

Clinical History, Skin Prick Test and RAST in the Diagnosis of Birch and Timothy Pollinosis

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The diagnostic efficacy of clinical history (CH), skin prick test (SPT) and RAST was estimated in relation to nasal and conjunctival provocation tests (NPT, CPT) in 69 patients with seasonal rhinoconjunctivitis. The extracts used were freeze-dried, and biologically standardized birch and timothy allergen preparations matched to the extracts on Phadebas RAST® discs. Based on single determinations the sensitivity, specificity and predictive values were calculated. There were highly significant ($P < 0.001$) correlations between all parameters: NPT, CPT, CH, SPT and RAST. For birch the combination of SPT and RAST made the PTs superfluous as both sensitivity and specificity then reached 100%. With timothy the sensitivity was 97% and with the addition of CH 100%. However, the specificity was only 79% through combining CH, SPT and RAST. The present study using the same standardized allergen preparation in all tests showed a good correlation between indirect test results and provocation tests.

Key words: allergy; birch pollinosis; conjunctival provocation test; nasal provocation test; RAST; rhinoconjunctivitis; skin test; timothy pollinosis

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A precise diagnosis is a prerequisite when working with allergic rhinoconjunctivitis (1). In principle, the diagnosis can be established by elimination and exposure or by provocation tests (PT). Skin prick test (SPT) and *in vitro* serum tests show only the presence of specific IgE attached to mast cells in the skin and circulating specific IgE, respectively. Scoring systems utilizing skin tests (ST), RAST and/or clinical history (CH) have also been used (10, 11, 18). In this investigation *in vivo* and *in vitro* diagnostic materials were matched. No such matched systems have been available for routine use previously, nor have stable freeze-dried extracts with defined potency been used, which is of the greatest importance, as the number of positive SPTs will increase with increasing potency of the extract (17).

Purified, biologically standardized and freeze-dried preparations of birch and timothy pollen allergens matched to Phadebas/Phadezyme

RAST® system for detection of circulating specific IgE, have been developed. When these extracts were made available we decided to investigate the diagnostic precision of SPT and RAST and the possibility of replacing time-consuming and potentially dangerous PT with SPT and/or RAST as confirmation of a positive clinical history.

MATERIAL AND METHODS

Patients and study design

Sixty-nine referred, nonhyposensitized patients (48 men and 21 women) with rhinitis and/or conjunctivitis, seasonal or perennial, were selected consecutively at the Allergy Service Department, County Hospital, Karlskrona, Sweden. Sixty-five cases gave a history of rhinoconjunctivitis and four of rhinitis. In addition, 21 of the patients also showed slight broncho-

obstructive symptoms. The mean age was 26.6 (range 14–53) and the history ranged between 1–30 years (mean 8.2). The study was carried out in October 1980–March 1981 when the patients were free from symptoms and drugs.

A careful CH was recorded regarding symptoms during both the birch and the grass pollen season. The CH was graded as: 1) negative; 2) doubtful; 3) probable; and 4) convincing. In calculations, grades 3 and 4 were regarded as positive (18). As some patients did not show a history (grades 1–2) of birch or grass pollinosis, they acted as a control group. SPT, RAST, conjunctival (CPT) and nasal (NPT) provocation tests were performed in all subjects with birch as well as timothy pollen extracts.

Allergen preparations. In all SPT and PT the same batches of freeze-dried, highly purified, biologically standardized and immunologically characterized allergen preparations, 50,000 BU/ml, of birch (Batch No. EM 15917) and timothy (Batch No. D 19359) were used (Spectralgen®/Pharmalgen®, Pharmacia AB, Uppsala, Sweden). Reconstruction was made with albumin diluent (sodium chloride 0.9%, phenol 0.4%, human serum albumin (0.03 %)). Solutions were stored at +4–+8°C and used at room temperature within 1 week.

Conjunctival provocation test (CPT). Thirty µl (one drop) of the concentration 50,000 BU/ml was instilled into the inferior recess without touching it. The diluent was used as a control in the other eye. Reactions were recorded after 15 min. Injected, red conjunctiva and either congested conjunctiva and/or swollen caruncula lacrimalis were regarded as a positive result (35, 38). Conjunctival symptoms were controlled with Antasten-Privin® (Antazolin. sulf., naphazolin. nitr., Dispersa, Switzerland) and/or Ultracortenol® (Prednisolon. pivalas, Dispersa, Switzerland) eye drops.

Nasal provocation test (NPT). The vestibulum nasi was opened with a nose speculum to expose the front edge of the inferior concha where 30 µl of the test solution was placed without touching the mucosa (31, 34). The challenge started with

one drop of diluent in one nostril. If no reaction occurred within 15 min, the allergen preparation was placed on the other inferior concha. End-point titration was performed with 15 min intervals using the concentrations 100, 1000, 10,000, and 50,000 BU/ml. Subjects with at least two of the following signs were regarded as positive: sneezings, nasal blockage and rhinorrhea. Eye and throat symptoms were not taken into consideration. A positive reaction was not treated in any way. Even after a negative response, the patient was observed for at least 30 min. If a late reaction occurred at home, it was recorded and regarded as a positive reaction. The interval between the challenges with birch and with timothy was at least 1 week. If no reaction occurred in CPT, the NPT could be performed after at least 60 min the same day with the same allergen.

Skin prick test (SPT) was performed by directing a tuberculin needle of 20 gauge through the allergen droplet at an angle of approximately 20 degrees to the skin with a slight lifting motion (33). Single prick tests were performed by the same investigator using the allergen preparations at 50,000 BU/ml concentration. The results were evaluated according to the recommendations of the Standardization Committee of the Northern Society of Allergology (4, 5). The weal reactions elicited by the allergen preparation were recorded 1+ (25%), 2+ (50%), 3+ (100%), 4+ (200%) in relation to the histamine reference (histamine HCl 1 mg/ml) weal reaction. A reaction $\geq 2+$ was considered positive. The diluent was used as a negative reference.

Radioallergosorbent test (RAST). Specific birch and timothy antibodies were determined by Phadebas RAST® (Pharmacia AB, Uppsala, Sweden) using the same raw material as Spectralgen/Pharmalgen. The results were expressed in classes 0–4 with RAST class ≥ 1 regarded as positive.

CALCULATIONS

A positive result of CPT and/or NPT indicated a clinical allergy (1). The results of CH, SPT

Table 1
Test characteristics

<i>Specificity</i> : Percent of negative test results among nonallergic patients	
	$\frac{TN}{TN + FN} \times 100$
<i>Sensitivity</i> : Percent of positive test results among allergic patients	
	$\frac{TP}{TP + FN} \times 100$
<i>Efficiency</i> : Percent of all results that are true results, whether positive or negative	
	$\frac{TP + TN}{TP + TN + FP + FN} \times 100$
<i>Predictive value of negative test (PV_{neg}) results</i> : Percent of cases without allergy among negative test results	
	$\frac{TN}{TN + FN} \times 100$
<i>Predictive value of positive test (PV_{pos}) results</i> : Percent of cases with allergy among positive test results	
	$\frac{TP}{TP + FP} \times 100$
<i>Bayes' theorem</i> : Includes the prevalence of the disease	
PV _{neg}	$\frac{(1-p) \text{ specificity}}{(1-p) \text{ specificity} + p \cdot (-\text{sensitivity})} \times 100$
PV _{pos}	$\frac{p \cdot \text{sensitivity}}{p \cdot \text{sensitivity} + (1-p) (1-\text{specificity})} \times 100$
TN = true negative TP = true positive FN = false negative FP = false positive p = proportion of individuals with the disease in a population	

and RAST were correlated with the PT results. SPT and RAST results were also correlated with the CH, and SPT was correlated with RAST.

The agreement or concordance of true results according to all results was calculated as test efficiency (Table 1). The diagnostic precision of the different test, i.e. their ability to exclude or detect clinical allergy, was determined by calculating the specificity and sensitivity of each test method and combination of tests (21, 30) (Table 1). Specificity and sensitivity were independent of the number of nonallergic and

allergic people included in the investigation. The diagnostic value is given as the predictive value (PV) for a negative or positive test result. The PV depends on the specificity and sensitivity of the test and the prevalence of clinical allergy in the group of patients studied calculated by means of Bayes' theorem (Table 1) (21, 30). To compare different species, a pretest probability of 0.5 was chosen, that is 50 % of the subjects tested were assumed to have clinical allergy for each of the allergens according to Eriksson (18). Since we found 55 % of the subjects positive in PTs to birch and 52 % to timothy (Table 2), no adjustment of the figures was needed.

As indicated in Fig. 1, all calculations were based on CH ≥ 3 , SPT ≥ 2 and RAST class ≥ 1 as positive (F). In addition, the specificity and sensitivity were calculated with different cut-off points (A-D).

Statistics

Chi-square tests in 4-fold table with Yates' correction for continuity were performed in the correlations of the diagnostic methods.

RESULTS

In the CPT and NPT, none reacted to the diluent and no systemic side effects were observed. Six hours after the PT, one subject noticed slight itching from the throat. In SPT,

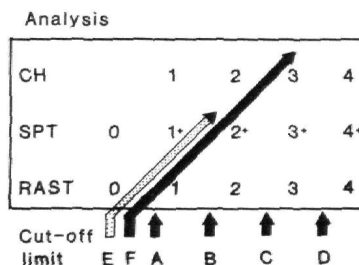


Fig. 1. Different cut-off points (A-D) according to the single analyses: CH, SPT and RAST. E means the cut-off point used when SPT and RAST are combined, and F with the addition of CH. E and F are used in calculations.

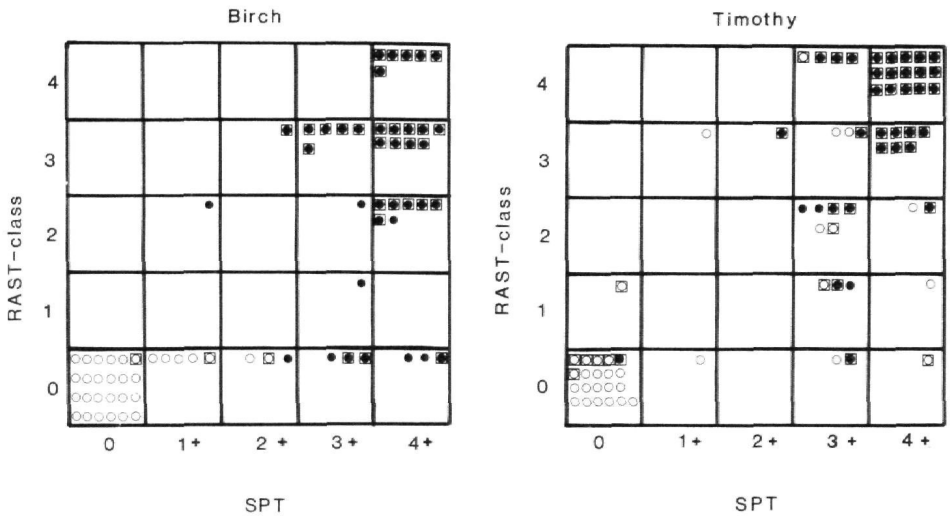


Fig. 2. Correlation between RAST classes 0-4 and skin prick test 1+ - 4+.: (●): subject with a positive provocation test; (○): with a negative provocation test; (□): subject with a positive clinical history.

Table 2
Outcome of different diagnostic parameters

	Positive findings						Negative findings	
	Birch		Birch/Timothy		Timothy*		n	%
	n	%	n	%	n	%		
Provocation tests	15	22	21	30	17	25	16	23
Clinical history	11	16	22	32	21	30	15	22
Skin prick test	13	19	26	38	19	27	11	16
Phadebas RAST	10	15	21	30	23	33	15	22

Table 3
Correlation between conjunctival and nasal provocation tests

No. of patients	Nasal provocation test		
	Neg	Pos	
Conjunctival provocation test	Pos	2	33
	Neg	31	3
	Pos	3	29
	Neg	33	4

the mean of the individual mean weal diameter for the histamine reference was 4.3 mm (range 2-6.5, SD $\pm$ 0.9 mm) and the median 4.0 mm. Most patients reacted with larger weal sizes to birch and timothy than to the histamine reference (Fig. 2). Most patients showed RAST class 3 for birch and class 4 for timothy (Fig. 2). Data on PT, CH, SPT and RAST are summarized in Table 2.

The concordance between CPT and NPT was 93% for birch ($P < 0.001$) and 90% for timothy ($P < 0.001$) (Table 3).

There was a high positive correlation between PT and CH, SPT and RAST respec-

Table 4

Correlation between provocation tests and different diagnostic parameters

No. of patients		Clinical history		Skin prick test		Phadebas RAST		
		Neg	Pos	Neg	Pos	Neg	Pos	
Provocation test	Pos	8	30	1	37	7	31	Birch
	Neg	28	3	29	2	31	0	
	Pos	3	33	1	35	2	34	Timothy
	Neg	23	10	23	10	23	10	

Table 5

Correlation between clinical history and indirect test methods

No. of patients		Skin prick test		Phadebas RAST		
		Neg	Pos	Neg	Pos	
Clinical history	Pos	2	31	6	27	Birch
	Neg	28	8	32	4	
	Pos	7	36	8	35	Timothy
	Neg	17	9	17	9	

Table 6

Diagnostic precision (%) for different diagnostic parameters*. Cut-off limit used is point F in Fig. 1

		Sensitivity	Specificity
Birch	CH	79	90
	SPT	97	94
	RAST	82	100
	SPT + RAST	100	100
	CH + SPT	97	96
	CH + RAST	87	100
	CH + SPT + RAST	100	100
Timothy	CH	92	70
	SPT	97	70
	RAST	94	70
	SPT + RAST	97	72
	CH + SPT	100	81
	CH + RAST	100	81
	CH + SPT + RAST	100	84

* When combined, the results of the single analyses are concordant

tively for both birch and timothy ($P < 0.001$ for all parameters) (Table 4).

There was also a high positive correlation between CH and SPT and RAST for birch and

timothy ($P < 0.001$ for both parameters) (Table 5).

A positive correlation was found between SPT and the RAST classes (Fig. 2). The results of SPT and RAST agreed in 87 % for birch and in 94 % for timothy ($P < 0.001$).

Diagnostic precision

Sensitivities and specificities are given in Table 6 with cut-off limits to single analyses indicated as F in Fig. 1. With different cut-off points, specificity and sensitivity cross at a point where maximum diagnostic accuracy is found (0 in Fig. 3). When a cut-off limit to the left of this point is chosen, the proportions of both true positive (TP) and false positive (FP) results are increased but true negative (TN) and false negative (FN) are reduced. Conversely, with a cut-off point to the right (x in Fig. 3) TP and FP are reduced and TN and FN are increased.

In Fig. 4 the specificity and sensitivity of the single analyses and combinations are given. The true results (TN + TP) are marked on the left and below the curves, respectively. The

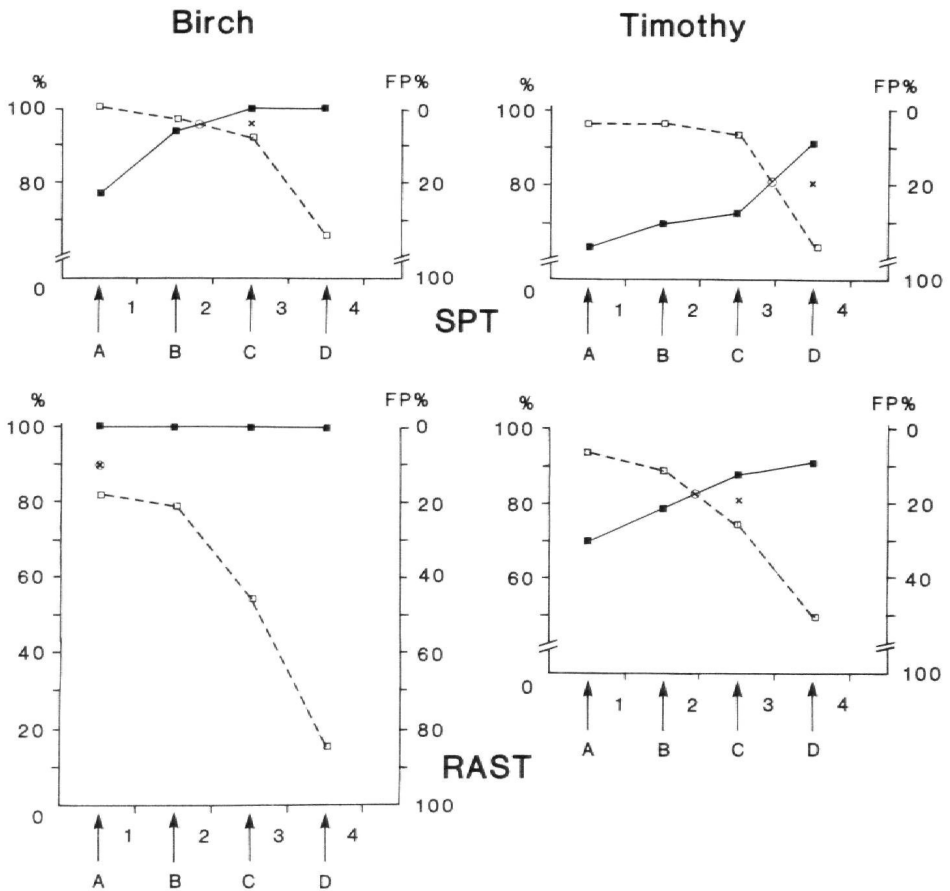


Fig. 3. Specificity (■—■) and sensitivity in % (□-----□) at different cut-off points (A-D) for skin prick test and RAST. FP% = 100% - specificity in %. Sensitivity = TP%. The optimal cut-off point: (○); best for hyposensitization: (x).

space on the right and above the curves corresponds to the false results (FP + FN) where the diagnosis can only be achieved by combining the analyses or carrying out PT.

Birch SPT showed a very high discriminative ability with both the sensitivity and specificity near the PT point (Figs. 3, 4). The maximum diagnostic accuracy of birch-RAST coincided with the best cut-off limit for both sensitivity and specificity but birch-RAST gave many FN results irrespective of the cut-off point (Fig. 3). However, the curve of CH values was separated

from those of SPT and RAST and the diagnostic reliability of the single analyses increased in the following order: CH, RAST and SPT (Fig. 4).

SPT and RAST to timothy, and CH for grass pollinosis, also showed similar curves, with either high sensitivity at low cut-off points, or high specificity at the highest cut-off point. However, the curves did not reach the PT point (*) not even when CH, SPT and RAST were combined (point F, Fig. 4) which means that it was not possible to completely discriminate

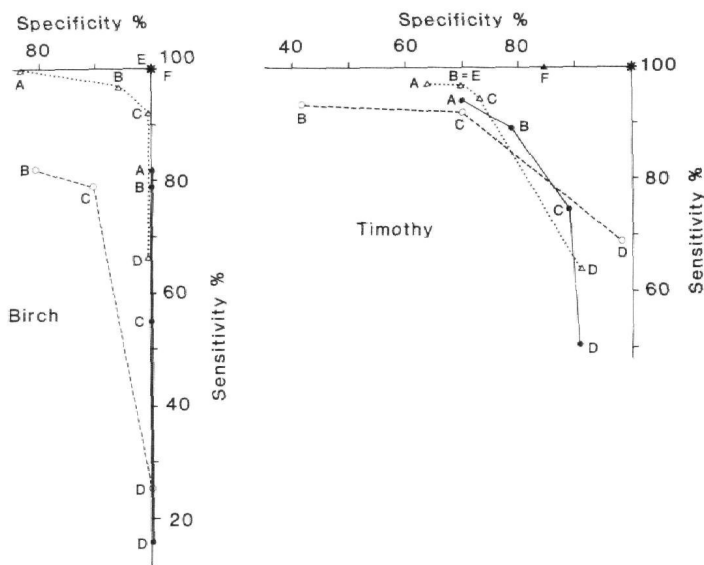


Fig. 4. Specificity (%) and sensitivity (%) at different (A-F, F = $\blacktriangle$) cut-off points for CH ($\circ$), SPT ($\triangle$) and RAST ($\bullet$) (see Fig. 1 for explanation). Positive PT: (*).

between clinical (sensitivity) and nonclinical allergy (specificity) to timothy.

Diagnostic value

The CH of birch allergy (PV_{pos} 91%) more easily indicated clinical allergy than did the CH of timothy (PV_{pos} 77%). Clinical allergy of timothy (PV_{neg} 88%) was more easily excluded by CH compared with birch (PV_{neg} 78%).

The prediction of birch pollinosis was possible with RAST (PV_{pos} 100%) and almost possible with SPT (PV_{pos} 95%). The combination of SPT and RAST was conclusive ($PV_{pos} = PV_{neg} = 100\%$), making PT superfluous. A negative SPT alone was nearly as good at excluding birch (PV_{neg} 97%) as timothy (PV_{neg} 96%) pollinosis. Neither a negative birch-RAST (PV_{neg} 82%) alone, nor the combination of a negative birch-RAST and a negative CH (PV_{neg} 88%) excluded birch allergy completely. In 4% (1/28) a positive challenge to birch was combined with a negative CH and

SPT to birch and in 13% (4/32) when CH and RAST were negative.

Clinical allergy to timothy was easier to exclude than include with the indirect test methods. A positive SPT or RAST in combination with a positive CH was not conclusive for clinical allergy. There were three cases (9%, 3/34) with all three positive but with negative PT.

DISCUSSION

A test method cannot at the same time give the highest sensitivity, the highest specificity, the highest PV for a positive result and also the highest efficiency (21). When the test results, as in our study, yield a scale of values, it is possible to choose a discrimination point along the scale — the cut-off point (18, 30). The selection of this point has to be interpreted according to the consequences, which in the case of pollinosis could be hyposensitization. As this treatment is time-consuming and includes the risk of allergic

reactions, it is advisable to choose a cut-off point which gives more false negative than false positive test results. That means that a high specificity and a high PV_{pos} are preferable (18). This is indicated in Fig. 3 with a cross to the right of the maximum diagnostic accuracy. However, few trials concerning allergic rhinoconjunctivitis have sought out this cut-off point and, when this had been done, nonstandardized allergen preparations were used (18).

For birch, we have found a better agreement between SPT and PT with 50,000 BU/ml than in previous studies not using biologically standardized materials. For timothy, we have reached about the same results as in earlier reports (e.g. 18, 34). When SPT gave completely negative results for birch and timothy — i.e. a low cut-off point was chosen, SPT excluded clinical allergy. A very large weal size (3+, 4+) was conclusive for birch but not for timothy pollinosis. This is in accordance with the results of other investigators (8, 18).

The SPT results in this study may have been influenced by the use of single prick tests. Duplicate and even quadruplicate tests will raise the precision (17). The majority of SPT reactions were found to be double the histamine reference, a result explained by concentration used (17).

Previously false positive reactions in SPT in the absence of a true CH or a positive PT have been explained as the eliciting of nonspecific reactions by irritants in nonpurified extracts (2). Such irritants have not been possible to demonstrate in pollen extracts (26). The existence of "latent allergy" (29) — positive test results in patients who have not yet developed clinical allergy, or who have outgrown their allergy to a certain allergen, is supported by a population survey among Finnish adolescents performed by Haahtela (22, 23) using both purified and nonpurified extracts. The findings were neither confirmed with PT nor CH and the patients were not followed later to confirm a latent allergy. However, such findings may also be explained by the definition of a positive test result. These results support the convention that a positive skin test reaction indicates sensitization of the patient but not necessarily the

presence of a shock organ. In a follow-up study, a positive skin test with nonpurified extracts was associated with a higher risk in developing allergic rhinitis (24). Thus, the clinical significance of a positive or a negative test is not the same in a normal population as in patients with symptoms. The latter have a more pronounced tendency to respond to allergen exposure with IgE production and the development of shock organs.

An average agreement of about 75–80% between RAST and PT results is a common finding in extended studies with several inhalant allergens. The agreement differs between different allergens but our findings for birch-RAST support earlier studies (7, 18), whereas we got a better agreement between timothy-RAST and PTs (18).

The frequency of positive RASTs among a symptom-free population has been found to be 0.6%–17% (10, 11, 12, 22). Analogously to the SPT results, a positive RAST may precede clinical symptoms (19, 25).

The false positive RAST results as well as the false negatives may be explained by the variation in the RAST method (18) and with the season (9, 28). However, our negative RAST results were evenly distributed from October to March.

An even better agreement between RAST and PT has been obtained by repeating RAST with other batches in discordant results with negative RAST (11). As the discs in our study were prepared from the same crude extract as Spectralgen, insufficient representation of important allergens on the RAST discs is less probable but will be checked. Further, we used 0.35 PRU (Phadebas RAST units) as a cut-off for class 1 RAST, the normal cut-off used in Europe, whereas 0.1 PRU is normally used as the cut-off in the USA. Differences in cut-off points and extracts may explain the variations in agreement in different studies. To investigate the effects of lower cut-off levels of birch-RAST, further studies are required. Both the false positive SPT and the RAST results may depend on the dose of allergen extracts used in PT, which is discussed below.

In combination with CH, SPT and RAST

may replace each other, according to earlier investigations (6, 27, 37). This was confirmed in the present study for timothy but not for birch.

The majority of false positive CHs to timothy found in our study may be explained by sensitization to other species causing symptoms during the grass pollen season. The false negative CH may be explained by a sensitization during the previous season. To confirm this, a prospective study with a follow-up period including reexamination is needed to establish the true predictive value of the present diagnosis as well as the predictive/prognostic value of indirect test results.

The difference in results found between CH and PT reflects the dilemma of choosing the right indicator of true clinical allergy. For the species studied the CH is often very clear. However, diverging opinions have been expressed regarding the value of the CH (2, 13, 16, 18, 34).

In this study, clinical allergy was proved by a positive PT (1, 18). When combining CH and ST for several species, Eriksson (18) had to challenge 53% to establish a correct diagnosis and when adding RAST only 25% of the patients. A correct diagnosis has been found when combining strong ST reactions and high RAST classes (10, 18, 34). In our study, it was possible to avoid the PTs to birch but not to timothy, not even in the case of a very strong SPT reaction and RAST score.

Since this trial was designed, it has been shown that, in a sample of patients included in clinical trials, the threshold concentration in PT shows a normal distribution (17). The doses used in PT (100–50,000 BU/ml) in this study can be discussed. A positive PT is defined as the dosage of allergen material eliciting the symptoms typical for hay fever in the patients (e.g. 2, 32). Conell (14) estimated the inhaled number of pollen grains of ragweed to 320/h during the pollen season. To provoke an allergic nasal reaction, 2–3 times more of the corresponding extract was needed. According to Aas (3) this is equal to 1000 BUs. One hundred mg of timothy pollen contains approximately 10 million pollen grains and 100 mg timothy pol-

len/ml of extraction releases 5 million BU. Thus, one BU is equivalent to two pollen grains. We challenged with 0.03 ml of 100–50,000 BU/ml which means 3–1500 BU or 6–3000 pollen grains, corresponding to the finding of Creticos et al. (15) of nasal mucosa sensitivity to 10–5000 grains of ragweed. Further, the reactions of PT seem to be specific, as in patients with perennial rhinitis no reactions have been elicited either with pollen grains in supraphysiological doses (14, 36) or with purified extracts (20). This and the very high correlation between CH, SPT and RAST for timothy (Fig. 4), and especially between SPT and RAST, indicate that the concentration used in the PTs may be too low.

Inconsistencies among different studies reflect the problems with study design, selection criteria, choice of extracts and cut-off levels.

In conclusion, using biologically standardized birch and timothy allergen preparations prepared from the same allergen raw material as that used for the preparation of RAST discs, a very high overall correlation was found between the single CH, SPT and RAST analyses and the PTs. Also, a high diagnostic precision and a high diagnostic value were found for both SPT and RAST. Disparate results in the diagnostic precision among different allergen preparations may be partly a question of dose. In further studies, we suggest the use of higher concentrations in PTs, several concentrations in SPT, and a continuous scale in RAST. Further, we propose that in further prospective studies, a broader panel of allergens which may induce symptoms during the seasons be considered.

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