

Hypersensitivity to *Parietaria officinalis* pollen in newcomers to the area with the plant

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Hypersensitivity to *Parietaria officinalis* (wall pellitory) pollen and other environmental allergens was studied in pollinosis patients allergic to *P. officinalis* pollen who were born in areas without *P. officinalis* and later moved to the city of Split, where *P. officinalis* is responsible for some 65% of pollinosis cases. Highly significant positive correlations were found for both the intensity of skin test reaction and concentration of specific serum IgE with the length of residence in the area. In contrast, the respective data on subjects hypersensitive to *P. officinalis* pollen allergen, but born and living in the area of Split, revealed a tendency to negative correlation between age and intensity of hypersensitivity to *P. officinalis*. A number of patients from both groups were tested for presence of serum IgE antibodies specific for 14 common environmental allergens. Hypersensitivity to *P. officinalis* pollen was associated with hypersensitivity to olive, mugwort, and birch pollen in newcomers; hypersensitivity to birch and, to some extent, olive pollen was significantly more frequent in newcomers than in autochthonous patients who were allergic to *P. officinalis* pollen. Regardless of whether the patients were autochthons or newcomers to the area with *P. officinalis*, hypersensitivity to *P. officinalis* mostly excluded hypersensitivity to *Dermatophagoides farinae* and *D. pteronyssinus*, and vice versa.

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Parietaria officinalis (wall pellitory) pollen is one of the major allergens causing pollinosis in southern and western Europe (9, 10, 12, 18). The percentage of pollinosis patients sensitive to this allergen ranges from 9.9% in children and 30.8% in adults in the Naples area (13) to 65% in southern Italy in general (19) and southern Croatia (12). In general, it is considered to be the major Mediterranean allergen (6, 10), but it may also have a significant role in the UK (15).

In the present study, we analyzed two aspects of hypersensitivity in patients allergic to *P. officinalis* pollen who had been born in (inland) areas where the plant does not grow and later moved to the Adriatic coast, in the area of the city of Split, where they were exposed to *P. officinalis* pollen and developed the respective hypersensitivity. We took advantage of two factors specific to this part of Croatia (the city of Split and a wide surrounding area): 1) sensitivity to this allergen has been well studied, so we had a fairly good overview of the situation (11, 12); and 2) after World War II the city of Split

received many immigrants from the interior of the country. The immigration has continued to the present day, and we were able to find all kinds of pollinosis patients reporting to our institution: those who had been born out of our *P. officinalis* area and had moved into it, as well as hypersensitive autochthons. By comparing the intensity of *P. officinalis* hypersensitivity and pattern of hypersensitivity to other environmental allergens in the two groups of patients, we conducted an original study and were able to draw important conclusions on the nature of hypersensitivity to this pollen.

Patients and methods

Patients

The study included 950 autochthonous subjects and 95 newcomers hypersensitive to *P. officinalis* pollen. Among autochthons, there were 550 men (mean age 48 years, ranging from 17 to 80) and 400 women (mean age 40 years, ranging from 17 to 68). The mean duration of pollinosis in men was 18 years

(range, 2–50 years) and in women 13 years (range 2–45 years). Family history of atopy appeared in 365 men and 290 women. Among the newcomers, there were 30 men (mean age 35 years, range 22–63 years) and 20 women (mean age 32 years, range 19–58 years). The mean duration of pollinosis in men was 10 years (range, 5–15) and in women 9 years (range, 6–17). Family history of atopy appeared in 15 men and 10 women.

The two groups of subjects did not differ statistically in any of the parameters listed. Control groups contained 1) 50 healthy persons with similar general characteristics, and 2) 111 patients allergic to anything but *P. officinalis* pollen allergen.

Most of the subjects whose history included *P. officinalis* hypersensitivity claimed that the weed grew on the walls of their houses and partition walls, and that every harvesting or removal of *P. officinalis* provoked skin, conjunctival, and nasal symptoms, as well as wheezing with cough in some subjects (12). Most of the symptoms appeared from April to the middle of autumn, starting already in March during mild winters. During summer (July and August), the symptoms usually ceased, reappearing in September.

Allergens

The preparation of the *P. officinalis* allergen has been described in detail elsewhere (11).

Skin testing

Skin testing was performed at the volar side of the arm by 0.02-ml intracutaneous injections with needles 0.5 mm in diameter. The negative control was an injection of the same volume of NaCl with 0.5% phenol, and the positive 0.1 mg/ml histamine chloride. Urticarial wheal sizes were measured 20 min after the testing. The reaction intensity was expressed as the mean of the longest wheal diameter and the diameter perpendicular to it. The criterion applied to interpret the data was that of Chai et al. (8), which considers the reaction to be significantly positive when the wheal diameter exceeds the negative control by at least 6.0 mm.

IgE RAST

Specific IgE antibodies against *P. officinalis* allergen were determined by the RAST method (radioallergosorbent test, Pharmacia, Uppsala, Sweden) in duplicate serum samples. Positive results were classified as class I (weakly positive), class II (clearly positive), and classes III and IV (highly positive) (16).

Determination of serum IgE antibodies against a panel of allergens

The Matrix microautomatic method (2) was used. The system uses 0.1 ml of the testing serum, and determines the concentration of the antibodies by a colorimetric ELISA method, with antigens fixed on nitrocellulose filters 5.0 mm in diameter. The test includes a semiquantitative determination of IgE antibodies against the following allergens: Bermuda grass (*Cynodon dactylon*), birch (*Betula*), mugwort (*Artemisia vulgaris*), olive (*Olea europaea*), *P. officinalis*, plantain (*Plantago lanceolata*), timothy (*Phleum pratense*), *Alternaria* (*Alternaria tenuis*), *Aspergillus fumigatus*, cat epithelium, dog epithelium, house-dust mite (*Dermatophagoides pteronyssinus* and *D. farinae*), and *Penicillium notatum*. Positive results were classified as low, moderate, high, and very high (2). For this study, we did not distinguish the levels of positivity.

Statistics

Simple correlations were used to correlate the length of exposure to *P. officinalis* allergen and the intensity of hypersensitivity (skin test and RAST) to it. Association of presence/absence of IgE antibodies specific for different allergens was calculated as χ^2 -value and tested by Fisher's exact probability test.

Results

Correlation of age and skin test reaction in 950 *P. officinalis* pollinosis patients autochthonous to the Split area is shown in Fig. 1. The correlation coef-

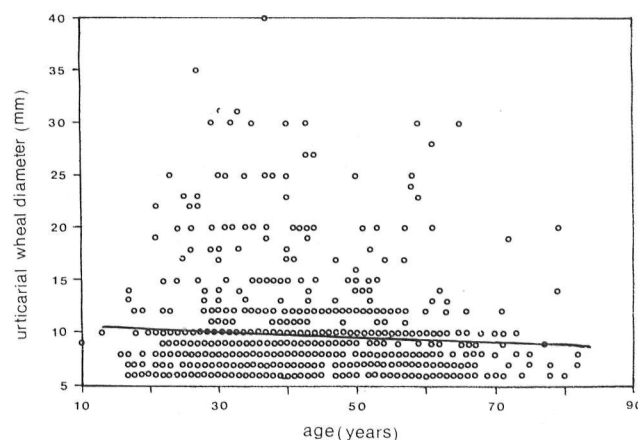


Fig. 1. Correlation between age and intensity (diameter) of skin test reaction to *P. officinalis* pollen allergen. Determined in 950 patients, autochthonous to Split area, 400 women and 550 men. Some points overlap; $r = -0.0778$, $P = 0.05$ (not significant). Slope of constructed regression line reveals theoretic 0.02691 mm/year decrease in intensity of reaction.

ficient was -0.0778 , with probability being 0.05 exactly. This should not be considered to be significant, but the tendency of the reaction to diminish with age is present. It could be calculated that the average decrease of the reaction diameter was 0.02691 mm per year.

Correlation of autochthons' age and the concentration of serum IgE antibodies specific for *P. officinalis* proved to be of the same type (negative) but considerably more significant (Fig. 2, $r = -0.4171$; $P < 0.001$); that is, RAST significantly decreased with age (approximately 0.02441 per year).

Regardless of the age of newcomers to Split who then developed hypersensitivity to *P. officinalis* pollen, the duration of environmental exposure to *P. officinalis* positively correlated with both intensity of skin test reaction (Fig. 3, $r = 0.524$; $P < 0.001$) and serum concentration of *P. officinalis*-specific serum IgE antibodies (Fig. 4, $r = 0.342$; $P < 0.015$). When the data were corrected for age of the tested subjects (on the basis of data shown in Figs. 1 and 2), the observed correlations increased, but the general picture of significant positive correlation of the duration of exposure and the intensity of the reaction remained basically the same as in Figs. 3 and 4 (data not shown).

Our next approach in studying the hyperreactivity in autochthons and newcomers to the area with *P. officinalis* was an analysis of the pattern of reactivity to common environmental antigens in two groups of patients. On the basis of skin test reaction and history of the disease, 95 autochthons (randomly selected) and 95 newcomers were included in the study. Among the autochthons, 37 were sensitive to *P. officinalis* pollen and 58 to some other allergen; among the newcomers, 42 were allergic to

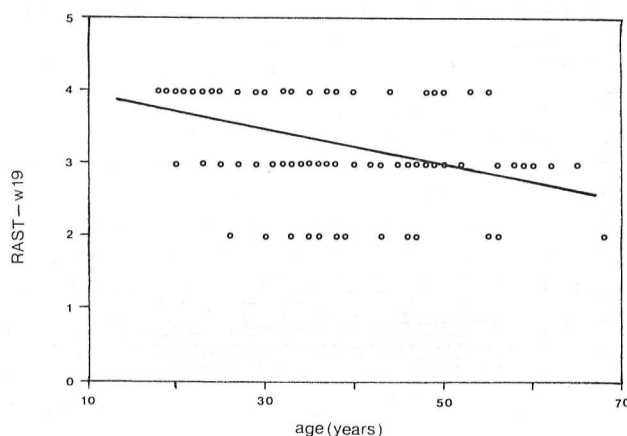


Fig. 2. Correlation between age and serum concentration of specific IgE antibodies (RAST-w19) against *P. officinalis* pollen in 100 patients (48 women and 52 men), autochthonous to Split area. Some points overlap; $r = -0.4171$, $P < 0.001$. Slope of constructed regression line reveals theoretic 0.02441 RAST-w19 decrease per year of age.

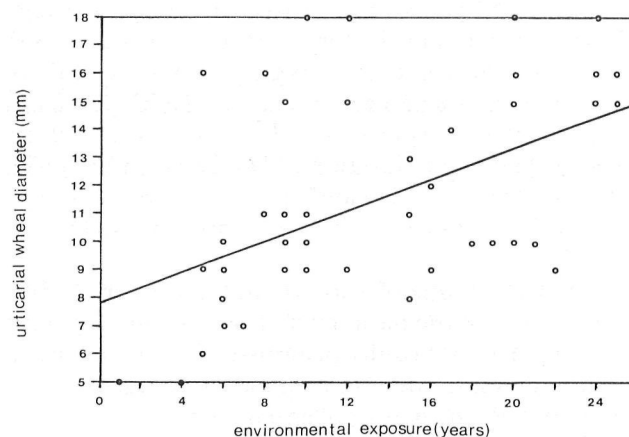


Fig. 3. Correlation between duration (years) of residence in area with *P. officinalis* and intensity (diameter) of skin test reaction to *P. officinalis* pollen allergen in 50 pollinosis patients (20 women and 30 men) who were born in areas without *P. officinalis*. Some points overlap; $r = 0.524$, $P < 0.001$.

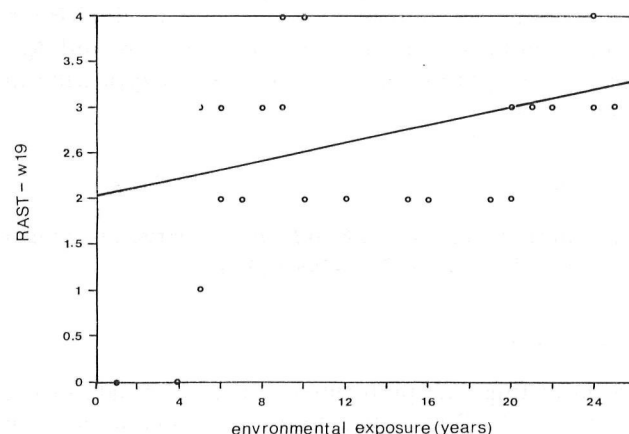


Fig. 4. Correlation between duration (years) of residence in area with *P. officinalis* and serum concentration of specific IgE antibodies (RAST-w19) against *P. officinalis* pollen in 23 patients (10 women and 13 men); $r = 0.342$, $P < 0.015$.

P. officinalis pollen and 53 to some other allergen. There was no significant sex and age difference between the autochthons and newcomer patient groups (see Patients and methods section).

All patients were tested for the presence of serum IgE specific antibodies against the following allergens: *D. farinae*, *D. pteronyssinus*, *Alternaria*, *Aspergillus*, *Penicillium*, cat, dog, Bermuda grass, timothy, birch, olive, mugwort, *P. officinalis*, and plantain. The results are shown in Table 1; frequencies of reactive and nonreactive patients are shown according to patients' origin (autochthons and newcomers) and reactivity and nonreactivity to *P. officinalis* pollen.

Associations (positive or negative) of reactivity to the allergens listed with reactivity to *P. officinalis* pollen allergen were calculated as χ^2 -values. A high

Table 1. Reactivity to various environmental allergens in patients allergic to *P. officinalis* pollen (*P. off.* +) or to some other allergen (*P. off.* -). Hypersensitivity was analyzed in patients autochthonous to the Split area (southern Croatia) and in newcomers to the area

Allergen	No. of positive patients ^a					
	Autochthons			Newcomers		
	<i>P. off.</i> +	<i>P. off.</i> -	χ^2	<i>P. off.</i> +	<i>P. off.</i> -	χ^2
<i>D. farinae</i>						
positive	10	36	12.39 ^b	9	32	18.69 ^b
negative	28	21		36	18	
<i>D. pteronyssinus</i>						
positive	11	40	15.58 ^b	33	16	16.21 ^b
negative	27	17		12	34	
<i>Alternaria</i>						
positive	1	3	0.39	1	2	0.24
negative	37	54		44	48	
<i>Aspergillus</i>						
positive	5	10	0.32	6	7	0.58
negative	33	47		39	43	
<i>Penicillium</i>						
positive	0	0	-	0	2	0.27
negative	38	57		45	48	
Cat						
positive	1	3	0.39	4	0	4.63
negative	37	54		41	50	
Dog						
positive	0	0	-	0	0	-
negative	38	57		45	50	
Bermuda grass						
positive	21	28	0.14	22	28	0.23
negative	17	29		23	22	
Timothy						
positive	20	34	0.45	24	24	0.26
negative	18	23		21	26	
Birch						
positive	6	7	0.23	10	5	2.66 ^c
negative	32	50		35	45	
Olive						
positive	8	14	0.15	11	2	8.38 ^d
negative	30	40		34	48	
Mugwort						
positive	6	8	0.06	8	7	4.77 ^e
negative	32	49		37	48	
Plantain						
positive	12	12	1.34	9	8	0.26
negative	26	45		36	42	

^a Determined by the presence of specific serum IgE antibodies.^b $P < 0.0001$.^c $P < 0.05$.^d $P < 0.005$.^e $P < 0.03$.

level of association of reactivity to *P. officinalis* pollen allergen with reactivities to *D. farinae* and *D. pteronyssinus* was found both in autochthonous and newcomer patients. A significant association of reactivity to the *P. officinalis* pollen allergen with reactivity to birch, olive, and mugwort pollen allergens was detected in the newcomer patients (Table 1). On the other hand, in patients who were not hypersensitive to *P. officinalis* pollen allergen, the frequency of reactivity to olive pollen allergen was significantly higher in autochthonous than in newcomer patients ($\chi^2 = 8.85$; $P < 0.003$).

With respect to the association of reactivity to *P. officinalis* pollen allergen with reactivity to *D. farinae* and *D. pteronyssinus* allergens (Table 1), two types of reactivity were found: positive reactivity to *P. officinalis* and negative to *D. farinae* and *D. pteronyssinus* (31.6% of all patients), and negative to *P. officinalis* and positive to *D. farinae* and *D. pteronyssinus* (35.8% of all patients). The frequency of the two types of reactivity did not differ between the groups of autochthonous and newcomer patients (Table 2).

Since the reactivities to birch, olive, and mugwort

Table 2. Associations of reactivity to *P. officinalis*, *D. farinae*, and *D. pteronyssinus* in autochthonous and newcomer pollinosis patients in Split area

Allergen			Patients (no. positive)		Total (no./%)
<i>P. off.</i>	<i>D. far.</i>	<i>D. pter.</i>	Autochthons	Newcomers	
+	+	+	10	7	17/8.9
+	+	-	0	2	2/1.1
+	-	+	1	3	4/2.1
+	-	-	27	33	60/31.6
-	+	+	36	32	68/35.8
-	+	-	0	0	0/0
-	-	+	4	4	8/4.2
-	-	-	17	14	31/16.3
Total			95	95	190/100.0

pollen allergens were shown to be associated with reactivity to *P. officinalis* pollen allergen in newcomers and not in autochthons (Table 1), the two most common types of reactivity (*P. officinalis* +, *D. farinae* -, *D. pteronyssinus* -, and *P. officinalis* -, *D. farinae* +, *D. pteronyssinus* +) were tested for frequency of concomitant reactivity to birch, olive, and mugwort pollen allergens in the two groups of patients (Table 3). Fisher's exact test for the $P < 0.05$ probability level was applied. The testing showed that in newcomers allergic to *P. officinalis* and nonreactive to *D. farinae* and *D. pteronyssinus*, reactivity to birch pollen was significantly more frequent than in autochthons with the same type of reactivity. Reactivity to olive pollen allergen also tended to be more frequent in newcomers allergic to *P. officinalis* pollen allergen but not allergic to *D. farinae* and *D. pteronyssinus*, but the difference from autochthonous patients was not significant; the frequency of reactivity to mugwort pollen allergen did not differ in the two groups of patients (Table 3).

Discussion

The age-dependent decrease in the intensity of hypersensitivity to *P. officinalis* allergen in autochthons to the area with *P. officinalis*, as determined in the present study (Figs. 1 and 2), agrees with the findings of Barbee et al. (3) on age-dependent decrease of skin reactivity. In part, it may also be due to a spontaneous desensitization in some patients, as has been described for occupational allergy in bakers (14). In contrast, in newcomers to the area, an opposite trend was observed: the intensity of hypersensitivity to *P. officinalis* positively correlated with the duration of environmental exposure to the allergen (Figs. 3 and 4). Taken together, opposite findings in the two groups of patients suggest that, although probably largely genetically determined (17), pollinosis is not a discrete phenomenon, but rather a quantitative set of changes slowly building up under exposure to the eliciting agent (allergen). Concor-

Table 3. Frequencies of reactivity to birch, olive, and mugwort pollen allergens in autochthonous and newcomer allergy patients with two patterns of hyperreactivity: 1) *P. officinalis* +, *D. farinae* -, *D. pteronyssinus* -, and 2) *P. officinalis* -, *D. farinae* +, *D. pteronyssinus* +

Pattern of reactivity	No. of positive patients		P
	Autochthons	Newcomers	
<i>P. officinalis</i> + <i>D. farinae</i> - <i>D. pteronyssinus</i> -			
Birch +	1	9	0.02
Birch -	26	24	
Olive +	1	6	0.08
Olive -	26	27	
Mugwort +	2	2	0.61
Mugwort -	25	31	
<i>P. officinalis</i> - <i>D. farinae</i> + <i>D. pteronyssinus</i> +			
Birch +	3	2	0.56
Birch -	33	30	
Olive +	5	1	0.13
Olive -	31	31	
Mugwort +	3	1	0.35
Mugwort -	33	32	

dant with this notion is the observation that hypersensitivity ceases shortly after cessation of exposure to the allergen (unpublished observation).

Another possible explanation of the difference in time-dependent changes of the intensity of hypersensitivity to *P. officinalis* pollen allergen in autochthonous and newcomer patients (Figs. 1-4) may lie in the fact that autochthons did and newcomers did not contact the allergen during the first months of life. Transitory, newborn immunodeficiency could be responsible for penetration of aeroallergens through bronchial epithelium and early sensitization. This could constitute a basis for later development of hypersensitivity at even minute concentrations of the respective allergens (1, 7, 20). *P. officinalis* may be particularly significant in this respect, inasmuch as it has a long flowering season, with maximal air accumulation of pollen grains in May and June (19, 23). Indeed, sensitivity to *P. officinalis* pollen was correlated with birth in May, and not in April and June (22).

In general, our analysis of hypersensitivity patterns in autochthonous and newcomer patients allergic to *P. officinalis* pollen or some other allergen revealed the following: 1) hypersensitivity to *P. officinalis* pollen was associated with hypersensitivity to olive, mugwort, and birch pollen in newcomers (Table 1); 2) hypersensitivity to birch and, to some extent, olive pollen was significantly more frequent in newcomers than in autochthonous patients

who were allergic to *P. officinalis* pollen (Table 3); 3) regardless of whether patients were autochthons or newcomers to the area with *P. officinalis*, hypersensitivity to *P. officinalis* mostly excluded hypersensitivity to *D. farinae* and *D. pteronyssinus*, and vice versa (Table 2; 67.4% of all patients).

Inasmuch as the birch does not grow on the eastern Adriatic coast, the hypersensitivity to birch pollen in newcomers could be explained by childhood sensitization in the birth area. Indeed, a correlation was demonstrated between the month of birth and later appearance of asthma caused by hypersensitivity to birch pollen allergen (4). Since there is no birch pollen in the Split area, the observed association of hypersensitivity to birch and *P. officinalis* in newcomers (Table 1) requires further investigation, possibly of the cross-reactive pollen antigenic components.

Hypersensitivity to olive pollen allergen is frequent in the Mediterranean area, whereas data are not available for mugwort. Olive hypersensitivity may cause serious pollinosis (5). It appears that this pollinosis is not due to cross-reactivity among the respective pollens (unpublished observation). In the present study, olive hypersensitivity was associated with reactivity to *P. officinalis* in newcomers, but in autochthons it tended to be associated with nonreactivity to *P. officinalis* (Table 3). It is thus possible that in newcomers who had been exposed neither to *P. officinalis* nor to olive in childhood, later exposure to the allergens enhanced mutual development of the respective hypersensitivities.

In general, the environment encountered at birth may have a decisive role in the development of allergic respiratory diseases. In this respect, hypersensitivity to pollen allergens, because of the defined flowering periods, can often be correlated also with month of birth. It is interesting, however, that hypersensitivity to mite antigens, which are constantly present, also may correlate with the month of birth of allergic patients (7). Thus, the observed tendency of our patients (both autochthons and newcomers) to have exclusively either *D. pteronyssinus* and *D. farinae* or *P. officinalis* hypersensitivity (Table 2) may suggest a competitive relationship of hypersensitivity development between the two groups of allergens.

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