ALLERGE



Focus on Non-T.R.U.E. **Test Allergens: Lyral** and Fragrance Mix II

BY SHARON E. JACOB, M.D., AND MICHAEL SHELLING, B.S.

n 1997 the U.S. Food and Drug Administration granted an indication for the use of the Thin-layer Rapid Use Epicutaneous (T.R.U.E.) Test Panels 1.1 and 2.1 as valuable, first-line screening tools in the diagnosis of allergic contact dermatitis (ACD). Many of you utilize this standard tool in practice and refer to contact dermatitis referral centers when the T.R.U.E test fails to identify a relevant allergen.

Specifically, the T.R.U.E. Test screens for 46 distinct allergens and the Balsam of Peru mixture. The test is thought to adequately *identify an allergen in approx*imately 24.5% of patients with allergic contact dermatitis.1 This being said,



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many relevant allergens are not detected by use of this screening tool alone, and, for this reason, the "Allergen Focus" column has been expanded to cover the notorious Allergens of the Year and the Up-and-Coming T.R.U.E. Test panel 32, as well as the North American Contact Dermatitis Standard Allergens.

This month, "Allergen Focus" will highlight Fragrance Mix II (FMII), which has been included on the North American Contact Dermatitis 2007 65 Allergen Standard Screening Series. In addition, the column will discuss FMII component, Lyral, which is also available for extended fragrance testing and has been chosen for inclusion on the up-and-coming T.R.U.E. Test Panel 3.²

We will answer some of the most frequent questions relating to the origin of these allergens and their most common uses. But first, an overview of the contact dermatides.

CONTACT DERMATIDES

The contact dermatides include, irritant contact dermatitis, contact urticaria, and allergic contact dermatitis.

Irritant contact dermatitis, the most common form, accounts for approximately 80% of environmental-occupational-based dermatoses.

Contact urticaria (wheal and flare reaction) represents an IgE and mast-cell-mediated immediate-type hypersensitivity reaction that can lead to anaphylaxis; the foremost example of this would be latex protein hypersensitivity. Although this is beyond the scope of this section, we acknowledge this form of hypersensitivity due to the severity of the potential reactions and direct the reader to key sources.3,4

Allergic contact dermatitis (ACD) is an important disease with high impact both in terms of patient morbidity and economics. This type of dermatitis represents a T-helper cell type-1 [Th1] dependent,



IN 1919, ODO-RO-NO, A DEODORANT FOR WOMEN, BECAME THE FIRST COMPANY TO USE THE TERM "B.O." (MEANING, BUT NOT SAYING, "BODY ODOR") IN AN ADVERTISEMENT. PREVIOUSLY, DEODORANT ADS HAD CONFINED THEIR PITCH TO SUGGESTIONS ABOUT HOW THEY WOULD FOSTER DAINTINESS AND SWEETNESS.

delayed-type (Type IV) hypersensitivity reaction. The instigating exogenous antigens are primarily small lipophilic chemicals (haptens) with a molecular weight less than 500 Daltons. On direct antigen exposure to the skin or mucosa, an immunologic cascade is initiated that includes cytokines, i.e., interleukin 2 (IL-2) and interferon gamma (IFN- γ), T cells and Langerhan cells. This complex interaction leads to the clinical picture of ACD.

CLINICAL ILLUSTRATION

A patient presented to the University of Miami Allergic Contact Dermatitis Clinic for evaluation of an axillary dermatitis. He had been evaluated by the T.R.U.E. Test, and no positive allergic reactions were found. Of note, he frequently used aerosol deodorant.

THE HISTORY OF DEODORANTS

Archeologists have found the earliest evidence of cosmetics in Egypt dating back to 4000 B.C. Without regard for sex or status, therapeutic and aesthetic compounds (cosmetics) were developed including facial make-up, hair creams, oils, and perfumes.⁵

Early on it had been discovered that the addition of special citrus and cinna-

mon extracts rendered the perfumed oils resistant to decomposition by the heat. It is believed that the Arabian trade merchants brought their "aromatic customs" and the artistry of perfumery to the Western civilizations.⁶

According to the *Natural History* writings of Roman historian Plinus, to control bodily odors the early Egyptians had recommended a scented bath followed by the underarm application of perfumed oils.^{5,7,8} An integral component of the early Roman formulas, however, relied on the use of the natural deodorizing salt alum — a double sulfate of aluminum and potassium, which Plinus was among the first to describe "*Alumen Romanum*."

In his book *Natural History*, he described its manufacture through the repeated dissolution of alum slates of natural sulfates in water.

Interestingly, various ancient civilizations also harvested these crystals for a multitude of uses such as a therapeutic aid in internal inflammations; a treatment for leprosy and skin disease; and a mouthwash and therapy for gum disease.^{9,10}

The use of alum also dates back to ancient China more than 2000 years ago when this "natural" product was used for medicinal purposes in addition to its use as an odor-reducer.⁹ It is interesting to



"Just one hint of underarm odor, and a girl misses out with men." *Image courtesy of www.mum.org.*

note that these salt-based rock deodorants have stood the test of more than 2000 years of time and still remain a popular alternative to modern commercial deodorants in Thailand, the Far East, Mexico, and many other countries.¹¹

FIRST COMMERCIALLY AVAILABLE DEODORANTS

By the 19th century, modern-day commercial deodorants became a widely utilized commodity. An "unknown" inventor formulated the first commercially available deodorant in Philadelphia in 1888, trademarked the invention, and then "marketed it through his nurse."

This cream-based product (which was applied with the fingers) was aptly marketed and sold for its ability to maintain discretion, under the trade name "Mum"^{7,12} — a name that harkened to Shakespeare's "Henry VI", "seal up your lips and give no words but mmm."¹³

The 1926 advertisement asserted that "women who realize the great importance of daintiness are grateful to 'Mum' for the complete sense of protection it gives them against the unpleasant odor of perspiration."

EVOLUTION OF THE ROLL-ON, THE AEROSOL AND IMPROVED FORMULATIONS

In 1931, Bristol Meyers bought the Mum manufacturing company and launched the deodorizing product in the United Kingdom (c. 1939).

Around this same time, Argentine-Hungarian journalist László Bíró, frustrated with the cumbersome nature of the fountain pen, along with his chemist brother George, sought to design a new prototype for pens.¹⁴ The Bírós succeeded, and their innovative pen bore a tiny free turning ball bearing in its tip, allowing for smooth transfer of the ink from cartridge to paper.

A Mum deodorant production team member sporting the new Bíró pen caught the eye of research engineer Helen Barnett Diserens. Diserens, fascinated by the new pen, revolutionized the deodorant industry by translating the Bíró principle into a novel application method for deodorant — a glass deodorant holder with a rolling-ball tip.

The state-of-the-art roll-on deodorant product debuted in the United States in 1952 as "Ban Roll-On" and in the United Kingdom as "Mum Rollette".⁷ Advertisement campaigns featuring the new products touted, "Social success was only attainable when body odor was controlled."^{15,16} Capitalizing on anxiety over social status, a "critical self-consciousness" toward physical appearance was promoted, and consumers bought in.^{16,17}

In fact, a competing company called Odo-Ro-No took a much more direct approach. They told potential customers to take the "Armhole Odor Test" and warned them that social success hinged on eliminating "B.O." — an acronym for "body odor," which they had previously coined in 1919.¹⁷

The late 1950s ushered in an era of aerosol technology to dispense personal care products such as perfumes and shaving creams. It wasn't until 1965, however, that the Gillette company imple-



WHILE THE MODE OF DELIVERY MAY VARY AMONG ANTIPERSPIRANT-DEODORANTS, THE ONE KEY COMPONENT THAT HAS HISTORICALLY DEFINED THE COMMERCIALLY AVAILABLE MASS-MARKETED PRODUCTS IS THE FRAGRANCE ELEMENT, ADDED WITH THE INTENTION OF MASKING THE ODOR OF PERSPIRATION.^{11,18}

mented this technology and expanded its line to include the first aerosol antiperspirant-deodorant, Right Guard.^{7,18} This product was cleverly marketed as *the* perfect product and "right" way, to "guard" against foul odors, and it became a huge success. In fact by 1967, half the antiperspirants-deodorants sold in the United States were in aerosol form; by the early 1970s, they accounted for 82% of all sales.¹⁸

Formulation breakthroughs in ingredient technology continued to provide more drying and efficacious products. Interestingly, the deodorant sticks were the last to gain acceptance on the market, despite their original debut in the 1940s. Their subsequent rise in the 1970s was aided by two developments that drastically set back the aerosol formulations:

- **1.** The FDA banned products with aluminum zirconium, the major ingredient in aerosol.
- **2.** The Environmental Protection Agency strictly limited the use of chlorofluorocarbons (CFCs) in these propellants.⁸

In the mid-1980s, American consumers embraced sticks as an alternative to aerosols, and their market share swelled to greater than 35%.¹⁸ Their popularity continues today with sticks single-handedly maintaining the top spot for most popular antiperspirantdeodorant form.¹⁸

Of note, the deodorant-antiperspirant industry in the United States was estimated to have had nearly \$8.5 billion in sales in 1999, with the top-six deodorant-antiperspirant companies each grossing more than \$1 billion in 2000.¹⁵

HOW DEODORANTS WORK

The majority of the deodorants on the market today are alcohol-based, which increases their ability to inhibit the growth of odiferous bacteria. Some are formulated with antimicrobials such as triclosan, or with metal chelant compounds that retard bacterial growth.¹¹

In accordance with their name, deodorants reduce the amount of odor produced. However, they do not affect the amount of sweat the body produces.¹⁸

Because deodorants are generally



Chemical structure of lyral, which is a key ingredient in synthetic fragrances.

maskers of body odor, they are considered to be cosmetic products.

As a side note, antiperspirants such as aluminum chloride and aluminum chlorohydrate work by inhibiting the activity of sweat glands, so less moisture is produced (a physiologic response that classifies them as drugs).¹⁸

Although the mode of delivery may vary among deodorants, the one key component that historically defined the commercially available mass-marketed products is the fragrance element — added with the intention of masking the odor of perspiration.^{11,18}

It is interesting to note that these same fragrance chemicals are also widely used in fine perfumes. As with fine fragrances, there is individual chemical variation in the ingredients used to create the aromatic bouquet. That being said, 46% of all fine fragrances, 77% of all aerosol deodorants and 27% of all roll-on deodorants contain one common synthetic fragrance, Lyral.¹⁹

LYRAL: A SYNTHETIC FRAGRANCE

In the early 20th century, the Provence-Alpes-Côte d'Azur region of France became a major center for the perfumes and cosmetics industry. This region was responsible for the birth of essential oils and incorporation of natural aromatic plants into fragrances.

The development of synthetic fragrances followed soon thereafter. Specifically, the International Flavors and Fragrances (IFF) Company created and introduced Lyral in 1960.²⁰

This aromatic chemical is formed through the reaction of myrcenol and acrolein.²¹ (*See page 25 to view the chemical structure of lyral.*) According to the IFF, this product is a delicate floral, a "lily of the valley," noted for its extraordinary tenacity and diffusivity as a potent fragrance.^{22,23}

Also known as hydroxyisohexyl 3-cyclohexane carboxaldehyde, Lyral is

TABLE 1

FRAGRANCE MIX II COMPONENTS (FM II)

- Lyral
- Citral
- Farnesol
- Citronellol
- AHCA
- Coumarin



LYRAL WAS CREATED AND INTRODUCED IN 1960²⁰ BY THE INTERNATIONAL FLAVORS AND FRAGRANCES COMPANY. THIS AROMATIC CHEMICAL IS FORMED THROUGH THE REACTION OF MYRCENOL AND ACROLEIN.²¹ ACCORDING TO THE IFF, THIS PRODUCT IS A DELICATE FLORAL, A "LILY OF THE VALLEY," NOTED FOR ITS EXTRAORDINARY TENACITY AND DIFFUSIVITY AS A POTENT FRAGRANCE.^{22,23}

now a key ingredient in a large number of synthetic fragrance mixtures found with high frequency in personal care and household products.²⁴

According to the European Union, it is among the "top-10" scents of the past 25 years with total volume of use ranging between 10 and 1000 tons per year.²² While estimates vary, it has been reported that Lyral may be found in 33% and 46% of all these products.^{24,25}

Of note, Lyral is a lipophilic aldehyde fragrance that readily penetrates the skin.²⁴ Because it is easily transported across the stratum corneum, it readily interacts with cutaneous proteins to form covalent adducts. These adducts (haptens) may then become weak allergens, which with repeated exposures may lead to sensitization.²⁶

ALLERGY TO LYRAL®

Currently, fragrances represent the most common cause of cosmetic contact

allergy.²⁷ Most people in modern society are exposed daily to fragrance ingredients from a multitude of sources.

The Fragrance Mix I (FM I) and Balsam of Peru (BOP) components are widely screened for using the commercially available Hermal and T.R.U.E. Tests, in addition to inclusion on comprehensive testing.

Overall, FM I and BOP are considered to be good indicators of fragrance contact allergy in studies of the general population and are estimated to detect 81% of fragrance allergic patients.²⁸

This being said, it is important to understand that many persons may be susceptible to fragrance chemicals not included in FM I and BOP.^{29,30}

For example, Frosch et al found that patients with a "certain" history of fragrance intolerance had a 40% reactivity to Lyral versus 31.4% reactivity to FM I.²⁴ And in this study, patients with a "probable" history of fragrance intolerance had 24% versus 17.1% to Lyral and FM I, respectively.²⁴

Meanwhile, Lyral is estimated to have a reactivity rate of 2.7% in the general population, as compared to a reactivity rate of 11.3% for the FM I from studies in Europe.²⁴

The recognition of Lyral as a significant sensitizer has warranted the placement of Lyral onto standard patch testing series for increased surveillance.³¹

This being said, six new frequently used fragrance chemicals (in order of positive reactivity rate: Lyral>citral>farnesol>citronellol>alpha-hexyl-cinnamic aldehyde>coumarin), have been compounded into the new Fragrance Mix II (FM II). (**See Table 1.**) Of note, the reactivity order of the individual constituents of FMII was determined through investigative work at six dermatological centers throughout Europe.^{29,30}

TESTING FOR LYRAL SENSITIVITY

Considering the sensitivity, specificity and the frequency of doubtful reactions, a 14% concentration of FM II has been recommended as the most appropriate diagnostic screening tool.²⁹ And indeed, FM II has been included on the North

DEDICATION

This column is dedicated to master mentor in contact dermatitis, Dr. William D. James, for his inspiration and guidance.



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American Contact Dermatitis 2007 Standard 65 Allergen Screen.

Lyral 5% in petrolatum is also available for extended fragrance testing. Of note, Lyral has also been chosen for inclusion on the up-and-coming T.R.U.E. Test Panel 3.²

THE VALUE OF THIS PATIENT CASE

This patient was patch tested with the North American Contact Dermatitis Standard Series and an extended fragrance panel and found to be allergic to Lyral. The patient was educated on **avoidance** and available product substitutions and has been able to remain dermatitis free.

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Mr. Shelling is a third-year medical student and Class Vice President at the University of Miami — Miller School of Medicine.

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28 FEBRUARY 2007 SKIN & AGING

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