Dear Reader,

In this issue, we share with you research that demonstrates that chronic contact dermatitis associated with an orthopedic metallic implant can lead to a rare cancer. Talk about motivation for patch testing! We further the discussion of metal allergies by taking a closer look at palladium, dubbed the metal of the 21st century and a popular choice for dental devices and jewelry. Finally, we review the best strategy for avoiding false-negative reactions when patch testing with volatile agents such as fragrances and acrylates.

As 2014 draws to a close, we take special pride in two of our accomplishments this year—accomplishments that we believe have the potential to dramatically affect the practice of patch testing. First, the introduction of the TruVol™ Precision Allergen Dispenser is poised to help standardize how allergens are dispensed like never before by insuring that the same volume of an allergen is dispensed every time it is used. Such standardization can help improve the interpretation of reactions by eliminating a major cause of variability.

This year the SmartPractice® Allergen Bank was also launched with the intent of making it easier for clinicians who may not patch test full time to do so as needed. The ready availability of customized patch test panels is a cost-effective alternative for those who may use allergens only sporadically. It is also a good option for practices with patients who may need testing beyond screening series.

But we have no plans to rest on our laurels—check back in February for the latest in all things contact dermatitis. For now, all of us at SmartPractice wish you a safe, happy, and healthy holiday season!

Kind Regards,
Dr. Curt Hamann
President & CEO, SmartPractice

Chronic Contact Dermatitis from Metal Implant Linked to Skin Cancer

Posing a link between chronic inflammation and carcinogenesis is not new. As long as 1800 years ago, Galen proposed that tumors arose from inflammatory tissue injury. Recently, Demehri, Cunningham, Hurst, and coworkers from Washington University in St. Louis linked chronic allergic contact dermatitis (ACD) to the development of a rare squamous cell carcinoma known as Marjolin’s ulcer. These aggressive carcinomas involve previously traumatized or chronically inflamed tissue. Establishing the link between the carcinoma and ACD began with a patient with no history of skin cancer.

In her early 40s the patient had undergone internal fixation of an ankle fracture. After surgery she developed a wound that failed to heal over the site of the implanted metal rod. Eventually, she underwent patch testing and had a positive reaction to nickel, which was, indeed, found to be a component of her implant. About a year after her initial surgery, the implant was removed but the lesion persisted. Two years later she sought treatment for the erythemic, oozing, and painful lesion, which was diagnosed as a Marjolin’s ulcer by punch biopsy. Chronic sun exposure of the adjacent uninvolved skin was evident by the presence of solar lentigines. Fortunately, the carcinoma was resected with clear margins and has shown no signs of recurrence after 2 years of follow up. Happy as it may be, however, that’s not the end of the story.

The case led the researchers to investigate whether ACD associated with a surgical wound could lead to tumorigenesis in mice. Mice were exposed to a species-specific allergen, 1-flouro-2,4-dinitrobenzene (DNFB), or to acetone as a control. The mice also received one treatment on their back with 7,12-dimethylbenz(a)anthracene (DMBA), a known carcinogen that mimics sun damage. The mice were then randomized into three groups—DNFB plus a surgical wound, DNFB alone, and acetone plus surgical wound. After surgery the mice continued to be treated with DNFB or acetone according to their group for 14 more weeks.

None of the acetone-treated mice developed tumors despite their exposure to the carcinogen. Within 4-6 weeks, however, many of the DNFB-treated mice developed skin tumors, and the number of tumors increased over time. The tumors also tended

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to progress from papillomas to invasive squamous cell carcinomas, similar to the patient’s tumor. In another experiment, the researchers ruled out a direct effect of the DNFB on keratinocytes as the mechanism of tumorigenesis. The combined results led the authors to conclude that continuous exposure to an allergen causing chronic ACD can promote tumorigenesis in sun- or carcinogen-exposed skin.

As the population ages, the number of surgically implanted medical devices will continue to increase, raising the possibility that the prevalence of metal-related ACD will likewise increase. How to advise patients before they undergo placement of a surgical implant is already a topic of discussion as is what to recommend to patients who develop implant-related ACD after surgery. What criteria justify patch testing in the first case, and what criteria justify implant removal in the second?

The data available to answer these important questions are sparse and conflicting. For example, patients who have received implants containing metals to which they are known to be highly sensitive have shown no postimplantation adverse reactions, while the patient reported by Demehri and coworkers who developed the squamous cell carcinoma had no reported history of hypersensitive reactions to metal. The authors note that their findings underscore the importance of patching testing patients before they undergo implantation of a metal device, especially patients with known metal hypersensitivities. As discussed in the March 2014 issue of this newsletter, however, few clinicians tend to recommend routine patch testing before placement of metal implants unless a history of metal intolerance is present and even then only by a slight majority. Although it may be rare for chronic ACD to promote skin carcinogenesis, the finding may provide fresh impetus to the discussion about when candidates for metal implants should be patch tested.


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• Do not apply to skin that is injured or inflamed.

WARNINGS AND PRECAUTIONS
• Acute allergic reactions, including anaphylaxis, may occur.
• Sensitization to one or more of the allergens may occur with initial or repeat testing.
• Extreme positive reactions, excited skin syndrome, tape reactions, irritant contact dermatitis, persistent reactions, and late reactions at the test site may occur.

ADVERSE REACTIONS
• The most common adverse reactions (occurring in more than 1% of the study population) were burning, tape irritation, persistent reactions, erythema, and hyper/hypo pigmentation.
Palladium is a metal named after the Greek goddess of wisdom, Pallas Athena, because its discovery in 1803 by William Hyde Wollaston coincided with that of the second largest asteroid in the asteroid belt and which was given the same name. This transitional metal, primarily produced by South Africa, Russia, and the United States, was known to miners in Brazil as early as the 1700s as an alloy with gold, but it was considered worthless. Wollaston, however, extracted palladium from platinum, and marketed it as “new silver” based on its color. Today palladium is alloyed with gold, silver, copper and zinc in various ratios, depending on its application, and is valued for its resistance to corrosion and for a unique feature. Palladium can store as much as 90% of its weight in hydrogen, which is then released when the metal is heated. In other words, it can filter hydrogen and thus is used to purify the gas.

Dental implants, including orthodontic devices, are sources of metal exposure, including palladium. The most common dental application for palladium is in crowns where the alloy forms the core onto which porcelain is bonded to build an artificial tooth. It is also used in bridges. Palladium provides strength, stiffness, and durability while the metals with which it is alloyed provide malleability. In fact, in Japan, there exists a mandate that all governmentally subsidized dental alloys must contain a minimum of 20% palladium. Consequently, palladium alloys are used in about 90% of all dental procedures performed in the country, making Japan the largest consumer of the metal for dental applications.

Individuals can also be exposed to palladium from jewelry—it is the element that gives white gold its appearance and is used because it does not tarnish. With the advent of the European Nickel Directive, which restricted the use of nickel in products in prolonged contact with the skin, palladium has become a popular substitute. The metal is also used in making electronics, aircraft spark plugs, and surgical instruments. Its most widespread use, however, is in catalytic converters.

Symptoms of palladium sensitivity have included hand and body dermatitis, burning mouth syndrome, stomatitis and mucositis, and oral lichen planus. Palladium has also been implicated in allergic contact granuloma associated with ear piercing. Many of these patients have not only had positive patch tests to palladium, but their reactions have indicated that they are monosensitized to the metal. The case of a patient who developed dermatitis on the face at the sites of contact with metallic glass frames, which proved to contain palladium, has also been reported. In some cases, oral symptoms have disappeared after removal of dental restorations with palladium. Symptoms indicative of immediate hypersensitivity, such as swelling of the lips and cheeks, dizziness, asthma, chronic urticaria and other symptoms, have also been reported.

As a result of the increased use of palladium, sensitization to this metal also may be increasing. In one study, 4,446 patients suspected of having contact dermatitis underwent patch testing. Over the 10-year period of the study, the sensitization rate to palladium increased to a high of 9.7%, with a higher prevalence in females than in males. Most of the patients (92.8%) were sensitized to more than one allergen, but 7.2% were allergic to palladium alone. Subjects exhibited hand dermatitis (40.5%), body dermatitis (47.4%) and burning mouth syndrome (1.7%). In a study of nondermatological patients, 7% of 700 school children had a positive patch test to palladium, again higher in girls (11%) than in boys (1%). In a recent review of 10,778 patients reported in the literature between 1986 and 2008, on which this discussion is based, the median prevalence of palladium allergy was 7.8% for patients with dermatitis and 7.4% for dental patients. Again, the prevalence was higher for females than males. Unlike in the earlier study, however, the rate of monosensitization was only 0.2%.

That nickel and palladium belong to the same group in the periodic table suggests the possibility of cross reactivity. And, indeed, simultaneous positive patch test reactions to nickel and palladium have been reported. In a study from 1996, 8% of 11,516 dermatitis patients undergoing patch testing were considered to have a palladium allergy and 94.6% had a concomitant nickel allergy. In a study of 1,092 patch-tested patients from 2008, 11.7% had a palladium allergy, 97% of whom also had a nickel allergy. Several reports have ruled out cross contamination between the two metals as the cause while other studies favor cross sensitization as the underlying mechanism. Furthermore, substantial in vitro evidence supports cross reactivity between palladium and nickel. Positive patch test reactions to palladium have also been associated with reactivity to other metals such as cobalt, gold, chromium, copper, and platinum among others.

Overall, the accumulated data suggest that palladium allergy is relatively common and most likely to be clinically relevant in two types of patients: those with allergic contact granulomas associated with piercing and those with oral disease. Although the indications could change over time, especially if the use of palladium continues to increase, for now patch testing appears to be a wise choice for these two groups of patients.

Faurschou A, Menné T, Johansen JD, Thyssen JP. Metal allergen of the 21st century—a review on exposure, epidemiology and clinical manifestations of palladium allergy. Contact Dermatitis 2011; 64: 185-195

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When it comes to the stability of allergens—in terms of their shelf life and in terms of the length of time that they can be stored between being dispensed and being applied—one size does not fit all. Stability of allergens is an important consideration for patch testers because false-negative reactions can occur if allergens lose potency over time. Stability is defined as ±20% of the concentration before the expiration date. In general, allergens prepared in petrolatum are considered relatively stable. For example, no differences were found in the detected concentrations of fresh and 1-year-old preparations of methyl dibromo glutaronitrile when tested at 0.1, 0.3, 0.5, and 1.0% in petrolatum. Many other test allergens have been found to be stable for as long as 4 years when kept refrigerated at 4°C. Exceptions include triglycidyl isocyanurate and diphenylmethane-4,4’-diisocyanate.

It is important to remember that method of storage can affect the stability of allergens in petrolatum. For example, in one study, methyl methacrylate (MMA), 2-hydroxyethyl methacrylate (2-HEMA), and ethyleneglycol dimethacrylate (EGDMA) were stored in capped polypropylene syringes (with and without aluminum foil wrapping) and in one type of patch test chambers kept in their corresponding transport containers (without aluminum foil). The samples were placed in an airtight bag and shipped to Singapore and then were returned to Malmö, Sweden where they were analyzed. Total travel time was about 32 hours (28 by air, 4 by land). The concentration of the allergens shipped in the capped syringes, regardless of being wrapped in the foil, remained stable. However, allergens shipped in transport containers lost most of their allergen content. The loss could reflect evaporation, chemical degradation from reactions with air or moisture (the transport cases are not airtight), or spontaneous polymerization. The authors of this study concluded that volatile allergens should never be preloaded and shipped to users. How long these same allergens might last in similar conditions during refrigerated storage involving no transport was not tested.

In another study, MMA, 2-HEMA, and 2-hydroxypropyl acrylate (2-HPA), cinnamal, and eugenol in petrolatum were stored in three different types of test chambers at room temperature and refrigerated. Allergen concentration was tested at 0, 2, 8, 24, and 72 hours and at 7 days. The different allergens evaporated at different rates. For example, evaporation of MMA increased the first 2 hours but declined thereafter; in contrast, cinnamal evaporated at a relatively constant rate. The decrease in concentration was substantial in two of the three types of test chambers under both storage conditions for all of the allergens except the refrigerated 2-HEMA. For the third type of chamber, stability was acceptable when the allergens were stored in the transport container although MMA and 2-HPA required refrigeration to maintain their concentration.

The above studies all relied on chemical analysis of the stored allergens. Most recently, however, a study compared the reactivity of fragrance mixes I and II (FM I and FM II) when dispensed into one type of chamber and found that the results could be of clinical importance. The allergens were loaded into the chambers either immediately before being applied to a patient’s back or were dispensed and stored in the chambers for 6 days before application. The stored panels were wrapped in plastic bags and kept at room temperature. Significantly more patients had a positive reaction to the fresh FM I compared to the number who reacted to the 6-day FM II; reactivity was about the same. The authors attributed the differences in reactivity to FM I and FM II to the mostly lower vapor pressure of the ingredients in the latter compared to the former (lower vapor pressure is associated with lower volatility) although the study did not elucidate the role of any one particular ingredient in either mix.

At this point, the stability of very few of the more than 550 commercially available substances for patch testing has been evaluated. Overall, the results of the above studies suggest that the most conservative approach is to dispense volatile compounds such as acrylates and fragrances only immediately before application for patch testing, regardless of type of chamber used. Given the measurable decrease in the concentrations of the allergens tested after only 2 hours of storage, the strategy of waiting to dispense volatile compounds until the time of testing should help minimize the risk of false-negative reactions in your patch test practice.

References:
4. Frick M, Zimerson E, Karlsson D, Marand A, Skarping G, Isaksson M, Bruze M. Poor correlation between stated and found concentrations of diphenylmethane-4,4’-diisocyanate (4,4’-MDI) in petrolatum patch test preparations. Contact Dermatitis 2004; 51(2):73-8