



Hypersensitivity reactions to products and devices in plastic surgery

David E. Cohen, MD, MPH^{a,*}, Julie M. Kaufmann, BA^b

^a*The Ronald O. Perelman Department of Dermatology, New York University School of Medicine,
560 First Avenue, Room H100, New York, NY 10016, USA*

^b*Joan and Sanford I. Weill Medical College, Cornell University, NY, USA*

Hypersensitivity reactions

The plastic, reconstructive, and cosmetic surgeon currently has a large armamentarium of procedures and products designed to improve the aesthetic features of patients. Exposures to potential contact irritants and allergens are plentiful in these settings, and the clinician should be aware of adverse reactions to commonly administered products. The overwhelming majority of these reactions are treatable without sequelae when the cause is elucidated and avoidance and treatment is initiated. The objective of this article is to familiarize individuals who participate in aesthetic procedures with the most commonly encountered chemicals that result in hypersensitivity reactions.

There are three basic forms of cutaneous hypersensitivity, irritant contact dermatitis, allergic contact dermatitis, and contact urticaria, although many subgroups exist. Contact dermatitis as a group represents an important cause of inflammatory skin disease in the United States. Fifteen million Americans are estimated to have or have had contact dermatitis. Of these cases, the majority are caused by irritant contact dermatitis, which is a nonimmune-mediated dermatosis resulting from a direct toxic response of the skin to the offending agent. Consequently, sensitization and

allergy are not integral to the genesis of irritant contact dermatitis; however, the elaboration of cytokines and cellular infiltrates are requisites to the development of a frank eruption.

Irritant contact dermatitis

There are currently over 57,000 described irritants worldwide, ranging from weak or marginal irritants to strongly corrosive acids and bases (see Box 1).

Box 1. Common irritant chemicals

Acids and alkalis

- Organic and inorganic

Solvents

- Alcohols
- Aldehydes
- Ketones

Soaps, detergents, and surfactants

Petroleum

Tars

Metal salts

- Antimony
- Arsenic
- Chromium
- Cobalt
- Nickel
- Mercuric
- Zinc

* Corresponding author.

E-mail address: david.cohen@med.nyu.edu
(D.E. Cohen).

Extrinsic variables such as concentration, pH, temperature, duration of exposure, repetitiveness of contact, and occlusion impact greatly on the development of irritation. Hence, occasional exposures to weak irritants like soaps and detergents rarely cause an eruption, whereas repetitive exposures such as frequent hand washings will often result in irritant dermatitis [1]. Additionally, repetitive, harsh scrubbing with mechanical assistance (eg, brushes), as is frequently performed prior to donning gloves for surgery, also presents increased risk for surgeons and assistants [2]. The irritancy potential of specific products might be harnessed for the purpose of selectively destroying the superficial layer of the skin. Glycolic acid, salicylic acid, resorcinol, trichloroacetic acid, and phenol are commonly employed “peeling” agents that act as corrosive irritants in controlled settings. The quality and depth of the irritancy is determined in these settings by the agent used, the concentration, and the time of exposure. Predictive testing for marginal or weak irritants is currently not as reliable as that for allergic-based skin disease. The repeat insult patch test and measures of transepidermal water loss are among the surrogates for assessing irritancy of chemicals, but they might not reflect or predict the impact of various exposures on a large population of individuals.

Allergic contact dermatitis

Allergic contact dermatitis represents true delayed-type (type IV) hypersensitivity that presents as an eczematous dermatitis and comprises approximately 10% to 20% of all cases of contact dermatitis. This clinical scenario can range from mild erythema and scale with minimal itch to vesicular, bullous, indurated plaques that are intensely pruritic. Initial sensitization is required for the subsequent expansion of a reaction when exposure occurs again. Chemicals that are capable of eliciting allergic dermatitis are usually small molecular weight chemicals that complex with epidermal proteins prior to processing by Langerhans cells. These epidermal dendritic cells digest the allergen complex and display the antigenic site on their cell surfaces for presentation to T cells. Should genetic susceptibility exist, clonal expansion of lymphocytes occurs. Lymphocyte- and keratinocyte-derived cytokines such as interleukin 2 and γ -interferon recruit T cell infiltrates, which results in the classic clinical and histologic patterns of contact dermatitis. Diagnostic testing for delayed-type hypersensitivity reactions is accomplished through patch testing. Patch testing is distinct from prick or scratch testing, which require a breach in the

epidermal barrier for a reaction to be elicited. In patch testing, epicutaneous application of allergens is performed by placing standardized concentrations of allergen chemicals on flat metal chambers placed on tape. These patches are applied to intact skin on the back and remain in place for 48 hours. They are read at the time of removal and again 1 to 5 days later. The presence of induration or vesicles with erythema under a specific chemical test denotes a positive reaction. To date, more than 3000 chemicals have been identified as delayed-type hypersensitivity allergens [3].

Allergic contact urticaria

Allergic contact urticaria is immediate-type hypersensitivity that represents a true allergic reaction. As the name implies, reactions occur within minutes to hours and might be limited to the site of exposure on the skin or, in severe cases, reactions can be generalized. The pathophysiology is based on immunoglobulin E binding to protein allergens, resulting in the release of histamine and other mast cell products such as prostaglandins, leukotrienes, chemotactic factors, enzymes, cytokines, and proteoglycans. Nonallergic variations of contact urticaria have been reported that result in release of mast cell products in the absence of sensitization and specific IgE antibodies. Clinically, patients might describe localized itching on the exposed site with accompanying signs of urticaria (wheals and flares). In highly allergic individuals, mucosal exposures, or large exposures, the symptoms of immediate-type hypersensitivity can generalize and include conjunctivitis, cough, bronchoconstriction, hypotension, anaphylaxis, and (occasionally) death.

Natural rubber latex and rubber allergy

While the contact urticaria syndrome has been described from exposures to foods and chemicals, a substantial volume of literature exists for contact urticaria and immediate-type hypersensitivity to natural rubber latex. There are two types of allergy to rubber products: type I—immediate-type hypersensitivity/contact urticaria and type IV—delayed-type hypersensitivity/contact dermatitis. Contact dermatitis has been a well-recognized problem for decades; however, latex allergy was generally recognized in patients in the early part of the 1990s with anecdotal cases being reported earlier [4].

Contact urticaria—latex

Allergy to the proteins derived from the milky sap of the *Hevea brasiliensis* tree can produce the classic signs of immediate-type allergy described above. Patients at risk for these reactions include children and adults with histories of spina bifida, genitourinary tract abnormalities, multiple surgical procedures, frequent occupational or mucosal exposure to latex products, hand dermatitis, atopy, female gender, and fruit allergy. Inquiries regarding risk factors and symptoms of pruritus and rash associated with exposure to rubber products should be performed prior to surgery. The reconstructive surgical theatre provides many potential exposure sources for latex, including surgical gloves, drains, bandages, stoppers, pressure cuffs, and stockings. Glove powders can serve as airborne vectors for latex protein, which can result in systemic symptoms in susceptible individuals who breathe the aerosolized mixture. The reader is advised to refer to the references to familiarize themselves with the details of potential exposures [5,6]. The evaluation and diagnosis of latex allergy rests with the detection of latex-specific IgE or the provocation of a wheal and flare reaction when challenged with latex in a controlled setting. Radio allergeo-sorbent tests are commercially available and are FDA approved for the detection of these antibodies. In the presence of a negative test and a suspicion of allergy, use and prick tests can be undertaken [7]. Treatment is principally avoidance of latex products and performance of procedures in latex-safe environments. Patients experiencing immediate-type hypersensitivity reactions should be medicated commensurate with the severity of their reaction. Treatments include antihistamines, epinephrine, and corticosteroids.

Contact dermatitis—rubber

Allergic contact dermatitis to rubber products is the result of a delayed-type allergy to component chemicals added to the latex sap rather than the protein, as described in latex allergy. Classically, erythema, scale, and lichenification might be noted at the site of exposure to the rubber device, and they sharply demarcate where the exposure stops. Examples include dorsal hands with cutoff at the wrist from gloves or circumferential dermatitis on the lower abdomen from rubber in a waistband of underwear. Chemicals that are responsible for these reactions are typically the accelerators, which are added to control and catalyze the polymerization process of the latex sap. Such accelerators include thiurams, carbamates, mercaptobenzothiazole and its derivatives, and thio-

ureas. Antioxidants, vulcanizers, fragrances, and colorants can also contribute to contact dermatitis. Powders placed in gloves as donning aides can cause irritant dermatitis through the frictional action of repeatedly applying gloves. Treatment involves detection and avoidance of the provoking allergen and minimization of the eruption with topical steroids and other anti-inflammatory agents.

Biocides

Biocides are products that kill biologic agents including bacteria, fungi, and viruses. In the aesthetic arena, biocide exposure occurs in two settings: preoperative cleansers/preparation solutions and topical antibiotics.

Skin cleansers

The preparation of the skin prior to procedures accomplishes two important functions: removal of overt dirt and oil from the surface of the skin and reduction of viable, potentially infectious agents. Antiseptic biocides destroy or prevent the growth of microorganisms when applied to living tissue. They should ultimately retain this antimicrobial activity in the presence of tissue and body fluids without deleterious effects. Disinfectants destroy microorganisms on inanimate objects and should not harm the surfaces to which they are applied. Commonly used solvents such as alcohol and acetone are marginal irritants that rarely cause significant skin disease. Box 2 lists some commonly used antiseptics and disinfectants, most of which have been reported to cause allergic and irritant contact dermatitis. Discussed below are the agents that are most frequently implicated as sensitizers in the surgical setting. The practitioner should be cognizant of the potential for hypersensitivity reactions to these products. Perioperative or peri-incisional lesions that

Box 2. Topical antiseptics and disinfectants [34]

Mercury

Thimerosal (merthiolate)
Merbromin (mercurochrome)
Phenylmercurates (acetate, nitrate, bromide, benzoate)
Mercury chloride
Mercurous chloride

Iodine

Tincture of iodine
Povidone iodine (betadine)

Chlorine

Sodium hypochlorite
Chloramine
Chlorhexidine
Chloroxylenol
Chlorocresol
Hexachlorophene

Quaternium ammoniums

Benzalkonium chloride

Miscellaneous

Triclosan
Triclocarban
TEGO (dodecyl aminoethyl glycine
hydrochloride)
Benzoyl peroxide
Gentian violet

are erythematous, scaly, and indurated should have allergic and irritant contact dermatitis included in the differential diagnosis. When antibiotics are initiated for a presumed infection, consideration of changes in topical postoperative wound care should also be entertained. Future avoidance of suspect perioperative wound cleansers and topical antibiotics should also be considered.

Povidone-iodine is a frequently used antiseptic containing iodine in a base of Povidone or polyvinyl pyrrolidone. It is less irritating than a tincture of iodine, which can contain between 2% to 7% iodine and sodium iodide in alcohol. Cases of allergic and irritant contact dermatitis are reported in the literature as well as rare cases of immediate type hypersensitivity [8].

Thimerosal is an organic, mercury-based preservative that is used worldwide as an antiseptic and preservative. It has been frequently present in vaccines and ophthalmic products as a preservative and it is used as a topical wound antiseptic. Thimerosal is one of the most commonly encountered contact allergens in North America; 10.9% of individuals suspected of having allergic contact dermatitis were allergic to it. In the United States, the substitution of

mercurial antiseptics with less allergenic biocides has resulted in fewer clinically significant allergy test reactions. This lack of relevance has prompted the designation of Thimerosal as the “non” allergen of the year by the American Contact Dermatitis Society because the prevalence of reactivity is high, but actual clinically relevant exposure topically is quite low [9]. Caution should still be exercised when utilizing mercury-based compounds because the potential for allergic reactions remains high.

Chlorhexidine is a frequently used antiseptic for hands and operative sites because of its impressive anti-gram-negative and -positive bactericidal action even in the presence of body fluids. It has supplanted many of the ammonium antiseptics, and cases of contact dermatitis are rare. A few cases of immediate-type hypersensitivity and anaphylaxis have been reported following cutaneous exposure to Chlorhexidine-containing cleaners [10].

Quaternary ammonium preservatives such as benzalkonium chloride are frequently present in ophthalmic preparations as preservatives because they have largely replaced mercury-based preservatives in these product lines. These biocides are also commonly used as preoperative cleansers. Contact dermatitis is a reported adverse reaction to benzalkonium chloride, and in a large study of patch-tested individuals, 1.8% of individuals were allergic to it [11].

Antibiotics: bacitracin and neomycin

A perusal of the most common cutaneous allergens that cause allergic contact dermatitis in North America (Table 1) reveals that two of the top ten contact allergens are routinely utilized topical antibiotics. When other nonantibiotic biocides are included, this family of chemicals occupies five of the top ten positions.

Topical antibiotics are commonly employed for prophylaxis and treatment of postoperative and accidental wounds. Though use is often patient-initiated, these products are important causes of iatrogenic contact dermatitis. Severe cases of contact dermatitis from topical antibiotics can be mistakenly diagnosed as cellulitis with the subsequent provision of hospitalization and parenteral antibiotics. Current literature suggests that the routine use of topical antibiotics such as bacitracin does not provide protection from postoperative infections that is superior to the protection derived from petrolatum use [12].

Bacitracin is one of the most frequently utilized topical antibiotics. It is available in over-the-counter preparations as a sole antimicrobial in petrolatum or mixed with polymyxin and neomycin in combinations products. Bacitracin, which interferes with

Table 1
Top North American contact allergens in North America

Allergen	% ^a
Nickel Sulfate (metal)	14.2
Neomycin (antibiotic)	13.1
Balsam of Peru (fragrance)	11.8
Fragrance mix (fragrance)	11.7
Thimerosal (preservative)	10.9
Sodium gold thiosulfate (metal)	9.5
Formaldehyde (preservative)	9.3
Quaternium-15 (preservative)	9.0
Cobalt chloride (metal)	9.0
Bacitracin (topical antibiotic)	8.7
Methyl dibromoglutaronitrile (preservative)	7.6
Carba mix (rubber)	7.3
Ethylene urea melamine form (textile resin)	7.2
Thiuram mix (rubber)	6.9
Phenylenediamine (hair dye)	6.3
Propylene glycol (solvent)	3.8
Diazolidinyl urea (preservative)	3.7
Lanolin (emollient)	3.3
Imidazolidinyl urea (preservative)	3.2
Bromonitropropane (preservative)	3.2
MCI/MI (preservative)	2.9
Cinnamic aldehyde (fragrance)	2.8
Potassium dichromate (metal)	2.8
Ethylenediamine (stabilizer)	2.6
DMDM hydantoin (preservative)	2.6
Glutaraldehyde (biocide)	2.6
Tixocortol pivalate (corticosteroid)	2.3
Benzocaine (anesthetics)	2.0
Colophony (rosin)	2.0
Epoxy resin (adhesive)	1.9

^a Percentage of tested individuals with positive reactions. From Marks JG, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 1996–1998. *Arch Dermatol* 2000;136:272–3; with permission.

bacterial wall synthesis, is derived from the bacteria *Bacillus subtilis*. In 4103 patients with suspected contact dermatitis, 8.7% of individuals were allergic to Bacitracin, with more than 50% of those reactions deemed clinically relevant to the eruption that was being evaluated [13]. In a study of ambulatory surgery patients, 0.9% of bacitracin-treated individuals developed an allergic reaction. None of the petrolatum-treated individuals developed contact dermatitis, and there was no statistical difference in the frequency of infections between the groups [14]. Bacitracin has also been reported to cause immediate-type hypersensitivity reactions (including anaphylaxis) following application to skin surfaces [15] and during irrigation of wounds [9]. Reactions to topical antibiotics like bacitracin and neomycin might be delayed for several days, causing confusion regarding the cause of a worsening eruption. Clin-

ical, recognizable reactions might take several days of continuous application, thus disassociating a causal relationship in the differential diagnosis [16].

Neomycin is an aminoglycoside antibiotic that is currently the second most commonly tested contact sensitizer in North America [13]. Neomycin interferes with protein synthesis through its interference with the 30s ribosomal unit. It also interferes with the reliability of the translation of mRNA. Aminoglycoside antibiotics are derived from *Streptomyces* species, with neomycin being isolated from *Streptomyces fradiae* [17]. It is the most commonly used topical antibiotic and it is present in a variety of preparations for the skin, eyes, and ears. In 3436 patients suspected of having allergic contact dermatitis, 13.1% of individuals were allergic to neomycin and 46% were deemed to be clinically relevant [13]. In a population of volunteers without contact dermatitis, 1.1% of individuals were allergic to neomycin [18]. Allergic reactions to neomycin are even more prevalent in individuals with stasis ulcers, chronic otitis externa, and eczematous (atopic) dermatitis [19]. Neomycin is the allergen of choice for allergy screening to the aminoglycoside antibiotics. Individuals who react to neomycin might crossreact with other agents in the same class, including gentamicin, kanamycin, paromomycin, amikacin, tobramycin, spectinomycin, and streptomycin. Patients who are allergic to neomycin might develop widespread, eczematous-like dermatitis following the systemic administration of aminoglycoside antibiotics [20]. Caution should be used when employing aminoglycosides in patients with known cutaneous hypersensitivity to neomycin. Bacitracin and neomycin are chemically distinct moieties, so they probably do not crossreact; however, coreactions to both of these antibiotics are common. Consequently, the use of bacitracin in neomycin-allergic patients and vice versa might not provide adequate protection from allergic reactions. Mupirocin, erythromycin, and clindamycin are easily available alternative antibiotics in patients who are allergic to neomycin and bacitracin and have substantially lower reported prevalence of allergic contact reactions.

Local anesthetics

The importance of local anesthetics to dermatologic and plastic surgery cannot be overstated. While generally well tolerated, reports of adverse reactions to these agents are somewhat frequent. Patients often convey a previous allergy to local anesthetics; however, true immunologically mediated allergic reactions are rare [21]. Adverse events are more likely

attributable to the preservative, antioxidant, or metabolites, not to the anesthetic itself [22].

All local anesthetics share three structural components—a lipophilic group, an ionizable hydrophilic group, and a conjoining intermediate group. Variations in intermediate chains account for the principal differences between group I (ester) and group II (amide) agents (Table 2). The antigenicity of ester-type local anesthetics (eg, procaine hydrochloride) has been firmly established by patch testing [23]. Hydrolysis by plasma cholinesterase and other non-specific esterases produces p-aminobenzoic acid (PABA), a metabolite that is thought to be responsible for the relatively high incidence of allergic reactions to these agents. The more widely used amide-type local anesthetics include such agents as lidocaine and its structural derivatives [24]. These agents are stable to plasma hydrolysis, undergoing enzymatic degradation in the liver instead. Amide preparations are therefore not metabolized to the antigenic PABA; however, patch test-confirmed, delayed-type hypersensitivity reactions to amide preparations have been reported in the literature, albeit infrequently [21, 25–28,75–77].

Adverse reactions to injectable anesthetics might result from true allergy, normal or idiosyncratic toxic overdose, or non–drug-related reactions (eg, psychogenic or vasovagal reactions) [29]. Less than 1% of adverse events to local anesthetic preparations are true allergic reactions [24]. Immunologic disease (ie, true allergy) can be one of two specific types:

(1) IgE-mediated, “anaphylactic” reactions (urticaria, angioedema, bronchospasm, or, in severe cases, hypotensive shock), and (2) contact dermatitis—a T-cell mediated delayed-hypersensitivity reaction. IgE-mediated reactions manifest within minutes to hours of introduction of the offending agent, whereas cutaneous sensitization in the elicitation of contact dermatitis response might take as long as 72 hours.

Topical anesthetics can also generate allergic reactions. The allergenic ester derivative group, which includes benzocaine, procaine, and amethocaine (tetracaine), used to be popular for treatment of pruritus ani, hemorrhoids, or pruritus vulvae. Delayed-type hypersensitivity (eczematous dermatitis) has been commonly associated with topical application of ester preparations; however, reports of contact allergy developing after exposure to amide preparations are rare [26–28]. Thus, agents from the amide and other less allergenic classes have largely replaced the esters as topical agents of choice. Among the more commonly used agents is a quinolone derivative, dibucaine (cinchocaine). Though relatively less allergenic than the esters, this agent can cause allergic contact dermatitis and systemic contact dermatitis [13].

As use of the less allergenic amide topicals becomes more widespread, cases of sensitization by these agents accumulate. Contact sensitization to prilocaine is rare and has been primarily induced by EMLA (Astra, Astra Zeneca Pharmaceuticals LP, Wilmington, DE) cream, a eutectic mixture of local anesthetics [13]. EMLA is an emulsion of 2.5% lidocaine and 2.5% prilocaine. EMLA cream is useful as an anesthetic for procedures such as venopuncture, shave and punch biopsies, molloscum contagiosum curettage, split-thickness skin grafts, debridement of chronic leg ulcers, chemical peels, and vascular laser treatments. The agent is also useful as an adjunct to local anesthetic preparations in dermabrasion and laser resurfacing. EMLA is limited by its ineffectiveness on palmar and plantar surfaces. The onset of cutaneous analgesia is largely dependent upon anatomic location and the duration of application. Dermal analgesia typically peaks at 2 to 3 hours after application and persists for as long as 2 hours after removal.

Minor application-site side effects include paleness, redness, alteration in temperature, sensation, edema, itching, and rash. Local reactions can be exacerbated by repeated applications, but they usually resolve after discontinuation. A known history of sensitivity to amide-type local anesthetics is a contraindication for the use of EMLA [30]. Though rare, there are reports of EMLA-induced hypersensitivity [31]. In one report, five patients developed a purpuric reaction within 30 to 60 minutes of topical applica-

Table 2
Classification of topical anesthetics

Amides	Esters
Dibucaine hydrochloride	<i>Aminobenzoate esters</i>
Lidocaine	Benzocaine
Prilocaine	Procaine
Bupivacaine	Tetracaine hydrochloride
Mepivacaine	
<i>Aminoalkyl amide</i>	<i>Benzoic acid esters</i>
Dibucaine	Cocaine hydrochloride
	Hexylcaine hydrochloride
	Piperocaine hydrochloride
	Proparacaine hydrochloride
<i>Miscellaneous</i>	
Cyclomethycaine	
Dimethisoquin	
Dipero don	
Dyclonine	
Pramoxine	

tion of EMLA with Tegaderm (3M Company, St. Paul, MN) occlusion. A direct, toxic effect on capillary endothelium is thought to be responsible because subsequent immediate and delayed patch tests failed to confirm sensitization [32]. When true allergy is confirmed, skin testing will generally reveal a positive reaction to prilocaine but no reaction to lidocaine. Reports of allergy to lidocaine are rare and derived mostly from Australia, where products containing lidocaine are sold over the counter [13].

In general, extensive crossreactivity has been documented among esters, whereas amide preparations have not demonstrated significant crossreactivity [23]. Existing reports are contradictory, demonstrating the inherent difficulty of predicting specific cross-reactivity among amide anesthetics [21–23,26,27]. Of note, methylparaben is a widely used preservative in ester and amide preparations. Metabolism of this agent yields PABA; thus, PABA-allergic individuals might demonstrate apparent crossreactivity between members of both classes that contain this preservative agent [33]. Delayed-type hypersensitivity to a paraben mix was demonstrated in 1.7% of individuals with suspected contact dermatitis [34].

Allergy to local anesthetics should be considered in the differential diagnosis of a localized, delayed-type hypersensitivity reaction that develops and recurs at sites of surgical procedures. Testing to an anesthetic allergen series, which includes both ester and amide preparations, is recommended to confirm a positive suspected result and to include or exclude other relevant anesthetic allergens. Insofar as methylparaben is a standard ingredient of many local anesthetic preparations, sensitivity to this preservative must be ruled out when evaluating potential allergic reactions to local anesthetics. When applicable, testing with paraben-free and paraben-containing preparations should be performed [21]. Patch test results have obvious profound clinical implications because they help to define which—if any—anesthetics can be tolerated for future indicated procedures.

Injectable agents—bovine collagen

As individuals age, normal skin tension lines deepen. Accentuation of the lines of expression is most apparent and (oftentimes) least acceptable in such regions as the nasolabial folds, glabella, forehead, and creases of the mouth. For centuries, correction of such age-related changes has been performed by way of soft tissue augmentation employing a variety of natural and synthetic compounds. In the United States, the armamentarium available to practitioners includes

autologen, autologous fat, Botox (Botox, Irvine, CA), bovine collagen, dermalogen, micronized alloderm, particulate fascia lata, and numerous other soft tissue injectable fillers. Additional agents such as Artecoll (Artis Medical, San Diego, CA), Bioplastique, hyaluronic acid derivatives, and silicone are available internationally, although they are not approved for use in United States.

Bovine collagen implants are indicated for the augmentation of acne scars, frown lines, nasolabial folds, upper and lower lips, and various other soft tissue defects. Elimination of the antigenic portions of the bovine collagen molecule is achieved by enzymatic digestion with pepsin. The refined collagen product is available as either type I collagen (Zyderm I and II, INAMED Corporation, Santa Barbara, CA) or cross-linked collagen (Zyplast, INAMED Corporation, Santa Barbara, CA). The former is used to treat superficial rhytides, whereas the latter is injected deep into the dermis and is used to efface deeper defects. Optimal results are achieved in regions in which underlying skin has retained elasticity without excessive redundancy. Satisfactory results are difficult to obtain on older patients in whom the underlying soft tissue is exceedingly lax [35].

Advantages of bovine collagen are its ready availability, ease of use, affordability, and amenability to an office setting. Collagen augmentation is not permanent, however; it requires periodic maintenance. Other shortcomings include allergic reactions and transient swelling and cystic reactions at sites of injection [36]. Fortunately, complications are (for the most part) few and transient. In an initial study of the safety and efficacy of injectable collagen, 5109 patients were followed for 6 years by dermatologists and plastic surgeons. Adverse treatment responses manifested in 1.3% of subjects, with localized swelling and erythema occurring most commonly [37]. Because of the potential for allergenicity to injectable collagen, proper patient screening and skin testing are critical prior to bovine collagen therapy. Patients should be excluded from testing and treatment if they have a history of lidocaine sensitivity, an anaphylactoid event, or previous sensitivity to bovine collagen.

Fortunately, potential allergenicity can be reliably determined with skin testing. The skin test syringe screens allergy to all three forms of therapeutic collagen. A small amount of Zyderm solution is injected into the volar forearm and observed at 72 hours and again at 4 weeks. Swelling, induration, tenderness, or erythema that occurs or persists for more than 6 hours after test implantation constitutes a positive test. Evident in 3.0% to 3.5% of patients, a positive skin test is

an absolute contraindication to treatment [35]. Many clinicians now recommend double testing to reduce the risk of treatment-associated adverse reactions; up to 2% of patients will manifest a localized hypersensitivity reaction after Zyderm implants despite negative skin testing [38]. The second skin test is administered 2 weeks after the initial test into the contralateral forearm or periphery of the face. Treatment should not commence for at least 2 weeks after double testing. This regimen greatly diminishes the frequency of treatment-associated hypersensitivity. Additionally, when an individual presents for retreatment, and a period of at least 1 year has elapsed since prior successful treatment, single retesting should be performed as an additional precaution [35].

Almost all patients who manifest hypersensitivity reactions to bovine collagen express antibovine collagen antibodies. Adverse reactions involve the cellular and humoral types of immune response. Charriere et al reported a clinical follow-up of 705 patients who were treated with a bovine collagen implant. Sensitization was evaluated in all subjects by skin testing, and humoral response was evaluated in 166 subjects by measuring the level of circulating antibodies to bovine collagen. Anticollagen antibody presence strongly correlated to a positive skin test (92%) and to an adverse reaction to the implant (100%) [39].

The medical literature provides little instruction regarding appropriate management of bovine collagen hypersensitivity. These localized eruptions are generally self-limited, but if left alone they can persist for up to 1 year before resolution is complete. Corticosteroids have only a limited therapeutic role because the eruption tends to recur after cessation of therapy. Reports of successful therapy are largely anecdotal. Baumann and Kerdel describe resolution following a short-course of cyclosporine (5 mg/kg/day for 18 days) after failed trials of intralesional, oral, and topical corticosteroids [40]. Moody and Sengelmann describe a favorable response to 0.1% tacrolimus and corticosteroids [41].

Injectables—botulinum toxin

Wrinkles (rhytides) can be categorized as dynamic or static. The former, which include glabellar, crow's feet, and some forehead and nasolabial wrinkles, are caused by hyperkinetic muscles of expression. In contrast, static wrinkles are caused by exogenous sources such as smoking, gravity, and sun exposure. When the facial muscles responsible for producing rhytides are not functionally required, botulinum toxin can be injected to temporarily paralyze them,

thereby improving undesirable lines. Botulinum toxin type A has recently supplanted injectable filling agents as the mainstay of therapy for dynamic rhytides in the upper one-third of the face. After years of off-label use, Botox Cosmetic (Allergan) has received FDA approval for cosmetic indications in adults aged 65 and younger.

Botox is a sterile, vacuum-dried, purified form of botulinum toxin type A. This highly potent neurotoxin complex inhibits acetylcholine release at the neuromuscular junction, thereby impeding neuromuscular transmission and reversibly paralyzing striated muscle. Botulinum toxin type A was first approved for the treatment of strabismus, benign essential blepharospasms, and facial dystonias. Its utility in non-surgical therapy for conditions such as spasmodic torticollis, tremor, and hemifacial spasm has been firmly established among neurologists. Observations that its injection for blepharospasm led to marked reductions in wrinkle lines inspired trials utilizing Botox for cosmetic indications. These trials demonstrated convincingly that Botox is a safe, effective, alternative therapy for crease lines and wrinkles that are attributable to hyperkinetic muscles of expression. Moreover, the procedure of administering the toxin by way of localized, pinpoint injections is simple, minimally invasive, and can be readily performed in an office setting [42].

Seven serologically distinct classes of botulinum toxin are termed types A to F. Type A, the most potent of the toxins, is the only form that is currently approved for use in the United States and others. It is commercially available as Botox and Dysport (Speywood Pharmaceuticals, London, UK). The two products differ in formulation, potency, and manufacturing process. Botulinum toxin A binds irreversibly to specific presynaptic receptors (SNAP-25). Peripheral neuronal sprouting commences within 28 days of toxin injection. Insofar as neuromuscular junction activity returns to normal within approximately 3 months, injection is repeated at that time to maintain muscle paralysis [43]. The effectiveness of subsequent Botox treatments might be diminished by the presence of neutralizing antibodies to botulinum toxin type A. Utilizing the minimal effective dose and lengthening intervals between injections are means of reducing this risk [44]. Additionally, some investigators are evaluating a possible role for types B and F in individuals who have developed antibodies to type A toxin [35].

Complications arising from Botox injections are generally minor and transient. Occasional reports of temporary bruising at the injection site or brief complaints of pain or headache after injection have

been described; however, reports of rashes are rare. In one study of adverse reactions to Botox therapy, 1044 Botox treatments were administered over 4 years to 232 patients. Three patients experienced generalized pruritus that persisted for up to 2 weeks after toxin injection. Subsequent injections (between one and eleven) were tolerated without incident [45]. Brin et al described the occurrence of a rash (unspecified) in 1 of 96 patients receiving Botox injections for oromandibular dystonia [46]. Cox et al described a fixed drug eruption on the nasal tip of a patient receiving Botox injections for severe blepharospasm. The base constituents of the botulinum toxin preparation (lactose, either alone or in combination with human serum albumin) were implicated [47]. In 1992, Bowden and Rapini described a case of a psoriasiform eruption in a patient treated for an ocular motility disorder with Botox injection [48]. Additionally, there are reports of urticaria and erythema multiforme resulting from Botox injections. Such adverse events are infrequent, however, and a causal relationship to the injected Botox remains unproven [44].

Injectables—silicone

Silicone is a long polymer of dimethylsiloxane, which comes in both liquid and solid forms. When first introduced into medical use, silicone was thought to be a nonreactive biomaterial. For more than three decades, silicone compounds have been used for construction of joint prostheses, breast implants, and tissue augmentation.

Tissue augmentation with silicone yields pleasing aesthetic results in many patients and it is permanent. Reports of complications such as inflammation, induration, discoloration, ulceration, migration, and formation of foreign body-type silicomas are somewhat frequent [36]. In one case, a granulomatous reaction to injections of liquid silicone for lip augmentation caused facial disfigurement that persisted for nearly 3 years [49]. These devastating outcomes can be caused by use of impure or adulterated silicone, improper administration technique, or injection of excessive amounts of silicone [50]. Fortunately, the medical community has an abundance of nonreactive biopolymers available for tissue augmentation, which reduces the need for silicone for this purpose. Thus, clinicians have seen fewer cases of granulomatous reactions, except those resulting from hematogenous or lymphatic migration of silicone from distal sites [51,52]. A recent report of cutaneous granulomatous lesions erupting in a patient who received acupuncture with silicone-coated nee-

dles raises concern about cutaneous manipulation with silicone-coated instruments [53].

Dressings and adhesives—benzoin and gum mastic

Wound adhesives and surgical tapes are critical to wound management after dermatologic and plastic surgical procedures. The postoperative use of wound adhesives decreases wound tension, helps to prevent skin separation, and favorably impacts postsurgical scarring. A tincture of benzoin USP, and gum mastic (Mastisol, Ferndale Laboratories, Ferndale, MI) are the two most widely used wound adhesives to augment surgical strips. These adhesives have wide applications and an overall low complication rate; however, wound adhesives are generally applied under occlusion, often on damaged skin, in a warm and moist environment. Furthermore, exposure tends to be chronic or recurrent over a short duration. All of the above factors naturally predispose to the development of allergic contact dermatitis.

Benzoin tincture consists of 10% benzoin in alcohol, whereas the compound formulation also contains 2% aloes, 8% storax (styrax), and 4% tolu balsam. Fisher describes benzoin as a common component of adhesives, water-repellent barrier creams, lozenges, benzoinated lard, and cosmetics. Benzoin tincture crossreacts with balsam of Peru, storax (styrax), eugenol, vanilla, pinene, benzyl alcohol, and benzyl cinnamate. Related compounds, for which reports of allergic contact dermatitis exist, include Arning's tincture (contains benzoin, ammonium tumenol, anthrarobin, and ether), greasepaint makeup, storax, and mastic. Fisher acknowledges that benzoin is a more potent sensitizer than formerly thought and cautions against its indiscriminate use as a medical adhesive [31].

In 1874, Tilbury Fox described the first instance of benzoin allergy in response to inhalation of a vapor containing compound tincture of benzoin. Since then, there have been dozens of reports of allergic contact dermatitis erupting after exposure to benzoin in the medical field and other settings [54,55]. Hoffman and Adams describe contact dermatitis to benzoin present in greasepaint makeup [56]. Several reports are among athletes and military cadets, who have for years applied benzoin tincture to their feet and various other parts of their skin as a means of blister prophylaxis [57,58].

Gum mastic (Mastisol) is derived from varieties of *Pistacia lentiscus* trees found in Mediterranean countries. This resin, which contains gum mastic, styrax

liquid, methyl salicylate, and alcohol, is used widely by surgeons and dentists to secure surgical dressings. Gum mastic is also found in chewing gums, incense, and varnish. In addition to its superior adhesive qualities, gum mastic has proven to be a less potent sensitizer than benzoin tincture [58,59].

Dressings and adhesives—wound dressings

Wound dressing such as hydrocolloids, hydrogels, alginates, and polyurethane foams are becoming increasingly popular. These dressings reportedly cause irritant contact dermatitis. Additionally, components of these dressings, particularly the tackifiers present in hydrocolloids, have been implicated as the source of sensitization. Pentalin (the pentaerythritol ester of hydrogenated rosin), a tackifying agent that crossreacts with colophony and Vistanex (Polyisobutylene, Exxon Mobil Corporation, Houston, TX), are the main allergens described [60,61]. In several patients allergic to hydrogel dressings, polypropyleneglycol (PPG) proved to be the source of sensitization [62].

Dressings and adhesives—acrylates

The adhesive matter in adhesive plasters can be composed of acrylic polymers or rubber with tackifiers such as colophony. Reports of allergic contact dermatitis to adhesive plasters have been attributed to acrylate monomers, rubber compounds, or colophony or other resins. Several cases of sensitization to the acrylates that are present in surgical tape are described by Jordan [63]. Daecke and others describe a case of urticaria induced by the acrylic acid present in Fixomull tape [64]. Polyacrylate-based adhesives, which are becoming increasingly common, sensitize less frequently than those that are formulated on a rubber and colophony base [65].

Acrylic resins are thermoplastics that are derived from acrylic acid ($\text{CH}_2=\text{CH}-\text{COOH}$). These agents are widely used and can cause allergic and irritant dermatitis [66]. The various acrylic monomers include acrylic acid and methacrylic acid and their esters, cyanoacrylic acid and its esters, acrylamides and acrylonitrile. Addition reactions between the various monomers generate a wide variety of polymers and resins. Polymers of the mono(meth)acrylate type, especially 2-ethylhexylacrylate, are often employed in the manufacturing of pressure-sensitive adhesives and other industry products such as leather finishes, paints, and coatings. The esters of multifunctional acrylates (ie, those with at least two reactive acrylic groups) include di(meth)acrylate

esters of dialcohols or tri- and tetraacrylate esters of polyalcohols. These esters are useful in acrylic adhesives, anaerobic sealants, and artificial nail preparations. Prepolymers refer to acrylate resins into which at least two reactive acrylate or methacrylate groups have been introduced. Acrylated epoxy resins, on which medical adhesives are sometimes based, are among the most commonly used prepolymers [67].

Cyanoacrylates are often called “superglues.” n-Butyl 2-cyanoacrylate and isobutyl 2-cyanoacrylate are the cyanoacrylates that are most commonly used in medical adhesives. Cyanoacrylate-based glues are employed widely as contact adhesives for biological materials including binding tissues and surgical wound sealants. The proposed mechanism for the bonding action of cyanoacrylates relates to the highly exothermic anionic polymerization, which occurs within seconds to minutes in the absence of catalysts. Insofar as the compound bonds to surface keratin nearly immediately, contact sensitization is considered to be extremely rare, although several case reports strongly suggest that cyanoacrylate can be the source of sensitization or irritation [19,68–71].

The high allergenicity of the monoacrylates is reduced by the introduction of a methyl group. Despite their relatively weak sensitizing capacity, however, methacrylates present in adhesive tapes have caused several cases of sensitization. Kanerva and Alanko describe a vesicular dermatitis that erupted 3 days postoperatively in a highly methacrylate-allergic female patient at the site at which an electro-surgical earthing plate was affixed. 2-hydroxyl ethyl methacrylate (2-HEMA), a component of the pressure-sensitive adhesive of the pad, proved to be the causative chemical. This was the fourth such report of allergy to earthing plate adhesives [66,72–74]. Interestingly, the patient was allergic to 2-HEMA, but not to 2-HEA. Thus, the authors concluded that use of ethyl acrylate (EA) as a screening agent for acrylate allergy is inadequate because some patients will test falsely negative. Prediction of the sensitizing potential of the various prepolymers can be challenging, although it is widely believed that epoxy acrylates are highly allergenic [67]. Contact sensitization to common medical acrylics such as methyl methacrylate, a frequently used bone and dental cement, was 1.6% in patients with suspected contact dermatitis.

Summary

The plethora of available materials that augment the aesthetic surgeon's capabilities to improve

patients' appearance has also expanded the possibilities of potential adverse events. As with all pharmaceutical products and devices, the adage of "no side effect—no effect" holds strongly true. Fortunately, the adverse events that stem from the chemicals used in cosmetic surgery are frequently benign and reversible, particularly with prompt recognition, withdrawal, and treatment.

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