

The reactivity of the back revisited. Are there differences in reactivity in different parts of the back?

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Summary

Background. In the contact dermatitis literature, it is regularly stated that the patch test reactivity on various areas of the back differs; this might have a large impact on the reproducibility of patch testing.

Objectives. To investigate the reproducibility of patch testing on the upper back with regard to the left as opposed to the right side and the medial as opposed to the lateral part of the upper back. The reproducibility over time and with regard to the reactivity pattern was also investigated.

Methods. Thirty-one subjects with contact allergy to the metals gold ($n = 19$) or nickel ($n = 12$) were patch tested with serial dilutions, in triplicate applications, on different locations on the upper back. The Friedman test was used for statistical calculations.

Results. No significant differences in the reactivity of the back were found. In all gold-allergic patients and 11 of 12 nickel-allergic patients, the allergy could be reproduced with regard to previous patch testing, but the degree of reactivity differed.

Conclusions. When a high level of standardization of the patch test technique with the same test system was used, there were no differences in patch test reactions and sites of application on the upper back.

Key words: anatomical site; angry back; contact allergy; excited skin syndrome; patch test; reactivity; reproducibility; serial dilution.

Introduction

Patch testing is, for practical reasons, performed on the upper back (1). In the contact dermatitis literature, it is regularly stated that there are regional differences in reactivity (2, 3). The lower back has been said to have lower reactivity than the upper part of the back; however, the results of studies are divergent.

Possible factors influencing the reactivity on the back have been described in articles reporting studies in which

different patch test systems were evaluated with the upper back as the test area (4). Differences in reactivity have been attributed to differences in the adherence of patch test material depending on anatomical site, pre-modified skin on one side of the back because of exogenous factors, the application of related substances in the same area, etc. (5, 6). Readings may not always be performed in a standardized manner, which can influence results (7).

With regard to differences in reactivity over time, the above factors can influence results. Other explanations for differences in reactivity over time for the same test preparation have been the angry back or excited skin syndrome (8, 9), and, for certain allergens such as nickel, hormonal factors have been suggested to affect patch test sensitivity (10). The present study was conducted in order to further investigate observations made in a metal study in which the same serial dilutions of gold and nickel were patch

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Fig. 1. The patch test reactivity pattern seen in some subjects when they were patch tested with exactly the same dilution series in triplicate.

tested simultaneously on different parts of the back. These observations (Fig. 1) initially pointed towards different patterns of reactivity on the upper back, and concern was raised with regard to the risk of differences in reactivity with a possible inherent pattern. This was the background for the exploratory study in which the patch test pattern in the subjects who participated in the above-described metal study was analysed in order to investigate differences in reactivity within the upper back and aspects of the reproducibility of patch tests.

Materials and Methods

Subjects

Thirty-one subjects, 19 of whom were allergic to gold sodium thiosulfate, previously patch tested at 2.0% wt/wt pet. (14 females; 5 males; mean age 52.5 years) and 12 with contact allergy to nickel sulfate, previously patch tested at 5.0% wt/wt pet. (11 females; 1 male; mean age 57.8 years), participated. Of the gold-allergic subjects, 7 had previously had a 3+ reaction, and 12 had previously had a 2+ reaction; of the nickel-allergic subjects, 2 had previously had a 3+ reaction, and 10 had previously had a 2+ reaction.

Patch testing

All subjects were patch tested with their known allergen in serial dilutions. Two weeks prior to the study and during the study period, the subjects were instructed not to undergo phototherapy, or use topical steroids or other immune-modulating therapy, near the sites of testing. Oral corticosteroids and other medications with a modulatory effect on allergic reactions were avoided during the study period. The subjects were asked to avoid using

any personal care products on the tested areas during the period.

With the baseline series in Malmö, patients are tested with gold sodium thiosulfate at 2.0% wt/wt pet. and nickel sulfate at 5.0% wt/wt pet. The dose is standardized at 40 mg/cm², corresponding to a 20-mg pet. preparation in an 8-mm-diameter Finn Chamber[®] (SmartPractice, Phoenix, AZ, USA) (11).

In this study, the allergens were tested with aq. as the vehicle to enable standardized concentrations in both the diluted samples and the samples tested at higher concentrations than in the commercially available patch test preparations.

Gold sodium thiosulfate (Chemotechnique Diagnostics AB, Vellinge, Sweden) was patch tested in aq. at 6.3%, 2.0%, 0.63%, 0.2%, 0.063%, and 0.02% (wt/vol); nickel sulfate hexahydrate (Acros Organics, Geel, Belgium) was patch tested in aq. at 16.0%, 5.0%, 1.6%, 0.5%, and 0.16% (wt/vol). If the subject had a prior 3+ reaction to gold, the serial dilution started at 2.0% and ended at 0.02%; and if the subject had a prior 2+ reaction, the dilution series started at 6.3% and ended at 0.063%. All of the nickel-allergic subjects were patch tested with the same dilution series. Each subject was thus patch tested with three identical dilution series, and the metal that they had not previously reacted to: 2.0% wt/wt pet. gold sodium thiosulfate if they were nickel-allergic, and 5.0% wt/wt pet. nickel sulfate if they were gold-allergic. Patch testing was performed with 8-mm-diameter Finn Chambers[®] (SmartPractice), with one filter paper mounted on Scanpor[®] tape (Norgeplaster, Oslo, Norway) (12).

A volume of 15 µl of test solution was applied to the chambers with a micropipette (13). Each serial dilution was placed separately on one test strip consisting of five chambers, and each subject was patch tested with three serial dilutions, with the highest concentration on the proximal part of the back.

Twenty-two subjects were patch tested on the left side, and 9 were patch tested on the right side. All subjects were patch tested with serial dilutions, in triplicate applications on the same test occasion, but on different locations with regard to distance from the spine (Fig. 2).

The patch test material was carefully marked, and extra tape (Norgeplaster) was used to secure the patch test material, to ensure that the material was equally occluded to the back on both sides. The patch tests were removed from the back after 48 h by the subjects themselves, and readings were carried out by a dermatologist on day (D) 3 and on D7. The patch tests were read according to ICDRG guidelines (14). Regarding the investigation of the possible significance of anatomical localization for the patch

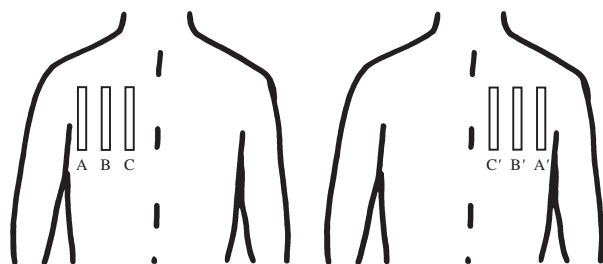


Fig. 2. Triplicate applications of the same serial dilution were made on either the right or the left side of the back.

test result, gradings additional to strong + and ++ reactions were used, these being registered as + (+) and ++ (+). The different steps, including the intermediate steps, are thus defined as follows: +, erythema and infiltration; + (+), erythema, infiltration, and a few papules; ++, erythema, infiltration, and papules; ++ (+), erythema, infiltration, papules, and a few vesicles; +++, intense erythema, infiltration, and vesicles (10).

Analysis of reproducibility over time. The reproducibility over time could be confirmed by comparing the previous test results with those obtained with the present aqueous patch test solutions, both at the highest concentration patch tested and at the concentrations of 2.0% for gold and 5.0% for nickel.

The comparison was thus made between 2.0% pet. and 2.0% aq. in 7 gold-allergic subjects with an initial +++ reaction, and between 6.3% aq. and 2.0% aq. for 12 gold-allergic subjects with an initial ++ reaction.

For all 12 nickel-allergic subjects, the comparison was made between 5.0% pet. and both of the aqueous concentrations at 16.0% and 5.0%. Independently of comparison, the strongest reaction for the present testing on D3 or D7 was used. In these calculations, no additional grading of the readings was used; that is, a + (+) reaction was registered as a + reaction.

Analysis of anatomical reproducibility. For study of the anatomical reproducibility, all readings performed were used; D3/D4 readings and D7 readings were analysed separately. Both the ordinary ICDRG gradings and the additional gradings were used for the summarized test score (STS) calculations.

Analysis of reproducibility of allergic reactions at simultaneous patch testing. Each subject was tested with 15 aqueous test solutions representing three test strips, each containing the same five concentrations in defined doses in mg/cm² in a dilution series. These 15 tests could be expected to result

in various numbers of +++, ++, +, (+) and – reactions. For each contact-allergic reaction (++++, ++, +), there were thus two other tests performed with exactly the same dose. The results of each one of these two tests could be positive, defined as a +++ or ++ or + reaction. For all positive contact-allergic reactions, a calculation was made of whether both tests at the same dose had resulted in an allergic reaction independently of the intensity of the reaction (100%), only one of the two tests (50%), or neither of the two tests (0%).

Analysis of patch test reactivity with regard to patch test dose. The three dilution series used simultaneously thus gave rise to three patch test reactions at each concentration for each subject. All reaction types for each concentration, that is, dose, were calculated separately in order to visualize the distribution of negative, irritant, doubtful, +, ++ and +++ reactions.

Statistical analysis

When patch tested in the study, 1 subject, who was nickel-allergic, did not have a reproducible reaction at all. The result from this subject was included when reproducibility over time was measured, but, with regard to anatomical reproducibility, the subject was excluded, as no reaction could be elicited.

To enable statistical calculations concerning the possible significance of anatomical localization for the patch test result, the test reactions were transformed to numerical values: –, 0; (+), 0.5; +, 1; + (+), 1.5; ++, 2; ++ (+), 2.5; and +++, 3 (10).

The reactivity could thus be measured in two ways: either as an STS, where the scores for all reactions in one patch test series were summed, or as a minimal eliciting concentration (MEC), defined as the lowest concentration eliciting at least a + reaction.

The positive reactions were not always continuous. When the numbers of negative and/or doubtful reactions were followed by the same or a greater number of positive reactions, the lowest positive reaction was registered as the MEC (10). In Tables 1 and 2, the individual STS and MEC values are given. The Friedman test was used for statistical calculations to compare the reactivity responses for both STS and MEC.

Ethics

The subjects were informed of the nature of the test and possible adverse reactions. Informed written consent was obtained from all of the subjects, and the study was approved by the Regional Ethical Review Board, Lund, Sweden.

Table 1. Minimal eliciting concentration (MEC) and summarized test score (STS) for patients tested with gold sodium thiosulfate in serial dilutions

Subject	Day 3						Day 7					
	A		B		C		A		B		C	
	MEC	STS	MEC	STS	MEC	STS	MEC	STS	MEC	STS	MEC	STS
1*	2.0	3.5	0.63	5.0	0.63	3.0	2.0	3.5	2.0	4.5	0.63	3.0
2*	0.063	10.0	0.063	13.0	0.063	8.5	0.063	9.0	0.063	9.0	0.063	9.0
3*	0	0	6.3	2.5	2.0	3.5	6.3	1.5	2.0	5.0	2.0	7.0
4*	0.63	6.5	0.63	8.5	0.63	8.5	0.2	9.5	0.2	11.0	0.063	12.0
5*	0	0	0	0	2.0	2.0	0	1.0	0	1.5	2.0	4.0
6*	0.2	8.5	0.63	7.5	0.63	7.5	0.63	5.5	0.63	6.5	0.63	7.0
7*	0.063	8.0	0.063	9.5	0.063	11.5	0.063	9.0	0.063	10.0	0.063	9.0
8*	2.0	3.5	6.3	2.5	2.0	2.5	2.0	3.5	2.0	3.0	2.0	3.5
9*	0	0	6.3	1.5	0	0.5	0	0	0	0	6.3	1.0
10*	0.2	12.0	0.063	13.0	0.063	14.0	0.2	10.0	0.063	12.0	0.063	13.0
11*	0.63	4.0	0.63	3.0	2.0	2.0	2.0	4.5	0.63	5.5	2.0	2.5
12*	6.3	1.0	0	0.5	0	0	2.0	3.0	6.3	1.0	6.3	1.0
13†	0.63	4.5	0.2	6.5	0.063	7.0	0.63	5.0	0.2	7.0	0.02	9.0
14†	0.02	12.5	0.02	10.0	0.02	11.0	0.02	9.0	0.02	8.0	0.02	8.5
15†	0	0	2.0	1.0	0	0	0	0	2.0	1.5	0	0
16†	0.063	9.0	0.063	10.5	0.063	9.5	0.063	8.0	0.02	12.0	0.063	10.5
17†	0.063	11.0	0.02	12.0	0.063	10.0	0.063	6.5	0.02	8.0	0.02	8.0
18†	0.63	4.5	0.63	3.5	0.63	3.0	0.2	5.5	0.63	4.0	0.63	4.5
19†	0.63	2.0	2.0	1.0	0	0	0.63	2.5	0	0.5	0	0

A, B, and C: tested areas on the back; bold type indicates subjects tested on the right side of the back. All other subjects were tested on the left side.

*6.3%, 2.0%, 0.63%, 0.2% and 0.063% aq.

†2.0%, 0.63%, 0.2%, 0.063% and 0.02% aq.

Table 2. Minimal eliciting concentration (MEC) and summarized test score (STS) for patients tested with nickel sulfate hexahydrate in serial dilutions, that is, 16.0%, 5.0%, 1.6%, 0.5% and 0.16% aq.

Subject	Day 3						Day 7					
	A		B		C		A		B		C	
	MEC	STS	MEC	STS	MEC	STS	MEC	STS	MEC	STS	MEC	STS
20	1.6	4.5	0	0	5.0	4.0	1.6	5.5	5.0	3.0	1.6	6.0
21	5.0	3.0	5.0	3.0	16.0	3.0	16.0	2.5	5.0	3.5	5.0	2.5
22	1.6	8.5	1.6	6.0	1.6	6.0	1.6	6.5	1.6	5.5	1.6	6.5
23	0.5	6.0	1.6	5.5	5.0	4.0	1.6	5.5	1.6	5.5	5.0	2.0
24	1.6	6.0	5.0	4.5	16.0	2.5	1.6	5.0	5.0	5.5	16.0	3.0
25	1.6	5.5	5.0	6.0	0.5	9.0	1.6	5.0	1.6	6.0	0.5	8.0
26	0.5	5.5	0.5	5.5	0.5	7.0	0.5	4.0	0.5	4.0	0.5	5.5
27	5.0	5.0	1.6	8.0	0.5	8.5	5.0	6.0	1.6	7.0	0.5	8.5
28	5.0	3.0	5.0	2.0	16.0	1.0	1.6	3.0	5.0	2.0	5.0	3.5
29	0	0.5	0	0.5	0	0	0	0.5	16.0	1.0	16.0	1.0
30	5.0	5.0	1.6	5.5	1.6	5.5	5.0	5.0	1.6	5.5	1.6	6.5

A, B, and C: tested areas on the back; bold type indicates subjects tested on the right side of the back. All other subjects were tested on the left side.

Results

Reproducibility over time

For all nickel-allergic subjects except one, an allergic reaction was reproducible (nickel 11/12, 91.7%; and gold 19/19, 100%). For the gold-allergic subjects, the results

were as follows. Among those with a previous 3+ reaction ($n = 7$) when patch tested at 2.0% aq., 3 of 7 had reproducible 3+ reactions, 2 of 7 had 2+ reactions, and 2 of 7 had + reactions. Among those with 2+ reactions ($n = 12$) when patch tested at 2% aq., 4 of 12 now had stronger reactivity (3+ reaction), 5 of 12 still had 2+ reactions, 2

of 12 now had + reactions, and 1 did not have a reproducible reaction on retesting with 2% aq. At 6.3% aq., however, all subjects had allergic reactions. Among the nickel-allergic subjects, the 2 with 3+ reactions had the same reactivity when patch tested at 5.0% aq., and of those with a 2+ reactions (n = 10) when patch tested at 5.0% aq., 1 of 10 had increased reactivity, 5 of 10 had the same reactivity, 2 had + reactions, and in 2 an allergic reaction could not be reproduced. When they were patch tested at 16.0% aq., an allergic reaction reproduced in all but 1 subject, and for 6 subjects the reactivity increased. In no subject was the intensity of the reaction at 16.0% lower than that at 5.0%.

Anatomical reproducibility: reproducibility with regard to horizontal change, that is, with regard to the left and the right sides of the back

Tables 1 and 2 show the individual STS and MEC values for the different dilution series A, B and C for each subject. There was no statistical difference when the STS ($p > 0.3$) and MEC ($p > 0.3$) were analysed with regard to whether the patients had been tested on the most lateral part of the left side A or the most lateral part of the right side A', and there were also no significant differences with regard to B versus B' and C versus C'. Furthermore, no significant differences could be found with regard to whether there was the same reactivity on the middle of the back as on the lateral part, that is, whether the STS results of test panel A differed from those of test panel B or test panel C, and with regard to whether the right side A was equivalent anatomically to C', and whether C was equivalent to A'. The A, B and C panels were compared for D3 and D7.

Analysis of reproducibility of allergic reactions at simultaneous patch testing

Taking into consideration the high degree of reproducibility with regard to anatomical location (see above), we also analysed the reproducibility at simultaneous patch testing and with different doses.

In Fig. 3a and b, for each step of reactivity (+, ++, +++), the degree of reproducibility with regard to whether any allergic reaction independent of intensity could be reproduced or not is shown. The two allergens are shown separately; however, the figures show a very similar pattern, indicating that, as the degree of reactivity decreases, the reproducibility becomes lower.

Patch test reproducibility with regard to patch test dose

Another way of indicating the reproducibility and how this changes with reactivity is to look at the reactivity

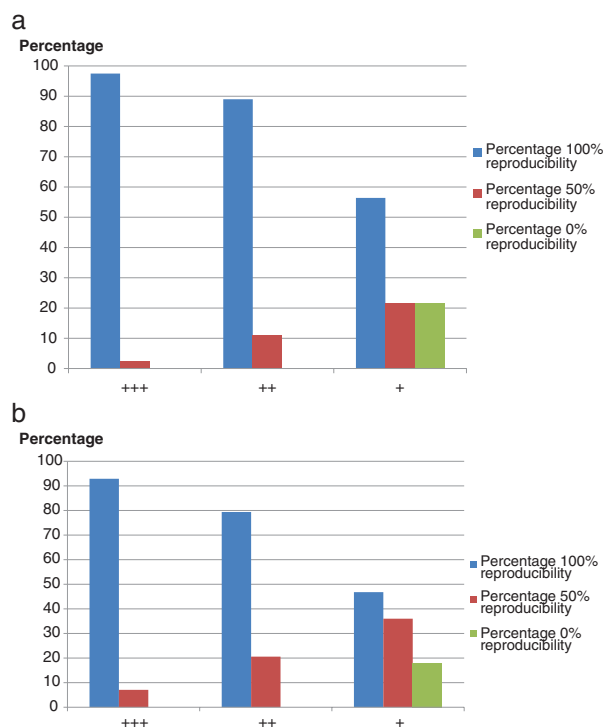


Fig. 3. (a) The reproducibility pattern for gold based on the intensity of the allergic reaction (+, ++, +++) at D3 when each subject was tested with three identical dilution series at the same time. For each contact-allergic reaction, the levels of reproducibility at that concentration step, that is, the three identical patch tested doses, were compared. The only comparison being made was whether there was 100% reproducibility, that is, all three showed allergic reactions (+, ++, +++) even if the reactivities of the reactions were not identical, or whether there was 50% reproducibility, that is, two of three reactions were positive, or whether there was 0% reproducibility, that is, if there was only one positive reaction and/or (+) or negative reaction. (b) The reproducibility pattern for nickel based on the intensity of the allergic reaction (+, ++, +++) at D3 when each subject was tested with three identical dilution series at the same time. For each contact-allergic reaction, the levels of reproducibility at that concentration step, that is, the three identical patch tested doses, were compared. The only comparison being made whether there was 100% reproducibility, that is, all three showed allergic reactions (+, ++, +++) even if the reactivities of the reactions were not identical, or whether there was 50% reproducibility, that is, two of three reactions were positive, or 0% reproducibility, that is, if there was only one positive reaction and/or (+) or negative reaction.

pattern at each concentration step, that is, each dose (Fig. 4a and b). As the dose decreases, there will, naturally, be an increasing number of doubtful and negative reactions, and at this level reproducibility will be significantly reduced.

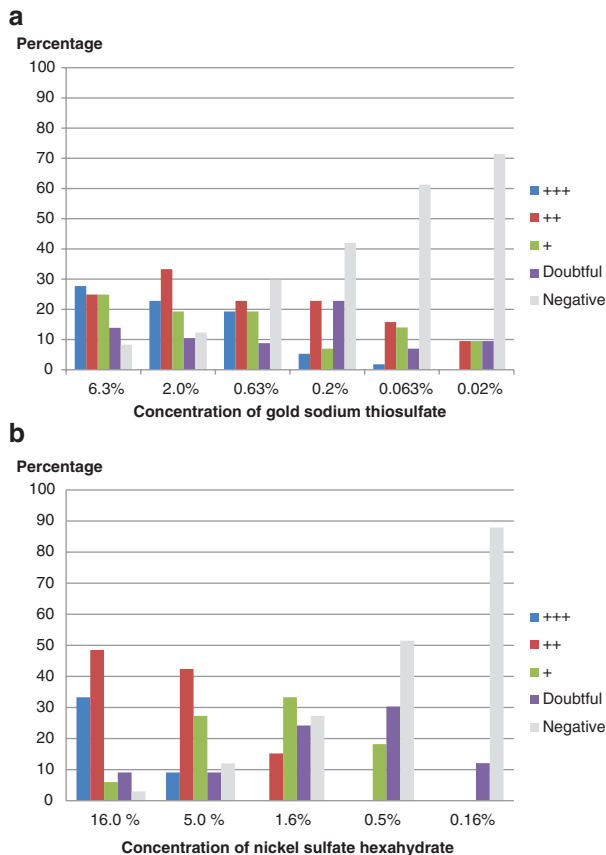


Fig. 4. Patch test reaction pattern at D3. (a) Patch test reaction pattern (percentage of total number patch tested defined according to the ICDRG as negative, doubtful, +, ++, or +++) for each patch tested concentration of gold sodium thiosulfate. (b) Patch test reaction pattern (percentage of total number patch tested defined according to the ICDRG as negative, doubtful, +, ++, or +++) for each patch tested concentration of nickel sulfate hexahydrate.

Discussion

Reproducibility with regard to anatomical location

Patch testing is usually performed on the upper back. This technique has been the gold standard for diagnosing contact allergy since the days of Jadahsson, but has been questioned (15).

Much work has been performed to standardize the patch test procedure (7, 11–13), not only regarding how the test substances are applied, but also in ensuring that the test panels adhere well to the back. The significance of the anatomical site with regard to patch testing has been investigated, and it has been found that the upper back is the preferred site. Patch testing, which is almost always performed with the baseline series and several additional test panels, is thus a standardized procedure. The patch

test panels are applied to the back from left to right. It is assumed that the test response is the same over the upper back. This, however, to the best of our knowledge, has not been investigated. The assumption is sometimes questioned when, at retesting, the patch test reproducibility is not the same (16–22).

In this exploratory study, which is part of a study on metal allergy, in which patients were patch tested with exactly the same allergen in defined doses in serial dilutions on different sites on the back, we saw the opportunity to analyse the possible difference with regard to the distance of the test panel from the spine, and to confirm prior findings that there is high reproducibility between the left and right sides. Initially, we saw a different pattern of reactivity (Fig. 1) on the upper back, but the calculations could not confirm a trend.

No significant difference was found with regard to reactivity on the left versus the right part of the upper back, confirming previous findings (5), and nor was there any difference with regard to the medial versus the lateral aspect of the back.

Reproducibility over time

Within the original group of 31 contact-allergic subjects, a contact-allergic reaction could be reproduced for 30. In our clinic, patients are routinely patch tested with gold sodium thiosulfate 2.0% pet., in the baseline series, and nickel sulfate 5.0% pet. Here, all patients were patch tested with aqueous solutions, and as serial dilutions were performed, this has to be taken into account when considering the reproducibility (23–25). On comparison of patch testing with aqueous solutions and pet. at the same concentration in 8-mm-diameter Finn Chambers®, the aqueous solution will give a dose corresponding to 30 mg/cm², whereas pet. will give a dose corresponding to 40 mg/cm². Despite this difference, a high degree of reproducibility over time was expected. Also, the fact that only subjects with previously high reactivity were included would logically result in a high degree of reproducibility. With regard to differences in reproducibility in contact allergy to nickel, one previous explanation has been hormonal changes in women during the menstrual cycle (10).

In this study, we aimed at minimizing these hormonal differences; however, 2 of the nickel-allergic subjects and 3 of the gold-allergic subjects females aged <42 years, and all others were post-menopausal. Even so, with regard to whether the allergic reaction as such was reproducible over time, this was the case except in 1 subject.

However, the intensity of the reactivity differed when reproducibility was studied; 7 of the subjects had lower

reactivity and 10 had higher reactivity when retested at the same patch test concentration. Also, it should be noted that every individual was actually patch tested three times with the same test concentration in this study; regarding the aqueous solutions of 5.0% nickel and 2.0% gold, ~10% of the patch test reactions would have been doubtful if these had been the only tested doses and if there had been only one retest and not three.

The concentrations recommended for diagnostic patch testing with most common allergens are usually above the concentrations used in the study, but a similar situation may occur when patients are tested with their own cosmetics, when some constituents may be present in very low concentrations, or when the threshold of reactivity for the patient is relatively high.

Another possible reason for changes in reactivity over time is the phenomenon of the angry back/excited skin syndrome (8, 9), where it is argued that, if an individual has many simultaneous positive reactions, there is a risk of false-positive reactions, that is, weak + reactions resulting from hyperirritability of the skin. Active dermatitis elsewhere is also considered to induce this phenomenon (26). A more recent additional theory is that possibly cross-reacting or closely related substances patch tested close to each other might 'drag' with them positive reactions that need not be reproducibly elsewhere on the back (6). In this study, only individuals who were already allergic were patch tested, and with their known allergen.

Reproducibility with regard to allergic reaction and patch test dose

Dilution series were made so the doses/cm² of the substances tested in close proximity to each other were actually the same. One way to find evidence for the previously described theories would be to study how many percentages that reacted for each degree at retesting, if the same reaction could actually be reproduced or at least reproduced as an allergic reaction at simultaneous patch testing.

Here, it is clearly seen that, for 3+ reactions, the reproducibility is almost 100%, whereas, as the reactivity decreases, reproducibility also decreases in a dose-response manner. The results shown in Figs. 3a and 3b also partly question, or at least do not support, the existence of the excited skin syndrome. In this study, there is a high degree of reproducibility, but the analysis also shows that retesting does not necessarily give the same patch test result, as there are >30% of the allergic

+ reactions to gold and nickel for which the reaction is not reproducible at all, showing that (as we know that these patients were actually allergic) a non-reproducible + reaction is not necessarily equivalent to a false-positive reaction, as has been argued.

How, then, do we explain this difference in reactivity? Both biological and technical factors may, of course, be responsible, even though great care was taken here to minimize technical reasons. The dose-response curve for a substance will influence the tendency for an allergen to cause a false-negative or doubtful reaction (27); this may be because of immunological factors and/or intrinsic factors of the allergen. Another reason may be local differences in the immunological status of the skin.

Conclusions

By the use of a high level of standardization of the patch test technique with the same test system, defined doses in mg/cm² in serial dilutions, and a test reaction classification with additional grades, good reproducibility of the patch test technique was found, independently of where on the upper back the patch test chambers were placed. However, it could be clearly seen that, when the reactivity is lower, the reproducibility will decrease. The fact that a 1+ reaction has lower reproducibility, as shown in this study, where known contact allergens were patch tested, also shows that if a 1+ reaction is not reproduced on retesting, this does not necessarily mean that the previously found reaction was false positive.

The findings are of interest for the general standardization of the patch test technique. In this study, the test substances were the same. Previously, it has been found that cross-reactivity or increased reactivity resulting from chemically similar haptens or possibly the same hapten (formed by, for example, metabolic activation of a closely related patch test substance, or caused by patch testing in close proximity) could be a possible reason when test results are not found to be reproducible (6). In this study, we could not find support for this suggestion.

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