

Gold Is Precious—But a Potent Sensitizer?



Werner Aberer, MD *Graz, Austria*

Metallic gold, carat jewelry alloys, and dental gold alloys are widely accepted as nonsensitizing materials. These substances are considered safe and inert when in contact with the skin or oral mucosa,¹ and this is attributed to the inertness of gold. In contrast, gold salts appear to be strong sensitizers, as shown by Kligman² in a human maximization test with gold chloride. But when gold sodium thiosulfate was added to a standard series for patch testing in Sweden, positive reactions were noted in 8.6% of 823 consecutive patients with a suspected contact allergy.¹ Gold then started to attract interest as a contact allergen. It was referred to as a controversial sensitizer,³ an important allergen,⁴ and even the Contact Allergen of the Year in 2001.⁵ In this issue of our journal, Yang et al⁶ performed a retrospective study and describe gold as the second most positive allergen on patch testing. However, this observation was of no clinical relevance in the majority of cases. Much ado about nothing? Apocryphal test results that could potentially lead to the unjustified removal of dental or endovascular implants, or the avoidance of decorative jewelry?

Epicutaneous patch testing is the gold standard (no pun intended) for establishing contact allergy.^{7,8} This is never equivalent to a diagnosis of allergic contact dermatitis. Contact allergy itself is not a disease; the sensitized person has contracted a property that is a prerequisite for the acquisition of allergic contact dermatitis, but only if there is demonstration of present exposure to the allergen and assessment of its clinical relevance.³

As a rule, 20 to 25 test preparations consisting of chemically defined compounds are grouped in a standard test series. This series should detect 70% to 80% of all contact allergies.⁹ The critical requirements for a sensitizer in a standard test series are well defined:¹⁰ the substance is commonly found in the environment; the contact allergy rate is above 0.5% to 1.0% in routinely tested dermatitis patients; reliable patch test results are obtained; they hold a high degree of clinical relevance; and test exposure bears minimal adverse effects especially regarding patch test sensitization.

Gold fulfills only some of these criteria. Being highly prevalent in the environment, the reported contact allergy rates range from 0.07% to 30.7% in patients with dermatitis.¹¹ Occurring at a

rate of 10.3% in the current study, it is the second most common sensitizer after nickel.⁶ The same was noted in Sweden in 1994.¹ The highly variable rates of contact sensitization to gold can best be explained by the use of different test allergens and different types of test readings. Elemental gold almost never elicits a positive patch test;¹² the same is true for gold salts such as sodium thiomalate or gold chloride.¹ In contrast, gold sodium thiosulfate provokes positive reactions quite frequently.¹ This gave rise to the notion that a positive skin test to gold sodium thiosulfate is indicative of gold allergy¹—a highly disputed and sweeping conclusion because a positive patch test may indicate sensitization to the specific test substance, but does never prove gold allergy per se. The degree of clinical relevance—which is the essential characteristic of an allergen—was very low in several studies.^{1,6} The type of test reading—mild reactions such as erythema were considered positive in some studies¹³—gives rise to a high percentage of reactors. And the high rate of late reactions might even indicate a large number of active sensitizations when testing with a high concentration of this specific gold salt.

Gold was shown to be the top allergen in a Mayo Clinic review.¹³ It achieved a 17.0% rate of “allergic reactions” after the introduction of the 2% gold sodium thiosulfate test concentration. The 0.5% preparation, tested simultaneously, yielded a rate of 9.2%, and the 0.25% preparation 5.8% positive reactions. All these preparations yielded a high rate (>50%) of allergic/questionably relevant reactions, and much lower rates of allergic/relevant reactions. Surprisingly, this remarkable fact was not discussed at all in this extensive publication except in the abstract, which stated that gold sodium thiosulfate, 0.5%, was associated with a lower reaction rate than in a previous report.¹³

The manufacturer’s leaflet for patch test substances states that a positive test reaction to gold sodium thiosulfate is indicative of a contact allergy to gold sodium thiosulfate (www.truetest.com). This information is absolutely correct; the positive reaction is indicative of sensitization, but nothing more. However, when the patient is told that “this substance is a fairly common sensitizer, eliciting symptoms linked to gold in jewelry, occupational exposure to gold, dental restorations, gold-plated intracoronary stents, and previous rheumatoid arthritis treatment,” it is becoming dangerous. Should the patient have the stent removed when he/she reacts positively to the gold salt? It may be correct, or even essential, but the statements have not been substantiated by hard evidence.¹⁴ Much ado about nothing?

Whether gold is a potent, a weak, or no contact allergen at all is not proven yet. Currently, gold or any gold salt has no place in any standard patch test series, as was decided by the North American Contact Dermatitis Group (NACDG) some years ago, citing persistent patch test reactions and patient concerns.¹⁵ The statement that gold, when tested as gold sodium thiosulfate (0.5% in pet), achieves positive reactions at a rate of 9.5% and is thus a more common allergen in North America than previously

Department of Dermatology, Medical University Graz, Graz, Austria

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication June 4, 2018; accepted for publication June 4, 2018.

Corresponding author: Werner Aberer, MD, Department of Dermatology, Medical University Graz, Auenbruggerplatz 8, 8036 Graz, Austria. E-mail: werner.aberer@medunigraz.at.

J Allergy Clin Immunol Pract 2019;7:294-5.
2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaip.2018.06.003>

reported¹⁶ does sound convincing. The conclusion from that data that gold might cause facial or eyelid dermatitis is less strong because the overall evidence is weak. In a review as early as in 1999, Bruze and Andersen³ stated: "There is a need for prospective studies on the significance of gold exposure for the development of dermatitis and stomatitis." Many studies have been published since then, but none was prospective. Although final answers to the currently open questions about gold as a sensitizer await further research, Fowler⁴ as well as Chen and Lampel¹¹ encourage continued patch testing with gold and a multidisciplinary approach to establish its clinical relevance—this did however not happen. And the decision by the American Contact Dermatitis Society Core Allergen Series Committee to again include gold sodium thiosulfate 2% pet in its Core Allergen Panel IV, stating potential relevance in specific patients,¹⁷ is controversially interpreted.¹¹

Should we continue as we have done in the last 25 years? Gold is a precious metal, and patch testing is the "gold standard" for the diagnosis of allergic contact dermatitis. Patch testing, when performed correctly and by the use of the appropriate test substance, does prove sensitization to a test substance, but not an allergic contact dermatitis. The complex interplay between gold and the human body is still poorly understood. Gold is currently too precious to be considered a potent contact allergen, or to recommend its avoidance. Further testing with the NACDG series as a means of investigating the full cause of contact dermatitis in any individual patient may yield a high number of positive reactions. However, the usefulness of an extensive NACDG series of 65 allergens is yet to be proven.¹⁸ The current evidence in regard to gold is insufficient, and the gold standard for the determination of true gold allergy is yet to be established—not by retrospective^{1,4,6,9,11,13,16} but by prospective, randomized, experimental studies.³

REFERENCES

1. Bjorkner B, Bruze M, Moller H. High frequency of contact allergy to gold sodium thiosulfate. An indication of gold allergy? *Contact Dermatitis* 1994;30: 144-51.
2. Kligman AM. The identification of contact allergens by human assay: II. Factors influencing the induction and measurement of allergic contact dermatitis. *J Invest Dermatol* 1966;47:375-92.
3. Bruze M, Andersen KE. Gold—a controversial sensitizer. European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 1999;40: 295-9.
4. Fowler JF Jr. Gold remains an important allergen. *Dermatitis* 2015;26:67-8.
5. Fowler JF Jr. Gold. *Am J Contact Dermat* 2001;12:1-2.
6. Yang B, Sundquist BK, Pasha MA. Determining the clinical relevance of patch testing to gold in evaluation of contact dermatitis. *J Allergy Clin Immunol Pract* 2019;7:292-3.
7. Aberer W, Andersen KE, White IR. Should patch testing be restricted to dermatologists only? *Contact Dermatitis* 1993;28:1-2.
8. Nelson JL, Mowad CM. Allergic contact dermatitis: patch testing beyond the TRUE test. *J Clin Aesthet Dermatol* 2010;3:36-41.
9. Holness DL, Nethercott JR, Adams RM, Belsito D, Deleo V, Emmett EA, et al. Concomitant positive patch test results with standard screening tray in North America 1985-1989. *Contact Dermatitis* 1995;32: 289-92.
10. Bruze M, Conde-Salazar L, Goossens A, Kanerva L, White IR. Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. *Contact Dermatitis* 1999;41:241-50.
11. Chen JK, Lampel HP. Gold contact allergy: clues and controversies. *Dermatitis* 2015;26:69-77.
12. Nonaka H, Nakada T, Iijima M, Maibach HI. Metal patch test results from 1990-2009. *J Dermatol* 2011;38:267-71.
13. Wentworth AB, Yiannias JA, Keeling JH, Hall MR, Camilleri MJ, Drage LA, et al. Trends in patch-test results and allergen changes in the standard series: a Mayo Clinic 5-year retrospective review (January 1, 2006, to December 31, 2010). *J Am Acad Dermatol* 2014;70:269-275.e264.
14. Echechipia S, Villarreal O, Iriarte P, Garces M, Sala-Cunill A, Daschner A, et al. Are all new allergens in TRUE Test(R) essential for a baseline set? *Contact Dermatitis* 2015;73:186-7.
15. Zug KA, Warshaw EM, Fowler JF Jr, Maibach HI, Belsito DL, Pratt MD, et al. Patch-test results of the North American Contact Dermatitis Group 2005-2006. *Dermatitis* 2009;20:149-60.
16. Fowler J Jr, Taylor J, Storrs F, Sherertz E, Rietschel R, Pratt M, et al. Gold allergy in North America. *Am J Contact Dermat* 2001;12:3-5.
17. Schalock PC, Dunnick CA, Nedorost S, Brod B, Warshaw E, Mowad C. American contact dermatitis society core allergen series. *Dermatitis* 2013;24: 7-9.
18. Cohen DE, Rao S, Brancaccio RR. Use of the North American Contact Dermatitis Group Standard 65-allergen series alone in the evaluation of allergic contact dermatitis: a series of 794 patients. *Dermatitis* 2008;19: 137-41.