

Gold Contact Allergy: Clues and Controversies

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Abstract: In 2001, gold was named Contact Allergen of the Year. More than a decade later, we continue to face several challenges in defining the role of gold in contact allergy. First, interpretation of gold reactions in the setting of epicutaneous patch testing may be difficult; in addition to being a common irritant, gold may be associated with significantly delayed and persistent reactions. Second, although gold compounds are commonly positive on patch testing, clinical relevance is relatively low and may be challenging to determine. Third, the complex interplay between gold and the human body is still poorly understood. In this review, we provide an overview of the literature concerning gold patch test positivity and present recommendations for epicutaneous patch testing with gold.

In 2001, gold was named Contact Allergen of the Year.¹ More than a decade later, we continue to face several challenges in defining the role of gold in contact allergy. First, interpretation of gold reactions in the setting of epicutaneous patch testing may be difficult; in addition to being a common irritant, gold may be associated with significantly delayed and persistent reactions that may be missed on standard testing or tough to distinguish from active sensitization.² Further, the ideal formulation for patch testing has yet to be determined. Second, although gold preparations are commonly positive on patch testing, clinical relevance seems to be relatively low and may be challenging to determine.³ Given the persistent nature of gold reactions, it may be difficult to ascertain what length of time would constitute an adequate trial of allergen avoidance⁴; moreover, the complex interplay between gold and the human body is still poorly understood as well as the amount of exposure required to sensitize a susceptible individual. In this review, we provide an overview of the literature concerning gold patch test positivity and present recommendations for epicutaneous patch testing with gold.

Gold as a Hapten

Gold (Au, atomic number 79) is elemental and can be found in many states, including an ionic state. As an element, it has several unique characteristics. Gold is easily malleable and, as a noble metal, is highly resistant to corrosion, thus prompting its use in the medical/dental field and in other industries. In its native elemental

form, it is fairly nonreactive with other metals. Gold is unaffected by most acids, a property that has been historically used via the “acid test” to determine whether a substance is pure gold; although gold is impervious to nitric acid (although other metals are dissolved), it is dissolved by a combination of nitric acid and hydrochloric acid, which is also known as “aqua regia.”⁵

The complex interactions between gold and the human body have yet to be fully characterized. Elemental gold requires ionization to become a hapten, and given its high resistance to corrosion, there is some debate about whether gold can ionize sufficiently to serve as a hapten. In cases of gold allergy, small amounts of inert gold are thought to be converted to a soluble form by amino acids in bodily fluids such as sweat and absorbed by the skin.⁶ Notably, experiments in vitro with simulated sweat/salt solutions demonstrated little to no gold ion formation.^{7,8} It is possible, however, that the presence of sulfur-containing amino acids in solution, specifically cysteine, may be critical for this process.^{9,10} Therefore, with regard to gold exposure and sensitization, the immediate surrounding fluid or tissue environment may play a pivotal role. In addition, it has been postulated that cosmetic powders that contain microabrasives such as titanium dioxide may abrade jewelry and act as carriers to the face.¹¹

The alloy of gold may affect its release and subsequent reactivity.⁶ White gold is a gold-based alloy with multiple constituents that lend its white color, and common alloys may include palladium, nickel, zinc, and cadmium, among others.¹² Of note, jeweler’s gold in reality does not contain gold but rather copper, zinc, and tin. Interestingly, increased copper content in gold alloy is associated with increased gold dissolution; thus, lower-karat gold may release more gold. This suggests that lower-karat gold may cause more intense skin reactions than pure gold in gold-sensitive patients.⁶

It should be noted that patch testing with metals can be both clinically and practically challenging. First, metals often elicit an irritant or doubtful reaction that may be difficult to distinguish from weak but true-positive reactions.¹² This may be especially difficult to interpret in the setting of atopic dermatitis, given an increased rate of false negatives and irritant reactions.^{12,13} Irritant

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reactions to metals have also been described in children with atopic dermatitis.¹⁴ Second, delayed reactions are common among metals, including gold sodium thiosulfate, gold chloride, potassium dicyanoaurate, palladium chloride, beryllium sulfate, nickel sulfate hexahydrate, and cobalt sulfate.^{15,16} Thus, some reactions may be missed with standard readings. Third, in vitro responses may not correlate with patch test results, especially in the case of weaker patch test results.¹⁷ Fourth, results may not be reproducible over time.¹⁸ Lastly, patients often patch test positive to multiple metals. For example, data gathered by the North American Contact Dermatitis Group (NACDG) between 1996 and 1998 found that, of 4101 patients, 9.5% had a positive patch test result to gold.¹⁹ Nickel and cobalt allergies were present in 33.5% and 18.3% of gold-allergic patients as compared with 14.2% and 9.0% of the total population. In another NACDG analysis, allergic reaction to gold was statistically linked to concomitant nickel allergy, and still another study associated gold and palladium allergy.^{20,21} It is difficult to distinguish cross-reactivity from coreactivity, and more research is warranted to further investigate the relationship between allergy to gold and other metals.

Recently, Basketter et al²² proposed a system to categorize the human sensitization potential of chemicals, with category 1 being the most sensitizing and category 6 representing essentially nonsensitizers. On the basis of a review of the literature and local lymph node assay results, the authors found gold chloride to be in category 2, a group deemed likely to sensitize 1% to 10% of those with regular exposures to moderate concentrations. At this time, it is unclear whether this calculation can be supported on a nontheoretical basis, given the insufficient data.

Available Haptens

Gold salts are the most widely used haptens in the epicutaneous patch testing of gold. Some available formulations of gold salts used in epicutaneous patch testing are gold (I) sodium thiosulfate dihydrate 0.25%, 0.5%, and 2% petrolatum (pet) as well as 75 $\mu\text{g}/\text{cm}^2$ (approximately equivalent to 2% pet) and potassium dicyanoaurate (I) 0.1% aqueous and 0.002% pet (Table 1). Compared with other gold salts, gold sodium thiosulfate has fewer reported irritant reactions.^{23,24} The most commonly tested gold preparation in North America may be gold sodium thiosulfate.^{16,25,26}

To capture all gold patch test–positive patients, different gold salts may need to be tested in the same patient and, sometimes, even different dilutions of each gold salt.^{16,27} Analysis of skin

samples below gold rings has demonstrated much lower levels of measured gold than are typically used in patch testing.⁶ It is possible that this may contribute to low rates of clinical relevance if currently used formulations are detecting gold positivity even in patients with higher thresholds of gold reactivity, in whom the low amounts of gold found in daily exposure might be insufficient to elicit a reaction. The same study also took skin samples from patients with systemic contact dermatitis to gold treatments and found that the amount of measured gold varied considerably, likely reflecting the wide variability that can be found in threshold of reactivity. Interestingly, Davis et al¹⁶ also showed that some patients reacted to gold sodium thiosulfate at a lower concentration but not at a higher one (0.25% versus 0.5%). This suggests that there are other factors beyond concentration and type of gold salt that determine reactivity. Such factors may include local amino acid interactions, pressure, friction, presence of damaged or eczematous skin, and fluctuations in the threshold of reactivity of the skin itself.²⁸ Overall, it is clear that the relationship of gold reactivity and exposure concentration is not linear. Further research is required to allow us to obtain an accurate, reliable, and reproducible patch test result.

Patch Test Controversies

The inclusion of gold in routine epicutaneous patch testing is controversial. The NACDG has eliminated gold testing from its standard allergen series, citing persistent patch test reactions and patient concerns (Fig. 1).²⁹ For example, of 31 subjects patch tested with gold sodium thiosulfate in 1 study, 8 (26%) subjects had long-standing reactions.³⁰ However, the American Contact Dermatitis Society Core Allergen Series Committee chose to include gold sodium thiosulfate 2% pet in its Core Allergen Panel IV, stating potential relevance in specific patients.²⁵ In addition, the Thin-layer Rapid Use Epicutaneous Test (Mekos Laboratories A/S, Hillerød, Denmark) has recently expanded, adding, among others, 75 mcg/cm^2 of gold sodium thiosulfate. Currently, the NACDG



Figure 1. Two sites of persistent positive gold reactions 2 months after patch testing.

TABLE 1. Gold Hapten Formulations

Gold Sodium Thiosulfate	Potassium Dicyanoaurate
0.25% pet	0.002% aq
0.5% pet	0.1% aq
75 mcg/cm^2	
2.0% pet	

aq, aqueous.

recommends targeted testing in patients with suspected jewelry allergy or in patients with facial or eyelid dermatitis.²⁹ The American Contact Dermatitis Society Core Allergen Series Committee also urges considering gold patch testing in patients with exposure through gold dental restorations.²⁵

It should be noted that the methodology of gold epicutaneous patch testing is also a source of controversy. Gold may be a late reactor, with some recommending a final patch test reading at 3 weeks to avoid missing any positive reactions.² Such late reactions have raised concern about active sensitization. Unlike other allergens, however, epicutaneous patch test sites that become positive up to 3 weeks after application are not thought to represent active sensitization. Instead, true cases of active sensitization might be suggested by reactions at prior or new testing sites upon retesting with serial dilutions of hapten.²

Epidemiology of Gold Patch Test Positivity

The data available regarding the prevalence of gold patch test positivity vary by study and test substance, with reaction rates ranging from 0.07% to 30.7% (Supplementary Table 1, <http://links.lww.com/DER/A3>).^{3,16,19,31–44} The NACDG noted an 8.7% positivity for gold sodium thiosulfate 0.5% pet during the study period 2003 to 2004, whereas the Mayo Clinic reported an 18.4% positivity for the same allergen and concentration during the period 2000 to 2009.^{16,32} At the last report of the NACDG patch test data with gold included (2003–2004), there was a statistically significant decrease in gold positivity compared with 2001 to 2002 and 1994 to 2002.³² The Mayo Clinic also reported a significant decrease in gold positivity in patch testing when comparing 2006 to 2010 with 2001 to 2005.³ In a study from Thailand, the most common reaction on patch testing was gold sodium thiosulfate 0.5% pet, at 30.7%, although clinical relevance was unclear.⁴¹ Reports from Japan found a possible decreased detection of gold allergy after changing the screening hapten to gold chloride (1% rate of positivity), as rates were 9.3% with prior use of gold sodium thiosulfate.⁴³

Women comprise most of the patients with gold allergy possibly because of greater use of jewelry. In addition, most have gold dental work, although no oral symptoms are usually present.⁴⁵ In 1 study, 34% of patients with gold dental restorations had positive patch test reactions to gold as compared with 11% of those without gold dental restorations.⁴⁶ Patch testing in children yields a 6% to 10% positivity rate.⁴⁷

It is important to note that our knowledge of gold allergy prevalence has been limited by the quality of our testing conditions because it remains unclear whether we have identified the appropriate screening agent, concentration, and time course for patch testing to gold.⁴⁸

Clinical Relevance

The clinical relevance of a positive patch test to gold has long been a matter of debate. Although gold sodium thiosulfate is one of the

most commonly positive compounds on patch testing, with patch test positivity reported to be as high as 30.7%, anywhere from 0% to 54% of positive reactions are felt to be clinically relevant, with the 2 largest studies showing clinical relevance in only 10% to 15% of cases (Supplementary Table 1, <http://links.lww.com/DER/A3>).^{31,33} To put this in perspective, in these studies, this rate of relevance was comparable with nickel (11.9%–16.2%) or balsam of Peru (11.7%–13.2%) and greater than cobalt (7.7%–12.5%) or thimerosal (1.8%–2.9%).

Other studies have supported low clinical relevance. Fleming et al³⁵ compared 1203 patients with suspected contact dermatitis with 105 volunteers without dermatitis and found similar rates of patch test positivity to gold sodium thiosulfate (3.2% in the dermatitis group versus 4.8% in the volunteer group). The authors found no differences between the 2 groups in terms of gold exposure and also no association between a positive patch test to gold and dental or therapeutic gold, or ear piercing. Still another study evaluated 8 patients with patch test positivity to gold sodium thiosulfate and found no clinical relevance after reviewing possible exposures.⁴⁴ Of 28 healthy volunteers who were found to have a positive reaction on patch testing to gold salts 10 years prior, none reported mucosal or skin reaction with gold contact.³⁰ Gold allergy in children has also demonstrated low clinical relevance. A review of 391 children patch tested by the NACDG between 2001 and 2004 found that 7.7% of the children tested positive to gold and that 3.6% of these were considered relevant positive reactions.⁴⁹

On the other hand, there are data that suggest that gold allergy may be clinically relevant in certain settings. Examples of possible evidence for gold allergy include the following: flaring at sites of previous contact dermatitis and patch test sites after exposure to systemic gold, improvement in dermatitis after gold avoidance, allergen-specific cytokine release in response to gold, and possible gold allergy in patients with gold-coated intracoronary stents. Blood levels of gold have been related to dental gold restorations, the number of dental gold restorations, and also to contact allergy to gold.⁵⁰ A correlation has also been demonstrated between the blood levels of gold and the intensity of the patch test reaction to gold: the higher the blood concentration, the stronger the positive patch test reactions and the lower the minimal eliciting concentration required to cause a positive reaction.^{51,52} Gold sensitivity has been hypothesized to be a cross-reaction common to transition metals because patients are often sensitive to other metals.²⁰ However, data gathered by the NACDG between 1996 and 1998 found that, of 4101 patients, 9.5% had a positive patch test result to gold and that gold was the only positive reaction in 15.2% of the gold-allergic patients.²¹ Nickel and cobalt allergies were present in 33.5% and 18.3% of the gold-allergic patients as compared with 14.2% and 9.0% of the total population.

It has been theorized that the low rate of clinical relevance may be due to the fact that it is difficult to solubilize metallic gold, so that the resultant small amount of gold released may not be sufficient to elicit a reaction in sensitized individuals. Thus, some gold-allergic patients may seem to tolerate most gold metal contact.¹

A summary of sources of gold exposure and reported reactions is provided in Tables 2 and 3, respectively.

Localized Contact Dermatitis to Gold

There have been numerous case reports regarding localized contact dermatitis to gold (Supplementary Table 2, <http://links.lww.com/DER/A3>), particularly involving the eyelids, ears, hands, and neck.^{21,36,45,53–63} This may take the form of a chronic papular eruption.⁶⁴ Airborne dermatitis has also been reported, particularly involving the eyelids and neck.^{65–67} Granulomatous and lymphomatoid reactions have been described at sites of piercings with gold jewelry.^{53,68–75}

Reported causes of localized contact dermatitis are often secondary to jewelry and occupational exposures. Bruze et al⁴⁵ found that patients suspected to be gold allergic did not have an increased incidence of positive patch tests to gold sodium thiosulfate in comparison with patients with no known sensitization to gold. In 106 patients who were noted to have positivity to gold, however, sites of dermatitis in areas exposed to gold jewelry, such as the ears and fingers, were overrepresented. Fleming et al⁷⁶ found that 2 of 8 patients with a positive patch test to gold had been suspected to have gold allergy before testing and noted resolution of their dermatitis with avoidance of gold jewelry. Trattner and David⁴⁰ found that 2 of 34 patients improved upon avoidance of gold.

Patch test reactions are often late and notably long lasting³⁸; similarly, gold allergy also tends to result in delayed reactions that are slow to appear and to subside.⁴⁸ Comaish⁵⁶ described a case of allergic gold ring dermatitis that persisted for several months after exposure to the gold had ceased. Repeated patch tests with scrapings from the 18-karat ring and pure gold leaf were negative, whereas testing with gold chloride showed a strong positive result, demonstrating the importance of testing with gold salts rather than to ring scrapings or gold foil, which typically do not elicit a reaction. In earlobe contact dermatitis caused by gold, scanning electron microscopy and x-ray microanalysis have shown small

TABLE 2. Sources of Allergic Contact Dermatitis to Gold

Local Allergic Contact Dermatitis

- Jewelry
- Occupational
 - Gold plating
 - Smelting
 - Gilding
 - Mining
 - Gold recycling
 - Dental workers

Systemic Allergic Contact Dermatitis

- Gold-coated stents*
- Dental implants
- Orbital implants
- Eyelid implants
- Gold-containing oral supplements
- Gold sodium thiomalate therapy

*No longer in use.

TABLE 3. Reported Manifestations of Allergic Contact Dermatitis to Gold

Local eczematous eruption	Lymphomatoid reaction
Generalized dermatitis	Lichenoid dermatitis
Chronic papular eruption	Perioral dermatitis
Airborne dermatitis	Oral manifestations (cheilitis, burning mouth, stomatitis, ulceration, lichenoid reaction)
Persistent granulomatous reaction	

dense fragments containing gold.⁷⁷ Gold incorporated in the dermis via piercing seems difficult to eliminate, and this may cause continual antigenic stimulation and patch test positivity. A prospective double-blinded study evaluated 60 patients with pierced ears who had positive patch test reactions to gold. For 8 weeks, half of the patients wore earrings coated with 24-karat gold and the other half wore a titanium nitride. Twelve patients who had received gold earrings and 5 patients who had received titanium developed a skin reaction ($P < 0.05$), predominantly on the earlobes. After excluding reactions of duration shorter than 1 week, 9 patients with reactions remained, 8 of whom had received gold earrings and 1 had received titanium ($P < 0.05$).⁷⁸

The long-lasting nature of gold reactions may present a diagnostic challenge. Sperber et al⁴ shared a case of papular dermatitis and persistent patch test reaction to gold sodium thiosulfate, where the eruption failed to improve after 2 months of gold avoidance. The authors were unable to ascertain whether the patient was having a persistent reaction to gold or an unidentified exposure to gold, or whether the dermatitis was secondary to a different etiology entirely, exemplifying the diagnostic challenges inherent to gold allergy.

In 1 double-blinded crossover trial of 24 patients with known contact allergy to gold, the patients were randomized into 2 groups where 1 group was topically provoked to gold (15-mg gold sodium thiosulfate applied to the shoulder for 48 hours) and 1 group to the control, then epicutaneously patch tested with 10 aqueous dilutions of gold sodium thiosulfate. Blood was drawn before exposure and after each patch testing read. After 6 weeks, the experiment was repeated and the group that had previously been provoked with gold was now provoked with the control and vice versa. Higher blood levels of gold were associated with a lower minimal eliciting concentration on patch testing.⁵²

Several questionnaire studies have evaluated the frequency with which patients with gold-positive patch tests experienced symptoms from gold contact. Bruze et al⁴⁵ found no difference between gold-positive and gold-negative patients (16.7% for the gold-positive patients compared with 15.9% for the gold-negative patients). On the other hand, Sabroe et al³⁶ in a similar study noted a large difference of 53.8% for the gold-positive group compared with 12.6% for the gold-negative group.

Systemic Contact Dermatitis to Gold

Systemic contact dermatitis occurs when an individual who is sensitized to an allergen via the cutaneous route subsequently

reacts to the same allergen or a cross-reacting allergen via a systemic route, including oral, intravenous, intramuscular, inhalational, transmucosal, or transcutaneous. One of the earliest such reports was a case of an extensive contact dermatitis in a patient reacting to a gold-ball orbital implant.⁷⁹ Subsequently, many more studies have substantiated the role of gold exposure in causing systemic contact dermatitis.

Intramuscular gold has been demonstrated to cause flares of previous patch test reactions to gold, as well as flares of dermatitis, in the setting of allergen-specific cytokine release. Moller et al^{80,81} challenged 10 gold-allergic patients with an intramuscular dose of gold sodium thiomalate and observed a flare of 1-week-old gold patch test reactions in all of them. Five patients also experienced a morbilliform eruption, 1 patient had a flare of a previous contact dermatitis site, and 4 patients had a transient fever. Plasma levels of tumor necrosis factor α (TNF- α), interleukin-1ra, sTNF-R1, and C-reactive protein were increased, particularly in those with fever. A double-blinded study of 20 gold-allergic patients challenged with intramuscular gold sodium thiomalate and/or oral nickel found that 6 of 10 gold-allergic patients reacted to the intramuscular gold.⁸² None reacted to nickel. Plasma levels of TNF-R1, TNF- α , and IL-1 were increased in only those gold-allergic patients challenged with gold.

Romagnoli et al⁸³ isolated gold-specific T cells from a gold-treated rheumatoid arthritis patient exhibiting delayed-type hypersensitivity response. T-cell activation seemed to occur via direct binding to the major histocompatibility complex (MHC)-peptide complex without requiring antigen processing by antigen-presenting cells. Similarly, Hashizume et al⁸⁴ immunologically characterized T cells from a patient with rheumatoid arthritis who developed fever as well as erythema, petechiae, and papules involving the trunk, extremities, face, and oropharynx after gold treatment. In contrast to control patients with rheumatoid arthritis, gold-specific CD4⁺ and CD8⁺ T cells were found that simultaneously activated Th0, Th2, and Tc1-like cytokine profiles. T-cell recognition of gold consisted of MHC-restricted and MHC-independent pathways, raising the possibility that gold may act as a superantigen in a fashion similar to that proposed for nickel, explaining the frequency of positive patch test results to gold.

There have been several other small studies evaluating gold sensitivity and systemic contact dermatitis in patients with rheumatoid arthritis receiving gold sodium thiomalate therapy. In these cases, patients have generally been screened with gold sodium thiosulfate because this is thought to provide greater sensitivity on patch testing.⁸⁵ Although Fleming et al⁸⁵ did not find any gold sensitivity in 55 patients with rheumatoid arthritis, Moller et al⁸⁶ found that patch test positivity to gold was quite common in a cohort of 77 patients with rheumatoid arthritis. It has been suggested that higher concentrations of gold sodium thiosulfate (ie, >0.5%) are required to detect gold allergy in patients with rheumatoid arthritis perhaps because of concomitant immunosuppressive medications or inherent immunosuppressive properties of the disease and that this may explain the discrepancy.⁸⁷

Svensson et al⁸⁷ evaluated 19 patients undergoing a first injection of gold sodium thiomalate for rheumatoid arthritis and found that 4 patients were patch test positive to gold. Contact allergy was corroborated by a statistically significant increase in serum TNF- α and IL-1 in gold-allergic patients but not in gold-negative patients. Only 1 of these patients became clinically symptomatic and developed malaise, vomiting, tachycardia, and a macular eruption over the abdomen 10 hours after injection.

A case of perianal itching that evolved into a generalized dermatitis was reported in a woman with a history of a gold dental crown who had recently started Aurocard, an over-the-counter gold-containing oral supplement indicated for the treatment of early heart failure.⁸⁸ The authors diagnosed her with systemic contact dermatitis and also hypothesized that excretion of gold via the fecal route might have contributed to her initial perianal dermatitis because 85% to 95% of gold is excreted in the feces. She cleared upon discontinuation of the Aurocard.

Four patients who developed eyelid dermatitis after gold weights were implanted in the lids to assist with difficulties in closing the eye have also been described. Patch tests were positive for gold sodium thiosulfate, and the localized dermatitis resolved with removal of the weights.⁸⁹

Endovascular Implants

Gold-coated stents have been found to release ions into surrounding tissue because the metal has been found in vessels retrieved from patients with these stents.⁹⁰ Gold-coated stents have also been associated with a 5-fold increased concentration of gold in blood compared with patients with stents not containing gold.⁵¹ A high prevalence of contact allergy to gold has been found in patients with gold stents,⁹¹ and multiple studies have shown that gold-containing stents are associated with an increased risk for in-stent restenosis.^{90,92–95}

In a retrospective study of 484 patients who were given stents with or without gold coating, a correlation was found between contact allergy to gold, gold stent, and restenosis.⁹³ Gold-allergic patients with gold stents were found to run a 3-fold higher risk for restenosis, and in the gold-stented patients, a significantly higher frequency of contact allergy to gold was seen on patch testing compared with a control group without stents (37% of gold-stented patients compared with 19% of controls, $P < 0.01$).^{93,94} There were no statistically significant differences in contact allergy to gold or nickel between nickel-stented patients and gold-stented patients, suggesting the presence of other sensitizing factors in addition to stent placement; however, the gold-coated stent demonstrated a trend toward statistical significance when other risk factors for contact allergy to gold were considered, such as dental gold and ear piercing (odds ratio, 1.43; 95% confidence interval, 0.95–2.16; $P = 0.09$). Overall, multivariate analysis showed a correlation between contact allergy to gold (gold-plated stents) and an increased frequency of restenosis (odds ratio, 2.3; 95% confidence interval, 1.0–5.1; $P = 0.04$).⁹³

It has thus been hypothesized that gold implants give rise to ions, perhaps in the setting of mechanical damage to the surfaces in the stent in place, leading to increased gold concentration locally as well as in blood that can cause sensitization in those not previously sensitized by other means such as dental material. Through continuous release of ions, a contact allergic reaction may manifest as an endotheliitis within the vessel where the stent is located.⁹³ Given the high rate of in-stent restenosis, the use of gold stents has been largely abandoned.

Dental Implants

Dental implants have long been suspected to be a source of sensitization and contact allergy to gold. Gold may be found in the dental amalgam on the enamel side of the tooth as well as in the metal post for dental implants. Schaffran et al⁴⁶ found that 34% of 71 asymptomatic patients with gold dental restorations had positive patch test reactions to gold as compared with 11% of those without gold dental restorations. Positive patch tests to gold in dental patients have also been corroborated in vitro through the lymphocyte proliferation test.⁹⁶

Multiple studies have suggested that localized exposure to dental gold may result in systemic gold exposure. A correlation between the blood concentration of gold and the amount of dental gold has been described.^{50,57,97} One study reported immediate elevation of gold blood levels after the placement of dental gold, and this elevation remained for more than a decade.⁹⁸ In addition, salivary gold levels also have been correlated to amount of dental gold.⁹⁷

There is some direct and indirect evidence that gold dental implants may cause contact allergy. Aside from case reports,^{27,57,99} a statistically significant and dose-dependent relationship has been shown between contact allergy to gold and the number of dental gold restorations, although no statistically significant relationship was found with respect to oral lesions.¹⁰⁰ In another series of 52 dental patients who patch tested positive to gold, 13 (25%) patients had a history of itching, irritation, or rash to gold jewelry and dental restorations.⁹⁶ With regard to specifically oral lesions, Laeijendecker et al¹⁰¹ evaluated 200 patients with persistent oral lesions attributed potentially to gold allergy and found that 17 patients patch tested positive to gold trichloride. Moreover, 1 patient with allergic contact stomatitis and 1 patient with allergic contact dermatitis healed completely with gold replacement, although improvement was noted more frequently in patients with oral lichen planus.

Positive patch test reactions to dental materials have been associated with cheilitis, perioral dermatitis, burning mouth, stomatitis, ulceration, and lichenoid reaction.^{99,101–103} With regard to lichenoid reactions, both oral and cutaneous lichen planus eruptions have been associated with allergy to gold and other metals in dental work. Patients with oral lichenoid reactions have been reported to have higher frequencies of positive gold reactions compared with frequencies in the general dermatitis population

reported by the NACDG in 1996 to 2003.^{32,33,104} In 51 patients with oral lichen planus, 20% had positive patch tests to gold, ranking it second only to mercury of 10 allergens.¹⁰⁴ Ahlgren et al¹⁰⁵ also found an increased frequency of patch test positivity to gold in patients with oral lichenoid lesions in comparison with patients undergoing evaluation of other dermatitis not affecting the oral region. In contrast, Martin et al¹⁰⁶ did not find an association between oral gold and oral lichen planus. The authors did, however, find an increased risk for oral lichen planus in the presence of dissimilar metals in contact with each other in the mouth as well as amalgam corrosion.

Clinical relevance in these cases is uncertain. When 121 patients with facial and oral pathology underwent patch testing to dental materials, the most common allergens detected were gold, nickel, mercury, palladium, cobalt, and 2-hydroxyethyl methacrylate. Most of the reactions to mercury seemed relevant to the authors, whereas gold and nickel positives were of uncertain clinical relevance.¹⁰² In addition, a study of 206 patients with oral lichen planus and stomatitis found that 28 patients had positive patch test reactions to dental metals.¹⁰⁷ Of note, fewer than 15% of the patients with lichen planus were thought to have a clinically relevant allergy. Only 4.9% of the patients demonstrated a positive reaction to gold possibly because of the use of a weaker concentration of gold sodium thiosulfate (0.25%) and the omission of a late reading.

Occupational Gold Allergy

Occupational exposure has been reported to occur in those who gild porcelain, enamel, and glass, where gold hydroxide, potassium, and sodium gold trichloride are often used.³⁸ Potassium and sodium dicyanoaurate have also been reported to cause dermatitis in workers involved in gold plating.¹⁰⁸ In addition, gold trichloride has been reported to cause dermatitis in photography.⁵⁵ Occupational dermatitis often presents on exposed acral sites.¹⁰⁹ Sperber et al⁴ shared a case of severe hand dermatitis in a jewelry saleswoman who had a positive patch test reaction to gold but not to nickel. She resolved completely after taking a leave of absence from her work. The authors also described a glass etcher with hand dermatitis who tested positive to gold. Her dermatitis was attributed to her gold-etching instrument, which resulted in the dispersion of gold particles while etching. She improved when she stopped etching glass. Airborne dermatitis has also been reported in those involved in gold smelting, gilding, and gold plating, particularly involving the eyelids and neck.^{65–67} Other workers who may be exposed to gold include gold miners, dentists, dental technicians, and those who work in gold recycling.³⁸

Conclusions and Recommendations

In conclusion, gold seems to be a cause of contact dermatitis in specific clinical settings (Table 4). We recommend screening for gold allergy in cases of eyelid and/or facial dermatitis or when jewelry allergy is suspected. Screening should also be strongly

TABLE 4. Gold Allergy Pearls

- Gold is largely inert unless in the presence of specific factors (ie, cysteine such as in some body fluids/sweat; microabrasives such as titanium dioxide; copper in lower-karat gold alloys).
- To capture all gold patch test–positive patients, different gold salts may need to be tested in the same patient and, sometimes, even different dilutions of each gold salt.
- Gold sodium thiosulfate is the most commonly used hapten when screening for gold allergy with epicutaneous patch testing.
- Gold reactions are often delayed (up to 3 weeks after application) and significantly long lasting.
- Positive gold reactions are often not clinically relevant.
- Screening for gold allergy is most helpful when evaluating patients with facial and eyelid dermatitis or when jewelry allergy is suspected. Screening should also be strongly considered when there is involvement of the ears, hands, and neck or a history of current exposure to gold dental materials.

considered when there is involvement of the ears, hands, and neck or a history of current exposure to gold dental materials. In addition, in the case of potential occupational exposure, patch testing to gold may be indicated.

Patch testing with gold can present unique challenges. Gold haptens may be irritating, so interpretation of results may require caution, especially in the setting of atopic dermatitis. When patch testing to gold, it is important to note that gold reactions may be delayed as many as 3 weeks after application and can be significantly long-lasting; thus, it is the opinion of the authors that routine patch testing to gold should be avoided. Currently, there is insufficient evidence to definitively recommend for or against a specific gold preparation for patch testing, although the most commonly tested form of gold in North America may be gold sodium thiosulfate 2% pet owing to its wide availability and decreased irritancy properties. To capture all gold patch test–positive patients, it may be necessary to test different gold salts in the same patient and, perhaps, different dilutions of each gold salt as well. Although this approach seems to increase sensitivity, specificity may decrease.

Determination of clinical relevance may be difficult because of the high rate of false or clinically irrelevant positives. Exposure is common, particularly in women and those with older dental restorations. We suggest obtaining a thorough history and maintaining a high index of suspicion for connubial and systemic sources of exposure.

Although the topic of gold contact allergy remains controversial, it is vital to both continue testing for gold allergy when appropriate and to report data regarding gold sensitivity. The story is not yet written, and we are hopeful that this article will renew dialogue about this provocative allergen. A multidisciplinary discussion and approach may help to elucidate the clinical relevance and role for patch testing to gold in the dermatologic community, with possible input from our colleagues—biochemical, metallurgical, and immunologic.

Future Research

Altogether, gold has many unique characteristics, and the interpretation of clinical relevance remains challenging. There is a clear

need for further research. Considerations include further testing to optimize gold-screening compounds such as testing with serial dilutions, different gold formulations, and different vehicles, as well as investigation into patch test sensitization, intradermal testing, the effects of systemic challenge, histopathologic and/or immunohistochemical findings, and the relationship between gold sensitivity and allergy to other metals. Randomized controlled trials and larger studies might be helpful in guiding evaluation of clinical relevance.

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