

Original Investigation

Patch Testing for Methylisothiazolinone and Methylchloroisothiazolinone-Methylisothiazolinone Contact Allergy

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IMPORTANCE Contact allergy to methylisothiazolinone (MI) or to the combined formulation of methylchloroisothiazolinone and MI (MCI-MI) has increased significantly, with a frequency of as much as 11.1% in patients with dermatitis; however, few cohort studies in the US population have been reported.

OBJECTIVE To investigate the prevalence of contact allergies to MI and MCI-MI and the outcomes of patients with positive patch test reactions to MI and MCI-MI.

DESIGN, SETTING, AND PARTICIPANTS Retrospective medical record review of all consecutive patients (n = 703) presenting with possible allergic contact dermatitis and subsequently undergoing patch testing at a tertiary referral center from January 1, 2012, through November 30, 2014. Patch testing used the North American Contact Dermatitis Group standard series. The MCI-MI concentration was 100 ppm; the MI concentration in the screening series increased from 200 to 2000 ppm in January 2013. Demographic data, exposures, and outcomes were reported for patients with positive patch test reactions to MI and/or MCI-MI. Data were analyzed from December 1, 2014, through January 31, 2015.

MAIN OUTCOMES AND MEASURES Positive patch test reaction to MI and/or MCI-MI and identification of the relevance of contact allergy to these preservatives. Follow-up after allergen avoidance was determined when available.

RESULTS Of the 703 patients who underwent patch testing, contact allergy to MI and/or MCI-MI occurred in 57 patients (8.1%), with 35 reactions to MI only, 5 reactions to MCI-MI only, and 17 reactions to both. Prevalence of contact allergy to MI increased from 6 of 236 patients (2.5%) in 2012 to 16 of 235 patients (6.8%) in 2014. The most commonly affected sites were the hands and face. Contact allergy to MI and/or MCI-MI was occupationally related in 4 cases. Cosmetics, soaps and cleansers (including wet wipes), and hair care products accounted for all identified sources. Twenty-three patients had follow-up data, and 17 of these (74%) improved with allergen avoidance.

CONCLUSIONS AND RELEVANCE The increasing prevalence of contact allergy to MI alone supports its addition to the standard series to identify cases missed by testing only for MCI-MI. Recent regulations by the European Commission have banned MCI-MI in all leave-on body products as of July 16, 2015. Currently recommended US regulations are less stringent; however, US regulatory agencies must act to ensure patient safety.

JAMA Dermatol. 2016;152(1):67-72. doi:10.1001/jamadermatol.2015.3606
Published online November 4, 2015.

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Methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) are preservatives that were first introduced in a fixed 3:1 ratio for industrial use in 1980.¹ The combination of MCI and MI is also used in cosmetic products, and MI alone was approved for use in personal health care products in 2005 at a maximum concentration of 100 ppm.¹⁻³ These preservatives can be found in more than 1000 cosmetic products, including baby lotions, bath products, makeup, hair care products, deodorants, skin care products, and sunscreens.² Patients can become sensitized and develop allergic contact dermatitis (ACD) to these preservatives.

Several studies have shown that MCI is a more potent sensitizer than MI.^{2,4,5} Subsequent studies of human patch test results⁵ indicated that concentrations of MI of as much as 600 ppm did not cause dermal sensitization. However, in 2013, Macias et al⁶ evaluated 751 patients, of whom 15 were allergic to MCI-MI at 100 ppm and available for repeated testing with MCI-MI at 100 ppm, MI at 200 ppm, and personal health care products. They reported that 7 patients were sensitized to MI at 200 ppm; 6 of these had an equally positive reaction to MCI-MI and MI, and 1 had a stronger reaction to MI.⁶ Isaksson et al⁷ also reported that of 9 patients allergic to MCI-MI at a concentration of 100 ppm on patch testing, 6 had a positive repeated open application test (ROAT) result to MI alone at a concentration of 1000 ppm and 6 had a positive ROAT result to an MI-containing cream at 100 ppm, likely owing to cross-reactivity between the two preservatives. In addition, a retrospective study⁸ found that the proportion of MI-allergic patients among those reacting to MCI-MI increased from 43% to 59% from 2009 through 2011, which indicates that widespread consumer exposure has led to the increase in primary sensitization to MI and in turn has led to a rise in MCI-MI cross-reactions.

Subsequently, an increasing number of published cases of ACD have been described, especially since 2009, when MCI-MI was added to the European baseline patch test series.¹ This rise is owing in part to increasing exposure to MI alone, which is present in concentrations approaching 100 ppm in leave-on and rinse-off cosmetics.¹ The rising incidence of contact allergy cannot be explained by MCI-MI exposure via cosmetics; rather, the rise is due to increasing exposure to MI.² The diagnosis of MI contact allergy was often missed because the concentration of MI in MCI-MI was too low to identify all patients with an allergy.⁹ An estimated 40% of patients with a contact allergy to MI alone were not detected with testing for MCI-MI.^{9,10} Similarly, a report by the North American Contact Dermatitis Group (NACDG)¹¹ suggested a significant increase in positive reactions to patch tests for several allergens, including MCI-MI. As a result, in 2012 we added MI at a concentration of 200 ppm to the standard screening series at our institution, which already included MCI-MI. The concentration of MI was subsequently increased to 2000 ppm in 2013 with its addition to the NACDG standard series. Methylisothiazolinone alone at concentrations of 2000 ppm was also added to the European baseline series in 2013.¹⁰ Methylisothiazolinone was named *allergen of the year* by the American Contact Dermatitis Society in 2013 to raise awareness of this important allergen.⁹

Most studies report rates of MI contact allergy of 7%, and few have included North American patients.^{10,12,13} Methyliso-

thiazolinone is also an important allergen in children. Schlichte and Katta¹⁴ surveyed 152 products marketed for infants and children and found 30 products containing MI, including hand wipes, sunscreens, moisturizers, and soaps. These products included labels of “gentle,” “sensitive,” and “hypoallergenic.”¹⁴ One case series by Chang and Nakrani¹⁵ in 2014 identified 6 children with ACD to MI in wet wipes, with rapid resolution of skin disease after discontinuing use of the offending products. We sought to determine the prevalence of contact allergy to MCI-MI and MI in patients at the Cleveland Clinic during the 3-year period from 2012 through 2014.¹⁶

Methods

We reviewed the medical records of all patients who underwent patch testing to the standard series of the NACDG from January 1, 2012, through November 30, 2014, in the Department of Dermatology at the Cleveland Clinic. The standard series included MCI-MI at a concentration of 0.01% and MI at concentrations ranging from 0.02% to 0.2% except in the pediatric standard series, which only included MCI-MI. Patch tests were applied using aluminum chambers, 8 mm in diameter (Finn Chambers; Epitest Ltd Oy) and secured with porous paper tape (Scanpor; SmartPractice) for 48 hours. The concentration of MI in the series increased after 2013. A total of 703 patients were included. Positive reactions were defined as 1 or greater (of a possible 1+ to 3+) at the first reading (2-3 days after patches were applied) or at the final reading (4-7 days). This study was deemed exempt by the institutional review board of the Cleveland Clinic under the program for the protection of human subjects participating in research.¹⁷ Patient data were deidentified.

All patients with a positive patch test reaction to MI, MCI-MI, or both were included in this study. Patients were diagnosed as having ACD according to clinical history, results of a physical examination, and relevant positive patch test reactions. Demographic information for each patient was collected and analyzed. Follow-up information regarding the extent of clearing of dermatitis was gathered when available. All follow-up until November 30, 2014, was included in the analysis, as mentioned above in the abstract. Not all patients required follow-up.

Data were analyzed from December 1, 2014, through January 31, 2015. For the description of the demographic characteristics of patients tested, we used the MOAHLFA index (*male*, *occupational dermatitis*, *atopic dermatitis*, *hand dermatitis*, *leg dermatitis*, *face dermatitis*, and *age* ≥40 years).¹⁸ Frequencies of sensitization (percentage of patients undergoing testing) were calculated as crude proportions. The commercially available statistical software package SAS (version 9.4; SAS Institute Inc) was used for data management and analysis.

Results

During the study period, dermatologists in our health care system billed code 692.9 from the *International Classification of*

Table 1. Demographic Description of Patients With Positive Patch Test Reactions Using the Items of the MOAHLFA Index^a

MOAHLFA Index Item	Positive Patch Text Reaction, No. (%) of Patients		
	MI Alone (n = 35)	MCI-MI Alone (n = 5)	MI and MCI-MI (n = 17)
Men	10 (29)	3 (60)	3 (18)
Occupational dermatitis	3 (9)	0	1 (6)
Atopic dermatitis	14 (40)	1 (20)	7 (41)
Hand dermatitis	17 (49)	0	4 (24)
Leg dermatitis	5 (14)	0	3 (18)
Face dermatitis	10 (29)	1 (20)	7 (41)
Age ≥40 y	7 (20)	3 (60)	5 (29)

Abbreviations: MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; MOAHLFA, male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis, and age 40 years or older.
^a Includes 57 of 703 patients who underwent testing.

Table 2. Distribution of Patients With Positive Patch Test Reactions

Allergen	No. (%) of Patients With Positive Reaction (n = 57)	Reactions, No. (%) of Patients					
		MI			MCI-MI		
		1+	2+	3+	1+	2+	3+
MI, 0.02%-0.2%	35 (61)	20 (57)	11 (31)	4 (11)	NA	NA	NA
MCI-MI, 0.02%	5 (9)	NA	NA	NA	4 (80)	1 (20)	0
MI and MCI-MI	17 (30)	4	5	8	15	0	2

Abbreviations: MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; NA, not applicable; 1+, weak positive; 2+, strong positive; 3+, extreme positive.

Diseases, Ninth Revision a total of 38 059 times, which includes the same patients billed more than once for 2 or more visits for the same skin condition. Seven hundred seventy-eight patients were referred for patch testing; consultation visits before patch testing were not required. Eighty-one patients failed to attend the scheduled visit, of whom 6 later rescheduled and underwent testing. Reasons for failure to attend included changes to the patient’s insurance coverage, the co-payment amount, resolution of the dermatitis, inability to miss work for 3 visits, a change of job or residence, and chronic missing of appointments to dermatology and other departments.

Seven hundred three patients were included in this study. Mean age was 49.4 (range, 3-95) years, with 495 female patients (70.4%). Of the 703 patients, 57 (8.1%) had positive patch test reactions to MCI-MI and/or MI.

The demographic characteristics of the patients with positive patch test reactions are described by relative proportion using the MOAHLFA index (Table 1). These characteristics differed slightly among those with positive patch test reactions to MI alone (35 patients), to MCI-MI alone (5 patients), and to both (17 patient). Prevalences of positive reactions for men ranged from 10 of 35 patients (18%) to MI and MCI-MI to 3 of 5 patients (60%) to MCI-MI alone; for occupational dermatitis, from 0 of 5 patients to MCI-MI to 3 of 35 patients (9%) to MI alone; for atopic dermatitis, from 1 of 5 patients (20%) to MCI-MI alone to 7 of 17 patients (41%) to MI and MCI-MI; for hand dermatitis, from 0 of 5 patients to MCI-MI alone to 17 of 35 patients (49%) to MI alone; for leg dermatitis, from 0 of 5 patients to MCI-MI alone to 3 of 17 patients (18%) to MI and MCI-MI; for face dermatitis, from 1 of 5 patients (20%) to MCI-MI alone to 7 of 17 patients (41%) to MI and MCI-MI; and for age of at least 40 years, from 7 of 35 patients (20%) to MI alone to 3 of 5 patients (60%) to MCI-MI alone. Mean duration of dermatitis was 28 months. Table 2 identifies patients who reacted to MI, MCI-MI, or both allergens, and Table 3 lists the most

Table 3. Common Sites of Skin Involvement for Patients With Positive Patch Test Reactions

Site	No. of Patients
Hands	21
Face	18
Extremities	11
Disseminated	9
Groin or buttocks	7
Trunk	6
Axilla	3
Feet	2

common sites of dermatitis. We found no significant difference in reaction pattern based on sex ($\chi^2 = 3.44$; $P = .18$), occupational dermatitis ($\chi^2 = 0.57$; $P = .75$), atopic dermatitis ($\chi^2 = 0.81$; $P = .67$), leg dermatitis ($\chi^2 = 1.00$; $P = .61$), face dermatitis ($\chi^2 = 1.18$; $P = .55$), and age ($\chi^2 = 3.73$; $P = .15$). Those with hand dermatitis were significantly more likely to have a positive patch test reaction to MI alone than were those with a positive reaction to MCI-MI alone or to both allergens ($\chi^2 = 6.28$; $P = .04$).

Four patients (7%) had occupational contact dermatitis with relevant allergies to MI or MCI-MI. Their occupations were masseuse, salon owner, hairdresser, and daycare worker. These preservatives were found in shampoos, lotions, and wet wipes used at work.

In addition, 40 patients (70%) identified MI or MCI-MI in personal health care products, most commonly in wet wipes (Figure), shampoos, and detergents. Twenty-three patients (40%) had a follow-up of at least 1 month (range, 1-9 months). Seventeen of these patients (74%) experienced clearance or near clearance with allergen avoidance. One patient required prednisone and allergen avoidance to clear his contact dermatitis.

Figure. Acute Contact Dermatitis of the Intergluteal Fold With Strong Positive Patch Test Reaction to Methylisothiazolinone (MI)



Discussion

We report a prevalence of contact allergy to MI, MCI-MI, or both of 8.1%. Our patient cohort had a sensitization rate to MI alone that increased from 6 of 236 patients (2.5%) in 2012 to 13 of 232 patients (5.6%) in 2013 and 16 of 235 patients (6.8%) in 2014, which we believe is caused by increased detection. Our test concentration of MI increased from 200 to 2000 ppm in January 2013 and likely contributed significantly to the increased allergy detection rate. Allergy to MCI-MI alone in 2012, 2013, and 2014 was found in 0 of 236 patients, 3 of 232 patients (1.3%), and 2 of 235 patients (0.9%), respectively; and allergy to MI and MCI-MI during the same period was found in 4 of 236 patients (1.7%), 11 of 232 patients (4.7%), and 2 of 235 patients (0.9%), respectively. Thirty-five patients reacted to MI only, 5 reacted to MCI-MI only, and 17 reacted to MI and MCI/MI. Three of the 5 patients who reacted to MCI-MI only (60%) were children.

The most common sites of involvement included the face and hands, and several patients also had disseminated dermatitis, as detailed in Table 3. As many as two-thirds of our patients with sensitization to MI would have been missed if they underwent testing for MCI-MI alone. Of the 5 patients who reacted only to MCI-MI, 3 were children who did not undergo patch testing to MI alone. Our findings agree with the increasing prevalence of MI allergy reported from Europe.^{10,12,13} Identification of contact allergy to MCI-MI and MI is crucial given the widespread use of these preservatives in cosmetic and industrial products. Of the 6 patients who did not report improvement in skin disease after allergen avoidance, contact allergy to other components of personal health care or industrial products as the offending agents should be considered.

In 2011, Lundov and colleagues² reported that MI contact allergy had a prevalence of 1.5% and that only 1% of cosmetics were preserved with MI. Three years later, a study of Belgian patients¹³

indicated that sensitization rates to MI had increased from 6% in 2012 to 7.2% in 2013. Similarly, the rate of contact allergy to MCI-MI had increased to 4.5% by 2012. In addition, Engfeldt et al¹² showed that up to 1.9% of all of their patients undergoing patch testing will react exclusively to MI and would be missed if patch testing only included MCI-MI. Furthermore, some patients required patch testing at concentrations of MI up to 2000 ppm to detect sensitization.¹²

Overall, occupational ACD caused by MCI-MI and/or MI has increased. Urwin et al¹⁹ report an annual increase in ACD of 3.8% in those exposed to personal care products in the workplace and a 6.3% annual increase in prevalence in manufacturing workers. Recently, commercial water-based paints containing MCI-MI and MI have been reported as potential causes of contact allergy. We did not ask our cohort directly about exposures to paints or newly painted surfaces. Lundov and colleagues²⁰ reported that MI in paints can cause severe allergic reactions. Emissions were found to peak within hours of paint application but were detectable for more than 42 days, with concentrations of MI of up to 300 ppm.²⁰ Schwensen et al²¹ randomly selected 71 wall paints commercially available in Europe and found that 93% contained MI, with concentrations of up to 180.9 ppm, and 24% contained MCI at concentrations up to 11.4 ppm. Emissions from paint containing MCI-MI and MI are important to consider as causes of facial dermatitis and airborne contact dermatitis, which may lead to respiratory difficulty.²² Current European regulations do not require paint manufacturers to list the isothiazolinone content of less than 1000 ppm.²¹

The European Commission has made regulatory changes following suggestions made by the Scientific Committee on Consumer Safety based in part on scientific publications from the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. Effective July 16, 2015, MCI-MI was banned in all leave-on body products sold in Europe but is still allowed at concentrations

Acute contact dermatitis was caused by MI-containing wet wipes.

up to 15 ppm in rinse-off products.²³ Human repeat-insult patch testing studies have shown that the risk for primary sensitization to MCI-MI after exposure in concentrations of up to 15 ppm in rinse-off products is negligible; in addition, elicitation of ACD is rare after exposure to these rinse-off products.²⁴ The European Commission believes that concentrations of MI at 3.8 ppm in leave-on products and 15 ppm in rinse-off products is acceptable.²⁵

In the United States, the Cosmetic Ingredient Review panel currently recommends MCI-MI concentration limits at 7.5 ppm in leave-on products and 15 ppm in rinse-off products.²⁶ The maximum allowable concentration of MI alone in rinse-off products has not been changed at 100 ppm; however, the Cosmetic Ingredient Review panel recommends that manufacturers formulate leave-on products to be nonsensitizing based on a quantitative risk assessment. However, a recent editorial by Magnus Bruze, MD, Wolfgang Uter, MD, Margarida Goncalo, MD, Jean-Pierre Lepoittevin, PhD, Thomas Diepgen, MD, PhD, and David Orton, MBBS, on behalf of the European Society of Contact Dermatitis states that quantitative risk assessment is a tool that has not been validated and has not yet been shown to protect consumers from sensitization.²⁷

Despite increased awareness of contact allergy to MI since 2013, Warburton and Wilkinson²⁸ reported in 2015

that the number of incident cases in the United Kingdom continues to rise although exposure is mainly via rinse-off products. Martin-Gorgojo and colleagues²⁹ also studied 46 patients with positive patch test reactions to MI and found that those sensitized to MI or MCI-MI had significantly higher odds of polysensitization to 3 or more unrelated allergens. Given the overwhelming evidence that MI is a significant contact allergen, the continued use of this preservative in household, consumer, and industrial products is extremely concerning. Even more stringent regulations, especially from regulatory agencies in the United States, will further positively affect the quality of life for many patients with ACD and are needed for public safety.

Conclusions

The increasing prevalence of contact allergy to MI alone supports its addition to the standard series to identify cases missed by testing for MCI-MI only. Recent regulations by the European Commission have banned MCI-MI in all leave-on body products. Currently recommended US regulations are less stringent; however, US regulatory agencies must act to ensure patient safety.

ARTICLE INFORMATION

Accepted for Publication: August 16, 2015.

Published Online: November 4, 2015.
doi:10.1001/jamadermatol.2015.3606.

Author Contributions: Drs Sood and Taylor had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sood, Taylor.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Yu.

Critical revision of the manuscript for important intellectual content: Sood, Taylor.

Statistical analysis: Yu.

Administrative, technical, or material support: Sood, Taylor.

Study supervision: Sood, Taylor.

Conflict of Interest Disclosures: Dr Taylor reported serving as a consultant to Procter and Gamble; receiving an honorarium from the Ontario Ministry of Health; owning stock in AstraZeneca, Johnson and Johnson, Merck, Express Scripts, and Opko Health; receiving research funding for his department from Samumed, Questor, Roche, and DUSA for work by other physicians; and that his adult, nondependent daughter is a vice president in pharmaceutical development for Pfizer. No other disclosures were reported.

Additional Contributions: Debra Murray, LPN, Department of Dermatology, Cleveland Clinic, and Sharon Bi, MCIS, Systems Analyst III, Department of Quantitative Health Sciences, Cleveland Clinic, provided technical assistance in identifying patients and locating medical records. No compensation was given to them for their assistance.

REFERENCES

- Gonçalo M, Goossens A. Whilst Rome burns: the epidemic of contact allergy to methylisothiazolinone. *Contact Dermatitis*. 2013;68(5):257-258.
- Lundov MD, Krongaard T, Menné TL, Johansen JD. Methylisothiazolinone contact allergy: a review. *Br J Dermatol*. 2011;165(6):1178-1182.
- Murad A, Marren P. Prevalence of methylchloroisothiazolinone and methylisothiazolinone contact allergy in facial dermatitis: a single centre Irish study [published online January 26, 2015]. *J Eur Acad Dermatol Venereol*. doi:10.1111/jdv.12956.
- Bruze M, Gruvberger B, Persson K. Contact allergy to a contaminant in Kathon CG in the guinea pig. *Derm Beruf Umwelt*. 1987;35(5):165-168.
- Burnett CL, Bergfeld WF, Belsito DV, et al. Final report of the safety assessment of methylisothiazolinone. *Int J Toxicol*. 2010;29(4)(suppl):1875-2135.
- Macias VC, Fernandes S, Amaro C, Santos R, Cardoso J. Sensitization to methylisothiazolinone in a group of methylchloroisothiazolinone/methylisothiazolinone allergic patients. *Cutan Ocul Toxicol*. 2013;32(2):99-101.
- Isaksson M, Gruvberger B, Gonçalo M, Goossens A, Le Coz CJ, Bruze M. Repeated open application test with methylisothiazolinone in individuals sensitive to methylchloroisothiazolinone/methylisothiazolinone. *Contact Dermatitis*. 2014;70(4):244-246.
- Geier J, Lessmann H, Schnuch A, Uter W. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? *Contact Dermatitis*. 2012;67(6):334-341.
- Castaneda-Tardana MP, Zug KA. Methylisothiazolinone. *Dermatitis*. 2013;24(1):2-6.
- Bruze M, Engfeldt M, Gonçalo M, Goossens A. Recommendation to include methylisothiazolinone in the European baseline patch test series—on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis*. 2013;69(5):263-270.
- Fransway AF, Zug KA, Belsito DV, et al. North American Contact Dermatitis Group patch test results for 2007-2008. *Dermatitis*. 2013;24(1):10-21.
- Engfeldt M, Bråred-Christensson J, Isaksson M, et al. Swedish experiences from patch testing methylisothiazolinone separately. *Acta Derm Venereol*. 2015;95(6):717-719.
- Aerts O, Baeck M, Constandt L, et al. The dramatic increase in the rate of methylisothiazolinone contact allergy in Belgium: a multicentre study. *Contact Dermatitis*. 2014;71(1):41-48.
- Schlichte MJ, Katta R. Methylisothiazolinone: an emergent allergen in common pediatric skin care products. *Dermatol Res Pract*. 2014;2014(2014):132564.
- Chang MW, Nakrani R. Six children with allergic contact dermatitis to methylisothiazolinone in wet wipes (baby wipes). *Pediatrics*. 2014;133(2):e434-e438.
- Yu SH, Murray D, Taylor JS, Sood A. Methylisothiazolinone (MI) and methylchloroisothiazolinone/methylisothiazolinone (MCI/MI): three-year patch test results from clinical practice. Presented at: 26th Annual Meeting of the American Contact Dermatitis Society; March 19, 2015; San Francisco, CA.

17. US Department of Health and Human Services. Basic HHS Policy for Protection of Human Research Subjects, 45 CFR §46.101 (b). <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>. Revised January 15, 2010. Accessed September 24, 2015.
18. Schnuch A, Geier J, Uter W, et al. National rates and regional differences in sensitization to allergens of the standard series: population-adjusted frequencies of sensitization (PAFS) in 40 000 patients from a multicenter study (IVDK). *Contact Dermatitis*. 1997;37(5):200-209.
19. Urwin R, Warburton K, Carder M, Turner S, Agius R, Wilkinson SM. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: an occupational perspective. *Contact Dermatitis*. 2015;72(6):381-386.
20. Lundov MD, Kolarik B, Bossi R, Gunnarsen L, Johansen JD. Emission of isothiazolinones from water-based paints. *Environ Sci Technol*. 2014;48(12):6989-6994.
21. Schwensen JF, Lundov MD, Bossi R, et al. Methylisothiazolinone and benzisothiazolinone are widely used in paint: a multicentre study of paints from five European countries. *Contact Dermatitis*. 2015;72(3):127-138.
22. Alwan W, White IR, Banerjee P. Presumed airborne contact allergy to methylisothiazolinone causing acute severe facial dermatitis and respiratory difficulty. *Contact Dermatitis*. 2014;70(5):320-321.
23. Consumers: Commission improves safety of cosmetics. European Commission Press Release Database. http://europa.eu/rapid/press-release_IP-14-1051_en.htm. Published September 26, 2014. Accessed July 8, 2015.
24. Fewings J, Menné T. An update of the risk assessment for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) with focus on rinse-off products. *Contact Dermatitis*. 1999;41(1):1-13.
25. Scientific Committee of Consumer Safety, European Commission. Opinion on methylisothiazolinone (P94): submission II (sensitisation only). http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_145.pdf. Revised March 27, 2014. Accessed July 8, 2015.
26. Bergfeld WF, Belsito DV, Klaassen CD, et al. Amended safety assessment of methylisothiazolinone as used in cosmetics. Cosmetic Ingredient Review. http://www.cir-safety.org/sites/default/files/mthiaz062014tent_0.pdf. Released June 20, 2014. Accessed July 8, 2015.
27. Incompetence and failure to regulate methylisothiazolinone. *Contact Dermatitis*. 2015;72(6):353-354.
28. Warburton KL, Wilkinson M. Contact allergy to methylisothiazolinone: has there been any change? experience of a UK centre. *Contact Dermatitis*. 2015;72(6):398-400.
29. Martin-Gorgojo A, Curto-Barredo L, Rovira-López R, Pujol RM, Gimenez-Arnau A. Is methylisothiazolinone contact allergy a risk factor for polysensitization? *Contact Dermatitis*. 2015;72(6):400-402.

NOTABLE NOTES

Remembering the Pioneers of Topical Agents

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While everyone remembers seeing a traveling salesman pushing "Dr Smith's Wonder Pills" or something similar in a Class B Western movie, many have forgotten that several serious dermatologic preparations carry the name of a colleague of the past. These former mainstays of dermatologic therapy are disappearing because proof of efficacy is lacking, a declining interest in compounding them, and the inclusion of ingredients no longer deemed suitable for topical use. We recall a few examples that, a generation ago, were prescribed daily by almost every dermatologist.

Burow solution is an aluminum acetate solution with astringent and antibacterial properties that was primarily used with wet dressings. Karl August Burow (1809-1874) was an ophthalmologist in Königsberg, East Prussia.

Castellani paint is a carbol fuchsin solution that is an effective antifungal and antimicrobial agent. It discolors the skin so badly that colorless forms were developed. Aldo Castellani (1877-1971) was an Italian physician with a broad range of interests, especially in tropical medicine. He was an enthusiastic Italian royalist and also supporter of Benito Mussolini as well as a peripatetic physician who practiced around the world, including New Orleans, Louisiana.

Lassar paste is a zinc oxide paste, still in use to treat diaper dermatitis. It was also one of the early vehicles used for anthralin in treating psoriasis. Oscar Lassar (1849-1907) was a flamboyant practitioner in Berlin, Germany, who had a flourishing private clinic, had an early moulage collection, and was a leader in developing public baths. He may have been the first dermatologist to die in an automobile accident.¹

Schamberg lotion is an inexpensive antipruritic formulation of zinc oxide with menthol and phenol. Because of the latter ingredient, it fell into disrepute. Jay Schamberg (1870-1934) established the Dermato-

logical Research Laboratories at the University of Pennsylvania, which was the only American supplier of a neo-arsphenamine during World War I. He plowed the considerable profits back into further research, helping establish Pennsylvania as a leading dermatologic center.

The Unna boot is a gauze bandage impregnated with calamine and zinc oxide paste used to treat stasis dermatitis and leg ulcers. Paul Gerson Unna (1850-1929) was a pioneer histopathologist who worked out of his own institute, the Dermatologium, in Hamburg, Germany. He was also an innovative therapist who trained a number of prominent dermatologists.²

Whitfield ointment is an inexpensive antifungal agent still in use. It contains 3% salicylic acid and 6% benzoic acid in a lanolin base. Arthur Whitfield (1868-1947) was a pioneer British dermatologist who started the program at King's College, authored a widely used small textbook, and was a founder of the British Association of Dermatology.³

Even as their compounds gradually fall victim to modernization, we should be thankful to these individuals for their highly personal contributions to the dermatologic treatment armamentarium.

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1. Scholz A. Oscar Lassar (1849-1907). In: Löser C, Plewig G, Burgdorf WHC, eds. *Pantheon of Dermatology: Outstanding Historical Figures*. Heidelberg, Germany: Springer; 2013:649-652.

2. Hollander A. Scientific work of Paul Gerson Unna. *Arch Derm Syphilol*. 1950;62(3):351-361.

3. Williams DI. Three British dermatologists: Arthur Whitfield, Erasmus Wilson, and Henry Radcliffe Crocker. *Arch Dermatol*. 1976;112(Spec no):1654-1658.