APHAKIC CYSTOID MACULAR EDEMA AND THE OPERATING MICROSCOPE: IS THERE A CONNECTION?

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INTRODUCTION

SINCE ITS FIRST DESCRIPTION IN THE EARLY 1950s,[1,2] AND ITS LATER CLASSICAL DESCRIPTION by Gass and Norton[3] in 1966, aphakic cystoid macular edema has been the subject of intense clinical and experimental investigations. However, despite numerous studies its exact nature and etiology remain obscure. Although much has been learned about its incidence and natural history in a wide variety of conditions and many theories have been proposed to explain it, there has been no agreement as to a definitive cause. Treatment has been empirical at best and has a distinct lack of uniform effectiveness.

In 1977, Henry et al[4] first suggested that aphakic cystoid macular edema might be caused by intense operating room lights or the light of the operating microscope. This suggestion was made on the basis of the apparent increase in incidence of macular edema with the coincidental increase in operating time, the use of brighter operating room lights and the introduction of the operating microscope to clinical practice, particularly during routine cataract extraction. Shortly thereafter, Hochheimer et al[5] and Calkins and Hochheimer[6] reported high levels of light emission from the operating microscope and experimentally produced macular burns in monkeys using the operating microscope. Subsequently Hochheimer[7] also suggested that this intense light might be a factor in the development of cystoid macular edema. Since then, particularly in the last 2 to 3 years, most discussions of cystoid macular edema in a variety of media have included some reference to light toxicity and the operating microscope.[8-12]

To my knowledge, no clinical study published to date suggests any correlation between cystoid macular edema and the operating microscope although preliminary data has been reported by Mannis and Becker[13] in a

letter prompted by Calkins and Hochheimer's report.[6] The current study was designed to investigate whether, in a routine cataract extraction with intraocular lens implantation, any suggestion could be found that cystoid macular edema is related to the use of the operating microscope and in particular to the blue light output of that instrument. Fluorescein angiography was used to evaluate patients following surgery using a microscope with and without a filter.

BACKGROUND: RETINAL PHOTOTOXICITY

DISCOVERY AND SEARCH FOR MECHANISMS

Until 1966 when Noell et al[14] reported the toxic effect of low levels of visible light on the retinas of rats, it was believed that retinal light damage was thermal in nature.[15,16] Noell's studies indicated that the action spectrum of this damage was in the visible light range; that the total retinal irradiance was too low to produce any significant temperature elevation of the retina; that repeated short exposures seemed to be additive in nature; and that increased body temperature produced a more severe lesion with similar total doses. Soon after, Friedman and Kuwabara[17] demonstrated visible retinal lesions in rhesus monkeys using an indirect ophthalmoscope and a relatively short exposure time (15 minutes). Major damage to both the retinal pigment epithelium and the outer segments of the photoreceptors resulted. They also confirmed that elevated body temperature reduced the damage threshold for a visible or histologically apparent retinal lesion. Since then, Kuwabara[18] using a rat model and Tso et al[19-21] using monkeys documented that there was evidence of retinal recovery from such damage. They contributed considerable light and electron microscopic histopathologic information about the location and response of the retina and retinal pigment epithelium to this injury.

Despite the fact that a number of these reports appeared in widely read clinical journals, the potential for retinal damage from the light sources of clinical instruments was either ignored or overlooked by clinicians for many years.

Re-evaluation of the retina irradiance associated with sun exposure[22-24] and a report of retinal injury from a welding arc[25] have suggested that not only sun gazing and eclipse blindness, but also rare cases of industrial light injury produce a phototoxic rather than thermal retinal injury.

The well executed studies of Ham et al[26-29] Ruffolo et al[30] and Lawwill et al[31-33] using primate models, demonstrated that not only the near ultraviolet but, more importantly, blue light (between approximately 400

nm and 500 nm) was much more damaging than longer wavelength light. Ham et al[26,27] demonstrated the blue light hazard (441.6 nm) and suggested for perhaps the first time the potential clinical significance for patients exposed to bright sunlight over long periods of time. They recommended precautions to shield the eyes from short wavelengths of solar radiation because of the possible significance for certain retinal pathologic conditions including age-related macular degeneration and retinitis pigmentosa. This has implications in the design of sunglasses and welders' goggles.

Lawwill et al,[31] using a primate model of chronic light exposure with both white light and several isolated laser-produced wavelengths, suggested that there was more than one mechanism of damage production which was not dependent on visual pigment and retinal pigment epithelium as Noell et al[14] had suggested. They found that short wavelength light was definitely more damaging than longer wavelengths and that damage can occur in all retinal layers although at threshold levels the outer segments seemed to be more sensitive. This certainly did not represent only a receptor phenomenon and it was noted that receptors were not necessarily affected before other layers. These findings suggested that the damaging light was being absorbed throughout the retina. It was further noted that the threshold for measurable permanent damage is surprisingly close to some everyday viewing conditions; this raised an important question. Could a lifetime of high light level exposure potentiate senile macular degeneration in susceptible people?

Subsequently Lawwill,[33] in an extensive review of a large primate investigation, outlined three major mechanisms of phototoxic retinal damage. These include a rhodopsin specific lesion which is the basic effect discovered by Noell et al[14] which documented rat retinal sensitivity peaking in the center of the visual spectrum. The second mechanism reviewed by Lawwill[33] was cone pigment specific. This process had previously been elucidated by Sperling et al[34] in reports of selective loss of sensitivity to the blue and green parts of the spectrum after intermittent repeated exposure to intense light (blue blindness). It was believed that this represented wavelength selective damage to cones sensitive to those wavelengths and that the mechanism involved repeated partial bleaching and recovery with differential absorption of light in those cones' photopigments. They found, as previously noted,[14,17,31] that exposure to steady light of similar wavelengths produced a different histologic picture. This mechanism is seen in combination with Lawwill's third mechanism, the short wavelength light effect. This mechanism has an action spectrum peaking in the short wavelength, blue end of the visual spectrum. All

layers of the retina are affected from the pigment epithelium to the nerve fiber layer. Lawwill's hypothesis[33] was that this effect is caused by a direct action of light on the mitochondria of different retinal layers. This produces inactivation of respirating enzymes which, if extensive enough in an individual cell, leads to cell death.

Recently, Ham et al[29] and Ruffolo et al[30] have suggested a possible basic mechanism to produce such damage. It has been noted by Feeney and Berman[35] and others, that oxygen toxicity with membrane damage by free radicals and light damage may have a common mechanism. The light-induced production of highly reactive free radicals and some of the mechanisms by which ocular tissues deal with them was reviewed. The data provided by Ham et al[29] and Ruffolo et al[30] demonstrated a marked reduction in the threshold for production of photochemical lesions in the presence of elevated oxygen levels in both *in vivo* and *in vitro* studies. This strongly suggests that damage by free radicals may be the basic mechanism for the production of photochemical lesions in the mammalian retina. Additionally, they showed apparent protection by known free radical stabilizers such as vitamin E and carotenes as well as some protection by intravenous corticosteroids. As they point out, this work needs to be extended in many directions and it is difficult to correlate this data to the human situation but it provides exciting new insight into at least one aspect of phototoxicity.

This finding may be of clinical importance in patients undergoing surgical procedures under conditions of elevated oxygen tension such as general anesthesia. Experimentally, Ham et al[29] found that an elevation of the arterial Po_2 by a factor of 3 in monkeys led to a corresponding decrease in radiant exposure threshold by a nearly identical factor.

FUNDUS PICTURE

The ophthalmoscopically observable as well as histologic retinal response to phototoxic insult varies widely. It depends on the species, wavelength of the source, the source radiance, pupil size, ocular transmission and scatter (thus retinal irradiance) and other factors.

As noted by Gladstone and Tasman,[36] solar retinitis, which has been recognized since antiquity and has been reported after both purposeful and accidental exposure, now appears to be a phototoxic rather than thermal lesion.[23,24,37] This exposure produces a yellow foveal exudate and macular edema, possibly with small foveolar cysts. Fluorescein angiography may show a slight hyperfluorescence in the foveolar area. With time, recovery is the rule, but small hyperpigmented lesions with tiny

associated scotomata may persist. In severe cases there is permanent visual loss.

Naidoff and Sliney[25] have reported a case of foveal injury from a prolonged exposure to a welding arc. Ophthalmoscopic examination showed a bright yellow foveal lesion situated deep in the retina which was about ¼ disc diameter in size and surrounded by pale yellow macular edema. The lesion gradually resolved with the development of pigment granules centrally in the macula and the disappearance of the pale yellow edematous area. This lesion was first observed 2 days following the insult. It was not known when visual symptoms related to the retinal injury first developed, but vision recovered to near normal levels.

Retinal lesions produced experimentally vary widely, again depending on the experimental situation, but they have in common a delay in their appearance from several hours to 2 days in contradistinction to a thermal lesion (such as produced by high energy lasers) which appears immediately. These lesions consist initially of variable degrees of retinal edema which gradually subsides and is usually followed by an area of irregular pigmentation, occasionally with a halo. Tso et al[19] noted that some eyes developed a slightly raised lesion centrally. With time, some lesions gradually diminished in size and the degree of pigmentation stabilizes. Occasional irregularity of the retinal surface has been noted.[19,33] No changes are generally seen in the optic nerve head or retinal vasculature.[33] Lawwill[33] performed fluorescein angiography on some animals and showed that window defects developed which persisted as long as the animals were followed. There was little evidence of fluorescein leakage but extensive late staining was common. It was believed that this occurred in the area of damage and was related to loss of pigment epithelial integrity. The retinal vasculature was not affected and there was no obvious leakage of fluorescein from the retinal vessels.

HISTOLOGIC CHANGES

Although damage is seen in all retinal layers, it is most striking in the pigment epithelium and outer segment areas. Damage to the pigment epithelium ranges from minor vacuolization and edema to the early presence of phagocytes and increase in lysosomes, followed by loss or distortion of pigment and finally to absence of the pigment epithelium, increasing phagocytosis and dead cells. The outer segments in the minimal stages show slight swelling or disorientation while in advanced stages they progress to more severe degrees of swelling, bizarre forms, and necrosis with final loss of the outer segments.

Tso and colleagues,[19-21] have described in detail electron microscopic changes. They noted disruption of the inner and outer segments of photoreceptor cells and the development of vacuoles and tubules in the photoreceptor lamellae. The invasion of macrophages in later stages with phagocytosis of cellular debris from necrotic pigment epithelium and damaged photoreceptor cells was noted. With the increasing macrophagic response, there was progressive depigmentation of the retinal pigment epithelium despite apparent activity of the remaining cells. Some new basement membrane was laid down and Tso et al[19] reported a placoid proliferation of retinal pigment epithelium in the center of lesions which appeared similar to that described as "fibrous metaplasia" in man. The spindle-shaped cells in the plaque were identified as modified retinal pigment epithelium. Although these plaques bore some resemblance to lesions seen in human macular degeneration, no invasion of blood vessels into the subretinal area was seen. Three to 5 months after exposure, regenerated photoreceptor cells were noted containing numerous tubules and vesicles suggesting unusually active metabolic processes. In a later work Tso and Fine[38] showed microcystic retinal edema 4 years after light exposure. However, the pathology of cystoid macular edema has been well described[39,40] and there is no similarity to phototoxic retinal lesions[41] such as those produced by Tso and Fine.[38]

In an attempt to develop an animal model of cystoid macular edema, Tso[41] and Tso and Woodford[42] carried out experiments with photic and other forms of injury. In spite of disruption of the blood-retinal barrier at the retinal pigment epithelium which persisted for years, no cystoid macular edema could be produced. In fact, none of the major studies of photic damage have produced a pattern of retinal edema resembling cystoid macular edema in humans. However, considerable clinical concern has arisen about such a possible connection.

THE OPERATING MICROSCOPE

Cystoid macular edema is one of the most studied of ophthalmic diseases with innumerable articles and annual symposia devoted to its investigation. Since its first description in the early 1950s, it has become a complication of major concern to cataract surgeons because its cause(s) is far from fully understood and treatments are not as successful as we would like.

Although the operating microscope was available for many years, it was not used routinely for cataract surgery until the early 1970s with the dawn of the age of "microsurgery." In 1976, Henry et al[4] suggested a possible connection between the operating microscope and cystoid macular ede-

ma. In their clinical observations they felt the probable causes or contributing factors to the development of chronic cystoid macular edema were an increase in operating time associated with the use of the operating microscope and fine monofilament sutures, and bright operating room lights and the light from the microscope. They noted an increase in the incidence of cystoid macular edema in their cases with these surgical changes. Although, as noted, there was no suggestion of cystoid macular edema in animal experiments, their recognition of a possible phototoxic effect on humans led to this very important possible correlation. They pointed out that the exposure levels required to produce lesions in animals were far less than the actual clinical exposures in humans and that research was essential to determine what constitutes a "safe" amount of light exposure. To reduce the amount of exposure, they suggested covering the pupil during wound closure when viewing the interior of the eye was unnecessary.

In 1979, Calkins and Hochheimer[6] reported measurements of light output from several popular surgical microscopes and devised a means for calculating a patient's retinal exposure from these instruments. New findings indicated that retinal irradiance was surprisingly high assuming the worst case situation of clear media, dilated pupils and a stationary eye. They demonstrated that the irradiance ranged from 0.10 to 0.87 W/cm^2, 1 to 10 times higher than that produced by an indirect ophthalmoscope.[17,43] Friedman and Kuwabara[17] in 1968 reported that only 15 minutes of exposure from an indirect ophthalmoscope produced a significant phototoxic injury. Calkins and Hochheimer's measurements of six microscopes available at the Wilmer Institute showed a moderate variation in retinal irradiance related to whether external fiberoptics or an internal bulb was used and to the exact optics of the individual instruments.[6] They used the American National Standards Institute laser safety guidelines to calculate a theoretical maximum permissible exposure and, from that, a "safe time" and thresholds for visible retinal change. While they admitted that these guidelines might not be appropriate for noncoherent (white) light sources, they pointed out that there was ample evidence in the literature to suggest that these standards might be too conservative. Surprisingly, the calculations showed a "safe time" for the different microscopes ranging from less than 10 seconds to 49 seconds. This correlated with a threshold time for a 50% chance of developing a retinal lesion (assuming a direct correlation is made to experimental lesions in monkeys) of 5 to 82 minutes. They summarized by stating "the average microscope produces over five times greater retinal irradiance than does the average indirect ophthalmoscope.[44] The same level reached by an average indirect oph-

thalmoscope on a medium voltage setting at 15 minutes (61 Joules/cm^2) is reached by operating microscope 6 after only 1 minute (worst case conditions are assumed for both instruments)."[6] They recommended a change in microscope design to allow extending safe time to perhaps 45 minutes and to eliminate as much of the blue end of the spectrum as possible without interfering with useful visibility. Additionally, as did Henry et al,[4] they suggested covering the cornea with opaque material during wound closure and noted that merely turning down the power of the microscope did not sufficiently decrease the retinal irradiance to consider the situation safe.

In a later report, Hochheimer[7] expanded on the theory that the operating microscope per se represented a cause of chronic cystic maculopathy. Although there was no direct clinical or experimental evidence, Hochheimer supported his theory by noting that aphakic cystic maculopathy and the operating microscope appeared at about the same time. He pointed out that there is considerable evidence that the operating microscope can produce retinal damage, citing from his experience[5] as well as the wealth of previously cited experimental data which used light sources producing comparable retinal irradiance. He noted that light can produce cystic changes in the retina. Support for this comes from Tso and Fine[38] in which cystoid changes in the outer plexiform layer were noted 4 years following light injury. The cystic changes consisted of enlargements of the intracellular spaces and were not noted on fluorescein angiogram 2¼ years following the insult in Tso's study. Later Tso[41] specifically attempted to produce cystoid macular edema using a photic injury. Although fluorescein leakage was produced from disruption of the blood-retinal barrier at the retinal pigment epithelium, no cystoid spaces were formed. He pointed out that this experiment further illustrated the distinct clinical pathologic differences between cystoid macular edema and photic maculopathy. Hochheimer[7] went on to note that light damage and aphakic edema initially develop in the parafoveal area and that solar retinitis produces similar retinal changes.

Although there was no direct evidence supporting his theory, Hochheimer[7] importantly noted the blue light hazard described by Ham et al[26] and in his own work[5] in which a phototoxic lesion was produced in a rhesus monkey with a 1 hour exposure to an operating microscope. Significant reduction in the severity of the lesion resulted when blue light (wavelengths less than 500 nm) was filtered out.

Following the report by Calkins and Hochheimer,[6] Mannis and Becker,[13] in a letter to the editor of the *Archives of Ophthalmology*, reported preliminary data from a study being conducted at Washington University

in St. Louis. Their investigation was similar to the current one. They reported angiographically demonstrable cystoid macular edema in 5 of 13 control patients and 2 of 15 protected eyes. These numbers are suggestive but not statistically significant. They noted no significant difference in the two groups in the final visual acuities at 4 months.

Tennant's report,[9] presented at the Third Annual Meeting of the American Intraocular Implant Society, suggested that ultraviolet light from the operating microscope appeared to play a role in the postoperative development of cystoid macular edema in his patients. Tennant recommended filters in the operating microscope, obscuring the pupil, spectacle glasses that remove ultraviolet light, and avoiding excessive solar exposure.

With increasing awareness of the transmission of various wavelengths[45] of light through the natural as well as artificial lens in pseudophakia and experimental evidence that near ultraviolet light does produce irreversible photic damage,[28] Keates and Gentsler[46] were prompted to point out that there was fairly good evidence that the operating microscope does not emit significant ultraviolet light. They stated that there is no ultraviolet (below 400 nm) produced by the operating microscope and further added that Zeiss, Inc, was designing a filter to eliminate wavelengths in the 400 to 450 nm range. They also noted that a lack of ultraviolet output from the operating microscope does not mean that the microscope does not contribute to the incidence of cystoid macular edema but that it was doubtful that ultraviolet irradiation from the microscope was a mechanism. It should be noted that, the report by Keates and Gentsler[46] to the contrary, Henry et al[4] did not see a decrease in incidence of postoperative cystoid macular edema when using an ultraviolet filter on the operating microscope. In addition the preliminary report by Tennant[9] indicates that postoperative filtration was also used, indeed an important variable. Tennant[9] also noted that an intact posterior capsule decreased the rate of cystoid macular edema. He felt that this was due to potential ultraviolet filtration (a factor that elsewhere has been shown not to be the case)[47] rather than some other mechanism associated with the capsules being open or not (such as free access of prostaglandins between anterior and posterior chambers).

Contrary to Keates and Gentsler's report,[46] however, is a recent clinical study of Berler and Peyser[48] which shows measurable although small amounts of ultraviolet light produced by two Zeiss operating microscopes used in their study. In this study, the investigators analyzed 310 cataract operations performed by 20 different surgeons randomly distributed between two operating rooms. Each room contained a microscope with

different light intensities. One microscope produced a corneal irradiance nearly threefold greater in intensity than the other. Visual acuity was measured postoperatively and a statistical correlation found for reduced visual acuity in patients who were operated on using the higher intensity microscope. Although increasing age was a factor, they could find no other correlations. They did not comment on operative time. This is an extremely interesting and thought-provoking study, as Dr Carl Kupfer pointed out in his very brief comments following its presentation at the American Academy of Ophthalmology Meeting in October 1982, but a number of variables exist which might have biased the results and the investigators recognized these factors.

The problem of light-induced maculopathy has become such an important topic that whole symposia[49,50] and chapters in textbooks[51] are devoted solely to its investigation. However, none of the literature and data presented to this point shows definite evidence of any variety of light-induced maculopathy, let alone cystoid macular edema, in any patient in a nonexperimental clinical setting. Unfortunately, there are two recent reports[52,53] describing 18 patients with retinal lesions characteristic of phototoxicity. On the first or second postoperative day, the lesions appeared as an oval area of yellow to white discoloration of the retina which gradually developed mottled pigmentation over the next few weeks. Fluorescein angiography revealed a characteristic fairly circumscribed lesion just above or below the fovea which corresponded to a paracentral scotoma. These areas appear identical to lesions produced in monkeys by several investigators as described above.

In some cases, ultraviolet filters were in place and, in one case, a piece of gelfoam covered the cornea after the intraocular lens was in position. McDonald and Irvine[52] did not record length of the procedure. These were reported as uncomplicated extracapsular extraction with lens implantation performed by senior residents (one might expect operating times on the order of 60 to 75 minutes). Boldrey et al[53] reported operating times of 55 to 175 minutes in their cases of macular burns. Boldrey et al[53] have reported a case with a central burn in spite of the piece of gelfoam covering the cornea after the intraocular lens was in place; operating time was 105 minutes. In contrast, Mannis and Becker[13] reported retinal light exposure times of 15.7 minutes in a protected group versus 56.9 minutes in their unprotected group of patients. These operating times need to be compared with the calculations done by Calkins and Hochheimer[6] and others.[54] Hochheimer et al[5] showed irreversible damage to a monkey retina by exposing it to an operating microscope for 1 hour. McDonald and Irvine[52] produced a lesion in rhesus monkeys identical to that seen in

their patients by exposing the monkey eye to 30 minutes of light from an operating microscope during cataract extraction and insertion of a posterior chamber lens followed by an additional 30 minutes of exposure. In a subsequent report, Irvine et al,[55] using a Zeiss OpMi 6 operating microscope (with power outputs measured in a range identical to that by Calkins and Hochheimer[6]), performed cataract extraction with posterior chamber lens implantation followed by differing times of additional exposure in a similar experiment. The reported duration of intraoperative light exposure was stable at 10 to 14 minutes and subsequent exposures of 4, 7.5, 15, and 30 minutes were recorded. In addition, an experiment was performed with intermittent exposure totaling 8 additional minutes. Clinically visible lesions identical to those previously described were produced with 30-, 15-, and 7.5-minute exposures. In the experiment with intermittent exposure totaling 8 minutes a characteristic lesion was produced. It is interesting to note that Noell's first report[14] of light damage in rats indicated no major difference in degree of damage with intermittent exposures compared to continuous exposures.

Cystoid macular edema was not a feature of the patients reported in these studies although case 3 reported by McDonald and Irvine[52] did indeed show some typical appearing cystoid macular edema adjacent to a phototoxic lesion just below the center of the macula.

MATERIALS AND METHODS

Fifty-five eyes of 47 patients requiring cataract extraction with intraocular lens implantation are included in this study. Patients known to have macular disease, significant glaucoma, corneal dystrophy, diabetes, or other ophthalmic or systemic conditions which might influence the development of macular edema or the outcome of the surgery otherwise were excluded. The nature and purpose of the study was explained to all patients and informed consent obtained prior to surgery. Patients were required to attend follow-up examinations and undergo two fluorescein angiograms at specified intervals in the postoperative period. The examinations were office visits scheduled at 1 to 6 days postoperatively, 7 to 21 days, 3 to 6 weeks, 7 to 10 weeks, 2.5 to 5 months, and 5 to 7 months. Fluorescein angiograms were read in a masked fashion routinely by two retinal specialists. Any difference of opinion as to the presence or absence of cystoid macular edema in borderline cases was resolved by a third opinion. Patients were randomized to a treatment or no treatment group by use of four computer generated randomization tables. Separate tables were used for men and women and for patients 71 years of age and

younger and those 72 years of age and older. This age division was made since a review of the ages of patients undergoing cataract extraction with implantation in this office showed a median age of 71.

In the control (no filter) group, patients were operated on using a Zeiss operating microscope Model OpMi 6 with a 175 mm objective. (This is operating microscope 4 in Calkins and Hochheimer's report).[6] According to routine operating room practice, the rheostat controlling microscope brightness was set at its highest (brightest) level. No exceptional precautions with respect to the eye and the microscope were taken, although if some nonsurgical event occurred (such as a major delay for a surgical instrument, suture, etc), the microscope was swung aside.

In the treatment (filter) group, the operating microscope was fitted with a 500 nm filter over the objective lens in the area of the light path from the fiberoptic illuminator. This produces a mild, but not objectionable, yellow cast to the field. In addition, at any time when the anterior chamber did not need to be visualized, such as during development of the groove, placement of sutures, handing off of instruments, etc, the cornea was covered with a piece of moistened gelfoam to shield the posterior pole from light exposure.

All surgical procedures were performed by the same surgeon and an attempt was made to perform exactly the same procedure in all cases reducing as much as possible variables such as length of procedure, placement of intraocular lens, capsulotomy, iridotomy, etc.

The standard procedure consisted of a local anesthesia with modified Van Lint and retrobulbar anesthesia using 0.75% Marcaine and 2% Xylocaine in a 50-50 mixture with hyaluronidase added. Six cubic centimeters of anesthetic was given in the lid block and 3.5 cc in the retrobulbar. A Honan balloon with the manometer set at 30 mm of mercury was used for 5 to 10 minutes over the closed lids to reduce ocular pressure. An Iliff-Park lid speculum was inserted and a 4-0 black silk superior rectus stay suture was placed to rotate the eye into position to expose the upper limbus. A conjunctival peritomy was performed superiorly for 4 clock hours developing a fornix based flap. Light bipolar cautery was used as necessary. A razorblade fragment was used to develop a 10 mm biplaned groove. Three 8-0 black silk mattress sutures were placed equally spaced in the groove and the loops retracted from the incision. The anterior chamber was entered at about the 10:30 to 11:00 o'clock position. The anterior chamber was deepened with 0.1% sodium hyaluronate (Healon) and an anterior capsulotomy formed in a can-opener fashion using a sharp tipped cystotome. The incision was then opened to the full extent of the groove using straight bladed corneal scissors. The nucleus was expressed

after further instillation of Healon. The sutures were temporarily tied and residual cortical material aspirated using the Cavitron-Kelman aspiration unit with a 0.3 mm aspirating tip. The posterior capsule was gently cleansed as necessary to remove major cortical material but no extensive polishing was performed. The sutures were loosened and the 12:00 o'clock suture retracted. The chamber was deepened slightly with Healon and Healon was inserted between the iris and capsule to facilitate placement of the lens haptics in the ciliary sulcus. The intraocular lens, a modified J-loop posterior chamber model, was inserted under Healon, placing the haptics in the ciliary sulcus. The sutures were drawn up, tied and cut. A small hook was used to rotate the lens 45 to 90 degrees so the haptics lie horizontally. The Healon was removed by aspiration with the irrigation-aspiration machine and the posterior capsule was opened with a bent 27 gauge needle. A small triangular central capsulotomy was attempted in all cases but occasionally the capsule split extending the capsulotomy beyond the optic. Acetylcholine chloride (Miochol) was injected to constrict the pupil and a postplaced 10-0 nylon running shoestring style suture was placed to reinforce the wound. Conjunctiva was closed with bipolar cautery and subconjunctival injection of 16 to 24 mg of gentamicin was given. No subconjunctival steroids were given.

Throughout the procedure, in patients in the "treatment" (filter) group, a square of moistened gelfoam was placed on the cornea at any time when the anterior chamber did not need to be visualized. The microscope was placed in position after placement of the superior rectus stay suture and was removed as soon as the subconjunctival injection was given.

Postoperative management included a combination steroid (dexamethasone) and antibiotic drop four times a day routinely. The patients were not routinely treated with pressure lowering agents. Postoperative steroid related pressure elevations were seen and were managed with switching from the dexamethasone preparation to fluometholone if continued steroids were deemed necessary. Steroids were generally continued for 6 weeks depending on the individual, but in all cases were stopped by the fourth postoperative visit. Discharge examination was considered the first postoperative visit at 1 or 2 days after surgery. If pinhole gave 20/20 acuity at the time of discharge, they were not refracted at that time but otherwise all patients were refracted at every visit.

The light output and calculated retinal irradiance of the microscope has been previously reported.[6] This microscope is not retrofitted with an ultraviolet filter from the manufacturer. The ultraviolet output less than 400 nm was not measured but one might expect it to fall somewhere between the zero output level suggested by Keates and Gentsler[46] and

the low levels reported by Berler and Peyser[48] in a similar although not identical microscope.

The 500 nm filter used throughout has previously[5] been shown to reduce radiant power to 81% of what it would otherwise be. The filter passed no wavelengths below 440 nm and markedly attenuated between 440 and 480 nm (less than 10%). Full transmission (90%) was not reached until between 550 and 560 nm.

RESULTS

Fifty-five eyes of 47 patients were included in the study; 8 patients required bilateral surgery during the course of the study. Twenty-six eyes were assigned to the no filter group (no corneal protection during the procedure and no filters in the microscope) and 29 eyes were assigned to the filter group (corneal cover used whenever the anterior chamber did not need to be visualized and 500 nm filter on the microscope at all times). The age range in the no filter group was 40 to 86 (mean of 64 and a median of 62). The age range in the filter group was 41 to 84 (mean and median of 62). In the no filter group there were 11 men and 15 women. In the filter group there were 13 men and 16 women. The right eye was operated on in 18 eyes in the no filter group and the left eye in 8 eyes. In the filter group the right eye was operated on in 12 instances and the left eye 17.

Postoperative fundus examination showed no patients with macular or paramacular retinal pigment epithelial changes similar to those reported by McDonald and Irvine[52] or Boldrey et al.[53] Four patients did show focal areas of mild depigmentation which behaved as pigment epithelial window defects on fluorescein angiography. They did not show the characteristic pigment changes and pigment blocking which was present in all the patients reported by McDonald and Irvine[52] and Boldrey et al.[53] There was no change or evolution of these window defects during the course of follow-up, either clinically or by angiography.

One patient was found to have a full thickness macular hole on the first postoperative day. This was believed to be a preexisting lesion; her vision remained at 20/200 throughout the entire postoperative period and is not included in the visual data.

Two patients had visually significant corneal changes in the immediate postoperative period. One was mild and a visual defect lasted for about 1 week and did not interfere with angiography. The second was severe and required more than 2 months to clear. This patient did not receive

fluorescein angiograms and her visual data is not included in the visual analysis. Final visual acuity was 20/25.

One patient developed a small wound leak adjacent to a suture which required resuturing. Visual acuity was 20/20 throughout and there were no other complications.

There were no other major operative or postoperative complications although a few patients had enough inflammation or haze in the immediate postoperative visit (1 or 2 days) to prevent accurate measurement of the vision. All cleared and had good vision at the second visit at 2 weeks.

One patient died of a stroke shortly after the second postoperative visit. The first fluorescein angiogram had been obtained and was normal. The eyes were obtained at postmortem and examination revealed no retinal changes suggestive of cystoid macular edema or retinal light toxicity.

Operative times ranged from 25 to 31 minutes; most cases took 27 or 28 minutes. Retinal exposure time in the filtered group was not measured in all cases but ranged between 6.5 and 8.5 minutes in those in which it was measured. In no case was prolonged intraocular manipulation (such as extended capsule polishing, difficulty in removing cortical remains or manipulation of the lens in the posterior chamber) which might have dramatically increased the retinal exposure time required.

Visual results in both groups were excellent. The final visual acuity (6 months) in the no filter group was 20/30 or better in all patients except the patient with the macular hole. In the filter group, final visual acuity was 20/40 or better in all patients. One patient had 20/40 acuity at 6 months (fluorescein angiogram at 2 months was positive) and one patient had 20/30 acuity at 6 months, also with a positive fluorescein angiogram at 2 months. Both have subsequently improved to 20/25. All remaining patients were 20/25 or better at 6 months and only two of those were 20/25.

The average visual acuity in the two groups showed an interesting but not statistically significant difference between the two groups in the first 2 months. The no filter group showed approximately one Snellen line poorer vision during the first 2 months compared to the filter group; both ended with identical final acuities. This suggests that the no filter group was slightly slower recovering vision after surgery, a finding that could be compatible with mild phototoxicity.

The fluorescein angiograms were graded on a scale of 0 to 4+ (Table I and II). All angiograms were considered readable. In several cases the amount of fluorescein leakage was so mild that they were read as questionable trace and trace positive. All angiograms read as trace were considered positive. In cases where one angiogram was read as questionable trace and the other angiogram was normal, they were counted as positive,

TABLE I*: NO FILTER

AGE	6 MO VISION	CLINICAL EDEMA	ANGIOGRAPHIC EDEMA	ANGIOGRAM 1 LEAKAGE	ANGIOGRAM 2 LEAKAGE
40	20/15	0	0	0	0
40	20/25	0	0	0	0
47	20/20	0	Y	?TR	0
50	20/15	0	0	0	0
52	20/20	0	0	0	0
53	20/15	0		NA	NA
54	20/25	0		NA	NA
55	20/20	0	Y	?TR	TR
57	20/15	0	Y	0	TR
58	20/20	0	0	0	0
58	20/15	0	0	0	0
58	20/20	0	0	0	0
62	20/20	S	Y	TR	1+
68	20/15	0	0	0	0
68	20/200†	0	0	0	0
71	20/20	0	0	0	0
71	20/15	0	Y	1+	0
72	20/25	0	0	0	0
75	20/20	0	Y	?TR	NA
75	20/20	S	Y	1+	1+
27	20/20	S		NA	NA
78	20/30	0	0	0	0
79	20/15	0	Y	TR	0
80	20/20	0	Y	TR	0
82	20/20	S	Y	?TR	1
86	20/50‡	0	0	0	NA

*NA, not available; Y, present; S, suspected; 0, absent; ?TR, questionable trace; TR, trace.
†Indicates macular hole.
‡Patient died, 2-week vision.

then as negative and corresponding percentages calculated (Table III).

The eight patients who underwent bilateral surgery during the study all had 20/20 or better acuity in each eye. The first eye was randomized in the usual fashion to the filter or no filter group. The second eye was done in the opposite fashion to serve as a built-in control. In five of the eight patients, both fluorescein angiograms in both groups were normal. Three patients had abnormal angiograms. In one patient, the eye in the no filter group showed trace fluorescein leakage in both angiograms. In one patient, the first angiogram was normal in both eyes and the second angiogram showed trace leakage in both eyes. In the third patient, the first angiogram showed questionable trace leakage in the first angiogram and was normal in the second angiogram in both eyes.

In the no filter group, fluorescein angiograms are available on 23 of the 26 patients (3 patients refused angiography after surgery was completed).

TABLE II*: FILTER

AGE	6 MO VISION	CLINICAL EDEMA	ANGIOGRAPHIC EDEMA	ANGIOGRAM 1 LEAKAGE	ANGIOGRAM 2 LEAKAGE
41	20/20	0	0	0	0
41	20/15	0	0	0	0
47	20/20	0	Y	?TR	0
47	20/20	S	Y	TR	0
54	20/20	0	0	0	0
55	20/15	0	0	0	0
55	20/15	0	0	0	0
56	20/15	0	Y	?TR	0
57	20/15	0	Y	0	TR
57	20/20	0	0	0	0
58	20/20	0	0	0	0
58	20/15	0	0	0	0
61	20/20	0	0	0	0
62	20/20	S	Y	TR	1+
63	20/20	0	0	0	0
64	20/20	0	0	0	0
68	20/15	0	0	0	0
68	20/20	0	Y	TR	0
69	20/20	0	Y	0	2+
69	20/20	0	0	0	0
69	20/25	0		NA	NA
69	20/20	0	Y	1+	0
70	20/15	0		NA	NA
70	20/20	0	0	0	0
75	20/20	0	Y	TR	2+
78	20/30	S	Y	0	TR
78	20/15	0	0	0	0
83	20/40	Y	Y	0	1+
84	20/25	S	Y	2+	2+

*NA, not available; Y, present; S, suspected; 0, absent; ?TR, questionable trace; TR, trace.

In two patients, only one angiogram is available (one refused a second angiogram, one died). In the filter group, 27 of 29 patients had two angiograms (1 patient refused angiography following surgery, 1 was not done due to corneal opacity).

For the purpose of this study, an angiogram with any evidence of fluorescein leakage was considered positive. No angiogram was read as greater than 2+ suggesting only moderate edema; none showed 360-degree petaloid perifoveal leakage. In the no filter group, 10 of 23 (43.4%) eyes with angiograms were positive. In the filter group, 12 of 27 (44.4%) eyes with angiograms were positive. If eyes with one angiogram read as questionable trace and the other angiogram normal are considered to show no angiographic cystoid macular edema, then 8 of 23 (34.7%) eyes in the no filter group and 10 of 27 (37%) eyes in the filter group showed

TABLE III:

	NO FILTER	FILTER
Clinical cystoid	15.3%	17.2%
Angiographic cystoid	43.4%	44.4%
Angiographic cystoid excluding ?TR*	34.7%	37%

*?TR, questionable trace leakage.

positive angiograms (Table III). The differences between these groups are not statistically significant in either case.

In this study, clinical cystoid macular edema was suspected if there was a drop of one Snellen line of vision from one visit to the next with subsequent recovery or if there was fundoscopic evidence of edema. In the no filter group, four patients met this criteria with three of these having positive angiograms. One patient did not have angiograms available. Therefore, 15.3% (4 of 26) patients were suspected to have transient edema clinically. In the filter group, 5 of 29 patients or 17.2% were thought to have transient edema, and all had positive fluorescein angiograms. This difference is not statistically significant.

In one of the no filter group patients, two observers believed that there was a probable macular branch vein occlusion with 1+ fluorescein leakage. However, because a positive diagnosis could not be made, these angiograms were included in the data analysis.

Only one eye met the usual criteria (otherwise unexplained 20/40 acuity and fundoscopic evidence of macular edema) of clinical cystoid macular edema. Although there was some mild haziness of the media, it was believed that retinal function was probably the cause of vision fluctuating in the 20/40 to 20/60 range. The first angiogram was normal and the second showed 1+ leakage. Vision which was 20/40 at 6 months subsequently did improve to 20/25.

In the no filter group, four eyes had both angiograms positive and three of them had suspected clinical cystoid macular edema (Table 1). In the filter group, three patients had both angiograms positive and two of those had suspected clinical cystoid macular edema (Table II).

Of interest in those eyes with fluorescein leakage is the visual acuity at the time of the angiogram. In the no filter group group, four eyes showed 1+ fluorescein leakage and all but one (suspected branch vein occlusion) had 20/25 or better acuity. Five eyes showed trace leakage and all had 20/25 or better acuity. In the filter group, three eyes were read as 2+ fluorescein leakage. One eye had 20/40 acuity at the time of the first angiogram which improved to 20/25 with no change in the angiographic

findings on the second angiogram; the others all had 20/25 or better acuity. Three eyes were read as 1 + fluorescein leakage on the angiogram; one had 20/40 acuity at the time of the angiogram and the others had 20/20 acuity. Six eyes showed trace leakage. Two had 20/30 vision and four were 20/20. Two patients showed questionable trace leakage. One had 20/20 and one had 20/15 acuity. Older patients seemed to develop edema more frequently and severely than younger patients.

Although more than 40% of the patients in each group showed angiographic macular edema at some time during their course, no patient appears to have developed chronic cystoid macular edema with persistently depressed acuity. Long-term follow-up acuities are not included here, but there is no evidence of worsening of vision in any patient.

DISCUSSION

There is ample evidence that low intensity light in both the visible and ultraviolet region can produce phototoxicity to the retina in experimental animals and in humans. Ham et al[26,27,54] have shown that the blue portion of the visible spectrum is particularly damaging. It has been well documented that in addition to xenon arcs and lasers that clinical light sources such as the indirect ophthalmoscope,[17,19] slit lamp,[43] intraocular fiberoptic illuminators[56] and, most particularly, the operating microscope[5,55] are capable of producing injuries. Indeed, McDonald and Irvine[52] and Boldrey et al[53] have recently documented phototoxic retinal lesions in patients undergoing otherwise routine cataract extraction with intraocular lens implantation, a complication predicted by many investigators.

Cystoid macular edema, a complication of cataract and other intraocular surgery and other disease states, has been an enigma to ophthalmic clinicians and investigators since its initial descriptions in the early 1950s. Although much has been learned about its nature, its exact pathogenesis still remains a mystery. It is probably multifactoral and includes to some degree inflammation and release of prostaglandins, systemic factors such as hypertension, diabetes, and age as well as potential drug effects.[10] Both medical and surgical therapy have produced disappointing results in long-standing chronic cases and is difficult to evaluate in short-term situations since it is known that the process clears spontaneously in a large percentage of patients.[10] Some decrease in the incidence of aphakic cystoid macular edema can be obtained by carefully controlling preoperative factors such as the type of cataract extraction, systemic disease, inflammation, etc, yet visually significant cases still occur.

Although Ham et al,[26] Lawwill et al,[31] and others previously suggested the potential clinical importance of light toxicity, Henry et al[4] in 1977 first suggested that the apparent increase in incidence of cystoid macular edema seen in clinical populations might be the result of increasing exposure of the retina to intense operating room lights and the operating microscope. Many subsequent investigators including Calkins and Hochheimer,[6] Hochheimer,[7] Tennant,[9] Drews,[8] Jampol et al,[10] Mannis and Becker,[13] and Yannuzzi,[11] and others have amplified and expanded this possibility. With the rising usage of intraocular implant lenses and the loss of ultraviolet filtering properties of the aphakic or psuedophakic eye, most of the concern is centered on the possible link between the operating microscope and the development of cystoid macular edema in the psuedophakic situation. Most reports have ignored the blue light hazard described by Ham et al[26] and have centered on possible ultraviolet toxicity despite reports that ultraviolet output of operating microscopes is extremely low. Indeed, there has been no experimental or well controlled clinical evidence (although preliminary and incomplete studies by Tennant,[9] Mannis and Becker,[13] and Kraff et al[12] have been presented) linking the operating microscope or light toxicity in general to cystoid macular edema. In fact, Jampol et al[57] have recently published a study showing no correlation between the development of cystoid macular edema and the ultraviolet output of the operating microscope. They point out that other portions of the spectrum may be a factor, however.

The current study was designed specifically to answer the question "Is there a connection between the light output of the operating microscope and cystoid macular edema in the psuedophakic eye?" The study was specifically designed to eliminate as many variables as possible including: multiple surgeons, widely varying operating times and techniques, variations in microscopes, different filters and covers, variable follow-up methods and times, patient population, etc. Constructing the study in this fashion had the major disadvantages that it limited the number of patients available for study within a reasonable period of time. Although the operating surgeon also performed the postoperative follow-up and knew which patients were randomized to which group at the time of surgery, the possible bias produced was minimized as much as possible by the randomization records being kept by a secretary. Group affiliation was not noted in office charts or operative notes. In addition, the patients were unaware to which group they belonged. Due to the time involved in the study, the number of patients, and number of visits made, it was impossible for the surgeon to remember which eye belonged to which group.

The fluorescein angiograms were read in a masked fashion by separate observers. All surgeries were performed in as close to an identical fashion as possible with the only difference being a 500 nm filter on the operating microscope and a cover on the cornea.

Analysis of the data showed angiographic proof of macular edema in 43% of the patients in the no filter group and in 44% of the patients in the filter group. The slight difference between these groups is not statistically significant.

Clinical cystoid macular edema—patients that showed visual or fundoscopic suggestions of macular edema—showed similar small differences (15% of the no filter group and 17% of the filter group clinically suspected of having edema). Only one patient in the combined groups (excluding the possible branch vein occlusion) met the usual criteria for clinical cystoid macular edema (20/40 acuity or worse otherwise unexplained and fundoscopic evidence of macular edema). In the no filter group, with the exception of one patient with a preexisting macular hole, all patients achieved 20/30 or better acuity at 6 months. In the filter group, all but two patients achieved 20/25 or better acuity at 6 months—the two exceptions being one patient with 20/30 (branch vein occlusion suspected) and one patient with 20/40 acuity. Both of these later improved to 20/25 with longer follow-up.

Although discovery of other phototoxic effects was not the goal of this study, none have been found. There were no lesions similar to those reported by McDonald and Irvine[52] and Boldrey et al.[53] Although the latter found no correlation of severity of lesion with operative time, times reported by them seemed excessive in some cases. The experimental evidence documenting the importance of exposure time is readily available.[54] It might be expected that long exposure times, in contrast to those reported here, would be more likely to cause a phototoxic injury. It is not believed that exposure time was a significant factor in the current study because the rate of cystoid macular edema development was similar to several previous reports.[58-60]

More sensitive tests (than fluorescein angiography and visual acuity) will be necessary to detect subtle forms of photic injury. Jampolsky[61] has suggested several such tests. Further examination of those patients with bilateral surgery will be the subject of a future report.

The data presented here indicates that there is no apparent effect on the incidence of cystoid macular edema in psuedophakic patients from an operating microscope when the total time of exposure to the light is reduced by the factor of 4 and the blue portion of the spectrum (docu-

mented by Ham et al[26] and others[33] as being the most damaging portion of the visible spectrum) is dramatically reduced.

Many investigators have suggested that the operating microscope is likely to be a factor in the development of cystoid macular edema. The question might be asked, "Why did this study not demonstrate such an effect?" There are three possible answers. (1) The study through either faulty design or too small a sample size did not detect the difference. (2) The action spectrum causing the macular edema remains in the portion of light reaching the retina—that is, it has not been filtered out by the 500 nm filter and sufficient energy reaches the retina during the 6 to 8 minutes of exposure to produce the effect. (3) The operating microscope has no effect on the incidence of cystoid macular edema.

Several comments on these three points can be made. The study was carefully designed to eliminate all variables other than the quantity and quality of the retinal irradiance produced by an operating microscope. It was believed that bias in the observer was minimized although it could not be eliminated entirely. The problem of sample size is a valid point. Assuming an incidence of cystoid macular edema of 40% in the no filter group as in this study, if the operating microscope made a 5% difference, reducing cystoid macular edema development to 35%, over 2900 patients would be necessary to detect a significant difference at the 0.05 level. If a larger effect exists and the incidence of macular edema decreased from 40% to 30%, over 700 patients would still be required. These numbers are beyond the capability of most individuals to obtain in a reasonable length of time. Indeed it is possible that because of the sample size of the current study, an effect from the operating microscope was missed. However, no trend was noted and it is suggested that this effect, if present, is small. If there is a connection, a very large sample study will be necessary to establish proof.

The possibility that the action spectrum causing macular edema in humans is something other than what was removed with the 500 nm filter is certainly possible but seems unlikely in light of the extensive experimental evidence suggesting that the blue portion of the visible spectrum as well as the ultraviolet is most likely to cause photochemical damage. This is certainly an avenue of potential further investigation. However, from a clinical standpoint the use of a 550 nm or higher filter on an operating microscope may interfere with visibility and cause so much annoyance to the surgeon as to be unusable by some. Such a filter is currently being evaluated.

The third possibility, that there is no effect of the operating microscope on the development of cystoid macular edema, seems most likely. There

is no evidence either in the literature or in the current study to suggest to the contrary.

It cannot be said, of course, that visible light, blue light, or ultraviolet light and the known phototoxic effects that they produce have *no* impact on the development of cystoid macular edema. Nor can it be said that the operating microscope, known experimentally and clinically to produce phototoxic lesions, is totally safe and can continue to be ignored as it has been in the past. Further study is needed to determine the action spectrum of and the methods of preventing lesions such as those reported by McDonald and Irvine[52] and Boldrey et al.[53] The operating microscope does not appear to be a significant factor in the development of cystoid macular edema but it surely continues to represent a phototoxic threat to the retina.

SUMMARY

The literature documenting the phototoxic effect of relatively low intensity light on the retina and the suggestions by several authors that this might influence the development of cystoid macular edema in the aphakic and psuedophakic patient is reviewed. In particular, the possibility that the operating microscope may be a factor has been emphasized. A study is presented, designed to investigate the possibility that the operating microscope is a factor important in the development of cystoid macular edema. No correlation was found. The need for further investigation into other phototoxic effects from the light of the operating microscope is stressed.

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