Shedding Light on Photophobia
Kathleen B. Digre, M.D.
Salt Lake City, UT

Keywords
photophobia, migraine, trigeminal nerve

Objectives
At the conclusion of this program, participants should be able to:
1. Enumerate three causes of light sensitivity
2. List three treatments for light sensitivity
3. Describe how light-sensitivity fits into the diagnosis of migraine

CME Questions
1. Name 3 causes of light sensitivity.
2. Name 3 treatments for light sensitivity.
3. Name one condition in which photophobia is part of the diagnostic criteria.

Introduction
Photophobia is a common symptom with almost all forms of migraine and neuro-ophthalmic disorders. It is even included as one of the major criteria of migraine in the International Headache Society Classification of migraine. It is listed as a major symptom in blepharospasm. The symptom is used to diagnose uveitis and iritis. We all see patients who have this vexing complaint, but for such a common symptom, so little understanding exists.

Nomenclature
The term photophobia is even somewhat of a misnomer. The word comes from two Greek words: photo “light” and phobia “fear or dread of”—hence, “fear of light.” In medicine, it has come to be thought of as a symptom of “abnormal sensitivity to light, especially in patients with measles and certain eye conditions” (Webster).1 Lebensohn, who first wrote about this symptom, said: “exposure of the eye to light definitely induces or exacerbates pain.”2 Cumming and Gittinger described “central dazzle” as an uncomfortable, but not painful, sense of excessive brightness to everything.

Loewenfeld described “Dazzling” as abnormal light scatter without ocular adaptation.3 “Hemeralopia” or “day blindness” describes blurring of vision due to light and is a frequent complaint in patients with retinal (e.g., cone dystrophy) and rarely optic nerve disorders. In these cases, patients report they see better in dim illumination. I have used the term “photo-oculodynia,” to describe pain or discomfort in the eye from a not usually painful light source.4 This term is in keeping with the pain literature that describes pain from a normally nonpainful stimulus (e.g., cutaneous allodynia).5,6 Lebensohn distinguished two different types of light sensitivity. One type is a “uncomfortable vision, based either on diffusion of light through the ocular media on a transient or permanent lack of adaptation.” He thought conditions such as albinism and corneal opacities belong to this type. This type of light sensitivity never had tearing or blepharospasm. Some people have called this “dazzle.”2 Lebensohn believed that people could have both photophobia with pain on exposure to light and an uncomfortable sense of glare.2 In this review, I have used photophobia generically with light sensitivity due to glare or associated with pain. In places I discuss photo-oculodynia, a term that describes an abnormally painful light sensitivity by a stimulus that ordinarily should not cause discomfort. We really haven’t settled on a term that describes an uncomfortable, but not painful, brightness. It may be difficult to distinguish between the two, since one person’s discomfort may be another’s pain. Dazzle, I believe, is an appearance that everything is very bright, and maybe a different phenomenon.

Conditions Associated with Photophobia
Anterior segment diseases such as iritis, cyclitis, blepharitis have long been known to cause photophobia. In fact, Lebensohn found that the more superficial the corneal lesion, the more severe the photophobia.2 Lebensohn thought this was because of the superficial position of the corneal nerves. Acute meningeal irritation causes photophobia as well. After meningitis or sub-arachnoid hemorrhage, photophobia is a common complaint8,9 Pituitary apoplexy and tumors have also been described to cause photophobia,10 presumably due to irritation of the basal meninges around the diaphragma sellae11 (See Table 1 for reported causes of photophobia).

Photophobia has also been thought to be a psychiatric disorder. In fact, in many neuro-ophthalmic clinics patients present with severe forms of photophobia and photo-oculodynia where they have virtually retreated from society, living in dark chambers with draperies drawn, wearing multiple pairs of sun-glasses.11 Some of these may have associated migraine. Authors report a high incidence of anxiety and panic disorder in these patients.11 Gowers, the famous 19th century London neurologist stated: “Apart from Ocular disease [photophobia occurs] in weak states of the nervous system, especially in women, and sometimes in association with symptoms of hysteria.”12 Although there may be underlying psychiatric disease, photophobia is a real symptom that has physiologic underpinnings.
Common Conditions Associated with Photophobia

Migraine

Probably the most common condition that has prominent photophobia is migraine. It is migraine that has really given us the most clues about the symptom of photophobia. Photophobia is one of the major diagnostic criteria associated with migraine from the International Headache Society Classification (1988, 2004). Photophobia is reported in about 80% of all patients with migraine. A recent study suggested that the presence of photophobia, disability, and nausea predicted migraine almost 98% of the time (ID Migraine Study). Furthermore, 30-60% of migraine attacks are triggered by light or glare. Different visual stimuli are known to provoke migraine including sunlight, flickering from motion pictures, television, and fluorescent lights. Patients with migraine often have many eye strain factors (see Table 2).

In animal models, flickering lights are known to precipitate spreading cortical depression, which has been associated with migraine pathophysiology. Patients with chronic migraine suffer from light sensitivity more than patients with episodic migraine. Migraine is associated with marked visual pathway dysfunction from the retina to the occipital lobes.

Drummond first showed that subjects with migraine were more light sensitive both during and in between migraine compared with non-migraine controls. Even subjects with tension-type headache had more light sensitivity than controls. Vanagaite et al. also reported that patients with migraine experienced increased light sensitivity to a progressively increased amount of light during and in between headache compared with controls. They concluded that photophobia “seems to be an intrinsic property of migraineurs.” Medication use did not change this threshold and patients with migraine with and without aura had similar lower threshold, even though patients with aura complained of light sensitivity more than patients without aura. They found that the longer the attacks the lower the pain threshold. Unilateral headaches brought the same amount of light sensitivity to each eye, even though testing of light sensitivity took place in each eye individually and bilaterally.

Drummond showed that migraine sufferers not only have a low tolerance to bright light and loud noises, but also suffer from motion sickness more readily. In an experiment where migraine and control subjects underwent optokinetic stimulation, subjects with migraine had more nausea, increased scalp tenderness, increased pain sensitivity, and increased light induced pain than normal controls. Drummond also stated that migraines may have true “photophobia” or fear that light will cause a migraine.

Psychiatric conditions

Photophobia has been reported in association with other phobias, notably agoraphobia. Patients with agoraphobia wear dark glasses more frequently and feel more relaxed in the darkness. Furthermore, light will frequently trigger anxiety reactions in these patients. In one study, comfortable illumination levels were reduced in patients with agoraphobia that actually normalized after cognitive behavioral therapy.

Gerbaldo and Thacker report that avoidance of light has been associated with depression since the 1500s. The classic picture of the person with depression hiding indoors in darkened rooms that do not allow any light of day has become almost a stereotypic picture. Gerbaldo and Thacker report that photophobia occurs in patients with “neurasthenia,” bipolar depression, and seasonal depression. In contrast, patients with schizophrenia are known to have “sun-gazing” tendencies without any discomfort. They tested binocular and monocular discomfort thresholds in patients with schizophrenia and schizoaffective disorder and found an increased threshold to light tolerability among those with schizophrenia and sun-gazing behavior. Depression, on the other hand, has been shown also to be associated with light sensitivity. One case report of a woman with bipolar depression revealed that she used eye patches during her depressive phase, and she used her light sensitivity to predict when she would be entering the depressive phase. As depression decreased in one study with bright light therapy, photophobia as well as irritation and other ocular symptoms decreased. Another case of depression was reported in which a 30 year old man who wore sunglasses and avoided reading and light exposure. The authors suggested that his anxiety and increased sympathetic tone may have contributed to his light sensitivity as well as a possible somatization disorder. Interestingly they credit a well-known neuro-ophthalmic textbook as the reference proving that severe light sensitivity is a conversion disorder. Clearly, more work is needed here, since many of the patients we see with photophobia have underlying psychiatric conditions.

Blepharospasm

Blepharospasm is a focal dystonia associated with involuntary blinking, squeezing and closure of the eyelids. The cause is unknown but is thought to be due to hyperexcitable brainstem interneurons. While blepharospasm has been known for years to be associated with photophobia, very little about this association has been studied. In one large survey of patients, Anderson found that eighty percent of patients with blepharospasm report that bright lights, stress, driving, television viewing, and reading aggravate blepharospasm. In fact, light alone is known to physiologically increase the light-blink rate. (See

132
Photophobia reads like a who’s who of neurology and problem in the corneal nerves and pointed the problem to pharospasm. 30 patients with a known photophobic below) Since little is known about light sensitivity in this disorder, we undertook a prospective look at light sensitivity in blepharospasm. We used similar methods as Vanigaite et al.\(^3\) We studied 30 subjects with blepharospasm, 30 patients with a known photophobic state—migraine—and 30 controls with no history of migraine or blepharospasm. First, we ascertained their symptoms using a questionnaire. Then we tested the light sensitivity by using a rheostat on a light source, and increased light sensitivity in 50 lux increments every 2 seconds to a maximum light intensity of 23,500 lux. Each subject was to stare at the light and let us know when the light became “uncomfortable” by saying “stop.” Each testing situation was repeated 3 times with a 3 minute rest in between each test. We found that patients with blepharospasm were as light sensitive as patients with migraine and that both were more light-sensitive than controls (see figure 1). Results have been submitted for publication\(^30\) and were presented as a poster at NANOS in 2002.\(^31\)

In addition, we queried members of the Benign Essential Blepharospasm Research Foundation about their symptoms of light sensitivity. There were 343 respondents (244 women, 80 men) average age 62-65. Ninety-three percent reported light sensitivity in which regular light not only provoked spasms in just less than half the patients, but was present all of the time in about half of the patients with blepharospasm. Bright light provoked spasms 95% of the time.\(^32\)

Early studies used various experiments to try to understand the symptom, and most of these localized the problem in the corneal nerves and pointed the problem to the trigeminal system. The historical figures interested in photophobia reads like a who’s who of neurology and ophthalmology. Lebensohn reported:

Magendie 1858 demonstrated that the retina was insensate as is the inner section of the optic nerve. Krause 1896 showed that removal of the gasserian ganglion resulted in the loss of photophobia on the ipsilateral side. Axenfeld 1902 showed that photophobia required an intact pupillary reaction, since with the use of mydriatics, photophobia resolved. Bjerrum then showed that photophobia occurred despite absent pupillary responses. Willbrand 1914 suggested that light may induce metabolites that could cause pain in ciliary nerves, while Peters in 1916 stressed that trigeminal hyperirritability is an “essential factor” and he showed that patients with chronic light sensitivity had sensitivity to pressure as well. Siegwart reported that in Vogt’s clinic in 1920, in 46 blind patients with various causes (phthisis, optic atrophy, glaucoma, congenital amaurosis) of blindness only 3 still showed light sensitivity. They proposed that the patients with light sensitivity had to have some vision. They also proposed that patients are only light sensitive to the visible spectrum and not infrared. Lebensohn concluded from these early studies that for photophobia to be present there must be an intact optic nerve and trigeminal nerve. He further concluded that local vasodilation, pupillary responses, light and trigeminal function were essential elements for photophobia to occur. He induced severe chemosis with mustard preparations to rabbit eyes and showed that pretreatment with corneal anesthesia blocked this chemotic reaction at least for a while. He stressed the importance of the vasodilation in the development of photophobia. Eckardt showed that vasodilation was not necessary for the development of photophobia and vasoconstricting substances had no effect in preventing it.\(^32\)

What Is Known Today about the Pathophysiology of Photophobia?

Photophobia is present in many eye conditions that affect the uvea (the pigmented portion of the eye) such that those with iritis, uveitis, and corneal disease complain of photophobia. Presumably this mechanism of photophobia in these cases is discomfort generated by irritation of the rich innervation to the eye supplied by the first division of the trigeminal nerve. The trigeminal nerve connections to the midbrain and thalamus have also been implicated in the pathophysiology of migraine.\(^33\)

What Do We Know about Light and Photophobia?

First, it is clear that the amount of light bothers some people more than others. We have all experienced a sense of discomfort going from a completely darkened environment (a movie theater matinee) to the sunshine. However, it is clear that there are individual “thresholds” of light sensitivity even in normal people. Most of the studies that have looked at thresholds of light in individuals showed some normal variation,\(^34\) but subjects with migraine and even tension-type and cervicogenic headache have lower thresholds.\(^20,35\) In these studies subjects and controls stare at a light that increases steadily in luminance until the subject reports discomfort. Light intensity definitely affects patients differently. Many studies have shown that there is a discomfort threshold for light that is lower in patients with migraine (in between attacks) than subjects without migraine.\(^36,37,38\) This threshold also exists similarly for patients with blepharospasm.\(^31\) Perhaps there are many other conditions that make individuals more sensitive to light (e.g., depression, fibromyalgia).
Light sensitivity may have seasonal changes. Vanagaite found that migraine patients and controls (less so) had lower pain thresholds to light in the winter months (November through January) than in the summer months (May through July). 20

We also know that there is a “net sum” of light that causes discomfort. Wirtschafter showed that binocular viewing lowered the threshold of light where unocular viewing raised the threshold. 29 This study result was also confirmed by Vanagaite and Stonner. 15 Ekhardt et al. showed that as the pupillary area increased after dilation of the pupil, so too did light sensitivity as measured by the blink rate. 30 Wirtschafter also showed that dilated pupils (mydriasis) also lowered the individual thresholds of light.

The interpretation of light brightness is dependent on the state of retinal adaptation (e.g., dark adaptation). 41, 42 The wave length of light may also affect a person’s comfort. For example, subjects with migraine in one study reported that using red overlays while reading were the least comfortable. 43 Main et al. found that low wavelength light (blue light) was more uncomfortable for subjects with migraine than subjects with tension-type headache or controls. 44 Furthermore, he reported that high wavelength light (red light) was also less comfortable for subjects with migraine. Good reported that visually provoked beta brain activity was suppressed by red light and enhanced with blue light. They postulated that the short wavelength light (blue) and hence this beta activity may excite the hypothalamus and thalamus more, stimulating migraine. 15

Flickering lights also cause visual discomfort in patients with migraine (with or without aura) compared with non-migraine subjects. 45 Wilkins found that the most unpleasant photogenic stimulus was 2-8 cycles/cm in migraine and in photogenic epilepsy. 47 Indeed, strobe lights can cause seizures in susceptible patients.

Light and patterns of light seem to affect patients with migraine in differential ways. For example, stripes and geometric patterns often with sharp contrast between dark and light are uncomfortable in migraine. Marcus et al. found that 82% of 38 migraine subjects found severe discomfort from stripes vs 18% of 22 subjects without migraine. 46 This “stripe-induced discomfort” has been thought of almost as a “test” for migraine and photoinduced epilepsy. 47 The whole movement of “Op Art painting” has been described as “assaulting the retina.” In this movement art objects are intended to generate visual discomfort and emotional reactions.

The hyperexcitable state of the occipital lobe also may be important in understanding light sensitivity. Many have shown through psychophysical tests that individuals with migraine have hyperexcitable cortices and increased sensitivity to stimulation (light, sound, odors, even touch).

Wray found that migraineurs detected lower levels of visual stimulation than non-migraine controls. She examined patients with migraine with aura and compared them with normal, non-headache controls. Each group performed tasks of “low-level” visual processing, e.g., detecting changes in line orientation vs “high level” visual processing, e.g., reading a word that had been visually degraded. They found that subjects with migraine performed superiorly on all “low level” visual processing and about the same as controls on “high-level” processing. They interpreted this finding as showing that the occipital cortex in migraineurs was more sensitive. 48 This psychophysical study parallels several studies using both magnetic stimulation and fMR techniques. Subjects with migraine show central neuronal hyperexcitability—in all senses (light, sound, odors and touch). 33 Aurora et al. showed that the occipital lobe responded to magnetic stimulation with phosphenes at lower levels than non-migraine, non-headache controls. 49, 50 Newer functional imaging techniques may improve our understanding of the trigeminal system and migraine. 51 This hyperexcitability of the occipital lobe plays directly into current thinking about migraine and its aura. 52

Patients with light sensitivity may have changes in photopigments, which act to protect the retina against light-induced oxidative damage through their ability to absorb phototoxic blue light and reduce free radicals. Deficiencies of these photopigments are associated with age-related macular degeneration. We used a novel, non-invasive objective method to quantify lutein and zeaxanthin in the human macula. This technique illuminates the macula with a low-power argon laser spot and measures Raman back-scattered light using a spectograph. This technique is sensitive, specific, and repeatable even in subjects with significant macular pathology. The main outcome measure is the Raman signal intensity generated by the carbon-carbon double-bond vibrations of lutein and zeaxanthin. 52 We showed in one study that patients with benign essential blepharospasm, a condition often accompanied by photophobia, have elevated levels of carotenoids in the retina. 53 (see figure 2.) In another study, 94 we confirmed that subjects with migraine also had increased carotenoid levels. How photopigments are altered is the subject of current investigations.

Biochemical changes associated with photophobia

Light is known also to generate an abnormal “catecholamine response” in migraine subjects vs controls. Stocia showed that norepinephrine increases after light exposure in non-migraine controls. However, in migraine subjects, this same light increases epinephrine. 55

Dopamine has also been postulated to be an important neuro-chemical modulator in light sensitivity. Under
certain conditions, dopamine reduced the light response by full-field illumination.\textsuperscript{54}

Substance P is released into the vitreous and aqueous when the trigeminal nerve is artificially stimulated in rabbits. In this instance, vasodilation and miosis occurs.\textsuperscript{55} Whether light alone can generate substance P is unknown.

Light suppresses melatonin secretion.\textsuperscript{56} How this may play into photophobia is unknown.

**The effect of light on pain**

Interestingly, light stimulation in subjects with migraine can decrease pain thresholds in the trigeminal and cervical regions compared with normal controls.\textsuperscript{57} In one study individuals endured progressive light stimulation until discomfort was reported and then each individual underwent algometric procedures (progressive pressure algometer, a device to measure pain sensitivity) over three predetermined trigeminal sites, occipital nerves, and temporal muscles. Algometry readings occurred before light stimulation, directly after and after time delay. All migraine subjects had reduced thresholds of light sensitivity (not unexpected), but they also had significant and sustained (beyond the second testing) lowering of pressure and pain sensitivity in both trigeminal and cervical sites. Controls did not exhibit this same phenomenon.\textsuperscript{57}

In a study on optokinetic stimulation of migraine symptoms, Drummond showed that light-induced pain increased with stimulation of motion sickness but not light-induced glare. He concluded that glare ratings do not necessarily increase during the headache phase and that photophobia that develops in migraine is linked more closely to pain processing and not necessarily visual perception.\textsuperscript{21}

**The Trigeminal Light Reflex**—The light blink reflex

The exact afferent pathway for reflexive blinking to a light source is unknown.\textsuperscript{58,59} The blink reflex has been found to be normal in patients with a unilateral occipital lobe lesion, absent in cortical blindness, and more variable with optic nerve atrophy.\textsuperscript{58} The occipital cortex was thought to play into this reflex since individuals without occipital lobes lose their light-induced blink reflex. However, some researchers report that a blink reflex remains in monkeys who have had bilateral striate cortex removal, and there are multiple reports of a persistent light blink reflex in human when cortical blindness has occurred.\textsuperscript{58} One case report of a man who suffered a cardiac arrest with intact blink to light reflex despite necrosis of cerebrum, basal ganglia, hypothalamus, several brainstem nuclei and superior colliculus suggests that the afferent pathway may involve the pretectum not the superior colliculi.\textsuperscript{50} In fact, Itoh and Takada reported such a pathway (a pretectal-facial motor nucleus pathway) in cats.\textsuperscript{51} Others have shown that in monkey lesion studies, destruction of the superior colliculus does not stop a light reflex blink pathway, but a lesion in the pretectal nucleus does.\textsuperscript{62}

Photophobia is present in blepharospasm, and blepharospasm is a “blinking” disorder. Patients with blepharospasm often present initially with a complaint of photophobia and eye irritation leading to an excessive blink reflex. This form of photophobia may possibly be related to sympathetic overdrive, since stellate and superior cervical ganglion blocks can ameliorate the symptoms.\textsuperscript{4,63}

**Where Then Could Photophobia Be Localized?**

The most likely anatomical localization of photophobia must be where there is a convergence of visual and pain pathways.

Trigeminal innervation of the eye and brain plays a role in photophobia. It is important to review its anatomy and realize the extent of the trigeminal system in the brain.

Cornea: The cornea has more sensory innervation than any structure in the body! These 1,000 or so small axons provide sensation from all layers of the cornea.\textsuperscript{64} They coalesce to form ciliary nerves, which then join the ophthalmic division of the trigeminal nerve. Some also join the orbital ciliary branch of the maxillary division. The central portion of the cornea has the greatest density of nerves where the limbus is less dense.\textsuperscript{4} The neuromodulators of the cornea include substance P, calcitonin gene-related peptide, cholecystokinin, and acetylcholine. Interestingly, sympathetic innervation also occurs in the cornea, while parasympathetic innervation has not been demonstrated.\textsuperscript{64} In addition to trigeminal innervation of the cornea, the uvea (iris, ciliary body, and choroid) are also richly innervated. Trigeminal afferents innervate the limbus, sclera, conjunctiva, eyelids, and orbit including the peri-orbita and sheath of the optic nerve, the intracranial dura. The lens, optic nerve and retina are not innervated by the trigeminal system.\textsuperscript{65}

The ophthalmic division of the trigeminal nerve innervates the eyeball, forehead, lacrimal gland, caruncle, and lacrimal sac. In addition, the tentorial nerve of Arnold innervates the dura of the frontal and middle cranial fossa and even tentorial branches go posterior toward the petrous bone, transverse sinus, anterior portion of the sagittal sinus. This division supplies blood vessels intracranially including the internal carotid artery and middle cerebral artery. The widespread innervation of the meninges may be important to explain the light sensitivity associated with meningitis and subarachnoid hemorrhage.

The three branches of the trigeminal nerve (ophthalmic, maxillary, mandibular) join at the Gasserian ganglion. From there they course through the trigeminal
photophobia, pain is produced. Before and after stimulation he showed that the irritated photophobia appeared. By using a "wink response rate" bia or photo-oculodynia—local causes in the eye and processes and reflexes. Photophobia one had to have a functioning optic nerve and photophobia. Lebensohn in 1934 stated that in order to get complaint in optic neuritis, but can occur in papilledema due to elevated intracranial pressure. Patients who experienced glare, photosensitivity, and a major contributor to the symptom with input into the mesencephalic migraine generator. Malecze et al. found that patients who experienced glare, photosensitivity and photophobia after laser in situ keratomileusis (LASIK) had more activity with light stimulation in the visual association cortices during functional MR testing.

Early experimentation showed that irritation of the eye (cornea, iris) produced photophobia. These experiments showed that there really may be two types of photophobia or oculo-oculodynia—local causes in the eye and more central causes. Eckardt et al. performed several experiments that illustrate the diseased eye causing photo-oculodynia (pain with light stimulation). In this type of photophobia, pain is produced.

First, he found that by mechanically irritating the surface of the eye with a foreign body (silk thread), photophobia appeared. By using a "wink response rate" before and after stimulation he showed that the irritated eye showed an increased wink response. A surface irritant (ethylmorphine hydrochloride, which causes vasodilatation and conjunctival edema) did the same. Winking immediately decreased and normalized by using a surface anesthetic (tetracaine) in both situations. This showed that irritation to the trigeminal afferents of the eye produced photophobia when exposed to light.

Eckhardt et al. also demonstrated that diseases of the iris provoke photophobia and increased blinking. Cycloplegics applied to this eye immediately slowed the blink rate.

Lebensohn had proposed that for the eye to exhibit photophobia, vasodilatation had to be present. Eckhardt et al. showed that after instilling a chemical surface irritant (ethylmorphine hydrochloride) there was profound vasodilatation and the usual increased blink rate. However, instillation of adrenaline, while completely ameliorating the vasodilatation, had no effect on the blinking response.

Eckhardt showed that surface sensitivity must be present to experience photophobia. When he repeated the above experiment with a chemical irritant and instilled tetracaine in one eye, the unanesthetized eye had 4-5 times the blink rate as the anesthetized eye. He further performed this experiment on an individual who had trigeminal nerve sectioning for tic doloreux, and the insensate eye had no increase in blink response after the chemical irritant was applied.

To determine if irritation to the trigeminal nerve (ophthalmic division) could result in photophobia, Eckhardt et al. injected sodium chloride into the frontalis muscle above the supraorbital margin. He showed that there was a 4-5 fold increase in the blink response on the affected side, which resolved as the pain decreased. This led Eckhardt et al. to conclude that trigeminal irritation anywhere along the ophthalmic division produces an increased light sensitivity and accounts for photophobia from local eye disease.

The lateral geniculate bodies may play a role in photophobia. The parvocellular pathway modulates color processing, while the magnocellular portion carries brightness. Both of these may be disturbed in migraine. It is the magnocellular neurons that are sensitive to luminance contrast that is so enhanced in migraine.

Eckhardt et al. looked to explain why photophobia was absent in Argyll-Robertson pupils, which are believed to occur because of dysfunction in the pretectal nuclei. This group demonstrated that there was no increased blink response from chemical irritation and this lack of photophobia was not due to the small pupil since even after dilating the pupil maximally, no increased blink response occurred. He proposed that these experiments localized photophobia to the pretectal nuclei (that connect to the mid-brain), that the sensory trigeminal system, together with the optic nerve produces photophobia and that the mechanism may be similar to "referred pain." They
further proposed (without experimental evidence), that the mesencephalic root and nucleus is involved since it is one component of the fifth cranial nerve with close connections to the optic fibers by way of the pre-tectal nuclei and the superior colliculus. They also proposed that the spinal nucleus and tract of V (caudal nucleus) must play a role since dysfunction of that nucleus causes a decreased corneal reflex similar to lesions in ophthalmic division of the trigeminal nerve.71

Cummings and Gittinger described a case of a man who after a stroke to the occipital lobe and thalamus developed “unusual sensitivity to bright light” that was not painful but “disagreeable.” These authors postulated that the delayed onset of the light sensitivity is similar to the delayed onset of dysesthesias and hyperpathia observed following thalamic infarctions, and that “central dazzle” or light sensitivity without pain is caused by a thalamic/midbrain/diencephalic lesion.7

Others propose that the occipital lobe is hyperexcitable in photophobia.72,73

Drummond proposes that photophobia is due to an enhancement of trigeminal and visual input into the brain stem. This can be accomplished by either some type of facilitation of excitatory mechanism into the input or by a reduction or release of the inhibitory mechanism of the visual input. Individuals with photophobia lose their normal inhibition to the sense of light.74 Furthermore he dissociated the pain with light from the perception of glare.21 Drummond also showed that the trigeminal nerve participates in photophobia but not phonophobia. He stimulated the trigeminal nerve of migraineurs by applying ice to the forehead. The visual thresholds of light sensitivity were lowered, but not the sound sensitivity threshold. This suggests that the trigeminal nerve definitely participates in photophobia of migraine but not phonophobia.75

Some suggest that visually elicited blink reflexes travel more through retinotectal projections than the occipital pathways. In this theory, it is postulated that light bypasses more visually related structures and is directed to the facial neurons via the tectum.75,76

Is there also a role for the sympathetic nervous system? We do know that the eye, orbit, and trigeminal branches receive extensive sympathetic input. Even the cornea may have sympathetic connections.77 It has been known for years that facial neuralgias that have been treated with trigeminal nerve sectioning can continue to produce pain that is only relieved by either sympathetic block or sectioning of the sympathetic ganglion branches (cervical or sphenopalatine ganglion).78 Early researchers like Davis and Pollock stimulated the superior cervical ganglion with current and produced evidence of pain on stimulation. They believed that the sympathetic input into the trigeminal nerves was the source of the pain.

Certainly, there is a large body of literature about sympathetic input to sensory nerves of the body in “reflex sympathetic dystrophy” or by its new name “complex regional pain disorder” (older names include causalgia or sympathetically maintained pain disorder). In general, any limb or area of the body may be injured, and in certain individuals, a continuous pain syndrome develops that can be followed by certain findings such as coolness to the skin, vascular discoloration, and occasionally dystonia. Usual treatment of this disorder involves sympathetic block to the involved limb. The proposed mechanism is sensitization of more central neurons (spinal in this case) with possible up-regulation of alpha-adrenoreceptors at the peripheral primary nociceptive afferents. The sympathetics arise in the hypothalamus, traveling down the spinal cord to C8-T1 where they synapse, exit, and rise to the cervical ganglion and form the internal carotid plexus. The sympathetic efferents follow the carotid artery to join the ophthalmic and nasociliary branches of the trigeminal nerve. Short ciliary nerves carry sympathetic supply to the blood vessels in the orbit and the long ciliary nerves supply sympathetic innervation to the pupil. Even the cornea receives sympathetic innervation. We considered that perhaps photosensitivity could be related at least in part to sympathetic stimulation.

We tested this observation in 6 patients who presented with severe light sensitivity that developed after corneal transplant for Fuch’s dystrophy, keratoconus, chemical keratitis, and head trauma. Individuals complained of severe light sensitivity. Our first patient had severe unrelenting pain and discomfort after her corneal transplant. She tried multiple medications before treatment to ameliorate the pain including tricyclic antidepressants and anticonvulsants. She became so dizzy after taking one anticonvulsant that she broke her leg. She underwent sympatholysis as a trial with such a great response that a controlled trial was undertaken in a masked fashion. Subsequently, four patients underwent 2 double-masked blocks of the superior cervical ganglion. All four had marked reductions in their symptoms with the local anesthesia but not the saline placebo. All patients had reduced spontaneous pain, light triggered pain, and interestingly there was also decrease in blinking, blepharospasm and dry eye sensation in most of the patients.79

This initial work led to second study in which 19 patients with photosensitivity and idiopathic blepharospasm underwent controlled sympatholysis. This study showed that 13/19 reported objective and subjective improvement in both the light-induced discomfort and the subsequent blepharospasm. Ocular surface disease was present in 18 of 19 of the individuals. The authors concluded that in some patients with blepharospasm with
ocular surface disease (dry eyes), a sympathetic mechanism may play a role.\textsuperscript{80}

**Hypotheses Related to Photophobia**

Lebensohn communicated to Frank Walsh (reported in the third edition): “Photophobia may accompany a lesion in any area supplied by the ophthalmic division of the trigeminal nerve. Whatever the cause, true photophobia is based invariably on the iris constriction to light; the only reaction that light evokes which is demonstrably capable of producing pain. The pupillary light reflex is not painful ordinarily and only becomes so after the iris has been sensitized to the trigeminal axon reflex producing vasodilatation and hyperalgesia. This common factor, the trigeminal pupillary reflex, is the link connecting all sources producing photophobia. The blink reflex is not a valid criterion of photophobia.”

Harold Wolff, the father of modern headache and migraine, was also interested in photophobia. He thought the “entire central mechanism of the sensory trigeminal including the mesencephalic root and nucleus constitute, together with the optic nerve, the neural mechanism for photophobia.”\textsuperscript{78}1 Furthermore, he proposed that although photophobia occurs with eye disease, the most dramatic and common causes are from the neurologic axis. He suggested that there are two types of photophobia: The first type is inflammation of the iris and ciliary body and that this type can be treated with cyclopia. His attention was directed to investigation of central causes. He proposed that the components of photophobia were skeletal muscle (blinking), smooth muscle (vasodilation), glandular (lacrimation) and sensory (pain). However, the central mechanism of photophobia involved the brainstem (possibly pre-tectal nuclei) and the cerebral cortex. He thought the best way to quantify photophobia was measure blink rate.

Wolff’s explanation for photophobia is:

“The afferent impulses from light entering the colliculus through the retina exert by spread an excitatory influence on the facial nerve nucleus causing the increase in winking frequency. The spread of the excitation from the site of noxious stimulation in the eye involves much of the trigeminal nerve nucleus. After spreading throughout the trigeminal nuclei, these afferent impulses exert additional excitatory influence on the facial nerve nucleus so as to augment further winking frequency. …. Afferent impulses from light on the retina entirely separate from those that go to the colliculus enter the external geniculate body. There through a synapse secondary disturbances are conveyed to the cerebral cortex. At neither the brain stem nor thalamic level is it possible for neurons involved in vision to be influenced or modified by spread of excitation from neurons involved with noxious stimuli. Such phenomena can take place only at the level of the cerebral cortex.”\textsuperscript{81}

More recently Pearce\textsuperscript{82} stated “photophobia and phonophobia are almost certainly primary cerebral mechanisms of excitation or of a heightened arousal of the special senses.”

Peter Drummond has come closest in thinking about photophobia. He believes that the sensitivity to light and glare is part of the hyperexcitability of the brain state especially in migraine, but the problem of light causing pain per se is the result of activation of trigeminal pain pathways and migraine aptly shows this distinction.\textsuperscript{19}

It seems there are really two sources of photophobia: anterior segment inflammation and stimulation of the corneal nerves. In this situation, dilation of the pupil may bring relief. However, there is clearly photophobia where pupillary dilation has no effect. This other type of photophobia must be from more central pathways. We do not know whether anterior segment inflammation uses the same pathways as more central causes (migraine, subarachnoid hemorrhage).

**How Do You Treat Photophobia?**

There are few neuro-ophthalmic problems that can be so vexing for practitioners to treat. Are there really any known treatments? What treatments exist for light sensitivity?

One treatment is to decrease the dark adapted state. Patients with severe photophobia who wear darkly tinted lenses should be encouraged to reduce the dark adaptation.

**Tinted Lenses**

Lebensohn early on cautioned that “tinted glasses as a symptomatic remedy for chronic photophobia is to be condemned because of both their ineffectiveness and their habit forming tendency. Later in 1951, however, he recommended the darkest shades of sunglasses.\textsuperscript{83}

Patients wearing sunglasses to an eye clinic has led many physicians to consider the patient to have some type of psychiatric disorder.\textsuperscript{84}

Sunglasses do make sense in the bright sunlight for patients with migraine, tension-type headaches and light sensitivity. Sunglasses with UV protection may further protect individuals from macular degeneration and cataract.\textsuperscript{85}

In ophthalmology clinics, patients are routinely urged not to wear sunglasses indoors. Sunglasses cause a dark adaptation—so that when one goes into the sunlight, the light is experienced more intensely. That would indicate that staying in the dark would make going into the light that much more painful. Think of how many people
without migraine wince coming out into the light after a matinee movie.
There have been reports that certain tinted lenses can reduce migraine. In their study in England, Good et al. found that FL-41, a rose-colored tint, reduced migraine frequency in children by over one-half. The authors contend that the FL-41 tint filters 80% of short wavelength 50 Hz flicker light that is seen with fluorescent lights, and therefore this reduces the number of headaches in patients with migraine. The primary affect as reported by the subjects was that there was a decrease in photophobia and glare in between attacks, but no change in the light sensitivity associated with the migraine attack.

We studied FL-41 tinted lenses and their effect in reducing light sensitivity and found that they increased the threshold to discomfort in all subjects (controls, migraineurs, and patients with blepharospasm), but they did not differ from gray tinted lenses in reducing light sensitivity. To test whether patients preferred FL-41 tint over gray tinted spectacles, we performed a double cross-over study of subjects with blepharospasm using gray and FL-41 tint. We found that patients preferred FL-41 tint over gray spectacles and that patients felt it significantly reduced their symptoms. (See presentation by Blackburn et al. at this meeting, NANOS 2005.)

Red-tinted contact lenses have been tested in individuals with photophobia and have been found to be successful in blocking all wavelengths of light, especially blue light. Why would red or pink tinted lenses show this effect? If the lateral geniculate body is involved in the sense of light sensitivity, diffuse red light (and not white light) is known to suppress magnocellular neurons. In addition, some authors have found that vision improved with red-tinted glasses or contact lenses in patients with cone dystrophy. Furthermore, red tinted lenses may block wavelengths of light that have been found to be most irritating to photosensitive individuals. A recent study showed that gray sunglasses that reduce all light transmittance improved photosensitivity thresholds for patients with migraine and blepharospasm. FL-41 tint in this preliminary study did not improve light sensitivity over traditional sunglasses. However, some patients with blepharospasm prefer these lenses over traditional gray lenses (See Blackburn, et al., NANOS 2005).

Medications
Lebensohn reported that cycloplegics can be used to give some relief when local factors are present. Sedatives that reduce "trigeminal irritability" are helpful (e.g., barbiturates), and allow for prolonged sleep and closed eyes.

Injections to the supraorbital nerve have been reported to reduce light sensitivity. Alcohol (40-60%) injected into the orbit (1.5 cc) was reported to be helpful in cases of ocular inflammation to reduce photophobia and did not influence visual acuity. Anti-inflammatory drops have been tested in reducing light sensitivity after cataract surgery and have not been found to be helpful. Lidocaine has been used after cataract surgery without decrease in light sensitivity. Sympathetic blockade was first reported by Magitot. Fine and Digre showed that superior cervical blockade by lidocaine did improve light sensitivity in some patients with photophobia as discussed above. This treatment may be best in patients who have had known injury to the anterior segment who, despite complete resolution of treatment, have continued photo-oculodynia and possibly depression. If depression is present, it would make sense to treat depression with anti-depressants.

This paper is taken in part from Digre, KB. Light sensitivity in migraineurs. Headache 2003; 43: 917-920. The work presented here in relation to blepharospasm was supported in part by a grant from the Benign Essential Blepharospasm Research Foundation.
Table 1: Causes of Photophobia

Ocular causes
Anterior segment
  Iritis, Cyclitis
  Keratoconjunctivitis
  Corneal diseases (e.g., Ichthyosis Follicularis Allopecia, Photophobia [IFAP])
  Uveitis
  Blepharitis
  Conjunctivitis
  Dry eyes
  Asthenopia
Posterior segment
  Vitreal disease (vitritis)
  Retinal causes: Cone dystrophy, Albinism, Achromatopsia, Retinitis pigmentosa
Optic Nerve
  Optic neuritis
  Papilledema, Idiopathic intracranial hypertension
Chiasmal
  Pituitary tumors (Kawasaki, Purvin)
  Craniopharyngioma
  Acromegaly (growth hormone pituitary tumor)

Occipital lobe
Meningeal: Meningitis
  Sub-arachnoid hemorrhage
Other: Blepharospasm
Neurasthenia (Lebensohn)
  Fibromyalgia
  Migraine
  Head injury
Psychiatric: Depression and agoraphobia

Table 2: The prevalence of eye strain factors in the headache group (from Arnaud et al.)

<table>
<thead>
<tr>
<th>Precipitation of HA</th>
<th>Aggravation of HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bright light</td>
<td>29.3%</td>
</tr>
<tr>
<td>Reading</td>
<td>16.0%</td>
</tr>
<tr>
<td>Computer screen</td>
<td>14.5%</td>
</tr>
<tr>
<td>Watching TV</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td>73.4%</td>
</tr>
<tr>
<td></td>
<td>56.3%</td>
</tr>
<tr>
<td></td>
<td>31.3%</td>
</tr>
<tr>
<td></td>
<td>27.7%</td>
</tr>
</tbody>
</table>

Table 3: Symptoms in 30 subjects with blepharospasm, migraine and controls. From Adams et al. (submitted for publication)

<table>
<thead>
<tr>
<th></th>
<th>Symptoms aggravated by light</th>
<th>Limitations because of light</th>
<th>Symptoms worsened during testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>———</td>
<td>29%</td>
<td>———</td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>41%</td>
<td>41%</td>
<td>52%</td>
</tr>
<tr>
<td>Migraine</td>
<td>48%</td>
<td>48%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Figure 1
This graph plots the log lux vs the test subjects. Subjects with blepharospasm and migraine are more light-sensitive than controls in all conditions. Both gray and FL-41 lenses raised the threshold of light sensitivity in all groups. (From Adams, et al., submitted).

Figure 2a
Thirty-one migraine patients underwent Raman measurements and were compared to 30 controls. Migraine patients follow the normal trend of having a decrease in Raman count with increasing age. The mean Raman measurement of each group was taken and compared decade to decade with control subjects. Raman values were increased in every decade compared to control subjects.

Figure 2b
Lutein and zeaxanthin measurements are higher in benign essential blepharospasm than in normal controls (p= 0.050). Blepharospasm patients follow the normal patient trend of decreasing Raman count with an increasing age.
CME Answers

1. Migraine, blepharospasm, psychiatric conditions, corneal disorders, meningitis, sub-arachnoid hemorrhage, (see table for complete list)
2. Colored spectacles, superior cervical ganglion block, anticonvulsants

References


78. Davis L, Pollock LJ. The role of the sympathetic nervous system in the production of pain in the head. *Arch Neurol Psychiatry* 1932; 27: 282-293.


