaluate the effect of 0.5% ketorolac tromethamine ophthalmic solution (1 drop four times daily for 1 month) in patients with acute (present 4 months or less) clinical CME.

Materials and Methods. During an 18-month period during 1988 and 1989, 350 patients underwent planned ECCEs with the implantation of an intraocular lens. These patients were screened for the presence of clinical (vision less than 20/40 by Snellen testing) CME at monthly intervals during the first 4 months following their cataract surgery. During this interval, 24 patients demonstrated a best corrected visual acuity of less than 20/40 as measured by Snellen visual acuity testing, which was associated with the presence of fluorescein angiographic signs of CME. Following their diagnosis, these patients were educated as to the nature of their postoperative problem, the clinical study and its goals, and the risks and potential benefit for themselves should they choose to participate in the study. Informed consent was obtained from each individual who decided to participate in this 2-month study after lengthy discussions including questions and answers.

Patients were excluded from the study if (1) they had used corticosteroids or NSAIDs within the previous 4 weeks, (2) they had uncontrolled diabetes mellitis or systemic hypertension, (3) they had ocular disease preventing adequate examination of the anterior segment of the eye or retina, (4) they had preexisting macular disease preventing adequate retinal evaluation or confusing the diagnosis of CME, or (5) they had a history of allergy to NSAIDs.

Patients were given a complete ocular examination within 1 week before the initiation of treatment to confirm the diagnosis of acute clinical CME. Visual acuity was determined at distance with Snellen testing after a careful refraction. The Snellen row of letters was selected that was most consistent with the patient's distance visual acuity. All refractions were performed by the same examiner using the same examination lane. This investigator was unaware of the treatment regimen. Furthermore, this examiner was unaware of results of fluorescein angiograms and slit-lamp observations.[149,151] Slit-lamp examination of the periocular and ocular structures was performed by a different investigator. A dilated retinal examination using direct and indirect ophthalmoscopy and Hruby lens examinations was used to make a tentative diagnosis of CME. This diagnostic impression was confirmed by performing a fluorescein angiogram.

The angiograms were graded at baseline and at 30 days and 60 days after each respective treatment. The grading system was as follows: grade 0, no fluorescein leak in the macular area; grade 1, semicircle of fluorescein leak in the macular area; grade 2, full circle of fluorescein leak, less than the size of the optic nerve; and grade 3, full circle leak greater than the optic disk in the macular area. Intraocular pressures were performed by applanation tonometry. This same examination was performed at baseline, 30 days after initiation of the first treatment regimen, and 30 days after initiation of the second treatment regimen.

Each patient included in the study initially received 30 days of treatment with either 0.5% ketorolac ophthalmic solution or vehicle solution of the same pH and tonicity packaged in an identical container (each preparation was supplied by Syntex Corp, California) and distributed with a computer-generated predetermined randomization schedule in a double-masked fashion. Following completion of this initial treatment regimen, the patient was given the remaining treatment regimen in a randomized, double-masked fashion for the subsequent 30 days. During each treatment period, 1 drop (50 μL) of solution was used 4 times daily in the involved eye. Following each treatment regimen, patients returned for reexamination, and their treatment bottles were collected and examined to confirm compliance. The final examination was performed at the 60-day visit.

Results. From the group of 24 patients enrolled during the 18-month period, 22 patients completed the 2-month study. The 2 patients eliminated from the study during the first 10 days consisted of 1 drug-treated patient (lost medication) and 1 vehicle-treated patient (moved to different state). These patients are not included in this report.

The 22 patients who completed this study were evenly distributed between the drug-treated first group and the placebo-treated first group. These 2 groups of patients are comparable in terms of age; sex; eye involved; presence of pupil abnormalities; type of intraocular lens; presence of diabetes mellitis, systemic hypertension, or arteriosclerotic vascular disease; initial visual acuities; and initial angiography grades as summarized in Table XII.

Following the first 30-day treatment period, 4 (36%) of 11 drug-treated patients (group I) had an improvement in vision (2 lines or more as measured by Snellen chart), and 2 (18%) of 11 vehicle-treated patients (group II) demonstrated improved vision. This difference is not statistically significant. Following the crossover in treatment regimens, group I (now vehicle-treated) had 2 of 11 additional patients with improved vision following treatment. Group II (now drug-treated) had 3 of 11 additional patients with improved vision. These data are summarized in Table XIII. A decrease in vision while treated with vechicle was observed in 3 patients,

TABLE XII: TREATMENT OF ACUTE CME: PATIENT CHARACTERISTICS

PATIENT NO.	AGE	SEX	RACE	EYE	DURATION OF CME (MO)	INITIAL VISUAL ACUITY	INITIAL ANGIOGRAM	IOL	DM	↑BP	IRIS ABNORMAL*
					GROUP I = KETOROLAC 0.5% FIRST						
1.	79	M	W	OD	2	20/50	1	PC	+	-	+
2.	66	M	W	OD	3	20/50	2	PC	-	+	0
3.	84	M	W	OS	2	20/60	1	PC	-	-	+
4.	74	M	A	OD	2	20/60	1	PC	-	+	0
5.	82	M	W	OD	2	20/200	3	PC	-	-	0
6.	61	M	B	OS	3	20/70	2	PC	-	+	0
7.	56	M	W	OD	2	20/60	1	PC	-	+	0
8.	68	M	W	OS	3	20/70	1	PC	-	-	0
9.	75	M	W	OD	2	20/200	1	AC	-	-	+
10.	80	M	W	OS	2	20/100	2	PC	+	-	0
11.	67	M	A	OD	3	20/200	1	PC	-	+	0
					GROUP II = VEHICLE FIRST						
12.	66	M	W	OS	3	20/70	2	PC	-	-	+
13.	88	M	W	OS	2	20/50	1	PC	-	-	0
14.	62	M	B	OD	2	20/80	1	PC	+	+	0
15.	82	M	W	OS	2	20/100	3	PC	-	-	0
16.	65	M	W	OS	3	20/100	2	PC	-	-	+
17.	75	M	W	OS	3	20/50	1	PC	-	+	+
18.	75	M	W	OD	2	20/200	3	PC	-	+	0
19.	73	M	W	OD	3	20/50	2	AC	+	+	+
20.	77	M	A	OD	2	20/50	1	PC	-	-	0
21.	82	M	W	OS	2	20/70	2	PC	-	-	0
22.	77	M	W	OD	2	20/80	1	PC	-	-	0

A, Asian; AC, anterior chamber; B, black; PC, posterior chamber; W, white.
*Iridectomy, updrawn pupil, iridotomy, iris to wound.

but no patients demonstrated decreased vision while treated with drug. Both treatment regimens were well tolerated by the patients. There were no complaints about burning or stinging following eye drop instillation. Furthermore, none of the patients developed any signs of ocular toxicity during the study.

During 1995, each patient's record was reviewed to determine the interim ophthalmic treatments. In addition, each patient's visual acuity at last examination was recorded. Their visual data and comments are included in Table XIII. During the interim, the patients received no further treatment for CME. All patients had improved vision except 2 who had a

TABLE XIII: TREATMENT OF ACUTE CME: SUMMARY OF CHANGES IN VISUAL ACUITY

PATIENT NO.	SNELLEN DISTANCE VISION (JAEGER NEAR VISION) INITIAL (DAY 0)*	DAY 30	DAY 60	FINAL (YR)	COMMENTS
	GROUP I = KETOROLAC FIRST				
1	20/50 (J2)	20/20† (J1)	20/30 (J2)	20/25↑ (1994)	Deceased
2	20/50 (J8)	20/50 (J6)	20/40 (J3)	20/30↑ (1994)	—
3	20/60 (J8)	20/70 (J8)	20/70 (J10)	20/30↑ (1993)	Deceased
4	20/60 (J10)	20/50 (J10)	20/60 (J6)	20/40↑ (1992)	Deceased
5	20/200 (J12)	20/200 (J12)	20/70† (J10)	20/70↑ (1990)	Deceased
6	20/70 (J8)	20/40↑ (J2)	20/25↑ (J2)	20/30↑ (1995)	Needed posterior capsulotomy
7	20/60 (J2)	20/25↑ (J1)	20/30 (J1)	20/20↑ (1991)	—
8	20/70 (J2)	20/70 (J6)	20/50† (J4)	20/40↑ (1992)	Lost to follow-up
9	20/200 (J12)	20/400 (J12)	20/200 (J12)	20/30↑ (1989)	Lost to follow-up
10	20/100 (J8)	20/50↑ (J4)	20/50 (J2)	20/30↑ (1994)	
11	20/200 (J12)	20/100 (J12)	20/200 (J12)	HM↑ (1993)	Optic nerve ischemia
	GROUP II = KETOROLAC SECOND				
12	20/70 (J6)	20/70 (J10)	20/50↑ (J6)	20/25↑ (1995)	—
13	20/50 (J6)	20/30↑ (J4)	20/40 (J3)	20/30↑ (1990)	Lost to follow-up
14	20/80 (J8)	20/80 (J8)	20/70 (J8)	20/70 (1991)	—
15	20/100 (J12)	20/80 (J12)	20/50↑ (J3)	20/30↑ (1992)	—
16	20/100 (J8)	20/80 (J8)	20/80 (J8)	20/20↑ (1992)	Deceased
17	20/50 (J4)	20/50 (J4)	20/50 (J2)	20/30↑ (1990)	Deceased
18	20/200 (J12)	20/200 (J12)	20/50↑ (J4)	20/50↑ (1991)	Deceased
19	20/50 (J2)	20/80↑↑ (J12)	20/100 (J12)	20/100(1992)	Glaucoma Deceased
20	20/50 (J2)	20/50 (J2)	20/50 (J2)	20/40 (1994)	—
21	20/70 (J6)	20/200 (J12)	20/200 (J12)	20/30 (1994)	—
22	20/80 (J8)	20/40↑ (J4)	20/50 (J4)	20/50↑ (1994)	—

*Initial vision measurements taken during 1987-1988.

↑2 lines improvement.

↓2 lines deterioration.

decrease in vision unrelated to CME. Eighteen of the patients had 20/50 Snellen or better.

Discussion. The results of this study suggest that the treatment of clinical CME within 4 months of its onset with 0.5% ketorolac ophthalmic solution does not shorten the treatment time needed for improvement in vision. The improvement in vision after 1 month of treatment with 0.5% ketorolac was not significantly different from that with placebo. A prior study of 26 patients with chronic clinical CME (present 6 months or longer) demonstrated a statistically significant improvement in vision only after 2 months of treatment with 0.5% ketorolac tromethamine ophthalmic solution.[149] Therefore, these results suggest that there is no advantage to treating clinical CME following cataract surgery earlier than 6 months following its diagnosis.

A review of the records of the 22 patients who were included in this study 7 years following the completion of the study reveals that all patients had improved vision without additional medical or surgical treatment at the time of their last examination except 2 patients, as summarized in Table XIII. One patient with poor vision has a diagnosis of anterior ischemic optic neuropathy, and the other has decreased vision due to glaucoma. Both disorders are unrelated to CME or postoperative inflammation. Therefore, the tendency for CME following cataract surgery to undergo spontaneous resolution is once again confirmed.[20,29,38,43,139,140]

Conclusion. The results of this study suggest that the duration of treatment required for an improvement in vision following the development of CME associated with cataract surgery is not shortened by early treatment with topical NSAIDs. Furthermore, this study confirms that the natural history of clinical CME following cataract surgery often includes spontaneous resolution, as other investigators have described. Therefore, this study suggests that it is reasonable to delay medical treatment and await spontaneous resolution for at least 6 months following the appearance of clinical CME after cataract surgery. This conclusion is in agreement with prior investigations.[13,15]

IV. ORAL ACETAZOLAMIDE AND THE TREATMENT OF CHRONIC CLINICAL CME FOLLOWING CATARACT SURGERY

The purpose of this investigation is to compare the effectiveness of orally administered acetazolamide with placebo in improving vision in chronic clinical CME following cataract surgery that has been unresponsive to other medical therapies.

Materials and Methods

During an 18-month period, 10 patients were enrolled with chronic clinical CME, defined as vision of 20/40 or less as measured by Snellen testing

and a fluorescein angiogram consistent with CME present for at least 6 months. All patients enrolled in this study were refractory to prior treatments with corticosteroids and NSAIDs. Each patient was fully informed about the potential risks and benefits of participating in the study. This included a comprehensive discussion of the potential toxicity of orally administered acetazolamide and treatment alternatives, including no treatment at all.

Following enrollment, patients were treated according to a predetermined randomization schedule with either 500 mg of acetazolamide given by mouth twice daily for 4 weeks or an identical placebo capsule given at the same intervals and for the same duration in a double-masked, randomized fashion. Acetazolamide in the form of 500-mg Sequels and identical placebo Sequels were supplied by Stortz Co, St Louis, Missouri. Treatment began within 1 month following an initial baseline examination designed to determine the patient's eligibility for inclusion in the study. Patients returned for follow-up examinations at 7, 14, and 28 days following initiation of treatment.

The ophthalmic examinations included distance Snellen visual acuity, external slit-lamp examination, intraocular pressure by applanation, dilated retinal examination using direct and indirect ophthalmoscopy and Hruby lens examinations, and a baseline fluorescein angiogram to confirm the presence of CME. Topical tropicamide 0.5% and phenylephrine 2.5% were used prior to retinal examinations.

Exclusion criteria included the following:

- Allergy to fluorescein or sulfonamide drugs
- Pregnant women or women trying to become pregnant
- Patients using NSAIDs or corticosteroids during the month prior to study
- Patients with the presence of severe systemic disease
- Patients with diabetes mellitis or systemic hypertension uncontrolled by medical therapy
- Patients with a history of ocular disease, including corneal disease, ocular infections, uveitis, uncontrolled glaucoma, optic atrophy, ocular tumors, retinal detachment, or macular disease
- Patients with an abnormal complete blood cell count or abnormal serum urea nitrogen, creatinine, or electrolyte levels

All visual acuities were determined by means of a refraction performed by one investigator. This investigator was unaware of each patient's treatment regimen, ocular examination results, or fluorescein angiogram result. He was not permitted to discuss anything concerning the study or the patient's side effects with the patient or his colleagues. This was important because of the difficulties in masking a placebo-controlled study of carbonic anhydrase inhibitors.[319]

Following completion of the initial treatment regimen, acetazolamide treatment was offered to placebo-treated subjects in an open-label manner. Patients were instructed to inform the primary investigator of all side effects, systemic and local, by telephone and/or at each office visit throughout the study.

Results. A summary of the characteristics of the 10 patients enrolled over the 18-month period is provided in Table XIV. These patients are evenly distributed between drug and placebo treatments. The treatment groups are comparable in terms of age, sex, eye, duration of CME, initial angiogram, initial vision, type of intraocular lens, presence of diabetes mellitis, and presence of iris abnormalities. However, systemic hypertension was more common in the drug-treated group.

Only 6 of 10 of the enrolled patients completed 1 month of treatment. All 5 patients treated with acetazolamide experienced side effects, and 4 of 5 requested early removal from the study and termination of treatment for

TABLE XIV: SUMMARY OF VISUAL RESULTS IN PATIENTS WITH CHRONIC CME TREATED WITH ACETAZOLAMIDE

PATIENT NO.	SEX	AGE	EYE	TREATMENT	INITIAL SNELLEN VISUAL ACUITY	FIRST SNELLEN VISUAL ACUITY	DURATION	COMMENTS
1.	F	77	(OS)	D	20/50	20/50	1 wk	D/C treatment, rash, fever, malaise
2.	F	82	(OD)	P	20/50	20/50	4 wk	
3.	M	76	(OS)	D	20/60	20/40	2 wk	D/C treatment, confused, disoriented.
4.	M	65	(OD)	P	20/200	20/200	4 wk	Complained of side effects
5.	M	83	(OD)*	D	20/60	20/40	1 wk	D/C treatment dizzy, lethargic
6.	M	71	(OD)†	D	20/60	20/50	1 wk	D/C treatment, syncope, metabolic disturbance
7.	F	79	(OD)	P	20/50	20/50	4 wk	
8.	M	83	(OS)*	D	20/200	20/80	4 wk	Paresthesias, nocturia
9.	F	79	(OS)	P	20/80	20/80	4 wk	
10.	M	72	(OD)	P	20/400	20/400	4 wk	

D, drug treatment; D/C, discontinue; P, placebo treatment

* Patient had 2-line improvement in visual acuity.

† Patient had 1-line improvement in visual acuity.

TABLE XV: PATIENT CHARACTERISTICS IN STUDY OF TREATMENT OF CHRONIC CARE CME WITH ACETAZOLAMIDE*

PATIENT NO.	SEX	AGE	EYE	TREATMENT	INITIAL VISION	GRADE ANGIOGRAM	DURATION CME	DIABETES	HYPER-TENSION	IOL
1.	F	77	(OS)	D	20/50	+2	4.5 yr	No	Yes	PC
2.	F	82	(OD)	P	20/50	+1	2 yr	No	No	PC
3.	M	76	(OS)	D	20/60	+1	2 yr.	No	No	PC
4	M	65	(OD)	P	20/200	+2	2 yr	Yes	No	PC
5.	M	83	(OD)	D	20/60	+2	1.5 yr	Yes	Yes	PC
6.	M	71	(OD)	D	20/60	+1	1 yr	Yes	Yes	PC
7	F	79	(OD)	P	20/50	+1	8 mo	No	No	PC
8.	M	83	(OS)	D	20/200	+3	7 mo	No	Yes	PC
9.	F	79	(OS)	P	20/80	+2	1 yr	Yes	No	PC
10.	M	72	(OD)	P	20/400	+3	1 yr	No	Yes	PC

D, drug treatment; P, placebo treatment; PC, posterior chamber lens

*All patients had round pupils without vitreous to wound or in anterior chamber except patient 6, who had an updrawn pupil.

reasons summarized in Table XV. In addition, 1 in 5 placebo-treated patients complained of severe side effects but elected to remain in the study.

A summary of the changes in visual acuity associated with each treatment is provided in Table XV. Within the drug-treated group, 4 of 5 patients demonstrate an improvement in Snellen vision. Three of these patients showed an improvement of 2 lines or more, and 1 patient demonstrated a 1-line improvement after only 1 week of treatment. No changes in visual acuity are observed in the placebo-treated group. Therefore, treatment with oral acetazolamide is associated with a subtle effect on vision as compared with placebo treatment (P=.053). However, patients did not demonstrate the complete disappearance of the macular edema during this study.

The open-label segment of the study included 2 of 5 patients who completed 1 month of treatment with acetazolamide without an improvement in vision. The 3 remaining patients consisted of 1 patient who was lost to follow-up and 2 patients who terminated treatment in less than 7 days owing to gastrointestinal upset and lethargy.

Discussion

It is difficult to make definitive conclusions about the potential benefit of acetazolamide treatment for patients with chronic clinical CME following cataract surgery from this small, double-masked, randomized study. However, the fact that 4 of 5 drug-treated patients demonstrated an improvement in vision, compared with none of the placebo-treated patients, supports the previously formed impression that this treatment may have potential benefit for some patients with reduced vision related to CME following cataract surgery.[318,321] This conclusion seems particularly well justified because all patients enrolled in this study had a history of being refractory to prior medical treatments with anti-inflammatory drugs. Therefore, the study population in this investigation represents a particularly difficult-to-treat group of patients with chronic clinical CME.

Although the pathogenesis of CME following cataract surgery remains obscure, the medical treatment of this syndrome usually involves anti-inflammatory therapy.[15,21,22,146,283] The present study describes several patients who were unresponsive to anti-inflammatory treatment but who responded to acetazolamide treatment. These results suggest that the pathogenesis of CME following cataract surgery involves more than inflammation in some patients.

Investigators have commented that acetazolamide treatment appears more effective in those disorders in which the retinal pigment epithelium (RPE), rather than retinal capillaries, appears to be the major source of the edema fluid.[180,318] It has been suggested that retinal edema within these patients may be due, at least in part, to a disturbance of the normal RPE

polarity, whereby the RPE moves ions, and associated water, from the neuroretina toward the choroid.[318] Cellular polarity may be influenced by transcellular and transmembrane pH gradients.[370] It is hypothesized that acetazolamide may restore cellular polarity by modulating ionic movements across the RPE cell membrane with consequent changes in transmembrane pH gradients. The present study suggests that an effect of acetazolamide on the retinal capillaries cannot be discounted as contributing to a therapeutic effect in patients with CME following cataract surgery, as has been suggested by others.[180]

Side effects were a major problem during this study. The thorough discussion of acetazolamide-related side effects provided during the informed consent influenced enrollment. Four patients elected not to participate in this study because they believed the potential risk was too great. Furthermore, all of the patients taking acetazolamide experienced side effects, and 4 of 5 found them intolerable and requested removal from the study. However, 1 placebo-treated patient experienced side effects and briefly considered removal from the study. Placebo-induced side effects in controlled studies of the carbonic anhydrase inhibitors during glaucoma therapy have been previously reported.[371] Finally, the side effects that accompanied acetazolamide treatment made the investigation difficult to mask. This problem was anticipated because problems associated with masking such studies are well described.[319] This made it imperative that the investigator taking the visual acuities did not discuss treatment with the patients.

Although not approved at the time of this study, topically effective carbonic anhydrase inhibitors are now available for the treatment of the glaucomas.[372-374] It is not clear whether topical treatment with these agents is capable of providing adequate levels of drug to the appropriate parts of the eye to result in an improvement in vision in patients with chronic clinical CME. However, we are planning such studies at present.

Conclusions

The results of this study suggest that orally administered acetazolamide may be of benefit in improving vision during the treatment of chronic clinical CME following cataract surgery. However, the presence of systemic side effects may limit the therapeutic usefulness of this treatment. In addition, the results of this study suggest that the pathophysiology of CME following cataract surgery involves more than simply inflammation in some patients.

SUMMARY AND CONCLUSIONS

Although the incidence of CME following cataract surgery is unknown, this syndrome continues to be the most common cause of decreased vision

following cataract surgery. CME is a nonspecific retinal manifestation of ocular disease that consists of the accumulation of intravascular transudate within cells or spaces in the outer plexiform and the inner nuclear layers of the retina. This intraretinal fluid accumulation is associated with retinal thickening and cyst formation, which can occasionally be visualized with an ophthalmoscope but is more easily identified with slit-lamp biomicroscopy. Fluorescein angiography is the most definitive diagnostic procedure.

CME may or may not be associated with reduced visual acuity. A patient's visual acuity does not always correlate with the severity of the retinal edema as visualized on the fluorescein angiogram. Therefore, during therapeutic studies, angiograms are important for confirming the diagnosis of CME but are of limited value in following visual changes. The natural history of CME includes the frequent occurrence of spontaneous resolution, which makes placebo-controlled studies not only ethical but essential for the evaluation of a therapeutic response.

The pathogenesis of CME following cataract surgery remains obscure. The imbalance in the vascular and tissue fluid dynamics that results in this abnormal accumulation of fluid is most likely the result of multiple factors, including inflammatory, vascular, chemical, and mechanical components. However, the association of CME with many inflammatory ocular diseases and the existence of abundant clinical, histopathologic, experimental, and pharmacologic evidence that ocular inflammation is associated with CME following cataract surgery all suggest that inflammation is an important aspect of the pathophysiology of this syndrome.

Therefore, many treatments for CME following cataract surgery attempt to prevent, reduce, or eliminate the presence or the results of excessive inflammation within the operated eye. These therapeutic attempts have included laser treatment, surgical vitrectomy, and the administration of NSAIDs and corticosteroids. In addition, efforts to influence the intergrity of the BRBs with the administration of acetazolamide or hyperbaric oxygen have attempted to restore better vision in these patients.

Additional important points relating to the incidence, pathogenesis, and treatment of CME following cataract surgery include the following (those relating to new studies within this thesis have an asterisk):

*1. The incidence of clinical CME following cataract surgery remains unknown, but it is significant. The reasons for the observed differences in the reported incidence of this syndrome have not all been identified.

*2. Inflammation is an important part of the pathogenesis of this syndrome. A study is described that strengthens this etiologic relationship by documenting an association between breakdown of the BAB

and slit-lamp signs of anterior ocular inflammation and subsequent development of CME following cataract surgery. However, the observation of a potentially beneficial effect on vision from acetazolamide treatment suggests that it is unwarranted to consider the Irvine-Gass syndrome as simply an inflammatory disease of the eye.

3. Topically applied NSAIDs are effective in the prevention of angiographic CME. However, no study has demonstrated a sustained angiographic effect beyond 1 year or more than a subtle, transient effect on visual acuity.

*4. Topical NSAID treatment is effective in improving vision in some patients with chronic clinical CME. However, some patients do not respond to treatment, and others require several months of treatment before any improvement in vision is observed.

   *a. There is no proven advantage for treating CME following cataract surgery earlier than 6 months after onset.

   *b. Clinical and laboratory studies have not identified which topical NSAID is the most effective anti-inflammatory drug in the treatment of chronic clinical CME. However, only ketorolac tromethamine 0.5% ophthalmic solution has been shown effective with prospective, randomized, double-masked, placebo controlled studies as of this publication.

   *c. The presence of diabetes mellitis, systemic hypertension, or several ocular anatomic findings (incomplete posterior capsule, anterior-placed intraocular lens, pupil abnormalities) does not appear to limit the effectiveness of topical NSAID treatment in some patients with chronic clinical CME.

5. No specific autacoid, including prostaglandins, is recognized as the etiologic agent for the development of CME following cataract surgery.

6. Corticosteroids have not been studied with randomized, placebo-controlled, double-masked investigations. However, experienced clinicians continue to use them in the treatment of chronic clinical CME following cataract surgery because they believe this treatment provides at least a transient beneficial effect.

7. A well-controlled investigation shows that the clinical course of patients receiving vitrectomy for the treatment of chronic aphakic CME with vitreous to the wound is better than that of the control patients. However, the patients in the vitrectomy group received corticosteroids, but the control group did not. Furthermore, the relevance of this study for pseudophakic patients is not clear.

8. A properly designed study of vitrectomy for chronic pseudophakic CME has not been completed. There is general agreement that surgical treatment should be preceded by conservative management.

The value of surgery in an anatomically normal, pseudophakic eye is unproved.

9. Controlled, masked, randomized studies have not been performed to confirm the usefulness and safety of hyperbaric oxygen as a treatment for CME following cataract surgery.

*10. The results of a small, double-masked, placebo-controlled study support the impression that orally administered acetazolamide may help improve vision in some patients with CME following cataract surgery. However, the side effects associated with acetazolamide ingestion may limit the usefulness of this treatment. The observation of a beneficial effect from acetazolamide treatment suggests that it is unwarranted to consider the Irvine-Gass syndrome as simply an inflammatory disease of the eye.

ACKNOWLEDGEMENTS

The invaluable assistance of the following investigators is recognized: Bernard Dolan, OD, who performed all refractions; Walter Stern, MD, who read fluorescein angiograms; Marilyn Donahue, BS, who assisted with laboratory experiments; and Richard Juster, who performed the statistical analyses. Special thanks goes to Margie Ong for preparing all tables.

APPENDIX

Summary Incidence of Cystoid Macular Edema Following Cataract Surgery

Year (Investigator)	Incidence	Comments
1958 (Welch, Cooper[248])	1.25%	Retrospective review of 1,600 cases.
1965 (Tolentino, Schepens[33])	1.7%	Follow-up on 1,000 cases taken from 2,200 surgeries. Noted association with vitreous traction.
1966 (Oliver[34])	9.6%	Retrospective study of 64/120 ICCE 3 wk to 9 mo after surgery. All cases 70 years of age or older.
1967 (Maumenee[247])	< 1%	Clinical impression.
1967 (Binkhorst, Leonard[36])	12%	"Macular disorders in pseudophakic eyes probably do not differ from those in aphakic eyes in frequency or pathogenesis."
1968 (Gehring[37])	7.6%	18/236 surgeries 5 to 8 wk after surgery. All had reduced vision.
1969	Unable to	Described in 64 eyes of 48 patients, but

(Gass, Norton[38])	determine from study	investigators believed series too small to comment on incidence. 50% resolved in 6 mo.
1971 (Irvine et al)	40%	Prospective study of 136 ICCE 4 to 16 wk postoperatively. Angiograms on 100/136. Investigators believe incidence greater. Peak incidence 6 wk.
1971 (Yoshioka[40])	60%	Prospective study with small number of patients.
1972 (Pearce[41])	5%	Retrospective study of 72 cases with iris clip lenses. Conclude iris clip lens not a problem.
1973 (Binkhorst[42])	3%	Reflects upon 14 years experience describing 26/865 iris clip lenses. Concludes ICCE higher incidence, but IOL does not matter.
1974 (Jacobson, Dellaporta[43])	No incidence reported	71.4% resolved in this 6-yr retrospective review. 33% needed more than 6 mo.
1974 (Jardine, Sandford-Smith[44])	19%	Iris supported lenses.
1975 (Hitchings, Chisholm, Bird[45])	53.5%	Prospective study of 101 consecutive cases 6-7 wk after surgery. 30 lost to follow-up. 38/71 positive angiograms, 12/28 positive in 6 mo.
1975 (Hitchings, Chisholm4[6])	47%	Study similar to reference 45.
1976 (Allen, Jaffee[47])	19% (4 mo) 16% (8 mo)	Investigators report "early results" 50% to 75% less frequent with ECCE compared with ICCE. Binkhorst lenses used.
1976 (Klein, Yannuzzi[48])	Less than 5%	One week after ICCE.
1976 (Dallas[49])	6.3% or 1.8%	Retrospective comparison: iris clip lens 6.3%, ICCE 1.8%.
1976 Meredith et al[50])	60%	Only 10% had reduced vision. Determined at 6 wk post ICCE. Only 50% surgeries had angiograms.
1977 (Miyake[51])	77% (placebo Rx) or 33% (topical Indocin Rx)	Prospective study of 119 eyes in ICCE (age 60 or more) all treated with steroids. Placebo 50% ↓ VA, topical Indocin 5% ↓ VA
1977 (Harris et al[52])	36%	Prospective study of 155 with IOL at 6 wk. Also describe retrospective study of 193 implants = 9% to 44.5% varying with vitreous loss and capsule presence. Conclude IOL does not influence, but presence of capsule does.
1977 (Berrocal[53])	5.5% to 15.7% (ICCE) or 1.7% to 7.0% (ECCE)	Summary of 16 surgeons' experience. All include IOLs.

1978 (Winslow et al[54])	36%	Study similar to reference 52.
1978 (Moses[55])	ICCE/IOL=8.5% (21/246) ECCE=4.4% (3/69) Phaco = 1.7% (4/236)	Review 551 cases 1 to 34 months post-operatively. All have IOL. Recommend leaving capsule intact.
1978 (Jaffee[56])	7.4% (Copeland lens) 1.4% (Binkhorst lens)	Retrospective summary of 10 years' experience and over 2,000 IOLs.
1978 (Jaffee[57])	4 mo. 8 mo. 16-24 mo. ECCE/IOL 6.7% 4.4% 3.4% ICCE/IOL 16.6% 12.4% 15.6%	Review 650 consecutive Binkhorst lenses Conclude IOL does not increase CME, but ECCE less than ICCE.
1979 (Meredith, Maumenee[24,25])	2.8%	Considerable underestimate.
1979 (Klein et al[58])	9% (oral Indocin Rx) 44% (placebo)	Nonrandomized study; 20/70 unable to finish Indocin.
1979 (Chambless[59])	2.8%	2.8% = 30/1055 cataract surgeries. Include 23 open capsules and 7 intact capsules.
1979 (Wetzig et al[60])	8% (ICCE) 1.2% (ECCE)	Review of 564 cases and conclude opening capsule increases CME.
1979 (Sorr et al[61])	23.3%	Prospective, nonrandomized, many lost to lost to follow-up, peak incidence 6 wk post-operatively. ECCE by phacoemulsification.
1979 (Miami Study Group[62])	4 mo 8 mo 16-24 mo ECCE/IOL 8% 6% 4% ICCE/IOL 17% 12% 15% ICCE 14% 15% 9%	Prospective, 67 yr old or more, lost over 100 patients to follow-up. Conclude open capsule and increase CME.
1980 (Francois, Verbraeken[63])	2.8%	Retrospective review of 1,000 consecutive ICCE. 50% associated with complications.
1980 (Berger et al[64])	28%-42%	Retrospective review of 26 mo on 59 eyes with vitreous loss.
1980 (Kunz et al[65])	ICCE = 13% ECCE = 2.1%	Review most 3 mo after surgery.
1980 (Lindstrom, Harris[66])	9.5%	Retrospective review of 595 cases with IOL All had decreased vision, 75% within 6 mo.
1980 (McGuinness et al[67])	38%	Prospective study of 145 surgeries at 4 wk postoperatively.
1981 (Poer et al[68])	0%	Retrospective study of 25 eyes in 18 children (7 mo to 14 yr) at 5 wk to 4 yr post-operatively.
1981 (Percival[69])	ECCE rupture capsule = 27% ECCE intact capsule = 13% ICCE = 23%	Conclude open capsule and increase CME and its severity.
1981 (Livernois, Sinskey[70])	Pseudophakic = 4% (open capsule 3.5%) Aphakic = 2%	Retrospective study of 142 eyes.
1981 (Wilkinson[30])	Not reported	66% resolved.

1981 (Jaffe et al[71])	3%	Prospective with retrospective control Angiograms 11 to 12 mo after surgery.
1982 (Kraff et al[14])	9.6% topical Indocin 18.5% placebo	Prospective study of 500 patients,all treated with steroids. 22% angiograms unreadable. Investigators believe incidence higher without steroids.
1982 (Jaffe et al[72])	Surgery Uncomplicated: Angio ØVA ICCE with IOL 15.4% 3.4% ECCE with IOL (AC) 4.5% } 0% ECCE/PC-IOL 2.9% } Surgery Complicated: ICCE/IOL 23% 11.6% ECCE/IOL 29% 18% ECCE/PC-IOL 24% 12.1%	Prospective review of 358 uncomplicated and 137 complicated cases 16 to 24 mo after surgery.
1982 (Hoyt, Nickel[73])	22.2%	Prospective study of children. Decreased vision in 4/27 = 14.8%.
1983 (Severin[74])	ECCE/IOL=ICCE/IOL = 7.4%	Retrospective, pooled data from 9 surgeons resulting in 1,464 cases. Range 1% 14.4%.
1983 (Tanabe[75])	18% (Indocin Rx) 61% (no Rx)	Angiograms at 3 to 5 mo after surgery.
1983 (Straatsma et al[76])	Faculty = 3.3% Residents = 5%	ECCE/IOL - not statistically different.
1983 (Gilbardet al[77])	4%	Retrospective study of 34 patients (48 eyes) congenital cataracts.17 patients (23 eyes) lost to follow-up.
1984 (Taylor et al[29])	ICCE = 2% ICCE/IOL = 9.9% ECCE/IOL-PC = 1.2%	Retrospective, 6 mo to 3 yr follow-up. All ↓ VA. Age-related: 50-59 = 26%; 80-89 = 1.5%
1984 (Kraffet al[78])	21.5% (intact capsule) 5.6% (open capsule)	All receive steroids. Only 57% readable angiograms.
1984 (Stark et al[28])	Transient Persistent PC-IOL 2% 0.3% Binkhorst 10% 1%	Prospective, nonrandomized study concludes PC-IOL decrease CME.
1985 (Jampol et al[79])	17%-21%	Prospective, randomized, all receive steroids 1/3 angiograms not readable.
1987 (Alpar[80])	13.3%	Retrospective study.
1988 (Severin, Severin[74,81])	ICCE/IOL = 12.7% ECCE/IOL = 3.5%	Retrospective study. Contrasts with prior study.
1988 (Wright et al[31])	Open capsule 24% Intact capsule 16%	Prospective, steroids to all patients, 96% angiograms read at 6 wk. (Overall: 6 wk 19% (2.5% ↓ VA) 6 mo 4% (2% ↓ VA)
1989 (Behrens et al[82])	4%	Prospective study at 6 wk. ICCE with Choyce IOL.
1990 (Flachet al[83])	21% (placebo Rx) 6% (ketorolac Rx)	Prospective, randomized, black patients, angiograms 6 wk postoperatively, no steroids, ECCE, angiographic CME.
1991	12.8%	Retrospective, vitreous loss.

(Hykin et al[84])		
1991 (Ruiz, Saatci[85])	2.6% (uncomplicated) 21.9% (vitreous loss)	Retrospective, 2,100 ECCE/IOL.
1991 (Cunliffe et al[86])	26%	Retrospective, ECCE with IOL.
1992 (Nikica et al[87])	ECCE/IOL-PC 1.5% ECCE/Vit loss 35.7% ICCE/IOL 9.0%	Retrospective, 6 wk to 6 mo postoperatively.
1992 (Johansen et al[88])	4% complicated cases	Prospective 2/49.
1992 (Pollack et al[89])	50% diabetics 8% controls	Prospective, 6 wk after surgery. ECCE with IOL.
1993 (Menchini et al[90])	Days 3 9 180 360 Normal 62% 33% 8.3% 0% Diabetes 68% 65% 43 24%	CME more common in diabetics but vision same. All receive steroids. Prospective, ECCE with IOL.
1993 (Desai[10])	1.2%	Retrospective study of 1,445 patients but ⅓ of records missing.
1994 (Bergman, Laatikainen[9])	12.5%	Review of 40 complicated cases with mean follow-up 23 mo.
1995 (Drolsum, Haaskjold[11])	3.6%	Review of 1,237 eyes collected over 3 yr.
1996 (Flach) (present AOS thesis)	9.6%	Prospective study of 350 consecutive ECCE/IOL. Angiograms performed on all patients patients with < 20/40. Six mo or less postoperatively.

REFERENCES

1. Irvine SR. A newly defined vitreous syndrome following cataract surgery. *Am J Ophthalmol* 1953;36:599-619.
2. Iwanoff A. Das Edema der Netzhaut. *Graefes Arch Clin Exp Ophthalmol* 1869;15:88-98.
3. Bangerter A. Zur Diagnose, Differentialdiagnose und Therapie des cystoiden Maculaodems (Maculacysten). *Ophthalmologica* 1945;109:102-122.
4. Duke-Elder WS. *Text Book of Ophthalmology. Vol III. Diseases of the Inner Eye*. St Louis: Mosby; 1941:2592
5. Vogt A. Weitere ophthalmoskopische Beobachtungen in Rotfreien Licht. Echte Netzhaut Faltchen. Cystische Degeneration der Macula Lutea. *Klin Monatsbl Augenheilkd* 1918;61:379-391.
6. Vogt A. Ophthalmoskopische Untersuchungen der Macula Lutea im rotfrein Licht. *Klin Monatsbl Augenheilkd* 1921;66:321-334.
7. Gass JDM, Norton EWD. Cystoid macular edema and papilledema following cataract extraction. *Arch Ophthalmol* 1966;76:646-661.
8. Gass JDM, Norton EWD. Fluorescein studies of patients with macular edema and papilledema following cataract extraction. *Trans Am Ophthalmol Soc* 1966;64:232-249.
9. Bergman M, Laatikainen L. Cystoid macular oedema after complicated cataract surgery and implantation of an anterior chamber lens. *Acta Ophthalmologica* 1994;72:178-180.

10. Desai P. The national cataract surgery survey: II. Clinical outcomes. *Eye* 1993;7:489-494.
11. Drolsum L, Haaskjold E. Causes of decreased visual acuity after cataract extraction. *J Cataract Refract Surg* 1995;21:59-63.
12. Ibanez HE, Lesher MP, Singerman LJ, et al. Prospective evaluation of the effect of pseudophakic cystoid macular edema on contrast sensitivity. *Arch Ophthalmol* 11993;11:1635-1639.
13. Jampol LM. Cystoid macular edema following cataract surgery. *Arch Ophthalmol* 1988;106:894-895.
14. Kraff MC, Sanders DR, Jampol LM, et al. Prophylaxis of pseudophakic cystoid macular edema with topical indomethacin. *Ophthalmology* 1982;9:885-890.
15. Milch FA, Yannuzzi LA. Medical and surgical treatment of aphakic cystoid macular edema. *Int Ophthalmol Clin* 1987;27:205-217.
16. Peterson M, Yoshizumi MO, Hepler R, et al. Topical indomethacin in the treatment of chronic cystoid macular edema. *Graefes Arch Clin Exp Ophthalmol* 1992;230:401-405.
17. Jampol LM, Sanders DR, Kraff MC. Prophylaxis and therapy of aphakic cystoid macular edema. *Surv Ophthalmol* 1984;28:535-539.
18. Easty D, Dallas N, O'Malley R. Aphakic macular oedema following prosthetic lens implantation. *Br J Ophthalmol* 1977;61:321-326.
19. Fung WE. Aphakic cystoid macular edema. In: Ryan SJ, Schachat AP, Murphy RB, Patz A, eds. *Retina*. St Louis: Mosby; 1989:767-779.
20. Irvine AR. Cystoid maculopathy. *Surv Ophthalmol* 1979;21:1-17.
21. Jampol LM. Pharmacologic therapy of aphakic cystoid macular edema. *Ophthalmology* 1982;80:891-897.
22. Jampol LM. Pharmacologic therapy of aphakic and pseudophakic cystoid macular edema-1985 update. *Ophthalmology* 1985;92:807-810.
23. Marmion VJ. Cystoid macular edema. *Proc R Soc Med* 1976;69:905-906.
24. Meredith TA, Maumenee AE. A review of one thousand cases of intracapsular cataract extraction: I. Complications. *Ophthalmic Surg* 1979;10:32-41.
25. Meredith TA, Maumenee AE. A review of one thousand cases of intracapsular cataract extraction: II. Visual results and astigmatic analysis. *Ophthalmic Surg* 1979;10:42-45.
26. Sears ML. Aphakic cystoid macular edema. The pharmacology of ocular trauma. *Surv Ophthalmol* 1984;28:525-534.
27. Spaide RF, Yannuzzi LA. Cystoid macular edema after cataract surgery. *Semin Ophthalmol* 1993;8:121-129.
28. Stark WJ, Maumenee AE, Fagadau W, et al. Cystoid macular edema in pseudophakia. *Surv Ophthalmol* 1984;28:442-453.
29. Taylor DM, Sachs SW, Stern AL. Aphakic cystoid macular edema. Longterm clinical observations. *Surv Ophthalmol* 1984;28:437-441.
30. Wilkinson CP. A long-term follow-up study of cystoid macular edema in aphakic and pseudophakic eyes. *Trans Am Ophthalmol Soc* 1981;79:810-839.
31. Wright PL, Wilkinson CP, Balyeat HD, et al. Angiographic cystoid macular edema after posterior chamber lens implantation. *Arch Ophthalmol* 1988;106:740-744.
32. Ward DA. Comparative blood-aqueous barrier stabilizing effect of topical flurbiprofen, diclofenac, tolmetin and suprofen. *Invest Ophthalmol Vis Sci* 1994;35:1885.
33. Tolentino FI, Schepens CL. Edema of posterior pole after cataract extraction-A biomicroscopic study. *Arch Ophthalmol* 1965;74:781-786.
34. Oliver M. Posterior pole changes after cataract extraction in elderly subjects. *Am J Ophthalmol* 1966;62:1145-1148.
35. Kraff MC, Sanders DR, Lieberman HL. The Medallion suture lens: Management of complications. *Ophthalmology* 1979;86:643-654.
36. Binkhorst CD, Leonard PAM. Results in 208 iris-clip pseudophakos implantations. *Am*

J Ophthalmol 1967;64:947-956.
37. Gehring JR. Macular edema following cataract extraction. *Arch Ophthalmol* 1968;80:626-631.
38. Gass JDM, Norton EWD. Follow-up study of cystoid macular edema following cataract extraction. *Trans Am Acad Ophthalmol Otolaryngol* 1969;73:665-682.
39. Irvine AR, Bresky R, Crowder BM, et al. Macular edema after cataract extraction. *Ann Ophthalmol* 1971;3:1234-1240.
40. Yoshioka H, Kawashima K. Macular edema following cataract extraction. *Acta Soc Ophthalmol Jpn* 1971;75:2269-2273.
41. Pearce JL. Long-term results of the Binkhorst iris clip lens in senile cataract. *Br J Ophthalmol* 1972;56:319-331.
42. Binkhorst CD. The iridocapsular (two-loop) lens and the iris-clip (four-loop) lens in pseudophakia. *Trans Am Acad Ophthalmol Otolaryngol* 1973;77:589-617.
43. Jacobson DR, Dellaporta A. Natural history of cystoid macular edema after cataract extraction. *Am J Ophthalmol* 1974;77:445-447.
44. Jardine P, Sandford-Smith JH. Federov iris-supported intraocular acrylic lens. *Br J Ophthalmol* 1974;58:718-724.
45. Hitchings RA, Chisholm IH, Bird AC. Aphakic macular edema: Incidence and pathogenesis. *Invest Ophthalmol Vis Sci* 1975;14:68-72.
46. Hitchings RA, Chisholm IH. Incidence of aphakic cystoid macular edema: A prospective study. *Br J Ophthalmol* 1975;59:444-450.
47. Allen AW, Jaffee NS. Cystoid macular edema—A preliminary study. *Trans Am Acad Ophthalmol Otolargyngol* 1976;81:133-134.
48. Klein RM, Yannuzzi L. Cystoid macular edema in the first week after cataract extraction. *Am J Ophthalmol* 1976;81:614-620.
49. Dallas NL. Intraocular implants. *Proc R Soc Med* 1976;69:903-905.
50. Meredith TA, Kenyon KR, Singerman LJ, et al. Perifoveal vascular leakage and macular oedema after intracapsular cataract extraction. *Br J Ophthalmol* 1976;60:765-769.
51. Miyake K. Prevention of cystoid macular edema after lens extraction by topical indomethacin (I): A preliminary report. *Graefes Arch Clin Exp Ophthalmol* 1977;203:81-88.
52. Harris WS, Taylor BC, Winslow RL. Cystoid macular edema following intraocular lens implantation. *Ophthalmic Surg* 1977;8:134-137.
53. Berrocal JAR. Incidence of cystoid macular edema after cataract operations. *Mod Probl Ophthalmol* 1977;18:518-520.
54. Winslow RL, Taylor BC, Harris WS. A one-year follow-up of cystoid macular edema following intraocular lens implantation. *Trans Am Acad Ophthalmol Otolaryngol* 1978;85:190-196.
55. Moses L. Macular edema following cataract extraction. *Am Intraoc Implant Soc J* 1978;4:17-22.
56. Jaffe NS: Results of intraocular lens implant surgery: The Third Binkhorst Medical Lecture. *Am J Ophthalmol* 1978;185:13-23.
57. Jaffe NS. Intraocular lenses: Secondary membranes; cystoid macular edema. *Trans Am Acad Ophthalmol Otolaryngol* 1978;85:157-163.
58. Klein RM, Katzin HM, Yannuzzi LA. The effect of indomethacin pretreatment on aphakic cystoid macular edema. *Am J Ophthalmol* 1979;87:487-489.
59. Chambless WS. Phacoemulsification and the retina: Cystoid macular edema. *Trans Am Acad Ophthalmol Otolaryngol* 1979;86:2019-2023.
60. Wetzig PC, Thatcher DB, Christiansen JM. The intracapsular versus the extracapsular cataract technique in relationship to retinal problems. *Trans Am Ophthalmol Soc* 1979;77:339-347.
61. Sorr EM, Everett WG, Hurite FG. Incidence of fluorescein angiographic subclinical

macular edema following phacoemulsification of senile cataracts. *Trans Am Acad Ophthalmol* 1979;86:2013-2018.
62. Miami Study Group. Cystoid macular edema in aphakic and pseudophakic eyes. *Am J Ophthalmol* 1979;88:45-48.
63. Francois J, Verbraeken H. Complications in 1,000 consecutive intracapsular cataract extractions. *Ophthalmologica* 1980;180:121-128.
64. Berger BB, Zweig KO, Peyman GA. Vitreous loss managed by anterior vitrectomy. *Arch Ophthalmol* 1980;98:1245-1247.
65. Kunz E, Kern R, Oppong MC, et al. Macular edema following implantation of Binkhorst lenses. *Klin Monatsbl Augenheilkd* 1980;176:690-693.
66. Lindstrom RL, Harris WS. Management of the posterior capsule following posterior chamber lens implantation. *J Am Intraoc Implant Soc* 1980;6:255-258.
67. McGuinness R, Kennedy I, Gole G. The Prince of Wales Hospital prospective aphakic macular oedema study. *Aust J Ophthalmol* 1980;8:247-251.
68. Poer DV, Helveston EM, Ellis FD. Aphakic cystoid macular edema in children. *Arch Ophthalmol* 1981;99:249-252.
69. Percival P. Clinical factors relating to cystoid macular edema after lens implantation. *Am Intraoc Implant Soc J* 71981;43-45.
70. Livernois R, Sinskey RM. Complications of late capsulotomy. *Am Intraoc Implant Soc J* 1981;7:242-243.
71. Jaffe NS, Luscombe SM, Clayman HM, et al. A fluorescein angiographic study of cystoid macular edema. *Am J Ophthalmol* 1981;92:775-777.
72. Jaffe NS, Clayman HM, Jaffe MS. Cystoid macular edema after intracapsular and extracapsular cataract extraction with and without an intraocular lens. *Ophthalmology* 1982;89:25-29.
73. Hoyt CS, Nickel B. Aphakic cystoid macular edema. Occurrence in infants and children after transpupillary lensectomy and anterior vitrectomy. *Arch Ophthalmol* 1982;100:746-749.
74. Severin SL. Clinical cystoid macular edema with intracapsular cataract extraction and posterior chamber lens implantation. *Ann Ophthalmol* 1983;15:631-634.
75. Tanabe N, Sagae Y, Hara K. Effect of topical indomethacin treatment for cystoid macular edema after lens extraction. *Folia Ophthalmol Japonica-Bull Jpn Ophthalmol* 1983;34:178-182.
76. Straatsma BR, Meyer KT, Bastek JV, et al. Posterior chamber intraocular lens implantation by ophthalmology residents. A prospective study of cataract surgery. *Ophthalmology* 1983;90:327-335.
77. Gilbard SM, Peyman GA, Goldberg MF. Evaluation for cystoid maculopathy after pars plicata lensectomy-vitrectomy for congenital cataracts. *Ophthalmology* 1983;90:1201-1206.
78. Kraff MC, Sanders DR, Jampol LM, et al. Effect of primary capsulotomy with extracapsular surgery on the incidence of pseudophakic cystoid macular edema. *Am J Ophthalmol* 1984;96:166-170.
79. Jampol LM, Kraff MC, Sanders DR, et al. Near-UV radiation from the operating microscope and pseudophakic cystoid macular edema. *Arch Ophthalmol* 1985;103:28-30.
80. Alpar JJ. Diabetes: Cataract extraction and intraocular lens. *J Cataract Refract Surg* 1987;13:43-46.
81. Severin TD, Severin SL. Pseudophakic cystoid macular edema: A revised comparison of incidence with intracapsular and extracapsular cataract extraction. *Ophthalmic Surg* 1988;19:116-118.
82. Behrens-Baumann W, Quentin CD, Eckhardt B, et al. Grading and evaluating cystoid macular edema. *Klin Monatsbl Augenheilkd* 1989;194:16-21.
83. Flach AJ, Stegman RC, Graham J, et al. Prophylaxis of aphakic cystoid macular edema

without corticosteroids. A paired comparison, placebo controlled double-masked study. *Ophthalmology* 1990;97:1253-1258
84. Hykin PG, Gardner ID, Corbett MC, et al. Primary or secondary anterior chamber lens implantation after extracapsular cataract surgery and vitreous loss. *Eye* 1991;5:694-698.
85. Ruiz R, Saatci A. Visual outcome in pseudophakic eyes with clinical cystoid macular edema. *Ophthalmic Surg* 1991;22:190-193.
86. Cunliffe IA, Flanagan DW, George NDL, et al. Extracapsular cararact surgery with lens implantation in diabetics with and without proliferative retinopathy. *Br J Ophthalmol* 1991;75:9-12.
87. Nikica G, Ljerka HP, Jelena P, et al. Cystoid macular edema in anterior chamber lens implantation following posterior capsule rupture. *Doc Ophthalmol* 1991;81:309-315.
88. Johansen J, Theodorsen FP, Corydon L. Visual outcome following complicated extracapsular cataract extraction. *J Cataract Refract Surg* 1992;18:577-581.
89. Pollack A, Leiba H, Bukelman A, et al. Cystoid macular oedema following cataract extraction in patients with diabetes. *Br J Ophthalmol* 1992;76:221-224.
90. Menchini U, Bandello F, Brancato R, et al. Cystoid macular oedema after extracapsular cataract extraction and intraocular lens implantation in diabetic patients without retinopathy. *Br J Ophthalmol* 1993;77:208-211.
91. Kraff MC, Sanders DR, Jampol LM, et al. Effect of an ultraviolet-filtering intraocular lens on cystoid macular edema. *Ophthalmology* 1985;92:366-369.
92. Kraff MC, Sanders DR, Jampol LM, et al. Factors affecting pesudophakic cystoid macular edema: Five randomized trials. *J Am Intraoc Implant Soc* 1985;11:380-385.
93. Bonnet M, Grange JD, Pingault C. Frequency of macular edema after cataract extraction. *Ann Ocul (Paris)* 1975;208:217-220.
94. Stern AL, Taylor DM, Dalburg LA, et al. Pseudophakic cystoid maculopathy. A study of 50 cases. *Ophthalmology* 1981;88:942-946.
95. Drews RC. The present understanding of cystoid macular edema. *Trans Ophthalmol Soc UK* 1985;104:744-747.
96. Irvine AR. Cystoid macular edema, Irvine-Gass syndrome. In: Fraunfelder FT, Roy FH, eds. *Current Ocular Therapy*. Philadelphia: Saunders; 1980:517-519.
97. Freedman J, Jordan AJ, Kokoris N. Cystoid macular edema in aphakic black patients. *Ann Ophthalmol* 1979;11:1699-1701.
98. Jampol LM. Aphakic cystoid macular edema: A hypothesis. *Arch Ophthalmol* 1985;103:1134-1135.
99. Miyake K. Prevention of cystoid macular edema after lens extraction by topical indomethacin (II) A controlled study of bilateral extractions. *Jpn J Ophthalmol* 1978;22:80-94.
100. Alpar JJ. Barrier deprivation syndrome. A case report. *Am Intraoc Implant Soc J* 1978;4:6-7.
101. Roper DL, Nisbet RM. Effect of hyaluronidase on the incidence of cystoid macular edema. *Ann Ophthalmol* 1978;10:1673-1678.
102. Kraff MC, Sanders DR, Jampol LM, et al. Effect of retrobulbar hyaluronidase on pseudophakic cystoid macular edema. *Am Intraoc Implant Soc J* 1983;9:184-185.
103. Frost NA, Sparrow JM, Strong NP, et al. Vitreous loss in planned extracapsular cataract extraction does lead to a poorer visual outcome. *Eye* 1995;9:446-451.
104. Katzen LE, Fleischman JA, Trokel S. YAG laser treatment of cystoid macular edema. *Am J Ophthalmol* 1983;95:589-592.
105. Baltazis S, Theodossiadis G, Velissaropoulos P. Irvine-Gass syndrome. Statistical and angiographic study. *Arch Ophthalmol (Paris)* 1976;36:21-32.
106. Bonnet M, Bievelez B. Iris fluorescein angiography and Irvine-Gass syndrome. *Graefes Arch Klin Exp Ophthalmol* 1980;213:187-194.
107. Iliff CE. Treatment of the vitreous tug syndrome. *Am J Ophthalmol* 1966;62:856-859.

108. Kirsch RE, Steinamn W. Spontaneous rupture of the anterior hyaloid membrane following intracapsular cataract surgery. *Am J Ophthalmol* 1954;37:657-665.
109. Michels RG, Machemer R, Mueller-Jensen K. Vitreous surgery: History and current concepts. *Ophthalmic Surg* 1974;5:13-59.
110. Robinson D, Landers MB, Hahn DK. An anterior segment approach to aphakic cystoid macular edema. *Am J Ophthalmol* 1983;95:811-817.
111. Bonnet M. Factors of prognosis in the Irvine-Gass syndrome. *Ann Ocul (Paris)* 1975;208:275-278.
112. Ferguson VMG, Spalton DJ. Continued breakdown of the blood aqueous barrier following cataract surgery. *Br J Ophthalmol* 1992;76:453-456.
113. Spaide RF, Yannuzzi LA, Sisco LJ. Chronic cystoid macular edema and predictors of visual acuity. *Ophthalmic Surg* 1993;24:262-267.
114. Goldberg I, Kolker AE, Kass MA, et al. Dipivefrin: Current concepts. *Aust J Ophthalmol* 1980;8:147-150.
115. Kolker AE, Becker B. Epinephrine maculopathy. *Arch Ophthalmol* 1968;79:552-562.
116. Mackool RJ, Muldoon T, Forier A, et al. Epinephrine-induced cystoid macular edema in aphakic eyes. *Arch Ophthalmol* 1977;95:791-793.
117. Michels RG, Maumenee AE. Cystoid macular edema associated with topically applied epinephrine in aphakic eyes. *Am J Ophthalmol* 1975;80:379-388.
118. Obstbaum SA, Galin MA, Poole TA. Topical epinephrine and cystoid macular edema. *Ann Ophthalmol* 1976;8:455-458.
119. Thomas JV, Gragoudas ES, Blair NP, et al. Correlation of epinephrine use and macular edema in aphakic glaucomatous eyes. *Arch Ophthalmol* 1978;96:625-628.
120. Aron-Rosa D, ed. *Pulsed YAG Laser Surgery*. Thorofare, NJ: Charles Slack; 1983:30, 53..
121. Krishnan MM, Lath NK, Govind A. Aphakic macular edema: Some observations on prevention and pathogenesis. *Ann Ophthalmol* 1985;17:253-257
122. Smith RT, Campbell CJ, Koester CJ, et al. The barrier function in extracapsular cataract surgery. *Ophthalmology* 1990;97:90-95.
123. Thompson JT, Glaser BM. Role of lensectomy and posterior capsule in movement of tracers from vitreous to aqueous. *Arch Ophthalmol* 1985;103:420-421.
124. Junge J. Cystoid macular edema associated with PVP coating of an intraocular lens. *Am Intraoc Implant Soc J* 1980;6: 28-29.
125. Shepard DD. The dangers of metal-loop intraocular lenses. *Ophthalmic Surg* 1977;8:93-95.
126. Obstbaum SA, Galin MA. Cystoid macular edema and ocular inflammation the corneoretinal inflammatory syndrome. *Trans Ophthalmol Soc UK* 1979;99:187-191.
127. Henry MM, Henry LM, Henry LM. A possible cause of chronic cystic maculopathy. *Ann Ophthalmol* 1977;9:455-457.
128. Hochheimer BF. A possible cause of chronic cystoid maculopathy: The operating microscope. *Ann Ophthalmol* 1981;13:153-155.
129. Iliff WJ. Aphakic cystoid macular edema and the operating microscope: Is there a connection? *Trans Am Ophthalmol Soc* 1985;83:476-500.
130. Li Z, Tso MOM, Jampol LM, et al. Retinal injury induced by near-ultraviolet radiation in aphakic and pseudophakic monkey eyes. *Retina* 1990;10:301-314.
131. McDonald HR, Irvine AR. Light-induced maculopathy from the operating microscope in extracapsular cataract extraction and intraocular lens implantation. *Ophthalmology* 1983;90:945-951.
132. Lewis H, Singer TR, Hanscom TA, et al. A prospective study of cystoid macular edema after neodymium: YAG laser posterior capsulotomy. *Ophthalmology* 1987;94:478-482.
133. Shammas HJF, Milkie CF. Cystoid macular edema following secondary lens implantation. *Am Intraoc Implant Soc J* 1981;7:40-42.

134. Apple DJ, Mamalis N, Loftfield K, et al. Complications of intraocular lenses. A historical and histopathological review. *Surv Ophthalmol* 1984;29:1-54.
135. Martin NF, Green WR, Martin LW. Retinal phlebitis in the Irvine-Gass syndrome. *Am J Ophthalmol* 1977;83:377-386.
136. Jaffe NS, Eichenbaum DM, Clayman HM, et al. A comparison of 500 Binkhorst implants with 500 routine intracapsular cataract extractions. *Am J Ophthalmol* 1978;85:24-27.
137. Epstein DL. Cystoid macular edema occurring 13 years after cataract extraction. *Am J Ophthalmol* 1977;83:501-503.
138. Severin SL. Late cystoid macular edema in pseudophakia. *Am J Ophthalmol* 1980;90:223-225.
139. Ffytche TJ, Blach RK. The aetiology of macular oedema. *Trans Ophthalmol Soc UK* 1970;90:637-656.
140. Hitchings RA. Aphakic macular Oedema: a two-year follow-up study. *Br J Ophthalmol* 1977;61:628-630.
141. Gas JDM. *Stereoscopic Atlas of Macular Diseases*. St Louis: Mosby; 1987:368-380.
142. Bovino JA, Kelly TJ, Marcus DF. Intraretinal hemorrhages in cystoid macular edema. *Arch Ophthalmol* 1984;102:1151-1152.
143. Gass JDM. Lamellar macular holes: A complication of cystoid macular edema after cataract extraction. *Arch Ophthalmol* 1976;94:793-800.
144. Gass JDM. Lamellar holes: A complication of cystoid macular edema after cataract extraction. A clinicopathologic case report. *Trans Am Ophthalmol Soc* 1975;73:231-250.
145. Lakhanpal V, Schocket SS. Pseudophakic and aphakic retinal detachment mimicking cystoid macular edema. *Ophthalmology* 1987;94:785-791.
146. Yannuzzi LA. A perspective on the treatment of aphakic cystoid macular edema. *Surv Ophthalmol* 1984;28:540-553.
147. Miyake K, Sakamura S, Miura H. Long-term follow-up study on prevention of aphakic cystoid macular oedema by topical indomethacin. *Br J Ophthalmol* 1980;64:324-328.
148. Fishman GA, Gilbert LD, Fiscella RG, et al. Acetazolamide for treatment of chronic macular edema in retinitis pigmentosa. *Arch Ophthalmol* 1989;107:1445-1452.
149. Flach AJ, Dolan BJ, Irvine AR. Effectiveness of ketorolac tromethamine 0.5% ophthalmic solution for chronic aphakic and pseudophakic cystoid macular edema. *Am J Ophthalmol* 1987;103:479-486.
150. Shahidi M, Fishman G, Ogura Y, et al. Foveal thickening in retinitis pigmentosa patients with cystoid macular edema. *Retina* 1994;14:243-247.
151. Flach AJ, Jampol LM, Weinberg D, et al. Improvement in visual acuity in chronic aphakic and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. *Am J Ophthalmol* 1991;112:514-519.
152. Nussenblatt RB, Kaufman SC, Palestine AG, et al. Macular thickening and visual acuity. Measurement in patients with cystoid macular edema. *Ophthalmology* 1987;94:1134-1139.
153. Shahidi M, Ogura Y, Blair NP, et al. Retinal thickness analysis for quantitative assessment of diabetic macular edema. *Arch Ophthalmol* 1991;109:1115-1117.
154. Mc Donnell PJ, de la Cruz ZC, Green WR. Vitreous incarceration complicating cataract surgery. A light and electron microscopic study. *Ophthalmology* 1986;93:247-253.
155. Michels RG, Green WR, Maumenee AE. Cystoid mauclar edema following cataract extraction (The Irvine-Gass Syndrome): A case studied clinically and histopathologically. *Ophthalmic Surg* 1971;2:217-221.
156. Norton AL, Brown WJ, Carlson M, et al. Pathogenesis of aphakic macular edema. *Am J Ophthalmol* 1975;80:96-101.
157. Wolter JR. The histopathology of cystoid macular edema. *Graefes Arch Klin Exp Ophthalmol* 1981;216:85-101.

158. Yanoff M, Fine BS, Brucker AJ, et al. Pathology of human cystoid macular edema. *Surv Ophthalmol* 1984;28:505-511.
159. Fine BS, Brucker AJ. Macular edema and cystoid macular edema. *Am J Ophthalmol* 1981;92:466-481.
160. Gass JDM, Anderson DR, Davis EB. A clinical fluorescein angiographic and electron microscopic correlation of cystoid macular edema. *Am J Ophthalmol* 1985;100:82-86.
161. Reese AB, Jones IS, Cooper WC. Macular changes secondary to vitreous traction. *Am J Ophthalmol* 1966;64:544-549.
162. Boniuk M. Cystic macular edema secondary to vitreoretinal traction. *Surv Ophthalmol* 1968;13:118-121.
163. Jaffe NS. Vitreous traction at posterior pole of the fundus due to alterations in the posterior vitreous. *Trans Am Acad Ophthalmol Otolaryngol* 1967;71:642-652.
164. Cunha-Vaz JG, Travessos A. Breakdown of the blood-retinal barriers and cystoid macular edema. *Survey Ophthalmol* 1984;28:485-492.
165. Cunha-Vaz JG. The blood-ocular barriers. *Surv Ophthalmol* 1979;23:279-296.
166. Starling EH. On the observation of fluids from the consecutive tissue spaces. *J Physiol (Lond)* 1896;19:312.
167. Klatzo I. Neuropathological aspects of brain edema. *J Neuropathol Exp Neurol* 1967;26:1-14.
168. Rapoport SI. *Blood-Brain Barrier in Physiology and Medicine*. New York: Raven Press; 1976.
169. Tso MOM, Shih C. Experimental macular edema after lens extraction. *Invest Ophthalmol Vis Sci* 1977;16:381-392.
170. Tso MOM. Animal modeling of cystoid macular edema. *Surv Ophthalmol* 1984;28:512-519.
171. Yamada E. Some structural features of the fovea centralis in the human retina. *Arch Ophthalmol* 1969;82:151-159.
172. Cogan DG, Guzak SV. Fluoroangiographic pattern of macular edema and retinal swelling in postmorten eyes. *Am J Ophthalmol* 1971;71:291-297.
173. Brownstein S, Orton R, Jackson BW. Cystoid macular edema with equatorial choroidal melanoma. *Arch Ophthalmol* 1978;96:2105-2107.
174. Domarus DV, Hinzpeter EN. Cystoid macular edema over a malignant melanoma of the choroid. *Klin Monatsbl Augenheilkd* 1978;172:751-756.
175. Newsom WA, Hood CI, Horwitz JA, et al. Cystoid macular edema: Histopathologic and angiographic correlations. *Trans Am Acad Ophthalmol Otolaryngol* 1972;76:1005-1009.
176. Reese AB. Defective central vision following successful operation for detachment of the retina. *Am J Ophthalmol* 1937;20:591-599.
177. Bonnet M. The Irvine-Gass syndrome. *Arch Ophtalmol (Paris)* 1972;32:705-720.
178. Classe JG. Epinephrine maculopathy. *J Am Optom Assoc* 1980;51:1091-1093.
179. Ito R, Yoshizumi M, Futa R. A case of epinephrine maculopathy. *Jpn J Clin Ophthalmol* 1976;30:809-813.
180. Chen JC, Fitzke FW, Bird AC. Long-term effect of acetazolamide in a patient with retinitis pigmentosa. *Invest Ophthalmol Vis Sci* 1990;31:1914-1918.
181. Fishman GA, Fishman M, Maggiano J. Macular lesions associated with retinitis pigmentosa. *Arch Ophthalmol* 1977;95:798-813.
182. Ffytche TJ. Cystoid maculopathy in retinitis pigmentosa. *Trans Ophthalmol Soc UK* 1972;92:265-283.
183. Fetkenhour CL, Charomokos E, Weinstein J, et al. Cystoid macular edema in retinitis pigmentosa. *Trans Am Acad Ophthalmol Otolaryngol* 1977;83:515-521.
184. Newsome DA. Retinal fluorescein leakage in retinitis pigmentosa. *Am J Ophthalmol* 1986;101:354-360.
185. Orzalesi N, Pierrottet C, Porta A, et al. Long-term treatment of retinitis pigmentosa

with acetazolamide. *Graefes Arch Clin Exp Ophthalmol* 1993;231:254-256.
186. Spallone A. Retinal fluorescein leakage in retinitis pigmentosa. *Am J Ophthalmol* 1986;102:408.
187. Spalton DJ, Bird AC, Cleary PE. Retinitis pigmentosa and retinal oedema. *Br J Ophthalmol* 1978;62:174-182.
188. Fishman GA, Jampol LM, Goldberg MF. Diagnostic features of the Favre-Goldmann syndrome. *Br J Ophthalmol* 1976;60:345-353.
189. Nasr YG, Cherfan GM, Michels RG, et al. Goldmann-Favre maculopathy. *Retina* 1990;10:178-180.
190. Bonnet M, Le Nail B. Prophylaxis of operative macular complications of retinal detachment by microsurgery. *Soc J Fr Ophtalmol* 1980;3:83-89.
191. Cleary PE, Leaver PK. Macular abnormality in the reattached retina. *Br J Ophthalmol* 1978;62:595-601.
192. Cleasby GW. Vitreous surgery as a supplement to cataract surgery. *Ann Ophthalmol* 1980;12:1200-1207.
193. Lobes LA Jr, Grand MG. Incidence of cystoid macular edema following scleral buckling procedure. *Arch Ophthalmol* 1980;98:1230-1239.
194. Machemer R. Experimental retinal detachment in the owl monkey. II. Histology of retina and pigment epithelium. *Am J Ophthalmol* 1968;66:396-410.
195. Meredith TA, Reeser FH, Topping TM, et al. Cystoid macular edema after retinal detachment surgery. *Ophthalmology* 1980;87:1090-1096.
196. Miyake K, Miyake Y, Maekubo K, et al. Incidence of cystoid macular edema after retinal detachment surgery and the use of topical indomethacin. *Am J Ophthalmol* 1983;95:451-456.
197. Nielsen PG. Macular oedema in the reattached retina. *Acta Ophthalmol* 1978;57:522-531.
198. Ryan SJ. Cystoid maculopathy in phakic retinal detachment procedures. *Am J Ophthalmol* 1973;76:519-522.
199. Tani P, Robertson DM, Langworthy A. Rhegmatogenous retinal detachment without macular involvement treated with scleral buckling. *Am J Ophthalmol* 1980;90:503-511.
200. Tannenbaum HL, Schepens CL, Elzeneiny I, et al. Macular pucker following retinal detachment surgery. *Arch Ophthalmol* 1970;83:286-293.
201. Yoshioka H, Sugita T, Kawashima K. Cystoid macular edema after cataract or retinal detachment surgery and contusion. *Acta Soc Ophthalmol Jpn* 1971;75:1027-1033.
202. Yoshioka H, Sugita T. Cystoid macular edema after retinal detachment surgery and treatment of retinal detachment with macular hole. *Folia Ophthalmol Jpn* 1972;23:774-777.
203. Alpar JJ. Keratoplasty with primary and secondary lens implantation. *Ophthalmic Surg* 1978;9:58-66.
204. Kramer SG. Cystoid macular edema after aphakic penetrating keratoplasty. *Ophthalmology* 1981;88:782-787.
205. West CE, Fitzgerald CR, Sewell JH. Cystoid macular edema following aphakic keratoplasty. *Am J Ophthalmol* 1973;75:77-81.
206. Bonnet M, Guille C. The macular complications of chronic posterior cyclitis. *Arch Ophtalmol (Paris)* 1974;34:453-462.
207. Diamond JG, Kaplan HJ. Lensectomy and vitrectomy for complicated cataract secondary to uveitis. *Arch Ophthalmol* 1978;96:1798-1804.
208. Maumenee AE. Clinical entities in uveitis. An approach to the study of intraocular inflammation. XXVI Edward Jackson Memorial Lecture. *Am J Ophthalmol* 1970;69:1-27.
209. Martin NF, Fitzgerald OR. Cystoid macular edema as the primary sign of neurosyphilis. *Am J Ophthalmol* 1979;88:28-31.

210. Smith RE, Godfrey WA, Kimura SJ. Complications of chronic cyclitis. *Am J Ophthalmol* 1976;82:277-282.
211. Ferris FL, Patz A. Macular edema. A complication of diabetic retinopathy. *Surv Ophthalmol* 1984;28:452-461.
212. Patz A, Schatz H, Berkow JW, et al. Macular edema-an overlooked complication of diabetic retinopathy. *Trans Am Acad Ophthalmol Otolaryngol* 1973;77:34-42
213. Scott DJ, Dollery CT, Hill DW, et al. Fluorescein studies of the retinal circulation in diabetes. *Br J Ophthalmol* 1963;47:588-589.
214. Friberg TR, Landers MC III. Aphakic cystoid macular edema after branch artery occlusion. *Ophthalmic Surg* 1980;11:192-193.
215. Gass JD. A fluorescein angiographic study of macular dysfunction secondary to retinal vascular disease. II. Retinal vein obstruction. *Arch Ophthalmol* 1968;80:550.
216. Gutman FA, Zegarra H. Macular edema secondary to occlusion of the retinal veins. *Surv Ophthalmol* 1984;28:462-470.
217. Hill DW. Fluorescein studies in retinal vascular occlusion. *Br J Ophthalmol* 1968;52:1-12.
218. Jensen VA. Clinical studies of tributary thrombosis in the central retinal vein. *Acta Ophthalmol* 1936;10:1-193.
219. Haas J. Uber das Zusammenvorkommen von Vernaderungen der Retina und Chorioidea. *Arch Augenheilkd* 1898;37:343-348.
220. Trese MT, Foos RY. Infantile cystoid maculopathy. *Br J Ophthalmol* 1980;64:206-210.
221. Michels RG, Ryan SJ Jr. Results and complications of 100 consecutive cases of pars plana vitrectomy. *Am J Ophthalmol* 1975;80:24-31.
222. Meyers SM. Macular edema after scatter laser photocoagulation for proliferative diabetic retinopathy. *Am J Ophthalmol* 1980;90:210-219.
223. Morse PH, Smith VC, Pokorny JM, et al. Fundus flavimaculatus with cystoid macular changes and abnormal Stiles-Crawford effect. *Am J Ophthalmol* 1981;91:190-196.
224. Chopdar A. Annular choroidal sclerosis. *Br J Ophthalmol* 1976;60:512-516.
225. Feldman RB, Mayo SS, Robertson DM, et al. Epiretinal membranes and cystoid macular edema in gyrate atrophy of the choroid and retina. *Retina* 1989;9:139-142.
226. Clarkson JG, Green WR, Massof D. Histopathologic review of 168 cases of preretinal membrane. *Am J Ophthalmol* 1977;84:1-17.
227. Steinmetz RL, Fitzke FW, Bird AC. Treatment of cystoid macular edema with acetazolamide in a patient with serpiginous choroidopathy. *Retina* 1991;11:412-415.
228. Deutman AF, Pinckers AJLG, Aan de Kerk AL. Dominantly inherited cystoid macular edema. *Am J Ophthalmol* 1976;82:540-548.
229. Fishman GA, Goldberg MF, Trautmann JC. Dominantly inherited cystoid macular edema *Ann Ophthalmol* 1979;11:21-27.
230. Notting JGA, Pinckers AJLG. Dominant cystoid macular dystrophy. *Am J Ophthalmol* 1977;83:234-241.
231. Pinckers A, Deutman AF, Notting JGA. Retinal functions in dominant cystoid macular dystrophy. *Acta Ophthalmol* 1976;54:579-582.
232. Fraunfelder FW, Fraunfelder FT, Illingworth DR. Adverse ocular effects associated with niacin therapy. *Br J Ophthalmol* 1995;79:54-56.
233. Gass JDM. Nicotinic acid maculopathy. *Am J Ophthalmol* 1973;76:500-503.
234. Jampol LM. Niacin maculopathy. *Ophthalmology* 1988;95:1704-1705.
235. Millay RH, Klein ML, Illingworth DR. Niacin maculopathy. *Ophthalmology* 1988;95:930.
236. Burns RP, Lovrien EW, Cibis AB. Juvenikle sex-linked retinoschisis: Clinical and genetic studies. *Trans Am Acad Ophthalmol Otolaryngol* 1971;75:1011-1019.
237. Berlin R. Zur Sogenannten Commotio Retinae. *Klin Augenheilkd Monatsbl* 1873;11:42-51.
238. Liem ATA, Keunen JEE, van Norren D. Reversible cone photoreceptor injury in com-

motio retinae of the macula. *Retina* 1995;15:58-61.
239. Mansour AM, Green WR, Hogge C. Histopathology of commotio retinae. *Retina* 1992;12:24-28.
240. Jaffe NS. Macular retinopathy after separation of vitreoretinal adherence. *Arch Ophthalmol* 1967;78:585-591.
241. Reese AB, Jones IS, Cooper WC. Macular changes secondary to vitreous traction. *Trans Am Ophthalmol Soc* 1966;64:123-134.
242. Reese AB, Jones IS, Cooper WC. Vitreomacular traction syndrome confirmed histologically. *Am J Ophthalmol* 1970;69:975-977.
243. Reese AB. In discussion of Gass JDM, Norton EWD. Follow-up study of cystoid macular edema following cataract extraction. *Trans Am Acad Ophthalmol Otolaryngol* 1969;73:681-682.
244. Schepens CL, Avila MP, Jalkh AE, et al. Role of the vitreous in cystoid macular edema. *Surv Ophthalmol* 1984;28:499-504.
245. Nicholls JVV. Concurrence of macular edema with cataract extraction. *Arch Ophthalmol* 1956;55:595-604.
246. Kottow M, Hendrickson P. Iris Angiography in cystoid macular edema after cataract extraction. *Arch Ophthalmol* 1975;93:487-493.
247. Maumenee AE. Further advances in the study of the macula. *Arch Ophthalmol* 71967;8:152-165.
248. Welch RB, Cooper JC. Macular edema, papilledema and optic atrophy after cataract extraction. *Arch Ophthalmol* 1958;59:665-675.
249. Dunnington JH, Regan EF. Late fistulization of operative wounds: Diagnosis and treatment. *Trans Am Ophthalmol Soc* 1949;47:63-76.
250. Duke-Elder WS. *System of Ophthalmology. Vol IX Diseases of the Uveal Tract*. London: Henry Kimpton; 1971:213-215.
251. McEntyre JM. A successful treatment for aphakic cystoid macular edema. *Ann Ophthalmol* 1978;10:1219-1224.
252. Dellaporte A. Fundus changes in postoperative hypotony. *Am J Ophthalmol* 1955;40:781-789.
253. Binkhorst CD. Corneal and retinal complications after cataract extraction: The mechanical aspect of endophthalmodonesis. *Ophthalmology* 1980;87:609-617.
254. Bito LZ. Prostaglandins: Old concepts and new perspectives. *Arch Ophthalmol* 1987;105:1036-1039.
255. Chandler PA. Complications after cataract extraction:clinical aspects. *Trans Am Acad Ophthalmol Otolaryngol* 1954;58:382-396.
256. Dugel PU, Rao NA, Ozler S, et al. Pars plana vitrectomy for intraocular inflammation-related cystoid macular edema unresponsive to corticosteroids: A preliminary study. *Ophthalmology* 1992;99:1535-1541.
257. Federman JL, Annesley WH Jr, Sarin LK, et al. Vitrectomy and cystoid macular edema. *Ophthalmology* 1980;87:622-628.
258. Miyake K, Sugiyama S, Norimatsu I, et al. Aqueous prostaglandins in persistent cystoid macular edema secondary to vitreous incarceration: Effects of pars plana vitrectomy. *Jpn J Ophthalmol* 1980;24:335-345.
259. Miyake K, Sugiyama S, Norimatsu I, et al. Prevention of cystoid macular edema after lens extraction by topical indomethacin (III). Radioimmunoassay measurement of prostaglandins in the aqueous during and after lens extraction procedures. *Graefes Arch Klin Exp Ophthalmol* 1978;209:83-88.
260. Neufeld AH, Jampol LM, Sears ML. Aspirin prevents the disruption of the blood-aqueous barrier in the rabbit eye. *Nature* 1972;238:158-159.
261. Peyman GA, Bennett TO, Vlchek J. Effects of intravitreal prostaglandins on retinal vasculature. *Ann Ophthalmol* 1975;7:279-288.

262. Podos SM. Prostaglandins, nonsteroidal anti-inflammatory agents and eye disease. *Trans Am Ophthalmol Soc* 1976;74:637-660.
263. Rao NA, Patchett R, Fernandez MA, et al. Treatment of experimental granulomatous uveitis by lipoxygenase and cyclo-oxygenase inhibitors. *Arch Ophthalmol* 1987;105:413-415.
264. Sanders MD. Retinal vasculitis. A review. *J R Soc Med* 1979;72:908-915.
265. Tsukahara S, Kohda N. The effects of prostaglandins on the blood-ocular barrier: II Blood-retinal barrier. *Acta Soc Ophthalmol Jpn* 1977;81:193-198.
266. Katz I. Indomethacin. *Ophthalmology* 1981;88:455-458.
267. Miyake K. Indomethacin in the treatment of postoperative cystoid macular edema. *Surv Ophthalmol* 1984;28:554-568.
268. Miyake K, Asakura M, Kobayashi H. Effect of intraocular lens fixation on the blood-aqueous barrier. *Am J Ophthalmol* 1984;98:451-455.
269. Podos SM, Becker B, Kass MA. Prostaglandin synthesis, inhibition and intraocular pressure. *Invest Ophthalmol* 1973;12:426-433.
270. Tennant JL. Is cystoid macular edema reversible by oral indomethacin, yes or no? In: Emery JM and Paton D, eds. *Current Concepts in Cataract Surgery. Selected Proceedings of the Fourth Biennial Cataract Surgical Congress*. St Louis: Mosby; 1976:310-312.
271. Van Haeringen NJ, Glasius E, Oosterhuis JA, et al. Drug prevention of blood-aqueous barrier disruption. *Ophthalmic Res* 1983;15:180-184.
272. Worst JGF. Biotoxizitat des Kammerwassers. Eine vereinheitlichende pathologische Theorie, begrundet auf hypothetische biotoxische Kammerwasserfaktoren. *Klin Monatsbl Augenheilkd* 1975;167:376-384.
273. Yamaaki H, Hendrikse F, Deutman AF. Iris angiography after cataract extraction and the effect of indomethacin eye drops. *Ophthalmologica* 1984;188:82-86.
274. Yannuzzi LA, Wallyn RH. Cystoid macular edema. A controlled treatment study utilizing indomethacin. In: Emery JM, Paton D, eds. *Current Concepts in Cataract Surgery. Selected Proceedings of the Fourth Biannual Cataract Surgical Congress*. St Louis: Mosby; 1976:313-316.
275. Baikoff G, Bechetoille A, Colin J, et al. Medallion intra-ocular lenses and fluorography of the anterior chamber. *J Fr Ophtalmol* 1980;3:165-169.
276. Yoshinao M, Hidetoshi N. Fluorophotometry of the intraocular barrier in aphakia and pseudophakia. *Cataract* 1984;25:12-15.
277. Miyake K. Vitreous fluorophotometry in aphakic or pseudophakic eyes with persistent cystoid macular edema. *Jpn J Ophthalmol* 1985;29:146-152.
278. Rao NA. Role of oxygen free radicals in retinal damage associated with experimental uveitis. *Trans Am Ophthalmol Soc* 1990;88:797-850.
279. Flach AJ. Nonsteroidal anti-inflammatory drugs. In: Tasman W, Jaeger EA, eds. *Duane's Foundations of Clinical Ophthalmology*. Philadelphia: Lippincott; 1994:1-32.
280. Blair NP, Elman MJ, Rusin MM. Vitreous fluouophotometry in patients with cataract surgery. *Graefes Arch Clin Exp Ophthalmol* 1987;225:441-446.
281. Burnett J, Tessler H, Isenberg S, et al. Double-masked trial of fenoprofen sodium: Treatment of chronic aphakic cystoid macular edema. *Ophthalmic Surg* 1983;14:150-152.
282. Vannas A. Fluorescein angiography of the vessels of the iris in pseudoexfoliation of the lens capsule, capsular glaucoma and some other forms of glaucoma. *Acta Ophthalmol Suppl* 1969;105:28-75.
283. Flach AJ. Cyclo-oxygenase inhibitors in ophthalmology. *Surv Ophthalmol* 1992;36:259-284.
284. Flach AJ. Nonsteroidal anti-inflammatory drugs in ophthalmology. *Int Ophthalmol Clin* 1993;33:1-7.

285. Flach AJ. Ophthalmic treatment of postoperative inflammation. *J Toxicol Cut Ocular Toxicol* 1991;10:253-277.
286. Flach AJ, Graham J, Kruger LP, et al. Quantitative assessment of postsurgical breakdown of the blood-aqueous barrier following administration of 0.5% ketorolac tromethamine solution.A double-masked, paired comparison with vehicle-placebo solution study. *Arch Ophthalmol* 1988;106:344-347.
287. Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. *Am J Ophthalmol* 1959;47:155-170.
288. Steinert RF, Wasson PJ. Neodymium YAG laser anterior vitreolysis for Irvine-Gass cystoid macular edema. *J Cataract Refract Surg* 1989;15:304-307.
289. Zweng HC, Little HL, Peabody RR. Laser photocoagulation of macular lesions. *Trans Am Acad Ophthalmol Otolaryngol* 1968;72:377-388.
290. Aaberg TM. Pars plana vitrectomy for persistent aphakic cystoid macular edema secondary to vitreous incarceration in the cataract wound. In: McPherson A, ed. *New and Controversial Aspects of Vitrectomy Surgery*. St Louis: Mosby; 1977:230-239.
291. Bonnet M, Bievelez B. Fluorescein angiography of the iris and Irvine-Gass syndrome (selection of indications for anterior vitrectomy) *Bull Soc Ophtalmol Fr* 1981;81:1001-1003.
292. Federman JL, Annesley WH, Sarin LK, et al. Vitrectomy and cystoid macular edema. *Ophthalmology* 1980;87:622-628.
293. Fung WE, Vitrectomy-ACME Study Group. Vitrectomy for chronic aphakic cystoid macular edema. Results of a national, collaborative, prospective, randomized investigation. *Ophthalmology* 1985;92:1102-1111.
294. Fung WE. Surgical therapy for chronic aphakic cystoid macular edema. *Ophthalmology* 1982;89:898-901.
295. Fung WE. Anterior vitrectomy for chronic aphakic cystoid macular edema. *Ophthalmology* 1980;87:189-193.
296. Fung WE. The national, prospective, randomized vitrectomy study for chronic aphakic cystoid macular edema. Progress report and comparison between the control and nonrandomized groups. *Surv Ophthalmol* 1984;28:569-576.
297. Harbour JW, Smiddy WE, Rubsamen PE, et al. Pars plana vitrectomy for chronic pseudophakic cystoid macular edema. *Am J Ophthalmol* 1995;120:302-307.
298. Ho PC, Tolentino FI. The role of vitreous in aphakic cystoid macular edema: A review. *Am Intraoc Implant Soc J* 1982;8:258-264.
299. Patel A, De Bustros S, Michels RG. Pars plana vitrectomy for aphakic cystoid macular edema. *Retina* 1985;5:11-15.
300. Patel A, de Bustros S, Michels RG. Pars plana vitrectomy for aphakic cystoid macular edema. *Retina* 1985;5:11-15.
301. Sebag J, Balaz EA. Pathogenesis of cystoid macular edema: An anatomic consideration of vitreoretinal adhesions. *Surv Ophthalmol* 1984;28:493-498.
302. Suga K, Okuda T, Shinomiya S, et al. Anterior vitrectomy for cystoid macular edema following cataract surgery. *Jpn J Clin Ophthalmol* 1980;34:1347-1354.
303. Young PW, Shea M. Pars plana vitrectomy in the management of the Irvine-Gass syndrome. *Can J Ophthalmol* 1980;15:172-175.
304. Fechner PU. Intraokularlinsen. Grundlagen und Operationslehre. Kapitel 12. Das zystoide Makulaodem. *Bucherei Augenarztes Heft* 1980;82:71-76.
305. Gartner S. Optic neuritis and macular edema following cataract extraction. *Eye Ear Nose Throat Monthly* 1964;43:45-49.
306. O'Connor GR. Periocular corticosteroid injections: Uses and abuses. *Eye Ear Nose Throat Monthly* 1976;55:83-88.
307. Abelson MB, Smith LM, Ormerod D. Prospective, randomized trial of oral piroxicam in the prophylaxis of postoperative cystoid macular edema. *J Ocular Pharmacol*

1989;5:147-153.
308. Fechner PU. Die prophylaxe des zystoiden Makulaodems mit indomethacin-Augentropfen. *Klin Monatsbl Augenheilkd* 1980;180:169-174.
309. Ginsburg AP, Cheetham JK, De Gryse RE, et al. Effects of flurbiprofen and indomethacin on acute cystoid macular edema after cataract surgery: Functional vision and contrast sensitivity. *J Cataract Refract Surg* 1995;21:82-92.
310. Hollwich F, Jocobi K, Kuchle HJ, et al. Zur Prophlaxe des zyztoiden maculaodems mit Indomethacin-Augentropfen. *Klin Monatsbl Augenheilkd* 1983;183:477-478.
311. Quentin CD, Behrens-Bauman W, Gans W. Prevention of cystoid macular edema with diclofenac eyedrops in intracapsular cataract extraction using the Choyce Mark IX anterior chamber lens. *Fortschr Ophthalmol* 1989;86:546-549.
312. Shammas HJF, Milkie CF. Does aspirin prevent postoperative cystoid macular edema? *Am Intraoc Implant Soc J* 1979;5:337.
313. Sholiton DB, Reinhart WJ, Frank KE. Indomethacin as a means of preventing cystoid macular edema following intracapsular cataract extraction. *Am Intraoc Implant Soc J* 1979;5:137-140.
314. Solomon LD, Flurbiprofen-CME Study Group I. Efficacy of topical flurbiprofen and indomethacin in preventing pseudophakic cystoid macular edema. *J Cataract Refract* Surg 1995;21:73-81.
315. Summary Basis of Approval for Profenal (Alcon's suprofen) subsequent to New Drug Application 19-387. Washington DC: Dept of Health and Human Services, Food and Drug Administration; 1989.
316. Yanuzzi LA, Klein RM, Wallyn RH, et al. Ineffectiveness of indomethacin in the treatment of chronic cystoid macular edema. *Am J Ophthalmol* 1977;84:517-519.
317. Yannuzzi LA, Landau AN, Turtz AI. Incidence of aphakic cystoid macular edema with the use of topical indomethacin. *Ophthalmology* 1981;88:947-954.
318. Cox SN, Hay E, Bird AC. Treatment of chronic macular edema with acetazolamide. *Arch Ophthalmol* 1988;106:1190-1195.
319. Farber MD, Lam S, Tessler HH, et al. Reduction of macular oedema by acetazolamide in patients with chronic iridocyclitis: A randomised prospective crossover study. *Br J Ophthalmol* 1994;78:4-7.
320. Fishman GA, Glenn AM, Gilbert LD. Rebound of macular edema with continued use of methazolamide in patients with retinitis pigmentosa. *Arch Ophthalmol* 1993;11:1640-1646.
321. Tripathi RC, Fekrat S, Tripathi BJ, et al. A direct correlation of the resolution of pseudophakic cystoid macular edema with acetazolamide therapy. *Ann Ophthalmol* 1991;23:127-129.
322. Ogura Y, Takahashi M, Ueno S, et al. Hyperbaric oxygen treatment for chronic cystoid macular edema after branch retinal vein occlusion. *Am J Ophthalmol* 1987;104:301-302.
323. Ploff DS, Thom SR. Preliminary report on the effect of hyperbaric oxygen on cystoid macular edema. *J Cataract Refract Surg* 1987;13:136-140.
324. Mizuno K, Miyake K. Pre- and postoperative therapy in cataract extraction. *Ophthalmic Surg* 1987;18:143-152.
325. Waitzman MB. Topical indomethacin in treatment and prevention of intraocular inflammation-with special reference to lens extraction and cystoid macular edema. *Ann Ophthalmol* 1979;11:489-491.
326. Bradford JD, Wilkinson CP, Bradford RH. Cystoid macular edema following extracapsular cataract extraction and posterior chamber intraocular lens implantation. *Retina* 1988;8:161-164.
327. Girard LJ. *Advanced Techniques in Ophthalmic Microsurgery. Vol 1. Ultrasonic Fragmentation for Intraocular Surgery*. St Louis: Mosby; 1979:149.

328. Fung WF. Cystoid macular edema (CME, cystoid maculopathy, Irvine-Gass syndrome). In: Fraunfelder FT, Roy FH, Meyer SM, eds *Current Ocular Therapy*. Philadelphia: Saunders; 1990:624-627.
329. Shepard DD. The fate of eyes from which intraocular lenses have been removed. *Ophthalmic Surg* 1979;10:58-60.
330. Jampol LM, Sanders DR, Kraff MC. Prophylaxis and therapy of aphakic cystoid macular edema. *Surv Ophthalmol* 1984;28:535-539.
331. Brune K, Glatt M, Graf P. Mini review: Mechanisms of action of anti-inflammatory drugs. *Gen Pharmacol* 1976;7:27-33.
332. Mishima S, Tanishima T, Masuda K. Pathophysiology and pharmacology of intraocular surgery. *Aust NZ J Ophthalmol* 1985;13:147-158.
333. Sanders DR, Kraff MC, Lieberman HL, et al. Breakdown and re-establishment of the blood-aqueous barrier following implant surgery. *Arch Ophthalmol* 1982;100:588-590.
334. Sanders DR, Kraff MC. Steroidal and nonsteroidal anti-inflammatory agents. Effects on postsurgical inflammation and blood-aqueous barrier breakdown. *Arch Ophthalmol* 1984;102:1453-1456.
335. Flach AJ, Jaffe NS, Akers WA, et al. The effect of ketorolac 0.5% solution in reducing postoperative inflammation: Double-mask, parallel comparison with dexamethasone phosphate 0.1% solution. *Ann Ophthalmol* 1989;21:407-411.
336. Flach AJ, Kraff MC, Sanders DR, et al. The quantitative effect of 0.5% ketorolac tromethamine solution and dexamethasone phosphate 0.1% solution on postsurgical blood-aqueous barrier. *Arch Ophthalmol* 1988;106:480-483.
337. Conquet PH, Plazonnet B, LeDourarec JC. Arachidonic acid-induced elevation of intraocular pressure and anti-inflammatory agents. *Invest Ophthalmol* 1975;14:772-775.
338. Sanders DR, Goldstick B, Kraff C, et al. Aqueous penetration of oral and topical indomethacin in humans. *Arch Ophthalmol* 1983;101:1614-1616.
339. Weisweiler PS, Barnett PS, Chen K, et al. Comparative comfort of flurbiprofen solution and indomethacin suspension eyedrops. *J Clin Res Drug Devel* 1988;2:233-239.
340. Kraff MC, Sanders DR, Peyman GA, et al. Slit-lamp fluorophotometry in intraocular lens patients. *Ophthalmology* 1980;87: 877-880.
341. Flach AJ, Lavelle CJ, Olander KW, et al. The effect of ketorolac 0.5% solution in reducing postsurgical inflammation following extracapsular cataract extraction with an intraocular lens: Double-masked, parallel comparison with vehicle. *Ophthalmology* 1988;75:1279-1284.
342. Sanders DR, Spigelman A, KraffC, et al. Quantitative assessment of postsurgical braakdown of the blood-aqueous barrier. *Arch Ophthalmol* 1983;101:131-133.
343. Sanders DR, Kraff MC, Leiberman HL, et al. Breakdown and re-establishment of blood-aqueous barrier with implant surgery. *Arch Ophthalmol* 1982;100:588-590.
344. Huang K, Peyman GA, McGetrick J, et al. Indomethacin inhibition of prostaglandin-mediated inflammation following intraocular surgery. *Invest Ophthalmol Vis Sci* 1977;16:760-762.
345. Podos SM, Becker B. Comparison of ocular prostaglandin synthesis inhibitors. *Invest Ophthalmol* 1976;15:841-844.
346. Van Haeringen NJ, Oosterhuis JA, Van Delft JL, et al. A comparison of the effects of non-steroidal compounds on the disruption of the blood-aqueous barrier. *Exp Eye Res* 1982;35:271-277.
347. Spalton DJ. Ocular fluorophotometry. *Br J Ophthalmol* 1990;74:431-432.
348. Drews RC. Management of postoperative inflammation: Dexamethasone versus flurbiprofen, a quantitative study using the new flare cell meter. *Ophthalmic Surg* 1990;21:560-562.
349. Ni M, Bloom JN, Lele S, et al. A laboratory evaluation of the Kowa laser flare-cell meter

for the study of uveitis. *Graefes Arch Clin Exp Ophthalmol* 1992;230:547-551.
350. Oshika T, Nishi M, Mochizuki M, et al. Quantitative assessment of aqueous flare and cells in uveitis. *Jpn J Ophthalmol* 1989;33:279-287.
351. Ohara K, Okubo A, Miyazawa A, et al. Aqueous flare and cell measurement using laser in endogenous uveitis patients. *Jpn J Ophthalmol* 1989;33:265-270.
352. Sawa M, Tsurimaki Y, Tsuru T, et al. New quantitative method to determine protein concentration and cell number in aqueous in vivo. *Jpn J Ophthalmol* 1988;32:132-142.
353. Sawa M. Clinical application of laser flare-cell meter. *Jpn J Ophthalmol* 1990;34:346-363.
354. Shah SM, Spalton DJ. Changes in anterior chamber flare and cells following cataract surgery. *Br J Ophthalmol* 1994;78:91-94.
355. Shah SM, McHugh JD, Spalton DJ. The effects of subconjunctival betamethasone on the blood aqueous barrier following cataract surgery: a double-blind randomised prospective study. *Br J Ophthalmol* 1992;76:475-478.
356. Shah SM, Spalton DJ, Smith SE. Measurement of aqueous cells and flare in normal eyes. *Br J Ophthalmol* 1991;75:348-352.
357. Yoshitomi T, Wong AS, Daher E, et al. Aqueous flare measurement with laser flare-cell meter. *Jpn J Ophthalmol* 1990;34:57-62.
358. Flach AJ. Factors associated with improvement in vision during treatment of cystoid macular edema following cataract surgery. *Invest Ophthalmol Vis Sci* 1993;34:2285.
359. Schwartz B. Physiological effects of corticosteroids on the eye. In: Schwartz B, ed. *Corticosteroids and the Eye*. Boston: Little Brown; 1980:753.
360. Davis JC, Dunn JM, Heimbach RD. Hyperbaric medicine: Patient selection, treatment porcedures, and side-effects. In: Davis JC, Hunt TK, eds. *Problem Wounds The Role of Oxygen* New York: Elsevier; 1990:225-235.
361. Herbstein K, Murchland JB. Retinal vascular changes after treatment with hyperbaric oxygen. *Med J Australia* 1984;140:728-729.
362. Kobayashi T, Murakami S. Blindness of an adult caused by oxygen. *JAMA* 1972;219:741-742.
363. Lyne AJ. Ocular effects of hyperbaric oxygen. *Trans Ophthalmol Soc UK* 1978;98:66-68.
364. Jampol LM. Oxygen therapy and intraocular oxygenation. *Trans Am Ophthalmol Soc* 1987;85:407-437.
365. Marmor MF. Hypothesis concerning carbonic anhydrase treatment of cystoid macular edema: Example with epiretinal membrane. *Arch Ophthalmol* 1990;108:1524-1525.
366. Marmor MF, Maack T. Enhancement of retinal adhesion and subretinal fluid absorption by acetazolamide. *Invest Ophthalmol Vis Sci* 1982;23:121-124.
367. Miyake Y, Awaya S, Takahashi H, et al. Hyperbaraic oxygen and acetazolamide improve visual acuity in patients with cystoid macular edema by different mechanisms. *Arch Ophthalmol* 1993;111:1605-1606.
368. Flach AJ. Topical acetazolamide and other carbonic anhydrase inhibitors in the medical therapy of the glaucomas. *Glaucoma* 1986;8:20-27.
369. Flach AJ, Smith RE, Fraunfelder FT. Stevens-Johnson syndrome associated with methazolamide treatment reported in two Japanese-American women. *Ophthalmology* 1995;102:1677-1680.
370. Caplan MJ, Stow JL, Newman AP, et al. Dependence on pH of polarized sorting of secreted proteins. *Nature* 1987;329:632-648.
371. Lichter P. Carbonic anhydrase inhibitors. *Am J Ophthalmol* 1978;85: 495-503.
372. Lippa EA, Carlson LE, Ehinger B, et al. Dose response and duration of action of dorzolamide, a topical carbonic anhydrase inhibitor. *Arch Ophthalmol* 1992;110:495-499.
373. Strahlman ER, Tipping R, Vogel R, et al. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt) timolol and betaxolol. *Arch Ophthalmol*

1995;113:1009-1016.
374. Wilkerson M, Cyrlin M, Lippa EA, et al. Four-week safety and efficacy study of dorzolamide, a novel, active topical carbonic anhydrase inhibitor. *Arch Ophthalmol* 1993;111:1343-1350.
375. Dixon WJ, Massey FJ. *Introduction to Statistical Analysis*. 3rd ed. New York: McGraw-Hill; 1969.
376. Hollander M, Wolfe DA. *Nonparametric Statistical Methods*. New York: Wiley; 1973.
377. Winer BJ. *Statistical Principles in Experimental Design*. 2nd ed. New York: McGraw-Hill; 1971.
378. Green WH. *Econometric Analysis*. 2nd ed. New York: MacMillan; 1993:236-238.
379. Suits DB, Mason A, Chan L. Spline functions fitted by standard regression methods. *Rev Economics Statistics* 1993;132-139.