

# Longitudinal variability of skin prick test results

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## Summary

The skin prick test (SPT) is a commonly used procedure for assessing a specific sensitization. The longitudinal variability of test results is of interest for clinical as well as epidemiological investigations. The sensitization to four common aeroallergens (grass pollen, birch pollen, *Dermatophagoides pteronyssinus*, cat dander) is investigated within the framework of three consecutive SPTs at 11-month intervals for a population of 587 schoolchildren. The prevalence of sensitization based on a weal diameter of at least 2 mm was between 12.9% (cat dander) and 23.9% (grass pollen) in the initial testing. The positive predictive values of the initial SPT were between 75.3% (birch pollen) and 88.2% (cat dander) for the two subsequent SPTs. In the case of initially negative tests with positive second and third SPTs the incidence ranged between 3.2% (cat dander) and 4.3% (birch pollen) per year. A clear increase in the intensity of reaction in subsequent tests was observed in a number of probands testing positively in the initial SPT. In conclusion, our data indicate a high long-term stability of a specific sensitization to aeroallergens in SPT.

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## Introduction

The skin prick test (SPT) with allergens is a common instrument for the assessment of specific sensitization. The SPT is supplemented in a clinical setting by a spectrum of additional information. Its clinical relevance with regard to allergic symptoms has been documented [1–3]. In epidemiological studies, the SPT generally serves as a screening method for large populations [1–3]. Sensitization in SPT can be interpreted as the correlate of a disease. Furthermore, it can also be a precursor of symptoms [4–6], or can persist without clinical relevance in the future. Finally, a positive test result may occur due to an error in measurement. A SPT reaction is considered positive if the weal is  $\geq 3$  mm in diameter [7]. However, in some studies a cut off limit of  $\geq 2$  mm in diameter has been used [8,9]. The use of SPT presupposes sufficient reproducibility. Short-term reproducibility has been adequately investigated [10–12]. Only little information is available concerning the longitudinal variability of SPT results within epidemiologic populations [13–15]. Using

SPT data on four important aeroallergens obtained from a longitudinal study over 2.5 years, we evaluated the long-term reproducibility of SPT with regard to the following aspects:

- 1 What is the predictive value of a single testing for two subsequent SPTs (stability of initially negative and positive tests)?
- 2 What increase of reaction intensity is to be expected for initially positive SPT in follow-up tests?

## Materials and methods

### Population

A population of 704 schoolchildren from the area of Freiburg city and one community in the Black Forest was randomly selected in October 1987 and examined from November 1987 to June 1988 and again in 1989 (mean interval 10.6 months, standard deviation [s.d.] 1.1 months) and 1990 (mean interval 11.0 months, s.d. 0.9 months). During the first phase of the investigation, 704 schoolchildren aged 7–16 years took part. In the second examination 88.5% of the study group participated again

( $n=623$ ), and 83.4% could be re-examined in 1990 ( $n=587$ ). To ascertain the initial medical history regarding bronchial asthma ('for your child/your husband/you has a doctor ever diagnosed asthma?') and hay fever ('for your child/your husband/you has a doctor ever diagnosed hay fever?') a standardized face-to-face interview was carried out with the child's mother. In addition to the sample of 704 children, information was gathered by a telephone interview from a non-selected sample of children not participating in the study ( $n=381$ ). Of these non-responders in 1988, the parents answered positively for asthma in the child in 3.9% and for hay fever in 13.1%. Further information about the initial population and about the clinical relevance of SPT-reactions in this population is provided in other publications [16,17]. The analysis is based on data of the longitudinal observation with three SPTs ( $n=587$ ).

#### *SPT procedure*

Four purified and immunochemically characterized aeroallergens (ALK, Denmark) were applied to the probands forearm (distance between allergens about 30 mm) in a standardized order with the aid of an uncoated Phazet needle. The reactions were recorded after 15 min [18]. The largest and the orthogonal diameter of a weal was measured by means of a transparent ruler and the arithmetic mean calculated. A reaction to the negative control was subtracted from the allergen value beforehand. Extracts from grass pollens (mixture of the six most common species), birch pollens, *D. pteronyssinus* and cat dander were used (concentration: 10 Histamine Equivalent in Prick testing). As control solutions histamine hydrochloride (10 mg/ml) and sodium chloride (9 g/l) were applied. The tests were carried out by the same two nurses during the whole study under supervision of a physician. Children with current anti-allergic medication were tested. The influence of a medical treatment on the SPT reactivity was not strong, because no child was found to have a weal to histamine smaller than 2 mm. An intra-individual influence of the pollen seasons was restricted by testing each child at a time, comparable to the previous test.

#### *Statistical analysis*

The assessment of variability of the SPT was estimated by two means:

(1) Predictive values are estimated comparing the result of the first measurement with the results of two subsequent SPTs for the total sample [19]. For four aeroallergens two cut off limits for a positive test were assessed both:  $\geq 2$  mm and  $\geq 3$  mm. The positive predictive value (p.p.v.) for

one subsequent year (for two subsequent years, respectively) provides information on how stable a single positive classification of a SPT would be over one year (two years, respectively). The negative predictive value (n.p.v.) assesses the stability of a negative finding in one single measurement throughout the following year(s).

(2) To detect an augmentation (increase) in those reactions with an initial weal diameter of 2 mm and more, which are classified as positive findings, in the subsequent years another concept was applied: the intra-individual variation is assessed for five disjunctive groups with different sizes of the mean of the three intra-individual weal diameters ( $< 3$  mm,  $\geq 3$  mm,  $\geq 4$  mm,  $\geq 5$  mm,  $\geq 6$  mm) by the s.d. of the weal diameters across three tests. However, assuming that the s.d.'s are not normally distributed, a cut off limit of two times the arithmetic averages of the group-specific intra-individual s.d. would be inappropriate to assess an increase. This is the reason why the 90th percentile of the intra-individual s.d. was used to classify weal diameter being increased in subsequent measurements after an initial positive finding.

Regarding incidence, two estimations are provided. The cumulative incidence is the crude proportion of new cases in the observation period (number of positives in 1989 or 1990/number of negatives in 1988). The 'certain' incidence is the yearly proportion of new cases in the second test which could be confirmed in the third investigation (number of positives in 1989 and 1990/number of negatives in 1988).

#### **Results**

During the course of the study, a loss of follow-up of 16.6% took place from 1988 to 1990 ( $n=704$  to  $n=587$ ). In 1988 5.1% of the children had a doctor's diagnosed asthma, in the year 1990 the proportion was 5.3%. The proportions in the year 1988 and 1990 for doctor's diagnosed hay fever are 11.5% and 11.9%. For a parental history of hay fever or asthma the respective proportions are 31.3% and 31.7%. Thus, the loss of follow-up did not change the composition of the sample.

In the initial testing 26 of the 31 cases with asthma (83.9%) were sensitized to at least one of the four aeroallergens compared to 16.1% of those without a doctor's diagnosis. Regarding hay fever, 58 of 70 cases (82.9%) and 15.9% of the children without the diagnosis were reactive to grass pollens. In children with a parental history of hay fever or asthma ( $n=186$ ) and in those without family history ( $n=400$ ), a sensitization to at least one of the four allergens was found in 45.7% and 29.8%, respectively. Table 1 presents the composition of the total sample according to age (mean age 11 years, s.d. 2.3 years) and sex (ratio of 1:1), as well as the corresponding

**Table 1.** Sample size, gender, age and prevalences of positive SPT (weal diameter  $\geq 2$  mm) in three consecutive years

| Allergen | Sex<br>% male | Age<br>in 1988<br>$\bar{x}/s.d.$ | Prevalence (1988)<br>( $n=587$ : 100%) |      | Prevalence (1989)<br>( $n=587$ : 100%) |      | Prevalence (1990)<br>( $n=587$ : 100%) |      |
|----------|---------------|----------------------------------|----------------------------------------|------|----------------------------------------|------|----------------------------------------|------|
|          |               |                                  | $n$                                    | %    | $n$                                    | %    | $n$                                    | %    |
| Grass    | 55.7          | 11.3/2.1                         | 140                                    | 23.9 | 146                                    | 24.9 | 153                                    | 26.1 |
| Birch    | 55.6          | 11.4/2.3                         | 81                                     | 13.8 | 92                                     | 15.7 | 116                                    | 19.8 |
| Mite     | 57.6          | 11.0/2.2                         | 92                                     | 15.7 | 117                                    | 19.9 | 121                                    | 20.6 |
| Cat      | 51.3          | 11.0/2.0                         | 76                                     | 12.9 | 93                                     | 15.8 | 97                                     | 16.5 |
| Total    | 49.9          | 10.9/2.3                         | —                                      | —    | —                                      | —    | —                                      | —    |

information on the subgroups which were defined as sensitized in 1988. In Table 1, an increase in prevalence is recognizable for each of the four allergens. The prevalence of sensitization to grass pollen, for example, rose from 23.9% in 1988 to 26.1% in 1990. Comparing the reaction to histamine hydrochloride (not normal distributed) in the three consecutive measurements, no change in median (4 mm) neither in 5%- and 95%-percentiles (3 mm and 6 mm, respectively) occurred. Table 2 presents the incidences and predictive values (with cut off limits of  $\geq 2$  mm and greater or equal to 3 mm, respectively) for the four allergens. For the period from the first to the third testing a cumulative incidence of 8.5% for 7–11 year olds, and of 5.9% for 12–16 year-olds is shown for grass pollen. The highest cumulative incidence of 11.0% and 12.2%, respectively, for both groups was found for *D. pteronyssinus* over a period of about 2 years (Table 2). Starting with the initial test results (1988), a calculation of the predictive values of this testing for the following 2 years generally revealed positive (p.p.v.) and negative (n.p.v.) predictive values between 80 and 90%. The high p.p.v.'s signify that approximately 80–90% of the prevalent cases categorized as being reactive in the following tests. The

same applies for the n.p.v., that is, SPT results where no initial skin reaction had taken place.

Being categorized with 2 mm versus 3 mm as the cut off limit, the p.p.v.'s did not differ systematically; the corresponding n.p.v.'s for 2 mm and 3 mm were close together. Of the four allergens, birch pollen was the only allergen with a p.p.v. below the average of the others. Figure 1 illustrates the intra-individual consistency over the period of observation based on the result of the first test. A negative test in 1988 followed by agreeing positive results in 1989 as well as 1990 is assumed to represent the 'certain' incidence. The incidence in this respect (1988 compared to 1989 and 1990) ranged from about 3.2% (cat dander; 3.5%/11 months) to 4.3% (birch pollen; 4.7%/11 months) per year (Fig. 1;  $< 2$  mm in 1988 and inconsistent in 1989 and 1990). Conversely, two agreeing negative results are shown to present the disappearance of a previously observed positive test result. When the test reaction to an allergen changed twice, it was indicated in Fig. 1 as an inconsistency exclusively in the second test (1989). For the grass, mite and cat dander allergens (Fig. 1), it can be seen that a single positive result in the initial test revealed a high repeatability in further tests. This applies for weal

**Table 2.** Cumulative incidences (weal  $\geq 2$  mm) over about 2 years (positive in 1989 or 1990/negative in 1988 100) by age and predictive values of the SPT in 1988 for two subsequent SPTs (weal diameters  $\geq 2$  mm respectively  $\geq 3$  mm in each test)

| Allergen | Cumulative incidence<br>%/negative (1988) |                    | Positive predictive<br>value for 1989/%<br>Weal diameter |             | Negative predictive<br>value for 1989/%<br>Weal diameter |             | Positive predictive<br>value for 1989 & 1990/%<br>Weal diameter |             | Negative predictive<br>value for 1989 & 1990/%<br>Weal diameter |             |
|----------|-------------------------------------------|--------------------|----------------------------------------------------------|-------------|----------------------------------------------------------|-------------|-----------------------------------------------------------------|-------------|-----------------------------------------------------------------|-------------|
|          | Age 7–11<br>years                         | Age 12–16<br>years | $\geq 2$ mm                                              | $\geq 3$ mm | $\geq 2$ mm                                              | $\geq 3$ mm | $\geq 2$ mm                                                     | $\geq 3$ mm | $\geq 2$ mm                                                     | $\geq 3$ mm |
|          |                                           |                    |                                                          |             |                                                          |             |                                                                 |             |                                                                 |             |
| Grass    | 8.5/276                                   | 5.9/171            | 90.7                                                     | 96.7        | 95.7                                                     | 95.1        | 87.1                                                            | 91.6        | 92.6                                                            | 93.6        |
| Birch    | 9.2/311                                   | 10.0/195           | 81.5                                                     | 79.3        | 94.9                                                     | 94.5        | 75.3                                                            | 62.1        | 90.7                                                            | 91.1        |
| Mite     | 11.0/300                                  | 12.2/195           | 90.2                                                     | 91.3        | 93.1                                                     | 94.2        | 84.8                                                            | 78.3        | 88.9                                                            | 92.3        |
| Cat      | 6.5/306                                   | 8.0/205            | 89.5                                                     | 86.8        | 95.1                                                     | 96.9        | 88.2                                                            | 80.9        | 93.0                                                            | 96.1        |

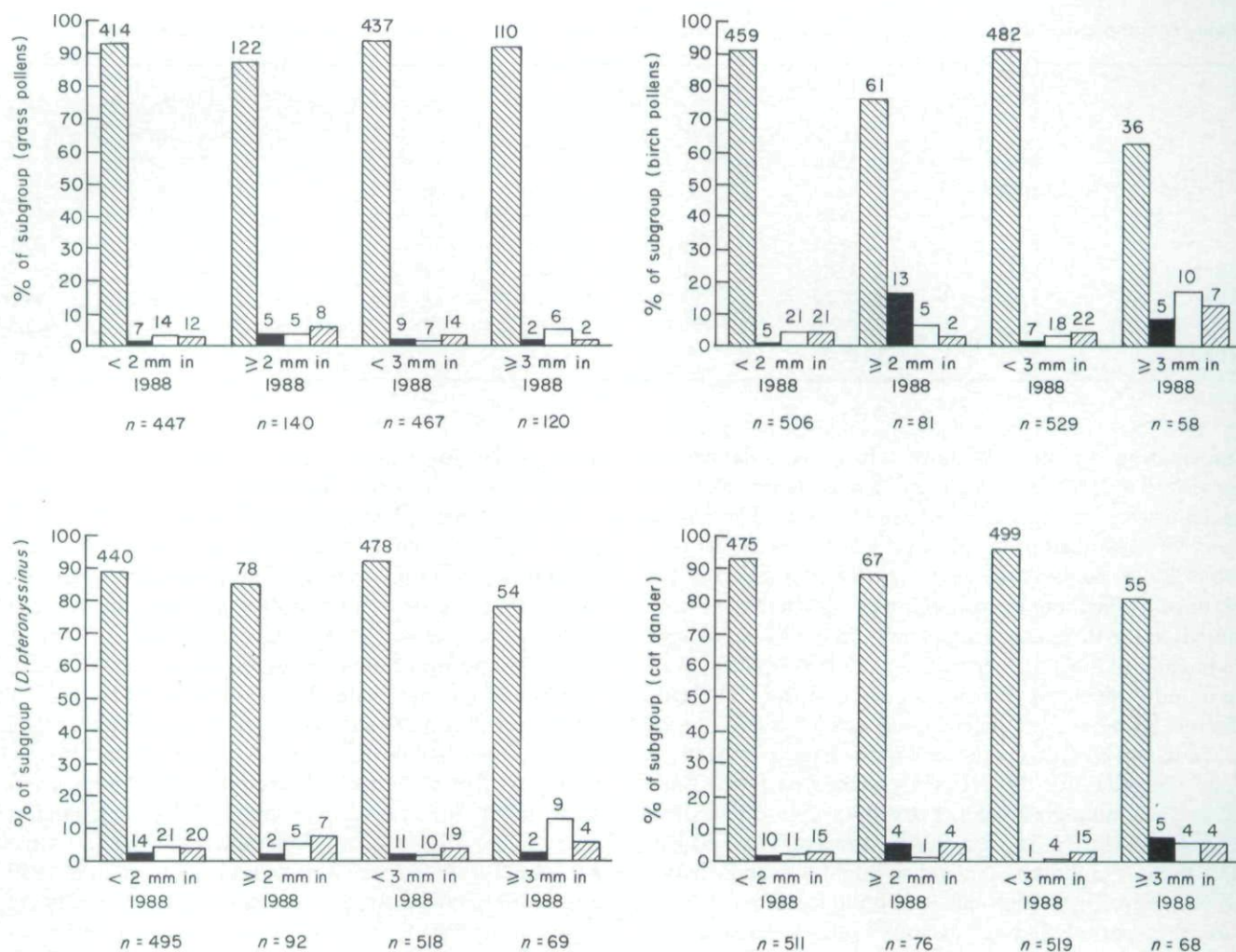


Fig. 1. Sensitization to different allergens. Predictive value of one test (in 1988) for two subsequent tests. Percentages and numbers (on top of the columns) of the sensitized and the not sensitized subgroups in 1988 (2 mm and 3 mm cut off limit, respectively). ■, 1989 & 1990 consistent. ■, 1989 inconsistent. □, 1990 inconsistent. ▨, 1989 & 1990 inconsistent.

diameters  $\geq 2$  mm and  $\geq 3$  mm. Such a degree of consistency was lacking for birch pollen (Fig. 1). Particularly for this allergen, even a 3 mm-cut off limit did not rule out that 12.1% of 58 initial positive reactions failed to indicate sensitization in the two following years. For the other aeroallergens, however, only about 5% of initial positive test reactions proved negative in the two following years. The intra-individual long-term variation of the weal diameter for the subgroup with an initial positive test is shown in the form of a standard deviation of the three measurements calculated for each child. The mean diameters of the three SPTs for each individual were assigned to one of the five size classes. Figure 2 presents the 90th percentiles of the standard deviation for the five resulting subgroups. A relative increase of the 90th percentile for weal diameters of 6 mm can be seen for grass pollen and

cat dander allergens. For house dust mite an increase of the 90th percentile is obvious for weal diameters  $\geq 5$  mm. This does not apply to birch pollen. Individual cases who exceeded the group-specific 90th percentile limit of the s.d. were classified as 'increased reaction'. By this means, following an initially positive reaction in 1988, an incidence of 'increased reactions' was observed for each group. It amounts to 19.3 for grass pollen, 18.5% for birch pollen, 19.6% for house dust mite and 9.2% for cat dander.

## Discussion

The reliability of SPT results depends on their reproducibility. A reliable inter-assay reproducibility of the SPT tested after short periods (day to day, week to week) is

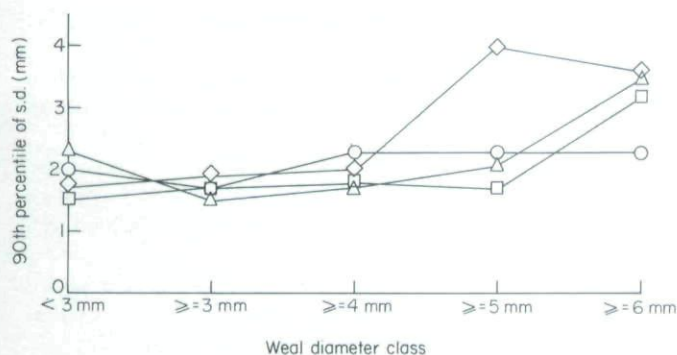


**Fig. 2.** Increase in weal size (90th percentile of the intra-individual standard deviation) dependent on crude categories of the mean weal sizes. Proband's were included if the weal diameter was  $\geq 2$  mm in the first test. Subgroups by mean weal diameter categories: grass pollens (< 3 mm:  $n=18$ ;  $\geq 3$  mm:  $n=20$ ;  $\geq 4$  mm:  $n=21$ ;  $\geq 5$  mm:  $n=39$ ;  $\geq 6$  mm:  $n=42$ ), birch pollens (< 3 mm:  $n=29$ ;  $\geq 3$  mm:  $n=22$ ;  $\geq 4$  mm:  $n=13$ ;  $\geq 5$  mm:  $n=11$ ;  $\geq 6$  mm:  $n=6$ ), *D. pteronyssinus* (< 3 mm:  $n=24$ ;  $\geq 3$  mm:  $n=20$ ;  $\geq 4$  mm:  $n=19$ ;  $\geq 5$  mm:  $n=17$ ;  $\geq 6$  mm:  $n=12$ ), cat dander (< 3 mm:  $n=9$ ;  $\geq 3$  mm:  $n=10$ ;  $\geq 4$  mm:  $n=17$ ;  $\geq 5$  mm:  $n=21$ ;  $\geq 6$  mm:  $n=19$ ). □, grass pollens. ○, birch pollens. ◇, *D. pteronyssinus*. △, cat dander.

described in the literature [10–12]. The variation coefficient for short-term inter-assays (s.d./mean  $\times 100$ ) ranges from less than 10% [11] to 30% [12] for histamine and from 47% to 56% for mite allergen [10]. The long-term reproducibility based on two measurements incorporates three aspects: stability (no conversion), change (conversion) and measurement error, which can be confounded in longitudinal analyses. However, if stability is predominant, the initial measurement encompasses predictive ability. Additionally, three measurements also allow an estimation of the stability of a prior change (conversion) in the third measurement. Barbee *et al.* showed for a score derived from SPT with five different allergens that reversion (positive to negative) is infrequent and that it did not occur in children up to 14 years of age [13]. Peat *et al.* investigated the variability of SPT with 13 common allergens in 380 schoolchildren [14]. Atopy was defined as a weal size of  $\geq 4$  mm to any allergen. The authors state that out of 80 atopic children only four reverted to non-atopic status. To our knowledge, the reproducibility of a specific sensitization in SPT is investigated only for bermuda grass in one study [15] indicating that only 4.1% with an initial positive reaction ( $> 1$  mm) were negative one year later. The results of our investigation, which deals with a population of schoolchildren (mean age 11 years), shows that sensitization indicated by means of SPT has a high rate of stability over a period of one and of two years, respectively. Prerequisites for these results

were, in addition to purified and standardized allergen extracts, a standardized SPT procedure carried out by the same trained staff.

The crude increase in prevalence, as a change observed over time (Table 1), shows that the incidence is greater than the disappearance of previously recorded positive SPT results (Fig. 1). The assumption of a net increase in prevalence is further supported by the high intra-individual consistency of positive results occurring once, measured against the predictive value (p.p.v.) (with a cut off limit  $> 2$  mm) for grass pollen, cat dander, and mite, with values exceeding 84% (Table 2). Yearly seasonal fluctuations of natural allergen exposure, which cannot be controlled for by investigations in comparable months entirely, might have been the cause for the lower repeatability (p.p.v.) of positive SPT-results to birch pollen. Consequently, an increase in the prevalence of sensitization ranging from 2.2% (grass pollen) to 6% (birch pollen) over the period of 22 months is to be noted for this age group of 7 to 16 year-olds (Table 1).

The high p.p.v. regarding four single allergens in this age-group is in accordance with findings of Barbee *et al.* on a SPT-score [13] as well as on bermuda grass as a single allergen [15]. Comparing the results (any reaction to one of the five antigens vs. no reaction) of the initial and the sixth survey (average interval: 8 years) for children up to 14 years of age ( $n=302$ ) no reversion (positive to negative) showed up [13]. This, however, could be due to a mutual exchange in sensitization to specific antigens or 'less stringent criteria that were required to be considered SPT-positive in this study' [13]. The authors report an increase in prevalence of 32%, which gives an average of about 4% per year for a combination of five antigens. Also Peat *et al.* in a longitudinal study (1982–1986) of 380 schoolchildren report an acquisition rate for atopy of 3.8% per annum [14]. Our findings in schoolchildren aged 7 to 16 years for an observation period of about two years result in a cumulative allergen related incidence between 6 (grass pollens) and 12 (mite antigen) per cent, which gives an average rate of three to six per year (Table 2). These incidences include sporadically positive tests exclusively in 1989 or 1990, which in part could be regarded also as a measurement error. However, if only those incidences recorded at the second testing were considered reliable which could be confirmed at the third testing (Fig. 1:  $\leq 2$  mm in 1988 and inconsistent in 1989 as well as in 1990) this would result in a 'certain' incidence in this respect (1988 compared to 1989) of about 3.2% (cat dander) to 4.3% (birch pollen) per cent per year. However, it was shown that skin test reactivity increases from childhood to the early third decade [15] which could be related to an increased incidence of SPT reactions in childhood. Moreover, it is important that the incidence of sensitization to a

single allergen is related to a pre-existing sensitization to other allergens. In the group 'pre-sensitized' to one of the other three allergens the crude incidence (e.g. from 1988 to 1989) is increased compared to the group without: grass pollens 14.1% vs. 2.6%, mite 20.5% vs. 2.9%, birch pollen 20.3% vs. 0.3%, and cat dander 18.0% vs. 0.5%.

As is the case with p.p.v. regarding sensitization, the negative predictive value (n.p.v.) of negative initial tests also demonstrated high reproducibility. An initially negative measurement was seldom to be associated with change in the following measurements. This is even more rare in the case of no pre-existing sensitization to other allergens (see above). The extent of inconsistency lies at 10% for mite and below 10% for grass and birch pollen and cat dander. About half of these changes could be viewed as incidences. Therefore, the proportion of false negative findings in 1988 amounts to an average of 5% for each allergen with respect to the total group. Sporadically occurring non-specific positive reactions (negative in 1988 and inconsistent only in 1989) are rare for the procedure applied (Fig. 1).

In general, the SPT can be estimated to be highly reproducible in children. This statement also applies to a cut off limit of 2 mm for the weal diameter. Figure 2 shows that the variability of the intra-individual standard deviation within the group with initial positive findings covaries with the mean weal diameter of three tests. Therefore, the 90th percentile of the individual s.d.'s derived from three measurements was stratified for different size classes in order to estimate the occurrence of an increase in the intensity of reaction over a period of time. Based on these criteria a clear increase in reaction for individuals sensitized in 1988 can be observed after two years, amounting to 9.2% (cat dander) to 19.6% (house dust mite). This verifies that test results based on a cut off limit which are 'qualitatively' stable over a period of time (p.p.v.), considerable quantitative changes occur. This can be of significance in immunotherapy studies in which changes of reaction intensity are to be correlated with therapy, and in epidemiological investigations in which changes in the intensity of skin test reaction are used for comparison with a potential subsequent incidence of symptoms.

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