

Course of contact allergy in consecutive eczema patients patch tested with TRUE Test™ panels 1 and 2 at least twice over a 12-year period

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Non-reproducibility of positive patch test reactions is common. In this retrospective study, we investigated the reproducibility of previously positive patch test reactions and the appearance of new positive reactions in a consecutive series of 264 eczema patients tested at least twice over a 12-year period using the TRUE Test™ standardized patch test system. Out of 297 positive reactions, 66% remained positive in a 2nd test, 10% were scored as doubtful and 24% as negative. Among the previously recorded doubtful reactions, 13% were positive in the 2nd test, 13% were again doubtful and 74% negative. In relation to the degree of patch test reactivity, 48% of the + reactions were reproducible, compared to 87% of ++ and +++ reactions. No difference in reproducibility was observed between patients tested with a short or a long-time interval between tests. With the use of the TRUE Test™ panels 1 and 2, methodological factors are minimized. The variation in patch test positivity may then be attributed to biological variation, which depends on several individual factors such as patch test reading, patient-related factors such as changed immunological sensitivity, regional variation of the skin on the back and the presence of more or less active dermatitis.

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The course of contact allergy over time is not well elucidated. Generally, contact allergies are often considered to be lifelong, but the loss of positive patch test reactions is not uncommon. Retrospective studies of the reproducibility of positive patch test reactions include a follow-up study by Nielsen et al. (1), where 365 subjects were re-patch tested with the TRUE Test™ (ALK-Abello A/S, Hørsholm, Denmark) after 8 years. Among 52, who previously had 1 or more positive patch test reactions, 37 (71%) still had 1 or more positive reactions at retest. Similar results was reported from Belgium, where 50 patch test-positive patients were retested after 3–25 months and the number of positive reactions decreased by 37%, giving a reproducibility of positive reactions of 63% (2). The patch test technique used was not specified. In another retrospective study by Keczek et al. (3), including 100 patients who were retested with the Al-Test™ (Imeco,

Södertälje, Sweden), 95 of 161 (59%) positive patch test reactions recurred and 44 (27%) showed a diminished reactivity after 10 years.

Variation in patch test reactivity is caused by methodological error as well as individual variation. The performance of diagnostic patch testing has been examined in experiments where duplicates of allergens have been applied symmetrically to the left and right sides of the backs of consecutive patients, and a test reaction positive only on 1 side was regarded as non-reproducible. Varying reproducibility of positive reactions has been reported for different patch test systems: the TRUE Test™ system gave a reproducibility of positives of 95% (413/435) and 82% (23/28) (4, 5), and the Epiguick™ system (Hermal, Reinbek, Germany) gave a similar high reproducibility of 96% (67/70) (6), while the manually filled Finn Chamber™ system (Epitest Ltd, Oy, Tuusula, Finland) gave a reproducibility of 56% (18/32), 62% (36/58) and 91% (76/84) in 3 investigations (5, 7, 8).

Some patients with recurrent or persistent dermatitis are patch tested several times over the

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years due to new suspicion of an eliciting allergenic factor in the environment, changed clinical characteristics of the dermatitis, poor effect of treatment and advice, and sometimes in order to verify an occupational allergy.

We analysed the reproducibility and development of new positive patch tests among patients tested twice or more between 1991 and 2002 at the Department of Dermatology, Odense University Hospital. This is the period of our use of the standardized TRUE TestTM panels 1 and 2.

Patients and Methods

264 consecutive patients have been tested with the TRUE TestTM at least twice between 1991 and 2002 and had a minimum of 1 positive patch test reaction (+). The total number of tests performed in this period was 6140. The time that had passed between the 2 tests spanned from 2 months to 10 years. If patients had been tested more than twice, only results from the 2 latest testing sessions were included. As a routine test procedure, test reactions were scored twice, on D3 and D5–7, by a trained nurse, and the test reactions were subsequently evaluated by the dermatologist at the last reading.

Results

As a routine procedure in our department, allergens causing ++ or +++ reactions in a patient are often removed from the test panel, when retesting is indicated to avoid strong patch test reactions to previously well-documented contact allergens. This applied to 50 of 297 positive reactions. It is reasonable to assume that these allergens would have caused positive responses in the 2nd test if included, and therefore, when an allergen has been removed from the 2nd test panel, a positive reaction has been anticipated for this allergen. Making this assumption, 196 or 66% of the 297 reactions that were positive in the 1st test also showed a positive reaction in the 2nd test. Consequently, 101 or 34% of the reactions were doubtful (31 reactions) or negative (70 reactions) at the 2nd testing session. The reproducibility of individual allergens was analysed and is shown in Table 1. Among the allergens with 10 or more positive reactions, thiuram mix, chloromethylisothiazolinone/methylisothiazolinone and colophonium were the most reproducible (84%, 75% and 75%), while more reactions to quaternium-15, formaldehyde and fragrance mix disappeared (reproducibilities of 60%, 55% and 62%). For some allergens, there was a tendency for positive reactions to be lost at

retests performed after only 2–3 years. For instance, 4/6 positive reactions to neomycin and 5/11 reactions to formaldehyde disappeared in patients who were tested after less than 2½ years. The same was seen for 6/17 reactions to potassium dichromate and 4/10 reactions to quaternium-15.

It was also analysed whether recurrence of the positive patch tests was related to the time period that had passed between tests. The patients were divided into groups according to the number of years that had passed between tests, and the reproducibility of positive reactions was found for each group (Fig. 1). Only small differences were observed in the reproducibility irrespective of the number of years having passed between tests.

Besides disappearance of some positive reactions, new allergies were also found during a later test session. A total of 117 previously negative patch tests, and 31 of previously doubtful reactions, were positive at the later test session. Most new positive reactions were recorded for carba mix (16 new positives), colophonium (15 new positives) and potassium dichromate (13 new positives). These reactions could either be explained by newly acquired allergies, false-positive reactions or to false-negative reactions in the 1st test.

Looking at reactions that were scored as doubtful in the 1st test, 13% were scored as positive in the 2nd test, 13% were again scored as doubtful and 74% as negative (Fig. 2). Of reactions that were scored + in the 1st test, about half (52%) were negative or doubtful on retesting, while only 13% of ++ or +++ reactions were negative or doubtful on retesting.

The pattern of reproducibility varied with the season of the year. We compared the 65 patients patch tested the 1st time in the warm months (April to September) and retested in the cold months (October to March), with the 64 patients patch tested in the opposite sequence. Doubtful reactions were considered negative in this analysis. The patients who were tested 1st in the summer had 0.66 new positives and 0.44 lost positives per patient, while the patients who were tested 1st in the winter had 0.56 new positives and 0.66 lost positives per patient (Fig. 3).

Discussion

When re-patch testing eczema patients, a multitude of factors may influence the outcome. Testing the patient within a period of more or less active dermatitis and individual variation in reactivity due, for instance, to UV irradiation

Table 1. The number of positive reactions in the 1st and 2nd testing sessions and the number of positive reactions reproduced for individual allergens of the TRUE Test™ system. The table also lists the number of positive reactions that newly occurred or were lost in the 2nd test

	Positives in 1st test	Reproduced positives [n (%)]	Positives in 2nd test	Lost positives	New positives
Nickel sulphate	56	37 (66)	48	19	11
Lanolin alcohol	7	2 (29)	5	5	3
Neomycin sulphate	6	2 (33)	10	4	8
Potassium dichromate	17	11 (65)	24	6	13
Caine mix	2	0 (0)	3	2	3
Fragrance mix	21	13 (62)	22	8	9
Colophonium	24	18 (75)	33	6	15
Epoxy resin	6	5 (83)	9	1	4
Quinoline mix	7	5 (71)	9	2	4
Myroxylon pereirae resin (balsam of Peru)	6	5 (83)	7	1	2
Ethylenediamine dihydrochloride	4	3 (75)	3	1	0
Cobalt dichloride	14	9 (64)	16	5	7
<i>p</i> -tert-Butylphenol-formaldehyde resin	3	2 (67)	8	1	6
Paraben mix	4	2 (50)	3	2	1
Carba mix	22	14 (64)	30	8	16
Black rubber mix	5	4 (80)	6	1	2
Cl + Me-Isothiazolinone	20	15 (75)	22	5	7
Quaternium-15	10	6 (60)	10	4	4
Mercaptobenzothiazole	2	1 (50)	2	1	1
<i>p</i> -Phenylenediamine	8	5 (63)	9	3	4
Formaldehyde	11	6 (55)	13	5	7
Mercapto mix	4	3 (75)	5	1	2
Thimerosal	19	12 (63)	20	7	8
Thiuram mix	19	16 (84)	27	3	11
Total	297	196 (66)	344	101	148

and hormonal influence may affect the results, together with methodological variation, difference between observers and seasonal variation. The use of the pharmaceutically standardized TRUE Test™ minimizes the methodological variation. The TRUE Test™ has shown a discordance of 5% and 18% in 2 previous right – left comparison studies (4, 5). This variation in results from simultaneous testing on both sides of the back has to be compared with the discordance found in this retrospective study showing a reproducibility of 66% of positive reactions.

It is important to remember that a positive patch test reaction is not automatically an indication of a related clinical problem. Diagnosis of allergic contact dermatitis using patch testing is not only a matter of identifying the positive reactions. The determination of relevance of positive reactions requires knowledge of the patient's history and the clinical picture. This study investigated patch test reactions only, without taking into consideration the relevance of such positive reactions.

Active sensitization from patch testing is a known, although minimal, risk. The risk is

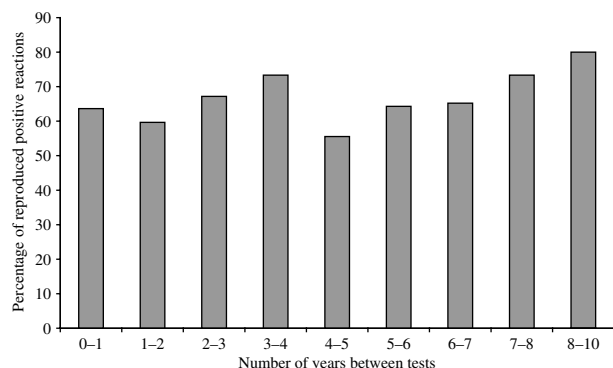


Fig. 1. The percentages of reproducible positive patch test reactions with the TRUE Test™ system. The graph shows the recurrence distributed according to the number of years having passed between tests.

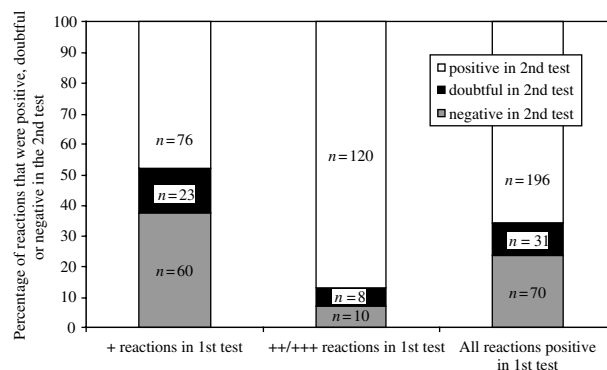


Fig. 2. Distribution of patch test results in the 2nd test of reactions that in the 1st test were + or ++/+++ reactions, respectively.

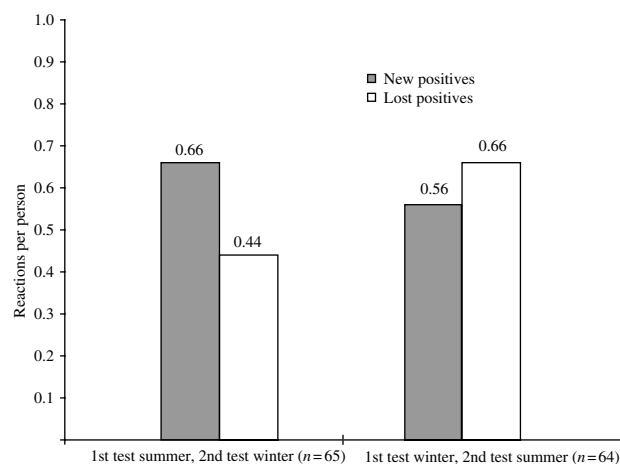


Fig. 3. New and lost positive reactions in patients tested and retested in opposite seasons.

particularly minimal with standard series allergens and is easily outweighed by the benefit of diagnosing relevant contact allergies, and furthermore they seldom cause disease (9). Our data show no tendency towards suspicion of patch test sensitization from any of the TRUE TestTM allergens.

Contact allergy is generally considered to be a long-lasting, often lifelong phenomenon, but immunological reactivity may diminish and patch test reactions may become negative. Avoidance of allergens is believed to diminish the sensitivity, but this is difficult to ascertain as most allergens are difficult to avoid completely. Studies with careful allergen avoidance have shown a loss of positive reactions of 25%, 26% and 29% (10, 11), but it is not possible to determine whether this decrease is caused by allergen avoidance or by other factors.

Reported reproducibility of positive patch tests for individual allergens are few and vary considerably. The studies are difficult to compare because of different study conditions such as patch test method, allergen concentration, size and characteristics of the study population such as initial sensitivity and environmental exposure to allergens. Nickel reproducibility has in later publications been reported to be 87% (87/100) (12), 79% (19/24) (10) and 68% (39/57) (13), and Memon and Friedmann (14) found duplicate dose – response curves, performed with serial dilutions of nickel, highly reproducible. In this study, we found a rather low reproducibility of 66% (37/56) for nickel sulphate. Considerable individual variations in patch test reactivity to nickel have been demonstrated (15), with individual differences in nickel sensitivity of up to 250 times. Individual fluctuation in sensitivity may be an important contributor to the loss of patch test reactions.

It might be reasoned that the more time passed between tests the greater the possibility of a negative reaction at retest, because of avoidance of contact with allergens or less-active dermatitis. However, this was not observed in our study. There was no difference in the reproducibility of positive reactions whether 1 or 8–10 years had passed between tests. Some allergens (neomycin, formaldehyde, potassium dichromate and quaternium-15) had already after 2–3 years lost several positive reactions, and patch test reactions scored as + were less reproducible compared to the stronger reactions. This is probably in part because of previous false-positive reactions, but may also be due to diminished reactivity. It has been documented that a lower sensitivity requires stronger exposure to elicit an inflammatory reaction (16), indicating that weak allergies are less easily maintained. The majority of doubtful reactions were not reproduced for the same reasons. Doubtful reactions are probably often false-positive irritant reactions, but may also be weak allergic reactions.

It is well known that the skin is more sensitive in the winter than in the summer, because of the cold and dry air and the lack of UV irradiation. As expected, most lost positive reactions were found in the group of patients who had been tested 1st in the cold season and then retested in the warm season. When retested in the summer, the skin was possibly less sensitive and fewer positive reactions appeared. The number of new positive reactions per patient was also, as expected, higher in the group tested 1st in the warm season and retested in the cold months, but this difference was small.

We found an increase in the number of new positive reactions compared to lost positives (Fig. 4). A probable explanation is that the population analysed in this study is selected. Patients tested twice are often individuals with multiple allergies and ongoing dermatitis problems, and it seems likely that the frequency of new positives is high in this group of patients, as they often are more susceptible to sensitization and develop new allergies more easily (17). We examined whether this was also the case within our study population. We selected the patients with at least 3 positive reactions either in the 1st or in the 2nd testing session ($n = 54$) and counted the number of new and lost positive reactions in this group. The number of new positives was 1.4 per patient and the number of lost positives was 0.87. In the remaining 210 patients, who consequently had 2 or fewer positive reactions in either testing session, the number of new reactions per patient was 0.34 and the number of lost positives was

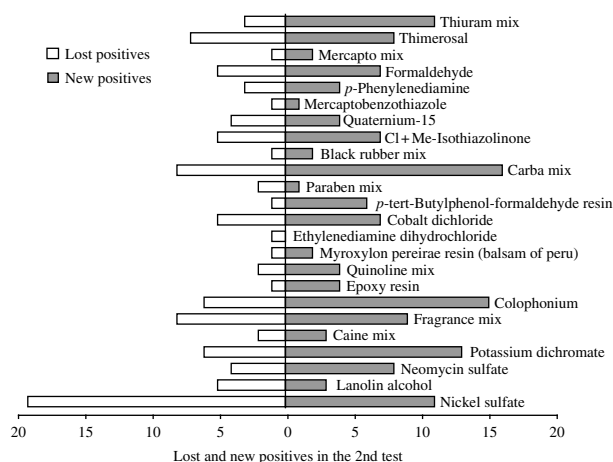


Fig. 4. The number of new positives (grey) compared to lost positives (white) in the 2nd test.

0.26 (Fig. 5). We see that the number of new positives is high in the 1st group compared to patients with 1 or 2 positives. The number of lost positives is also high, as would be expected since more positive reactions exist that may disappear in patients with multiple positives.

However, the many lost and new positive reactions may also be a reflection of the fact that this group of patients have extraordinarily sensitive, labile skin that gives significant fluctuations in patch test results, and therefore many new and lost positive reactions when retested.

Our knowledge is still inadequate regarding what explains the disappearance of some allergies and development of new ones. The question of relevance of positive patch test reactions, allergen

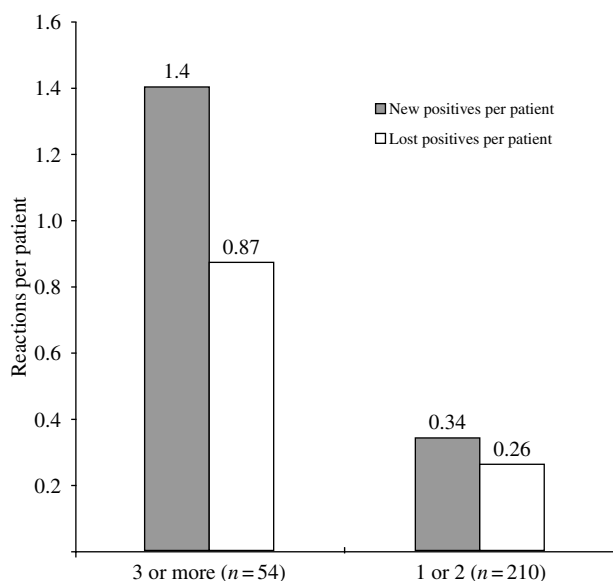


Fig. 5. New and lost positive reactions in patients with either 3 or more or less than 3 positive reactions in either test.

exposure, clinical picture and the possibility of allergen avoidance may all contribute to such variation. Diagnostic patch testing is never the final answer, but a very useful tool in the clinical evaluation of a suspected case of contact dermatitis.

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