# FRAGRANCES AND FLAVORANTS

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penditures for visits to health care providers and for medicaments.<sup>1</sup> Once patch testing is performed and a culprit has been identified, education becomes the

tact

Derma-

titis (ACD) is

an important disease

that notably affects

14.5 million Ameri-

cans each year.1 The

economic impact of

this disease is high in

terms of both patient

morbidity and loss of

income, school and

work, not to men-

tion significant ex-

critical intervention to ensure adherence to an avoidance regimen. With avoidance, remission of the dermatitis ensues. If the patient is unable to comply with the avoidance regimen, they become at risk for recurrent or sustained dermatitis or progression to a systematized presentation.<sup>2,3</sup> In fact, education of patients often begins before the diagnostic patch test is ever placed, to ensure that they have an appropriate understanding of potential outcomes, and their central role in both their disease and treatment.

At the initial consultation patients are often taught about the patho-physiology of ACD: its delayed presentation; its relationship with the immune system (sensitization to a chemical and

then elicitation of a dermatitis with reexposure); and that it can occur at any point in time, even to something that the patient has been using regularly for a short period of time or even intermittently for years. In certain cases, the topics of the other key players, such as irritant contact dermatitis (ICD) and contact urticaria, may be explained, as history (not patch testing) can point to these as the correct diagnosis for the patient. It is important to note that ICD, the most prevalent form of contact dermatitis, can at times precede or be a concomitant diagnosis with ACD.<sup>4,5</sup> Unlike ACD. ICD is not immune-mediated, but occurs secondary to contact with an irritating or abrasive substance. Contact urticaria (wheal and flare reaction), on the other hand, represents the least prevalent form of CD. It is important to note that it is an immune-mediated phenomenon whose hallmark is an IgE and mast cell-mediated immediate-type hypersensitivity reaction. We acknowledge this form of hypersensitivity due to the severity of the potential deleterious anaphylactic type reactions and direct the reader to key sources.6,7,8

In this column, we highlight ACD and explore top relevant allergens, regional-based dermatitis presentations, topic-based dermatitis presentations and clinical tips and pearls for diagnosis and treatment.

### FRAGRANCES AND FLAVORANTS

The ability of fragrances and flavorants to ignite the senses is a wonder that has created a great cultural impact. In ancient times, Egyptians "welcomed the gods" and sanctified their homes by burning the sacred temple incense, kyphi or kapet, in their dwellings.9 Kyphi recipes

and pictographs can be found written on the walls of ancient temples and on papyrus. The esteemed kyphi was thought to hold the power to heal, alleviate anxieties, increase dreaming, eliminate sorrow, treat asthma and act as a general antidote for toxins. This fragrance mixture is still in use today for its full-bodied bouquet with a relaxing, sweet, spicy and sensual aroma.<sup>10,11</sup> Another popular relaxation practice in ancient Egypt that is now widespread due to the wide array of tastes and aromas was wine drinking. Winemaking is said to have begun in the Neolithic period (8500 to 4000 B.C.) in the Near East and Egypt. Of interest, the wild grape was not native to ancient Egypt and its use was likely due to trade with modern-day Israel, the West Bank, Gaza and Jordan.12

The introduction of viniculture practice into Europe is largely associated with the expansion of Greek civilization across the continent.<sup>13</sup> Along these same lines, as spoils of his conquests, Alexander the Great is said to have brought perfumes to Europe in the 4th century B.C.14 History notes that when Alexander entered the tent of the defeated King Darius III, after the battle of Issos, he added insult to injury by pillaging the king's box of priceless ointments and perfumes. Alexander's obsession with aromas and anointment oils led him to send deputies on dangerous conquests across distant lands to Yemen and Oman to find new sources of the Arabian incenses.<sup>15</sup>

Despite Alexander's successes, early Romans had very limited access to fragrances and perfumes, but as the Empire expanded across the continents, there was an influx of conquered people from the 'Orient' into Rome and with them came a large number of aromatics, oils and perfumes.<sup>12</sup> The consumption of great quantities of fragrances by the Romans in the 1st century A.D. was so vast that new trade routes to Arabia, India and China had to be devised to keep up with the demands.<sup>16</sup>

In addition, while Greek civilization introduced viniculture to Europe, it was the Roman Empire that nurtured its foundation and growth. As early as the 1st century B.C., the Romans were exporting wine to Spain, Germany, England and Gaul (France), and by 1000 B.C., they had made vital contributions by way of grape classification, irrigation, fertilization and adaptation of wooden barrels for wine storage and transportation.<sup>13</sup>

Of interest, in the Book of Matthew 2:1, it is said that three wise men (kings) came "from the east to Jerusalem" bearing three gifts to the infant Christ. Two of these were fragrances, frankincense and myrrh, which were thought to be more valuable than the gift of gold; in fact, some scholars speculate that the third gift of gold actually may have been the gold-colored fragrant ambergris.13 Ambergris is a biliary concretion made to facilitate the gastrointestinal passage of hard objects, such inadvertently eaten bones in sperm whales.14 One of the most vivid descriptions of ambergris can be found in Melville's Moby Dick: "Dropping his spade, he (Stubb) thrust both hands in, and drew out handfuls of something that looked like ripe Windsor soap, or rich mottled old cheese; very unctuous and savory withal. You might easily dent it with your thumb; it is of a hue between yellow and ash colour. And this, good friends, is ambergris, worth a gold guinea an ounce to any druggist ... ", "Who would think, then, that such fine ladies and gentlemen should regale themselves with an essence found in the inglorious bowels of a sick whale!...".17

Later, in the 13th and 14th centuries, the trade of spices and perfumes was tremendously boosted by the explorations of Marco Polo, Christopher Columbus and Vasco de Gama into new lands. The American New World offered the exquisite scents of balsam of Peru (BOP) and Tolu, juniper, American cedar, sassafras and vanilla to the Old World.<sup>13</sup>These same scents became some of the many essential ingredients for the perfume industry, whose growth saw to the rapid emergence of department stores in Europe and the United States in the 20th century.

Furthermore, these fragrances are also used in the food industry. For instance, BOP, a viscous fluid produced by the Myroxylon balsamum tree, found mainly in El Salvador, contains >400 chemicals, many of which are used in both the fragrance and flavoring industry.<sup>18,19</sup> This sap was used by Peruvians and Aztecs to provide relief for ailments and wounds

Table 1. FOODS CONTAINING BALSAM OF PERU COMPONENTS <sup>19,38</sup>		
• Tomato (ketchup, BBQ sauce, tomato sauce)		
• Cinnamo	n	
• Soda/Cola		
• Chocolat	e	
• Vanilla e	xtract (ice cream)	
• Citrus (peel)		

and by the Spanish clergy as a sacred ointment.<sup>19</sup> Today, BOP and/or cross-reacting chemicals are used as fragrances in cosmetic products such as perfumes and lotions, but also as flavorings for toothpastes and mouthwashes, foods, drinks and liquid medicaments.<sup>18,19</sup> Foods and drinks such as tomato, soda, cinnamon, chocolate and vanilla extract contain naturally occurring constituents also found in BOP or synthetics that are likewise chemically similar.<sup>3,18</sup> (**See Table 1.**)

Fragrances and flavorants are complex mixtures of natural and synthetic materials used for improving the quality of life for those who wear or taste them. In fact, tasting is such an art that sommeliers, wine stewards, must accomplish four levels of intense training in order to be considered master sommeliers. This title is the only credential for those in the beverage field that is internationally recognized.<sup>20</sup> Once established, these experts incorporate extensive travel into their profession, visiting different regions to choose wine for their restaurants.<sup>21</sup> Wines are analyzed based on specific aspects of their appearance and aroma, as well as flavor.13 The aroma is best examined by swirling the glass for 10 seconds to vaporize the alcohol in order to release the wine's natural aroma, then taking a quick whiff, followed by a deep nasal inhalation, smelling scents such as oak, berry, floral bouquet, vanilla or citrus.<sup>22</sup> Flavor consists of three stages: attack, evolution and finish. After a small sip, the initial intensity and complexity are sensed, a mixture of alcohol content, tannin levels, acidity and residual sugar; this is the attack phase. The evolution phase refers to the actual flavor (fruity, spicy, woody or floral) as one rolls the wine around in his or her mouth. Lastly, the finish occurs after the sip is swallowed, and describes the length of time the flavor lasts, the wine's body and the aftertaste.<sup>21</sup>

Likewise, perfumes can be unique as well and are said to present "their wearers with an opportunity to create for themselves a virtually unforgettable, personal trademark."23 While flavor can be described in terms of stages, attack, evolution and finish, fragrances are described with a 'musical metaphor,'24 in which top notes, middles notes and base notes come together to create a scent. These notes mimic the stages of flavor in that top notes are immediately perceived as 'fresh, assertive or sharp;' middle notes refer to the 'heart' of the fragrance, smooth and melodious; and base notes are rich, sensed last, at least 30 minutes after application.<sup>24</sup> Fragrances can be constructed using natural ingredients, which are primarily distilled botanical extracts from plants such as BOP and Tolu, juniper, American cedar, sassafras and vanilla or prized animal by-products (eg, ambergris, musk, castoreum and civet). Musk and castoreum are obtained from the abdominal pheromone sacs from either a musk deer buck or Canadian beaver, respectively. Marketing of the dried gland utilizes specific terminology, such as "musk in pod" (ie, the whole gland) or "musk in grain" (the already extracted perfume). Likewise, covet is expressed from the perianal glands of a covet cat. This prized commodity is an oily substance secreted by the cat when marking its territory. Civet is used in the perfumery industry to enhance other scents.15 However, given the scarcity of natural products, these scents can be expensive, leading to the development of synthetic ingredients made possible by advances in the chemical industry. In fact, prominent discoveries in synthetic fragrances were made during the Industrial Revolution of 1889 to 1910: 1869 heliotropine, 1877 coumarin, 1888 artificial musk, 1890 vanillin, 1890 ionone, 1905 l'hydroxycitronellal.13

## FRAGRANCES TODAY

Around 90% of available fragrances on the market are synthetic chemicals rather than natural extracts, with more than 5,000 different compounds reported.<sup>25</sup> Globally, fragrance (and flavor) market sales are estimated to be between \$12 billion and \$15 billion per year. Perfume fragrances are thought to make up about \$3 billion of the total.<sup>26</sup> Fragrances are found in a wide range of products that include eau d'toilettes and colognes, cosmetics, cleaning supplies, medicaments, foods and flavored personal hygiene products.<sup>19,20</sup> Furthermore, cutting fluids, electroplating fluids, metalworking fluids, paints, rubber, plastics, insecticides, herbicides and additives used in air-conditioning water also contain fragrances.<sup>19</sup>

Fragrance allergy occurs predominantly in women, with a female to male ratio of 3 to 4:1, and may relate to an overall greater exposure to skin care products by women than men.<sup>15,27</sup> This is not surprising since, on average, 30 to 50 chemicals are used to create the fragrance composition of a perfume, and complex formulations of upward of 200 ingredients are not uncommon.<sup>18</sup>

The importance of allergen concentration (ie, occlusion), skin barrier (or disruption thereof, ie, shaving), and constitutional factors are important risk factors in the likelihood of becoming sensitized and the extent of the clinical manifestation.<sup>19,21</sup> Given that patients with atopic dermatitis (AD) have been shown to have defective epidermal barrier function, they could be at greater risk for sensitization to allergens that also have the potential to irritate,<sup>28</sup> such as fragrances and benzoyl peroxide.<sup>29,30</sup>

Classic localizations for fragrance contact allergy are the face, behind the ears, the neck, the axilla and hands.19 Oral and perioral dermatitis are common presentations of fragrance/flavoring ACD in toothpastes, chewing gums, mouthwashes and mentholated cigarettes.<sup>15</sup> Besides direct contact with fragrances, "consort" or "connubial" contact dermatitis also can occur by contact with products used by partners, care-givers, friends or coworkers. Airborne contact and systemic exposure by inhalation and ingestion (flavor and spices in foods) may also occur.19 Children may become sensitized to fragrances, especially through the use of baby products applied to areas of chronic dermatitis, such as diaper dermatitis.<sup>15</sup>

Notably, fragrances are the second most common class of substances identified to cause ACD, and the most frequent cause of contact allergy to cosmetics. Cosmetics account for 30% to 45% of these allergic reactions, with perfumes accounting for 4% to 18% and deodorants/antiperspirants 5% to 17% of cases.<sup>19</sup> Finally, it is important to note that fragrances can be

Table 2. OCCUPATIONAL SOURCES OF FRAGRANCE <sup>16,23,48</sup>	
Aromatherapists	
Beauticians	
Cleaning personnel	
Cosmetic industry (cosmetic chemists, people handling the raw materials, salespeople)	
Food industry* (bakers, cooks, caterers)	
Hairdressers	
Health personnel <sup>†</sup>	
Housewives	
Industry (metal furnace operator, potter or glass maker)	
Masseurs	
* Cinamates are the most common allergen among bakers † Eugenol is widely used by dentists	

contacted through occupational sources. (See Table 2.)

#### **PRODUCT LABELING**

Patients should be counseled on fragrance and flavor avoidance. Unfortunately, this is easier said than done, as product labeling can be complicated because labels may list individual fragrance names without indicating "fragrance," or may include inadvertently misleading labeling. For instance, the terms "unscented" and "fragrance-free," are not synonymous. "Unscented" simply means that a product lacks a scent; however, masking fragrances may be present in order to eliminate odor. "Fragrance-free" refers to the absence of chemicals added to enhance aroma or mask odor. The use of this terminology, however, may also be misleading, as chemicals used as fragrances may also be utilized for other purposes, ie, as preservatives or emollients.31 This, combined with the FDA code of federal regulations, title 21, volume 7, section 700.3 (d), stating that the term "fragrance" means any natural or synthetic substance or substances used solely to impart an odor to a cosmetic product,32 creates situations where products are labeled "fragrance-free" despite containing chemical fragrances as long as they are not used for their aroma, aka 'covert' fragrances. (See Table 3.)

## 'GREEN' PRODUCTS

Consumers must also be aware that 'natural' or 'green' products containing botanical essential oils, also pose an al-

lergen risk. Essential oils are widely used in perfumes, personal care products and aromatherapy. Not only have essential oils, such as lavandula angustifolia (lavender),<sup>33</sup> tea tree, orange oil, geranium oil, ylang-ylang, jasminum officinale, lemongrass, sandalwood and clove,<sup>34</sup> been shown to induce ACD, but naturally occurring fragrances/flavors that are known allergens, such as benzyl alcohol,<sup>35</sup> can be found as constituents of botanical essential oils, including hyacinth, jasmine and ylang ylang.<sup>36</sup>

### HOW FLAVORANTS STIMULATE FRAGRANCE ALLERGY

The terms "fragrance" and "flavor" both may refer to the same chemical experienced by different senses, ie, olfactory and gustatory, respectively. Balsam of Peru is an example of a contact allergen that is composed of many chemicals that are used as fragrances in personal care products and as flavors in multiple foods and beverages. Therefore, a patient with contact allergy to BOP may develop a systemic dermatitis or a worsened localized dermatitis from the ingestion of foods or drinks containing chemicals found in BOP as well.<sup>3</sup> In these instances, a balsam-restricted diet may be helpful in the treatment of the patient.<sup>3,19</sup>

#### ALLERGY TO FRAGRANCES AND FLAVORANTS

Allergy to fragrance was first indexed in the medical literature in 195737 and to flavorants in 1961.38 Increasing rates of sensitization to perfumes called for fragrance identification measures to be established in late 70s. Larsen<sup>39</sup> proposed a mixture of ingredients as a screening tool for fragrance contact allergy, after identifying the eight primary substances present in the Mycolog cream. These fragrances [combined as Fragrance Mix 1] are isoeugenol, eugenol, cinnamic aldehyde, cinnamic alcohol, hydroxycitronellal, geraniol,  $\alpha$ -amyl cinnamic aldehyde and oak moss absolute.<sup>21</sup> This composite is still used today for fragrance screening because of its current clinical relevance. And, notably in conjunction with balsam of Peru, it detects a significant proportion of fragrance allergies.<sup>40</sup> (See Table 4.)

## PRACTICALS OF PATCH TESTING

As mentioned above, patch testing is often necessary to distinguish ACD

• Benzyl alcohol		
• Bisabolol (chamomile oil)		
• Citrus oils		
• Ethylene brassylate		
<ul> <li>Essential oils of plants or flowers</li> </ul>		
• Farnesol		
• Maltol		
• Vanilla, Sweet almond oil, Menthol, Flavorings		
*Fragrances used for other properties and therefore may be in "fragrance-free" products. Pamela Scheniman, ML From Lecture at AAD 2011, Contact Dermatitis Course.		

Table 3 COVERT FRAGRANCES\*

from other causes of dermatitis, and to identify the relevant allergen(s) responsible. Screening patch test trays, which isolate the most common chemicals and offer the provider clues for potential sources, are available. The North American Standard Series includes allergens from several different categories;41 however, supplemental trays are also available, such as fragrance/flavors, and specifically balsam of Peru components at some institutions.42 The idea behind using supplemental allergens as well is that by including constituents and crossreactors of the allergen in question, the chance of detecting relevant positive reactions is greater.43 Along these same lines, many cosmetic products themselves can also be tested "as is." Dental and flavored products, however, may require preparation prior to testing.44

#### PEARLS OF TREATMENT: EVERY DOSE COUNTS

As alluded to in this preface, one may be exposed to and subsequently sensitized to a contact allergen such as fragrance for days to years before demonstrating the clinical picture of ACD. With each exposure, there is an increasing risk of reaching a point at which the immune system meets its metaphorical "threshold" and subsequent exposures at this point can lead to elicitation of a cutaneous response.<sup>4,18</sup> Just as repeated contact over time led to this immune response, repeated avoidance of the majority of exposures over time will be required to induce remission.

Avoidance of specific allergens in personal care products can prove to be a tedious task; however, there are programs

Table 4. TOP 25 SENSITIZING FRAGRANCES <sup>16,23,37,49,50</sup>	
	Fragrance ingredient
Myroxyl	on pereirae (balsam of Peru)*
	Benzyl alcohol
	Benzyl cinnamate
	Benzyl salicylate
	Vanillin
	Benzoyl benzoate
	Benzoic acid
	Nerodilol
Fragrand	e Mix 1
	lpha-amyl cinnamic aldehyde*
	Cinnamic alcohol*
	Cinnamic aldehyde*
	Eugenol*
	lsoeugenol*
	Hydroxycitronellal
	Geraniol
	Oak moss absolute
Fragranc	e Mix 2
	4-(4-hydroxy-4-methyl pentyl)- 5 petro- latum 3-cyclohexene-1-carboxaldehyde (Lyral)
	Citral
	Citronellol
	Coumarin
	Farnesol
	Hexyl cinnamic aldehyde
Various I	Fragrances
	Lavender
	d-limonene
	Jasminum officinale oil (jasminum grandiflorum)
	Majantol
* These a	re substituents of balsam of Peru as well

available to aid in this endeavor. Both the Contact Allergen Management Program (CAMP), a service offered through the American Contact Dermatitis Society,<sup>45</sup> and the Contact Allergen Replacement Database (CARD), de-

veloped by Mayo Clinic,<sup>46</sup> allow for a provider to enter a patient's known contact allergens, and produce a "shopping list" of products void of those particular chemicals. The programs also have the ability to exclude cross-reactors.

Some sources, however, require avoidance creativity and finding alternatives. For example, a cinnamate allergic patient may have to use a fennel or apricot flavored toothpaste. Educating patients to increase their awareness of sources of allergens and having the patient inform their health and dental professionals of their contact allergens is also important.

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