

# The significance of previous allergic contact dermatitis for elicitation of delayed hypersensitivity to nickel

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Several factors, such as amount of allergen, vehicle, anatomic site, immunologic status and previous eczema, may influence delayed hypersensitivity reactions. In an extended model, we have studied the significance of previous allergic contact dermatitis for elicitation of delayed hypersensitivity to nickel in 25 nickel-allergic females. On 3 occasions, 8, 4 and 1 months before the final challenge patch testing, an experimental allergic contact dermatitis from nickel was induced on the lower back. At the challenge patch testing, 4 identical dilution series of nickel were tested on 4 areas on the lower back: 3 with previous but healed dermatitis and 1 control area. The tests were read in a blind way. A significantly higher test reactivity was found at the areas with a previous allergic contact dermatitis, the shorter the time interval between the previous provocation and the challenge, the stronger the reaction. These results may be of importance for the understanding of factors contributing to chronicity of allergic contact dermatitis.

**Key words:** test model; nickel allergy; topical; re-challenge; memory function; immunological basis.  
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The better our understanding and knowledge of various factors of significance for the sensitization and elicitation of allergic contact dermatitis, the better the possibilities to diagnose, treat and prevent the dermatitis as well as to rehabilitate patients with eczema. An allergic contact dermatitis can be elicited not only from direct contact between the skin and the sensitizer but also from exposure via the airway and the gastro-intestinal tract. Our knowledge of the significance of ingestion and particularly inhalation of a sensitizer for allergic contact dermatitis is sparse, while we know more about direct skin exposure.

Commonly, an allergic dermatitis will heal when the exposure to the incriminated sensitizer ceases. Sometimes total avoidance of the sensitizer is impossible, e.g., for any ubiquitous sensitizer and when a patient with an occupational allergic contact dermatitis on the hands returns to work after a period of sick-leave. In this latter situation, the dermatologist should inform and, when desirable, cooperate with the employer to create the best conditions for a successful return to work. Even if the exposure to the sensitizer continues, the exposure

may be decreased by changing the work procedures. If the allergic contact dermatitis is not completely healed when returning to work, it is likely that re-exposure to the sensitizer will aggravate the dermatitis. Another question of significance is whether the previous, but clinically healed, allergic contact dermatitis will influence the likelihood that the dermatitis reappears when the previously diseased skin is re-exposed. Currently, our knowledge on this matter is insufficient. In this study, we have therefore investigated the significance of a previous allergic contact dermatitis for the elicitation of contact dermatitis on re-exposure to the same sensitizer, with respect to the time interval between the 2 events with allergic contact dermatitis.

## Materials and Methods

### Subjects

25 female patients hypersensitive to nickel, as demonstrated by patch testing with the European standard series, were enrolled in the study after approval by the Ethics Committee at Lund Univer-

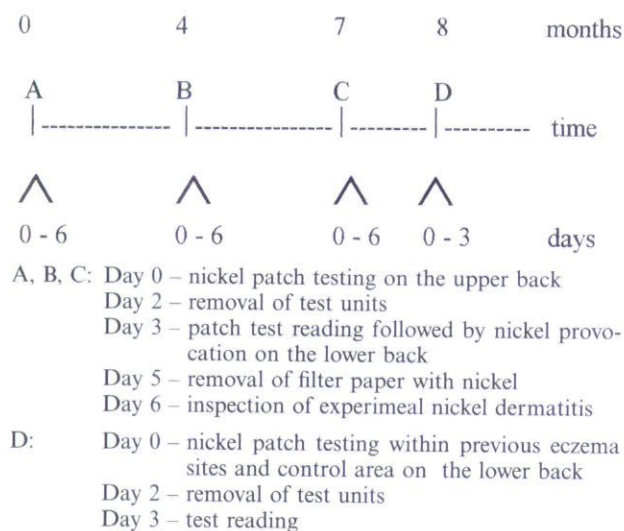


Fig. 1. Study design.

sity. Informed consent was obtained from each patient.

The nickel-allergic females belonged to 2 different groups, one with pompholyx ( $n=10$ ), mean age 44.3 years (range 24–54 years), and the other group without any hand eczema at all ( $n=15$ ), mean age 35.3 years (range 19–51 years). None of them were atopics, according to the criteria of Svensson et al. (1).

The study was performed from October to May to reduce any possible influence of ultraviolet radiation (2).

#### Experimental allergic contact dermatitis

On 3 occasions, the patients were provoked to nickel in exactly the same way (Fig. 1). Immediately before such a provocation, each patient was tested with a dilution series of nickel to determine the present degree of reactivity. An aqueous stock solution with nickel (nickel sulfate  $\times 6 \text{ H}_2\text{O}$ , Merck, Germany) at 12.5% w/v was prepared and further diluted with a factor 2.5 down to 0.0032% w/v. We have long experience in testing aqueous nickel solutions with the concentration 12.5% w/v (in combination with the used volume 15  $\mu\text{l}$ ) without eliciting irritant reactions. Each patient was tested with 10 consecutive test solutions within the range 12.5–0.0032% w/v. 15  $\mu\text{l}$  of the nickel solution were micropipetted onto filter paper discs of small Finn Chambers ( $\varnothing 8 \text{ mm}$ , Epitest Ltd Finland) on Scanpor (Epitest Ltd, Norgeplaster A/S, Norway). The tests were applied on the upper part of the back for 2 days and reading was performed 1 day later.

Immediately after the reading an allergic contact dermatitis was provoked on the back. On this occasion, 1.0 ml of the nickel test solution with the

lowest concentration resulting in a ++ reaction (according to ICDRG criteria) were micropipetted on to a  $6.0 \times 7.0 \text{ cm}$  filter paper and attached onto an  $8.0 \times 9.0 \text{ cm}$  hydrocolloid dressing (Duoderm, Convatec, Denmark). The lowest part of the back, an area where the patients had not been tested before and an area unusual for nickel dermatitis, was divided into 4 symmetrical parts. For each patient, randomization according to a Latin square table determined the test area to be used on each occasion. The hydrocolloid dressing test was applied under an adhesive tape (Mefix, Molnlycke, Sweden) on one area for 2 days and 1 day later, the area was inspected to assure that the experimeally provoked eczematous reaction was as expected (Fig. 2). 2 patients (24 and 25) missed 1 provocation each, one at 8 and one at 4 months before challenge patch testing. To enable exact localization of the experimeally-induced eczematous area even after healing, the distances from the most proximal and distal parts of the  $6.0 \times 7.0 \text{ cm}$  eczematous area from the spine were measured on each occasion with an experimentally-induced contact dermatitis. We also measured the shortest distances to the lowest part of the scapula, the most prominent vertebra of the neck, and the hip.

#### Challenge patch testing

1 month after provocation with the 3rd and last hydrocolloid dressing with nickel, the patients were patch tested with a serial dilution of nickel sulfate on the 4 symmetrical parts of the lower back, 3 of these being the areas where an eczematous reaction had been provoked 8, 4 and 1 months before, and 1 the remaining area where there had never been a dermatitis before (control area). Each individual was tested with 6 consecutive test preparations within the range 12.5–0.0013 % w/v (12.5, 2.0,

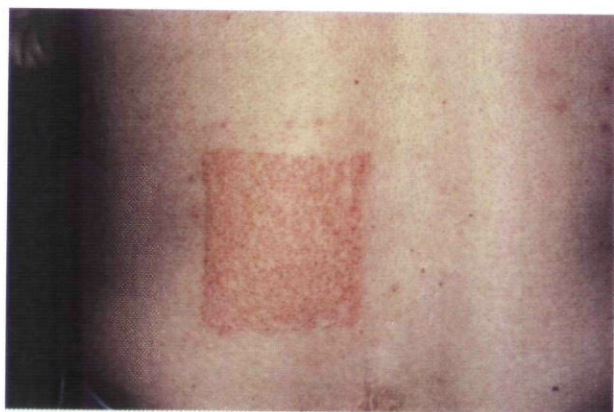


Fig. 2. Experimental allergic contact dermatitis from nickel on the lower back (day 3).

Table 1. Summarised test score (STS) and minimal eliciting concentration (MEC) for the 4 challenge sites in 25 nickel-hypersensitive females. (1–15 non pompholyx, 16–25 pompholyx)

| Patient no | Never eczema |       | 8 months |        | 4 months |        | 1 month |        |
|------------|--------------|-------|----------|--------|----------|--------|---------|--------|
|            | STS          | MEC   | STS      | MEC    | STC      | MEC    | STS     | MEC    |
| 1          | 2            | 12.5  | 3.5      | 2.0    | 3.5      | 2.0    | 2       | 12.5   |
| 2          | 6.5          | 0.32  | 11       | 0.008  | 8        | 0.32   | 8.5     | 0.008  |
| 3          | 1.5          | 12.5  | 1        | 12.5   | 0        | >12.5  | 0       | >12.5  |
| 4          | 7            | 0.32  | 9.5      | 0.05   | 7        | 0.32   | 7       | 0.05   |
| 5          | 5            | 0.32  | 5.5      | 0.32   | 3.5      | 2.0    | 6       | 0.32   |
| 6          | 5.5          | 0.32  | 3        | 0.32   | 6.5      | 0.05   | 9.5     | 0.05   |
| 7          | 7.5          | 0.32  | 12.5     | 0.008  | 6.5      | 2.0    | 8       | 0.32   |
| 8          | 5.5          | 2.0   | 7        | 0.32   | 6        | 0.32   | 9.5     | 0.008  |
| 9          | 8            | 0.05  | 7        | 0.05   | 6        | 0.05   | 7.5     | 0.05   |
| 10         | 0.5          | >12.5 | 3        | 0.32   | 3.5      | 2.0    | 3.5     | 2.0    |
| 11         | 6            | 2.0   | 9.5      | 0.05   | 8        | 0.05   | 5       | 0.008  |
| 12         | 1            | 12.5  | 0        | >12.5  | 2.5      | 12.5   | 1.5     | 12.5   |
| 13         | 6.5          | 0.05  | 3.5      | 2.0    | 8        | 0.32   | 7       | 0.32   |
| 14         | 5            | 0.32  | 6        | 0.05   | 6        | 0.05   | 5       | 0.32   |
| 15         | 5.5          | 0.05  | 5.5      | 2.0    | 6        | 0.32   | 7       | 0.05   |
| 16         | 8            | 0.32  | 13.5     | 0.0013 | 14.5     | 0.0013 | 17.5    | 0.0013 |
| 17         | 7            | 0.32  | 8.5      | 0.05   | 10.5     | 0.05   | 9.5     | 0.05   |
| 18         | 5            | 2.0   | 8        | 0.05   | 5.5      | 2.0    | 7       | 0.05   |
| 19         | 6            | 2.0   | 11       | 0.008  | 5.5      | 2.0    | 12      | 0.0013 |
| 20         | 10           | 0.05  | 11.5     | 0.008  | 7.5      | 0.05   | 11.5    | 0.008  |
| 21         | 1.5          | 12.5  | 4        | 2.0    | 4.5      | 2.0    | 4.5     | 2.0    |
| 22         | 5            | 2.0   | 4.5      | 2.0    | 4.0      | 2.0    | 4.5     | 2.0    |
| 23         | 10.5         | 0.05  | 6        | 0.32   | 8.5      | 0.05   | 9.5     | 0.05   |
| 24         | 2            | 12.5  | 6.5      | 0.05   | ---      | ---    | 4       | 0.05   |
| 25         | 7            | 0.32  | ---      | ---    | 7.5      | 0.008  | 11      | 0.05   |

0.32, 0.051, 0.0082, 0.0013 % w/v). 15  $\mu$ l of the nickel solutions were micropipetted on to filter paper discs of small Finn Chambers ( $\varnothing$  8 mm) on Scanpor and applied for 2 days. When reading was performed 1 day later, the patients were covered with a cloth just exposing the back. The patients were told not to communicate with the reader, who did not know the patients, the individual localizations of various provocation areas or to which eczema group (with pompholyx or without hand eczema at all) they belonged. The reactions were scored according to ICDRG criteria, with 2 classifications added between the 3 usual positive gradings: strong + and ++ reactions were graded as + (+) and ++ (+), respectively.

#### Statistical calculations

To enable statistically-based calculations, the scores were transformed to numerical values:  $- = 0$ ,  $(+) = 0.5$ ,  $++ = 1$ ,  $++(+) = 1.5$ ,  $+++ = 2$ ,  $+++ (+) = 2.5$ ,  $++++ = 3$ . Based on these numerical scores, the challenge patch test reactivity was calculated in 2 ways: (i) the scores for all reactions representing 1 area were summed (summarized test scores = STS) and for the same area, (ii), the minimal eliciting concentration (MEC) (3), which was defined as the lowest concentration eliciting at least a + reaction, was registered. The positive test reactions were not al-

ways continuous. When the number of negative and/or doubtful reactions were followed by the same number or more of positive reactions, the lowest positive concentration was registered as the MEC. In all other situations, the concentration above the 1st negative or doubtful reaction was registered as the MEC. For example, a patient could have positive reactions to 12.5, 2.0 and then 0.051%, meaning that 0.32% was negative or doubtful; in this case 0.05 % was registered as the MEC.

To compare reactivity response (STS as well as MEC) on the 4 challenge sites, the Page test (4) was used. The a priori natural way to order the challenge sites was: "never eczema", "8 months", "4 months", and "1 month". Moreover, pair-wise comparisons for "never eczema" versus "8 months", "8 months" versus "4 months", and "4 months" versus "1 month", were performed using the one-side Wilcoxon signed-rank test; the *p*-values were corrected for multiple comparisons according to the Bonferroni method. Exact calculations of *p*-values were performed using the statistical software StatXact 3 (CYTEL Software Comparison, Cambridge, MA, USA).

#### Results

We did not find any significant difference in challenge patch test reactivity between the 2 groups of

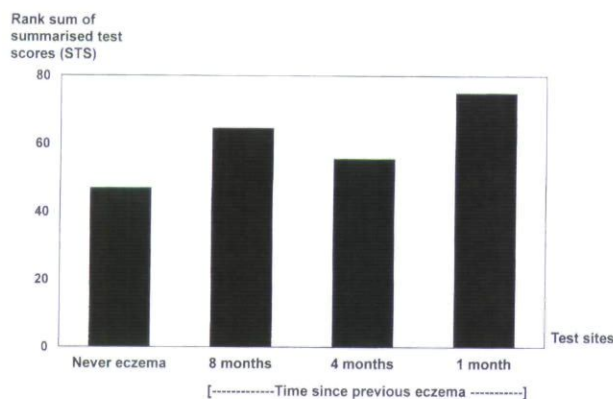


Fig. 3. Rank sum of summarised test scores (STS) for the nickel reactions on 4 test sites of the lower back.

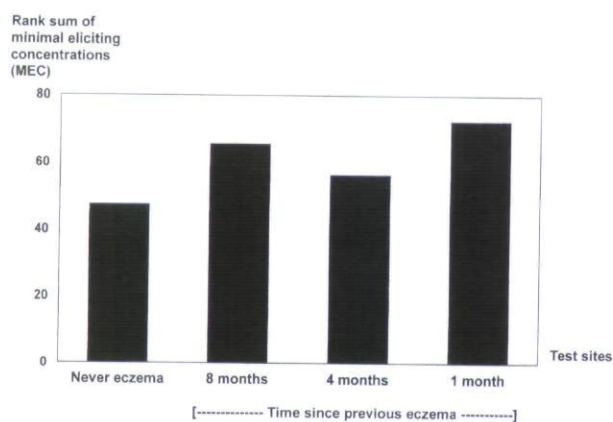


Fig. 4. Rank sum of minimal eliciting concentrations (MEC) for the nickel reactions on 4 test sites of the lower back.

patients (one with pompholyx, and the other without hand eczema at all), when comparing the STS and the MEC. Therefore, in the following, the results are presented for the total material of 25 patients.

In Table 1, the individual STS and MEC are given for the 4 challenge sites. The results of the STS and the MEC at the 4 challenge test sites are listed in Fig. 3 and 4, respectively. Statistical test results and  $p$ -values for Page test and pair-wise comparisons between the different test sites are illustrated in Table 2. With the Page test, a statistically significant tendency was found for both STS and MEC ( $p=0.009$  for STS and  $p=0.006$  for MEC), demonstrating a higher test reactivity at areas with previous allergic contact dermatitis; the shorter the time interval between the previous provocation and the challenge, the stronger the reaction. For the pair-wise comparisons of STS, significant differences were obtained for control skin versus the areas where an eczema had been located most remotely ( $p=0.03$ ), and between the 4-month-old and 1-month-old eczema sites ( $p=0.04$ ).

Table 2. Statistical test results- $p$ -values

| Response | Page test | Pair-wise comparisons*        |                           |                          |
|----------|-----------|-------------------------------|---------------------------|--------------------------|
|          |           | Never eczema* versus 8 months | 8 months* versus 4 months | 4 months* versus 1 month |
| STS      | 0.009     | 0.03                          | 0.5                       | 0.04                     |
| MEC      | 0.006     | 0.03                          | 0.3                       | 0.12                     |

\* One-sided Wilcoxon signed-rank test;  $p$ -values corrected for multiple comparisons according to the Bonferroni method.

The corresponding comparisons for MEC yielded a significant difference only for the control skin versus the area where an eczema had been located most recently ( $p=0.03$ ).

## Discussion

In this study, we have investigated the significance of a previous allergic contact dermatitis for the provocation of a dermatitis on topical re-exposure to the sensitizer, also with regard to the time interval between the 4 occasions. We have chosen nickel as the allergen, because the hypersensitivity as such is very common (5), as is the combination with hand eczema (6).

Especially chronic hand eczema of the pompholyx type is associated with nickel hypersensitivity (6). Therefore, we chose one group of patients with pompholyx and one without. Patients with atopy were excluded because the atopic state could interfere with the results due to compromised barrier function (7). We have dedicated much work to providing a test system producing an experimental allergic contact dermatitis with as homogeneous eczema as possible and with the intended intensity, to be able to compare the different test occasions with regard to the time interval only. Since there is a wide intra-individual variation in patch test reactivity to nickel from one test occasion to another, as recently described by us (8), we have, before each occasion with an experimentally provoked allergic contact dermatitis, patch tested each patient to assess the present degree of reactivity. Furthermore, in this study, an intra-individual reactivity variation up to 100  $\times$ , without any tendency for increasing or decreasing reactivity with time between the 3 test occasions, was demonstrated. We have divided the test area on the lower back into 4 symmetrical parts and made the experimental provocation of allergic contact dermatitis in a randomized order, to avoid any undesired influence of the anatomical site on the test result as earlier described (9), as well as to enable blind reading. The test area was chosen as it is an un-

usual location for nickel dermatitis and an area not used for patch testing.

Based on the STS as well as the MEC, as in the present study, a correlation between retest reactivity and time was observed. The site with the most recent allergic contact dermatitis resulted in the highest degree of reactivity, while the lowest reactivity was noted for the control area where there had never been an allergic contact dermatitis. The same relation of the increased retest reaction at earlier eczema sites is pointed out in an earlier publication in nickel-hypersensitive individuals (10). In guinea pigs, increased allergic retest reaction is noticed up to at least 5 weeks after both allergic and irritant inflammation (11).

The intra-individual variation in test reactivity means that the same intra-individual variation exists for the number of molecules required to elicit an experimental contact dermatitis of equivalent intensity. Theoretically, variation in residual nickel in the skin may also be a factor of significance for the final challenge. However, a statistically based calculation did not show any relationship between the final reactivity and the number of molecules required for the experimental contact dermatitis.

There are 2 other major possible explanations for the increased retest reactivity. Increased penetration of the allergen due to damage of the barrier function in areas of earlier eczema is one explanation. Such a mechanism is reported by Allenby & Basketter (3) regarding inflammation induced by irritants. Whether such a phenomenon exists in the present material regarding clinically-healed contact allergic reactions is not known. Anyway, it is unlikely that the barrier will not be restored within 8 months. Therefore, the increased test reactivity at the 8-month-old earlier eczema site speaks more in favour of the other major explanation, implying the preservation of a specific memory function in the skin facilitating the elicitation of allergic contact dermatitis on re-exposure to the sensitizer. Furthermore, the results of some other studies also speak in favour of this explanation.

Oral challenge with 1–5 mg nickel often results in flare-up reaction of previous eczema (12,13,14). This flare-up reaction is allergen specific (15) and, as recently pointed out, the intensity of the flare-up reaction is related to the time interval between previous eczema and oral challenge (16). Thus, the shorter the time between previous eczema and re-exposure, topically or orally, the stronger the reactions for both retest and flare-up reactions. Still, clinical experience shows that this increased reactivity may exist for several months or years in certain individuals (12).

Flare-up reaction and increased retest reactivity

to oral (17) and topical challenge (18), respectively, also exist in another type of specific allergic reaction, the fixed drug eruption. In this type of reaction we have described the presence of cytotoxic-suppressor T-cells along and above the basement membrane in healed lesions 3 weeks after challenge (17). However, this pattern is not observed in "healed" allergic eczema sites (unpublished data), so the true nature of the memory function in this condition still has to be defined.

In conclusion, we have found a stronger allergic contact dermatitis reaction in areas where there has been an allergic contact dermatitis before; furthermore, the shorter the time interval between the previous provocation and the challenge, the stronger the reaction. These observations may be of importance for the understanding of factors and events which ultimately may result in chronicity of an allergic contact dermatitis from nickel, or any other sensitizer, and also of importance for the clinical management of a patient with allergic contact dermatitis, with respect to the time required to eliminate or reduce allergen exposure to avoid a vicious circle leading to chronicity of the eczema. At the same time, the present study underlines the importance of early diagnosis by patch testing, so that the patient, when suffering from an allergic contact dermatitis, can be informed as early as possible as to how to avoid or reduce exposure to the antigen in question, as well as to cross-reacting substances.

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