

CONTACT DERMATITIS OF THE EYE

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Delayed hypersensitivity reactions involving the eyelids and conjunctiva frequently cause an individual to seek medical attention whereas cutaneous reactions elsewhere on the skin are less of concern. Because it is soft, pliable, and thin, eyelid skin increases the eyelid's susceptibility to contact dermatitis. The skin is capable of developing significant swelling and redness with minor degrees of inflammation. Contact dermatitis is the most common eruption of the eyelid.

COSMETICS AND CONTACT DERMATITIS

The most common cause of contact dermatitis of the lids and periorbital area is cosmetics applied to the hair, face, or fingernails rather than to the eye area itself. It is important to bear in mind that the sites to which some of these cosmetics are applied may not be affected. This is particularly true for hair dye and nail polish. Allergic and irritant reactions to face creams, makeup (foundation lotions and bases), and blushers may likewise be limited to the eyelids.²⁰ Stinging and burning of the eyes and lids on application of an eye-area cosmetic are the most common complaints. These subjective symptoms are usually transitory and unaccompanied by objective signs of irritation. Evaporation of volatile components such as mineral spirits, isoparaffins, and alcohol and the presence of potential irritants such as propylene glycol and soap emulsifiers in eye-area formulations are among the principal causes

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of irritation. In some instances, tolerance increases with subsequent applications so that the offending product does not have to be discarded.

Contact dermatitis attributable to eye-area cosmetics is classified as either *allergic contact dermatitis* or *irritant (toxic) contact dermatitis*.¹⁷ The morphologic features of these two forms are not always readily distinguishable. The degree of inflammation may be of the same magnitude (usually mild to moderate), and the time interval may be the same between the initial exposure and the onset of the dermatitis for each one of these classes. The potential irritants in general cosmetics and specifically in eye-area cosmetics are usually weak. Thus, repeated exposures are often required to induce a reaction. In addition, not all exposed individuals react as they generally do with stronger irritants.¹⁹

Irritation Due to Mascara

Water-based mascara usually contains emulsifiers such as sodium borate and ammonium stearate formed by the interaction of stearic acid with ammonium hydroxide. These water-based emulsifiers can be irritating to conjunctival surfaces in certain individuals who may otherwise tolerate an anhydrous, waterproof mascara. Interestingly, individuals who may not tolerate waterproof mascara or waterproof eyeliner may very well tolerate their water-based counterparts. In the event that either form of emulsifier cannot be tolerated, a cake mascara or cake eyeliner can then be tried. Various cosmetic manufacturers have intentionally decreased their physiochemical contents of cosmetic formulations in hopes of subsequently decreasing their sensitization rates, e.g., Maybelline Cake Mascara and Ultra Liner Cake Eyeliner (Maybelline, New York, NY), Lumilane Cake Mascara (Orlane, Paris, France), whereas others have retained their highly complex formulations, e.g., Chanel's Compact Mascara (Chanel, Paris, France). Similarly, individuals who cannot use cream eyeshadow may tolerate pressed-powder eyeshadow and vice versa.

Irritation Due to Eye Cosmetic Preservatives

Parabens are extremely common in the majority of eye-area products in use today. These esters of parahydroxybenzoic acid are commonly used with other antimicrobial agents such as phenyl mercuric acetate, imidazolidinyl urea (Germall 115), or quaternium 15 (Dowicil 200) to ensure adequate protection against yeasts, molds, and bacterial contaminants. Paraben-free cosmetic formulations commonly use sorbic acid as a preservative, e.g., Clinique's Resistant Eyeliner and Basic Eye Emphasizer (Clinique, New York, NY).

Paraben-sensitive individuals, however, must not necessarily avoid paraben-containing cosmetics.⁹ Interestingly, patients sensitized to parabens may nonetheless be able to tolerate paraben-containing cosmetics even on the thin skin of the eyelids, provided the paraben-containing

product is applied to normal skin that has not been previously involved in cutaneous reactions. This has previously been called the *paraben paradox*.

Quaternium-15 and imidazolidinyl urea are well-known formaldehyde generators; of the two, quaternium-15 is a more active formaldehyde releaser than imidazolidinyl urea.¹⁵ Hypersensitivity reactions may be induced by the antigenic content or by the released formaldehyde.⁷ It is thought that imidazolidinyl urea may represent a safer preservative than quaternium-15 for formaldehyde-sensitive individuals. Other compounds, including potassium sorbate, also have been used as a preservative in eye-area products, although potassium sorbate has also been reported to cause sensitization.⁸ *Di-isopropanolamine*, used in cosmetic gloss formulations such as eyeshadow and "blushing" gel, has been reported to produce cutaneous hypersensitivity reactions consistent with allergic contact dermatitis.⁵ *Ditertiarybutyl hydroquinone*, an antioxidant in eyeshadow products, has also been reported to produce an eyelid dermatitis,² as has eye cream owing to the presence of yellow D & C No. 11 dye.³

Nail Polish Dermatitis

Nail polish contains a toluene-sulfonamide formaldehyde resin that has been identified as a sensitizing agent. It is the dry nail polish that becomes polymerized and is not known to be a sensitizer.⁶ The cosmetic industry has developed "hypoallergenic" nail polish by replacing toluene-sulfonamide formaldehyde resin with a polyester resin, e.g., Clinique. Interestingly, the cutaneous hypersensitivity seen in sensitized individuals on the eyelids or on other parts of the body that come into contact with nail polish is not seen on nailbeds or paronychia areas. This form of dermatitis has been labeled as an *ectopic dermatitis*, i.e., sensitivity in areas other than the site of application of the sensitizing agent. Similarly, hair cosmetics (e.g., hair dyes, bleaching agents containing ammonium persulfate, perfumed hair sprays, hair setting lotions, and shampoos containing formaldehyde) may produce an ectopic form of cutaneous hypersensitivity, i.e., affecting the eyelids without producing scalp or forehead dermatitis. Sensitivity to paraphenylenediamine or ammonium persulfate commonly may produce marked edema of the eyelids.

Irritation Due to Conjunctival Deposition

Conjunctival pigmentation can be caused by the application of eyeliner to the conjunctival side of the lid instead of the exterior lid just in back of the lashes.^{14, 25} The observation of deposited eyeliner pigment is commonly missed on physical examination unless the upper lid is everted to bring the aggregates of pigment deposited along the upper margin of the tarsal conjunctiva into view. Eyeshadows may generate a radiopaque curvilinear supraorbital shadow on radiographic examina-

tion of the skull due to radiodense bismuth, magnesium silicate, and iron oxides found in many formulations.¹⁰ Although some patients complain of discomfort, tearing, and itching, most are asymptomatic and do not require treatment.

In addition to eyeliner and eyeshadow, artificial eyelashes are known to cause ocular hypersensitivity reactions. Artificial eyelashes consist of a variety of synthetic or natural fibers, including human hair mounted on a thin fabric strip. The adhesive used to attach artificial eyelashes is a mixture of rubber latex, cellulose gums, casein solubilized with a very mild alkali or other resins, and water. The adhesive is formulated to be nonirritating and to permit easy removal of the lashes by simply peeling them off. This rubber latex rarely irritates the eyelids and as yet no known cases of latex hypersensitivity reactions have been reported from this source.

Eyelash curlers and tweezers are commonly nickel plated and thus may induced reactions in nickel-sensitive patients. There are instruments made from stainless steel that provide an alternative to sensitive patients who use such items. There are also some older forms of rubber-tipped eyelash curlers that can induce a dermatitis from rubber sensitivity.

MEDICATIONS AND CONTACT DERMATITIS

The eye is a frequent site of involvement in contact dermatitis.¹¹ There is a significant incidence of conjunctival and eyelid contact hypersensitivity to neomycin sulfate in patients treated with this topical medication for conjunctivitis.²² This may lead to excessively prolonged conjunctivitis or presumed lack of therapeutic response and the addition of unnecessary topical antibiotics to the treatment regimen.

A typical victim of conjunctivitis medicamentosa is a patient who is initially treated for a "red" eye of an entirely different etiology. Topical medications for the eye are prescribed, and the patient's symptoms start to improve. The patient continues the topical application of the medication, and the eye starts to become more injected. More ocular medications, usually of a different type are used, and a vicious cycle of inflammation begins. It becomes difficult to tell whether the conjunctivitis is related to the original disease or the medication. Usually, the best treatment is to stop all eye drops, see the patient in a few days, and sometimes perform cultures and conjunctival scrapings.

The skin of the eyelids usually becomes erythematous, edematous, and ulcerated. The conjunctivitis may take on a more chronic form characterized by a papillary response, pronounced vasodilation, chemosis, and watery discharge. In more severe cases, a keratitis can develop that involves small to large corneal epithelial defects and opacities. Some of the most severe responses are associated with topical anesthetics. Some long-standing cases also have occurred with glaucoma medications.¹⁶

Irritation Due to Ophthalmic Preservatives

Preservatives have been shown to cause conjunctivitis and eyelid dermatitis in sensitized individuals.²⁴ Benzalkonium chloride and thimerosal (Merthiolate) are some of the most widely used ophthalmic preservatives. Chlorobutanol is a rare sensitizer and is commonly used when allergic reactions are present to thimerosal or benzalkonium chloride.

All multidose vials of ophthalmic agents usually contain a preservative. Preservative-free lubricants come in single-use disposable units and are more expensive. A multidose lubricant that is preservative-free contains sodium perborate as a preservative, which generates a low level of hydrogen peroxide within the solution. When the solution is placed in the eye, the sodium perborate immediately degenerates into water and oxygen via the enzymatic action of catalase. Catalase and glutathione peroxidase naturally occur in the human conjunctiva and have been shown to very quickly reduce topically applied H_2O_2 .⁴ It appears that H_2O_2 is not detectable by the human eye until one reaches concentrations greater than 210 ppm H_2O_2 .²¹ At concentrations from 400 to 800 ppm H_2O_2 , subjects reported transient, moderate stinging and conjunctival hyperemia. The clinical sensitivity to H_2O_2 resolves within 2 minutes after insertion and does not appear to decrease or slow down in patients over the age of 60 when compared with those under this age.¹⁸

Preservatives such as thimerosal are also found in contact lens cleaning solutions and may cause irritation. This ocular hypersensitivity reaction responds to changing to other cleaning solutions that are preservative-free. Interestingly, epinephrine hydrochloride in the form of Pro-pine, which is used in the control of glaucoma, has been found to cause a local ocular hypersensitivity in some patients as proven by patch testing.¹²

OTHER SOURCES OF IRRITATION

Paper

Facial tissue papers containing perfume, formaldehyde, or benzalkonium chloride may produce dermatitis in sensitized individuals. Newsprint and carbon paper products have been associated with eyelid dermatitis, particularly in certain individuals who are sensitized to formaldehyde.

Plants

Classically, the *Rhus* genus of plants, in particular, can produce marked swelling of the eyelids with minimum dermatitis to the face. Marked edema of the eyelids is often a feature of poison ivy and hair-

dye dermatitis. This can also occur from the burning of poison ivy leaves in the fall. Other airborne contactants that also can induce eyelid dermatitis include household sprays, insecticides, animal hairs, and occupational volatile chemicals. In the home, the oil of lemon peel and the dyes of Florida orange skin can cause eyelid dermatitis. In the winter months when wood fireplaces are in use, the phosphorous sesquisulfide in "strike anywhere" matches may produce marked eyelid dermatitis or contact urticaria.^{1, 13, 23}

DIAGNOSIS OF CONTACT DERMATITIS

The patch test is also used to diagnose the response to allergens and irritants on the eyelid or conjunctival surface. As in the determination of reactions at other sites, erythema and/or edema at the patch test site may be elicited by either a toxic or immune-mediated reaction. An eczematous vesicular reaction diagnostic of delayed allergic hypersensitivity in response to potential allergens in eye makeup is by no means the rule. Interpretation of patch test results may be difficult, and the likelihood of irritant false-positive reactions must be kept in mind.

The Draize test and its variants are the standard methods for determining the ocular injury potential of liquids and solids. The animal model has shown only a fair correlation to human ocular responses. Screening protocols have been developed for ophthalmic formulations. They include the following:

- A 1-day acute (short-term) ocular irritation test
 - A 5-day ocular irritation test
 - A 21-day topical ocular irritation test
 - Subchronic (i.e., 1–3 month) and chronic (1–2 year) topical ocular irritation test
1. The 1-day acute (short-term) animal model ocular irritation test uses multiples of the active ingredients (when possible) and includes a similar marketed product, if available, for comparison. This test is used prior to release of an ophthalmic formulation for ingredients that have been placed in Category I by US Food and Drug Administration (FDA) ophthalmic panel(s). In the 1-day test, 0.03 to 0.05 mL of the test materials are instilled every 30 minutes for 6 consecutive hours, using at least six eyes. The 1-day acute model does not reflect human usage, because most, if not all, over-the-counter and prescription ophthalmic formulations are to be used several times per day.
 2. The 5-day ocular irritation test uses multiples of the active ingredients and includes marketed products. The dosing regimen should be similar to the clinical regimen. This study is an extension of the 1-day test and may be in addition to or in lieu of the 1-day test for ingredients placed in Category I by FDA ophthalmic panel(s). It is used to confirm findings from the 1-day test. In the

5-day test, 6 eyes are used, and the animals are dosed at the regimen similar to that to be used clinically. The eyes are evaluated every day for 5 consecutive days by slit-lamp observations. Examinations are usually done 1 hour after the last dose of the afternoon.

3. The 21-day topical ocular irritation test is more commonly used for establishing safety. Drugs intended for chronic therapy are evaluated in a preclinical test system for a minimum of 1 year. Using multiples of the active ingredients, when possible, is essential, as is including a marketed product, when available. Dosing is according to the anticipated clinical regimen by the manufacturer. This study is used for ingredients that have not been previously used by the topical ocular route. Hematology, clinical chemistry, urinalysis, and histopathology testing is not included if the ingredients have adequate published safety data or an FDA panel has placed them in a Category I rating by some other route of administration.
4. The subchronic (i.e., 1–3 month) and chronic (1–2 year) topical ocular irritation test with systemic toxicologic studies also uses multiples of the active ingredient as well as a comparable marketed product. The regimen tested is similar to the clinical dosing regimen. Because the ingredients have not been investigated by any route and have no category rating by any FDA ophthalmic panel or there are no published toxicology data, systemic toxicity is monitored by including hematology, clinical chemistry, urinalysis, and histopathology testing of tissues, including the eyes.

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