

The Role of Contact Allergens in Chronic Idiopathic Urticaria

Meghan T. Hession, MD and Pamela L. Scheinman, MD

Objective: The objective of this study was to determine whether contact allergens play a role in chronic idiopathic urticaria (CIU).

Methods: We conducted a longitudinal prospective study of 23 patients with CIU. Patients were patch tested to a modified North American Contact Dermatitis Group standard, fragrance, and cosmetic series; other series were tested as warranted by relevant history and physical examination. Readings were performed at 48 and 72 hours. Patients were counseled to avoid proven contact allergens and were followed up 2 to 9 months after testing.

Results: Twenty-one of 23 patients were female. The mean age was 46 years. The mean duration of urticaria was 32 months. Of the 23 patients, 8 (35%) experienced improvement of their symptoms with allergen avoidance. Four (17%) experienced a complete remission, and 4 (17%) experienced partial improvement. Two of the complete responders challenged themselves to proven contact allergens and developed urticaria, which resolved upon allergen avoidance. The most common allergens were potassium dichromate ($n = 9$), nickel sulfate ($n = 7$), *Myroxylon pereirae* ($n = 6$), cobalt chloride, neomycin, *p*-phenylenediamine ($n = 5$); fragrance mix I, fragrance mix II ($n = 4$); cinnamic aldehyde ($n = 3$); and formaldehyde ($n = 2$).

Conclusions: Patch testing may be helpful in the evaluation of CIU patients for whom previous workup has failed to reveal an etiology.

CHRONIC URTICARIA is defined as hives that occur at least twice per week for at least 6 weeks.¹ Urticaria results from an increase in capillary permeability, followed by vascular leakage—the so-called “wheal” response. The ensuing pruritus results from release of histamine and other inflammatory mediators. Pruritus is nearly always severe, with a significant impact on quality of life for many patients.² When physical urticarias (delayed pressure, cholinergic, cold, dermatographism, solar, aquagenic) and urticarial vasculitis have been ruled out, the condition is considered chronic idiopathic urticaria (CIU).³ Chronic idiopathic urticaria is thought to affect at least 0.1% of the population.³ Identification of an etiology for CIU can be a frustrating endeavor, both for patients and their physicians. The workup for CIU involves a detailed history, especially screening for potentially causative medications and supplements.⁴ Evaluation for infectious diseases, autoimmune thyroid disease, or neoplasia should be pursued only if suggested by history and physical examination. A recent study investigating laboratory evaluations of patients with

chronic urticaria found that such evaluation rarely leads to changes linked to improved clinical outcomes.⁵

There is convincing evidence that approximately 25% to 45% of cases of CIU have an autoimmune etiology.³ These patients have functional antibodies to the α -chain of the high-affinity immunoglobulin E (IgE) receptor (Fc ϵ RI α) or, less commonly, to free IgE.³ Whereas Fc ϵ RI α autoantibodies may account for nearly half of cases of CIU, little is known about the etiology of urticaria in the remaining 55% of patients.

Diagnosis of allergic contact dermatitis is regularly done with patch testing. Although patch testing is not routinely performed in the evaluation of CIU, we have observed anecdotally that some CIU patients have positive patch test results. There are also several case reports in the literature of chronic urticaria induced by nickel.^{6–8} Furthermore, a 2007 study showed that 41% of patients with chronic urticaria were patch test positive to contact allergens, with nickel being the most common allergen. In all study participants, avoidance of allergens—including a low-nickel diet in nickel-allergic patients—led to complete remission.⁹ In this study, we aim to further elucidate whether contact allergens play a role in the etiology of CIU.

METHODS

Institutional review board approval was obtained for this prospective, longitudinal study. Local allergists, dermatologists, and internists were informed via letter and e-mail about our study

From the Dermatology Department, Tufts Medical Center, Boston, MA.

Address reprint requests to Pamela L. Scheinman, MD, Dermatology Department, Tufts Medical Center, 800 Washington St, Box 114, Boston, MA 02111. E-mail: PScheinman@tuftsmedicalcenter.org.

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investigating whether contact allergens are present in patients with chronic urticaria and whether avoidance of such allergens would lead to remission. Flyers about the study were also posted throughout Tufts Medical Center soliciting patients with a diagnosis of chronic urticaria. Referring physicians were asked to provide documentation of a history of chronic urticaria, defined as skin swellings lasting less than 24 hours, occurring daily or almost daily, over the course of at least 6 weeks. Most patients had extensive previous workups from their referring physicians, including complete blood count, hepatitis screen, thyroid function tests, liver function tests, and radioallergosorbent tests. Eligibility criteria for the study included (1) documentation of hives by a referring physician and/or symptoms of evanescent skin swellings for at least 6 weeks and (2) ability to come in for at least 3 clinical visits (patch test placement and 2 follow-up visits for readings). Exclusion criteria included (1) patients with dermatographism and any other physical urticaria, (2) those with hives remaining fixed for more than 24 hours, (3) patients with signs of dermatitis on examination, (4) pregnant or lactating women, (5) those unable to come in for at least 3 clinical visits (patch test placement and 2 follow-up visits for readings), and (6) those taking oral immunosuppressants for their urticaria or for concomitant diseases.

Patch testing was performed using a modified North American Contact Dermatitis Group (NACDG) standard series, as well as cosmetic and fragrance series. Other series were tested if warranted by relevant history or occupational exposure. Textile series were placed when urticaria was in a distribution on trunk and extremities consistent with a possible textile dye or formaldehyde textile resin allergy, a rubber series in patients complaining of hives under bra elastic or waistband elastic, and a hair series for patients with scalp symptoms who had colored their hair, and so on. All allergens were purchased from Chemotechnique Diagnostics (Vellinge, Sweden), except for individual fragrance mix I (FM I) components, which were purchased from Hermal (Reinbek, Germany). Readings were performed at 48 and 72 hours and graded according to the NACDG grading system of 1+ (weak reaction; papules with erythema), 2+ (strong reaction; papules plus edema or vesiculation), or 3+ (extreme reaction; spreading papulovesicles or bullae).

Patients were counseled to avoid relevant contact allergens topically and were given dietary information if documented allergens had food sources. All patients with potential systemic allergens were counseled to start dietary modification if their urticaria did not improve despite changes to personal care products within 4 to 6 weeks of patch testing. All patients were informed that their clinical progress would be followed after testing. Follow-up interviews were conducted either in clinic or over the phone between 2 and 9 months after patch testing. Patients were asked what steps they took to avoid their allergens, which allergens they avoided, and if this avoidance led to symptomatic improvement. Patients who noted clinical improvement were asked to quantify this improvement in terms of changes in the frequency of their urticaria.

Patients who improved were grouped into 2 categories: (1) complete remission and (2) partial remission, meaning their hives were reduced in frequency but did not completely resolve.

Data were stored in Microsoft Access 2007 SP2 and were analyzed using Microsoft Excel 2007 SP2 (12.0.6545.5004). Age, sex, mean duration of symptoms, allergens, and intensity of reactions were recorded. Reactions to specific categories of allergens, including metals, textiles, and potential systemic allergens, were also analyzed. The following allergens were considered potential systemic allergens: cobalt chloride, nickel sulfate, potassium dichromate, FM I and its individual components, fragrance mix II (FM II), *Myroxylon pereirae* (MP), parabens, propylene glycol, and formaldehyde. For analyses involving response rates, patients were divided into “responders” (ie, patients with either complete or partial resolution of symptoms) and “nonresponders” (ie, patients who did not experience clinical improvement).

DATA

Study Population and Clinical Characteristics

Twenty-three urticaria patients were eligible for study enrollment. Twenty-one were female, and 2 were male. The mean age was 46 years (range, 27–76 years). The mean duration of urticaria was 32 months (range, 3–120 months). One patient had Graves disease (Table 1, patient 9) and was clinically euthyroid. Upon follow-up after patch testing, 1 patient (patient 3) was found to have anti-FcεRIα antibodies. One patient had a history of rheumatoid arthritis, fibromyalgia, and Sjögren disease (patient 2). Only 1 patient (patient 5) underwent a biopsy before participating in this study; the rest of our patients had clinically diagnosed CIU.

Number and Strengths of Patch Test Reactions

We tested an average of 147 allergens per patient. All patients were tested to a modified NACDG series, cosmetic and fragrance series. Other series were placed based on history, physical examination, and occupational exposures. Of the 23 patients, 22 (96%) had at least 1 positive patch test reaction of 1+ or stronger, whereas 9 patients (39%) had at least 1 positive reaction of 2+ or stronger.

Summary of Allergens

The allergens resulting in positive patch test reactions for each patient are listed in Table 1. The most common allergens were potassium dichromate (n = 9), nickel sulfate (n = 7), MP (n = 6), cobalt chloride, neomycin, *p*-phenylenediamine (PPD) (n = 5); FM I, FM II (n = 4); cinnamic aldehyde (n = 3); and formaldehyde (n = 2).

Compliance and Clinical Outcomes

Among our patients, 2 were lost to follow-up, and 3 were non-compliant; that is, they did not wish to change any personal care

TABLE 1. Patch-Test Results, Avoidance Measures, and Outcomes for 23 CIU Patients

Allergens								
No.	Metals	Textiles	Fragrance	Other	Avoided Allergens?	Allergens Avoided	Remission	
1	Potassium dichromate 1 ⁺	DB 106 1 ⁺ ; MF 1 ⁺ ; RBLK 5 1 ⁺ ; DB 124 1 ⁺ ; UF 1 ⁺	Cinnamyl alcohol 1 ⁺ ; cinnamic aldehyde 2⁺ ; FM I 2⁺ ; FM II 1⁺	Benzalkonium chloride 1 ⁺ ; DMDM hydantoin 1 ⁺	No	N/A	None	
2	Cobalt chloride 1 ⁺	DB 106 1 ⁺ ; RBLK 5 1 ⁺ ; RB 238 1 ⁺	—	—	Yes	Metals, dark textiles	None	
3	—	—	—	Carba mix 2⁺ ; benzophenone4 1 ⁺ ; propylene glycol 1 ⁺ ; oleamidopropyl dimethylamine 1 ⁺ ; CAPB 1 ⁺	Yes	Changed personal care products	None	
4	—	—	—	Carba mix 1 ⁺ ; methyl methacrylate 1 ⁺ ; PPD 1 ⁺	LTF	LTF	LTF	
5	Potassium dichromate 1 ⁺	RBLK 5 1 ⁺ ; RB 238 1 ⁺ ; DB 106 1 ⁺	Cinnamic aldehyde 1 ⁺ ; FM II 1⁺	Benzalkonium chloride 1 ⁺	Yes	Changed personal care products; low chrome diet	None	
6	—	—	—	—	Yes	Hair dye‡	None	
7	Cobalt chloride 2⁺ ; nickel sulfate 3⁺	EU/MF 2⁺ ; MF 1 ⁺ ; UF 1 ⁺	MP 2⁺	Diazolidinyl urea 1 ⁺ ; DMDM hydantoin 2⁺ ; Grotan BK 1 ⁺ ; PPD 2⁺ ; formaldehyde 1 ⁺	Yes	Changed personal care products; changed uniform	None	
8	—	—	FM I 2⁺ ; cinnamic alcohol 1 ⁺	Neomycin sulfate 1 ⁺	Yes	Fragrance	None	
9	—	—	MP1⁺ ; FM I 1⁺	Benzalkonium chloride 1 ⁺ ; CAPB 1 ⁺ ; DPG 1 ⁺ ; MDA 1 ⁺ ; dodecyl mercaptan 1 ⁺	Yes	Fragrance	None	
10	Potassium dichromate 1 ⁺	—	MP 1 ; FM II 1⁺	Amerchol L 101 1 ⁺ ; lanolin alcohol 1 ⁺ ; sorbitan sesquioleate 1 ⁺	Yes	Fragrance, lanolin, metals	None	
11	Nickel sulfate 1 ⁺ ; potassium dichromate 2⁺	DB 153 1 ⁺	MP1⁺ ; FM I 1⁺	Ammonium persulfate 1 ⁺	Yes	Fragrance	Complete	
12	—	—	FM II 1⁺	Dithiomorpholine 1 ⁺ ; <i>formaldehyde 1⁺</i> ; Groton BK 1 ⁺	LTF	LTF	LTF	
13	—	1 ⁺ Acid red 118	—	—	Yes	avoided red dye	None	
14	—	—	—	Amerchol L 101 1 ⁺ ; lanolin alcohol 1 ⁺ ; PPD 1 ⁺	Yes	avoided lanolin and dyes	Complete	
15	Cobalt chloride 2⁺ ; nickel sulfate 3⁺ ; potassium dichromate 1⁺	—	—	Amerchol L 101 1 ⁺ ; benzalkonium chloride 1 ⁺ ; neomycin sulfate 1 ⁺	Yes	Amerchol L; benzalkonium chloride; metals	None	
16	—	DB 35 1 ⁺ ; DY 3 1 ⁺	—	Neomycin sulfate 1 ⁺	No	N/A	None	
17	Cobalt chloride 2⁺ ; nickel sulfate 3⁺ ; potassium dichromate 1⁺ ; GST3⁺	DY3 1 ⁺ ; DR17 1 ⁺ ; DB153 1 ⁺ ; DB35 1 ⁺ ; DB106 1 ⁺	MP1⁺ ; cinnamic aldehyde 1 ⁺ ; geraniol 1 ⁺ ; α-amyl cinnamaldehyde1 ⁺	Bronopol 1 ⁺ ; diphenylguanidine 1 ⁺ ; GTG2⁺ ; PPD 2⁺ ; n-phenyl-2-naphthylamine 1 ⁺ ; neomycin sulfate 2⁺ ; black rubber mix 1 ⁺ ; compositae mix 1 ⁺ ; ethyl acrylate 1 ⁺	Yes	Fragrance, metals, hair dye	Partial	
18	—	Fix CPN 1 ⁺ ; Fix NF1 ⁺ ; DB 85 1 ⁺ ; MF 1 ⁺	<i>Isoeugenol 1⁺</i>	benzophenone 3 1 ⁺ ; carba mix 1 ⁺ ; dithiomorpholine 1 ⁺ ; <i>paraben mix 1⁺</i> ; <i>butylparabens 1⁺</i>	Yes	Elastic/stretchy clothing	Partial	
19	GST 3⁺	—	—	—	No	N/A	None	

20	Nickel sulfate 1 ⁺ ; potassium dichromate 1 ⁺	—	—	Yes	CAPBS, MCI/MI§; metals	Complete
21	RBLK 5 1 ⁺ ; RB 21 1 ⁺ ; RB 238 1 ⁺	MP 1 ⁺	Neomycin 1 ⁺ ; PPD 1 ⁺	Yes	Fragrance; dark textiles	Partial
22	Nickel sulfate ; 3 ⁺ ; potassium dichromate 1 ⁺	FM I 1 ⁺	—	Yes	Fragrance	Complete
23	Cobalt chloride 1 ⁺ ; GST 2⁺ ; nickel sulfate 2⁺ ; potassium dichromate 1 ⁺	—	—	Yes	Avoided common sensitizers in personal care products	Partial

*Reactions to potential systemic allergens are italicized.

†Reactions of 2+ or 3+ are in bold.

‡Patient had questionable reaction to PPD.

§Patient had questionable reactions to these chemicals.

||Patient had questionable reactions to formaldehyde, FM I and MCI/MI.

DB indicates disperse blue; RB, reactive blue; RBLK, reactive black; EU/MF, ethyleneurea melamine formaldehyde; UF, urea formaldehyde; MF, melamine formaldehyde; Grotan BK, hexahydro-1,3,5-tris-(2-hydroxyethyl)triazine; DR, disperse red; DY, disperse yellow; FM II, fragrance Mix II; DPG, diphenylguanidine; MDA, methylendianiline (diaminodiphenylmethane); Fix NF, dimethyl dihydroxyethyleneurea; Fix NF, dimethyl dihydroxyethyleneurea; GST, gold sodium thiosulfate; PPD, para-phenylenediamine; GTG, glyceryl monothioglycolate; CAPB, cocamidopropyl betaine; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; LTF, lost to follow-up.

products or avoid ingesting potential systemic allergens. Eighteen were compliant with instructions to avoid relevant “topical” allergens. With the exception of patient 5, none of our patients were willing to perform dietary modifications, avoiding all foods potentially containing high contents of that particular allergen. Patient 5 followed a low-chrome diet without change in her symptoms. However, she chose not to follow a low-balsam diet, which might have been helpful based on her patch test results.

Of the 23 patients who were patch tested, 8 (35%) experienced improvement of their symptoms: 4 (17%) experienced a complete remission, and 4 (17%) experienced a partial improvement of symptoms. None of the 3 noncompliant patients experienced improvement in their symptoms. With regard to the 4 patients who had partial remission, response rates varied. One patient who experienced urticaria twice per week before patch testing is now symptomatic approximately twice per month (patient 18) with allergen avoidance, whereas another patient who experienced hives daily is now symptomatic only 1 to 3 times per week (patient 21). The last 2 patients were symptomatic 4 times per week before testing; with allergen avoidance, frequency of urticaria was reduced to once per week for 1 patient (patient 23) and 3 to 4 times per month for the other patient (patient 17).

The median disease duration before allergen avoidance for complete responders was 25 months (range, 10–120 months). The median disease duration of partial responders before allergen avoidance was 20 months (range, 18–96 months). These values were not statistically significant (Mann-Whitney *U* test, *P* = 0.27).

Of the complete responders, only 1 patient was male (patient 14). He had had urticaria for 10 years, and his symptoms resolved with change of personal care products. His hives recurred when he inadvertently used a product with lanolin and resolved when he stopped the lanolin-containing product. Patient 11, another complete responder, also developed urticaria upon reintroducing products she had avoided and experienced complete clearing again once she avoided such items.

Responders and Associated Allergens

For the responders, the following allergens were positive on testing: nickel sulfate and potassium dichromate (*n* = 5); MP and PPD (*n* = 3); FM I, gold sodium thiosulfate, cobalt chloride, disperse blue 153, and neomycin (*n* = 2); and *n* = 1 each for lanolin, Amerchol L 101, bronopol, cinnamic aldehyde, carba mix, dithiomorpholine, glyceryl monothioglycolate, ammonium persulfate, ethyl acrylate, paraben mix, butyl parabens, black rubber mix, diphenylguanidine *n*-phenyl-2-naphthylamine, compositae mix, disperse blue 35, disperse blue 106, disperse blue 85, disperse yellow 3, disperse red 17, reactive black 5, reactive blue 21, reactive blue 238, dimethylol dihydroxyethyleneurea, dimethyl dihydroxyethyleneurea, melamine formaldehyde (MF), isoeugenol, geraniol, and α -amyl cinnamaldehyde.

Of the compliant nonresponders (those patients who attempted to avoid at least “topical” allergens and were not lost to follow-up;

n = 10), reactions were to the following allergens: potassium dichromate, cobalt chloride, benzalkonium chloride, MP (n = 3); disperse blue 106, reactive black 5, reactive blue 238, cocamidopropyl betaine, nickel sulfate, FM I, neomycin, Amerchol L 101 (n = 2); and n = 1 to each of the following: carba mix, benzophenone 4, propylene glycol oleamidopropyl dimethylamine, cinnamic aldehyde, FM II, ethyleneurea melamine formaldehyde, MF, urea formaldehyde, diazolidinyl urea, DMDM hydantoin, Grotan BK, PPD, formaldehyde, cinnamic alcohol, diphenylguanidine, methylenedianiline (diaminodiphenylmethane), dodecyl mercaptan, lanolin, sorbitan sesquioleate, and acid red 118.

Types of Allergens in Responders Versus Nonresponders

For metal reactions, there were 5 positive nickel reactions in the responders (n = 8) versus 2 positive nickel reactions among the compliant nonresponders (n = 10). For cobalt, there were 2 positive reactions among the responders versus 3 positive reactions among the compliant nonresponders. For potassium dichromate, there were 5 positive reactions among the responders versus 4 positive reactions among the compliant nonresponders. Among the 8 responders, there were 12 positive reactions to textile dyes and/or formaldehyde textile resins versus 7 positive textile dyes and/or formaldehyde textile resins reactions among the nonresponders.

Our 23 patients showed a total of 130 definitive positive reactions (1+ or greater). Forty-seven of these definitive reactions ($47/130 = 36\%$) were to potential systemic allergens, that is, those with potential food sources. Among these systemic allergens, there were 13 "strong to extreme reactions" (2+ or 3+). Of the potential systemic reactions, all 3+ reactions were to nickel.

Our 1 patient with antibodies to Fc ϵ RI α (patient 3) showed a strong reaction to carba mix and otherwise weak reactions to propylene glycol, cocamidopropyl betaine, and oleamidopropyl dimethylamine. She complained of her hives flaring during testing. She did not improve with allergen avoidance.

Patient 13 flared during testing as did patient 10. The latter patient had her menses the week of testing, and she had associated her flares with her menses. Her urticaria resolved with menopause.

DISCUSSION

Although our study population was small, patient demographics and duration of symptoms were similar to larger studies on the prevalence and clinical course of chronic urticaria. The mean age was 46 years, at the high end of means encountered in other studies (35–45 years).^{10–12} In our population, 91% of patients were female, which is a slightly greater proportion than that encountered in other studies (60%–79%)^{11,12} yet still aligns with the trend toward increased prevalence in females.

Reports on the natural course of CIU vary. In 1 study, patients with CIU (and negative autoantibody testing) had a mean duration of symptoms of 22.5 months, but a very broad range of 2 months

to 42 years.¹² In our study, the mean duration of symptoms was 2.7 years; 26% had symptoms for 2 to 12 months, 61% for 1.1 to 5 years, and 13% for more than 5 years.

We had 3 patients with concomitant autoimmune disease. One patient who had thyroid disease (Graves disease, patient 9) was euthyroid. One patient with rheumatoid arthritis and Sjögren disease (patient 2) was referred specifically by her primary care provider to potentially help identify a cause of her urticaria. Patient 3 informed us she was found to have anti-Fc ϵ RI α antibodies at follow-up. We felt it was reasonable to include all 3 patients above in our analysis to see if we might elucidate contact allergens contributing to their disease and whose avoidance might ameliorate their symptoms.

Among study participants, 22 of 23 had at least 1 positive patch test reaction. This proportion is high compared with the results of the NACDG 2005–2006 patch test results, which found that 65.3% of patients with allergic contact dermatitis had at least 1 positive patch test reaction.¹³ This discrepancy may be explained by our small sample size of only 23 patients and the fact that our patients were tested to a large battery of allergens: an average of 147 allergens per patient, compared with only 65 per patient in the NACDG study. The top allergens for our urticaria patients were similar to national data published by the NACDG.¹³ Six of 8 of the most common allergens (nickel sulfate, MP, cobalt chloride, neomycin, PPD, FM I) were also within the 10 most common allergens reported in the NACDG 2005–2006 patch test results, and 7 of 8 (additionally, potassium dichromate) were within the top 15.¹³ Interestingly, potassium dichromate was the most common allergen for our patients. Although potassium dichromate is only the 11th most common allergen reported by the NACDG, a study by the Mayo Clinic found a statistically significant increase in the positivity rate for potassium dichromate in their patients (9.8%) compared with the NACDG data (5.8%).¹⁴ As with the Mayo Clinic data, our results suggest that the prevalence of allergy to potassium dichromate may be increasing—or perhaps simply higher in different geographic regions.

Our data suggest that contact allergens within personal care products and/or textiles are only rarely responsible for CIU. Only 4 patients achieved complete remission, avoiding allergens within such items. Other studies have attempted to examine the role of contact allergy in chronic urticaria. Sharma¹⁵ found that 11 (19%) of 57 patients with chronic urticaria had positive patch test reactions; over a 6-week period of allergen avoidance, 9 patients achieved complete remission, whereas the remaining 2 patients improved partially. As with our study, nickel sulfate, MP, and potassium dichromate were common allergens. In a larger study, Guerra et al⁹ found that 50 of 121 (41%) of chronic urticaria patients tested positive to contact allergens. Again, nickel was a common allergen. Interestingly, both the studies of Sharma and Guerra et al observed complete remission in all nickel allergic patients who followed a low-nickel diet.

In addition to these results, there are various case reports citing nickel allergy as a cause of chronic urticaria. Abeck et al⁶ described

a patient who had both types I and IV sensitivities to nickel, as well as a positive oral challenge test, whose urticaria resolved with a nickel-free diet. Similarly, Espana et al⁷ reported a case of chronic, generalized urticaria following implantation of nickel-containing dental prostheses. Radioallergosorbent testing for IgE antibodies to nickel was negative, but patch testing revealed a 3+ reaction to nickel sulfate. Following removal of the prostheses, the patient's symptoms resolved. These authors hypothesized that the type IV reaction was triggered by nickel released during chewing and subsequently ingested. Taken together, these studies and case reports suggest that nickel exposure—particularly systemically—may be a true cause of CIU.

Conversely, the results of Magen et al¹⁶ raise caution when interpreting studies aimed at identifying an etiology for chronic urticaria. The authors found that 9 (21%) of 43 patients had positive patch test reactions to various allergens, with the mean chronic urticaria severity scale improving significantly during a 1-month period of allergen avoidance.¹⁶ However, similar improvement was also seen in 34 patients with negative patch tests and 49 controls. These results highlight an important study limitation: we cannot exclude the possibility that the positive reactions observed in our patients simply reflect the background rate of contact sensitization in the general population and are not, in fact, clinically relevant. Indeed, the rate of contact sensitization in 1 unselected population was as high as 19% to nickel and 3% to fragrance mix.¹⁷ Thus, it is possible that our patients would have improved even without allergen avoidance—as was the case with the control subjects of Magen et al¹⁶—since the natural course of CIU is often that of spontaneous resolution. However, our patients were followed up for 2 to 9 months after testing, a longer time period than in the study of Magen et al, which would give us a longer period to assess patients' improvement. Additionally, 2 of our 4 complete responders had recurrence of their urticaria when using personal care products with proven contact allergens. The other 2 complete responders did not perform such challenges.

Because of the large number of allergens placed and the technical difficulties of placing large number of allergens in duplicate, we did not investigate our patients for contact urticaria, which is a limitation of this study. With regard to allergen avoidance, it is often difficult to assess compliance, as many allergens are ubiquitous in the environment and thus require tedious changes to daily habits. Thus, it is possible that patients who reported allergen avoidance were not fully compliant, resulting in persistent hives or only partial remission. Furthermore, none of our patients completed full dietary avoidance of potential systemic allergens; perhaps, our response rates would have been higher if patients had been willing to try dietary changes.

Despite these limitations, it is still important to consider contact allergy as a potential cause of CIU. The target cells for CIU are dermal mast cells and basophils. Thus, any hypothesis to explain how contact allergens result in urticaria must provide a mechanism by which mast cells are repeatedly activated to release histamine.

Despite the attention given to IgE-mediated urticaria, there are many other immunologic activators of the dermal mast cell, including neuropeptides, stem cell growth factor, and histamine-releasing factors (HRFs).¹⁸ Among these mediators, HRFs represent a heterogeneous group of cytokines released from peripheral blood mononuclear cells.¹⁹ Data suggest that diffusible HRFs do not involve cell-surface IgE antibody, instead activating the mast cell through their own unique receptors.²⁰ Multiple studies have demonstrated that CD4⁺ and CD8⁺ T cells are capable of stimulating histamine releasing activity from both mast cells^{20–22} and basophils.²³ Furthermore, unlike other subpopulations of peripheral blood mononuclear cells, which release HRFs spontaneously, synthesis of HRFs by T cells is significantly enhanced in the presence of antigen.²²

We theorize that HRFs are involved in the immunologic pathway by which contact allergens produce a type IV, T cell–mediated urticaria. As with allergic contact dermatitis, allergens absorbed through the skin or systemically are delivered to antigen-presenting cells, with subsequent activation of T cells. Here, however, the pathways of allergic contact dermatitis and allergic contact urticaria diverge. In some patients with CIU, we propose that an alternative pathway is activated whereby exposure to an allergen stimulates T-cell production of HRFs, which subsequently bind to mast cell or basophil receptors to initiate histamine release. The rarity of this phenomenon may be attributed to a high allergen threshold for T cell–mediated HRFs release. Alternatively, mast cell degranulation may require activation of a high threshold number of HRF receptors. In some patients, the combination of multiple contact and systemic allergens may act synergistically to surpass this threshold, presenting clinically as urticaria. Furthermore, the threshold for manifestation of delayed-type contact urticaria may differ among patients, helping to explain why some patients in our study achieved complete remission, whereas others had only partial improvement. In patients who improved, topical allergen avoidance may have decreased the allergen load below the individual's threshold for HRF-mediated mast cell activation. For other patients, topical avoidance may not be adequate. Indeed, many patients who did not respond to topical allergen avoidance reacted to potential systemic allergens, including fragrances and metals. If implemented, systemic avoidance measures may have resulted in clinical improvement for these patients.

Based on our results, we conclude that there is an association between contact allergen avoidance and clinical improvement; whether these reactions are, in fact, clinically relevant is a point of contention, as we may simply be capturing the background prevalence of contact sensitization. Still, patch testing may be useful in the management of CIU, particularly for patients with long-standing urticaria.

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