

Immunotherapy for mountain cedar pollinosis

A double-blind controlled study

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In this study, the effect of a single preseasonal course of injection therapy on the symptoms of patients with allergic rhinitis or asthma due to pollen from the conifer, mountain cedar, was evaluated in a double-blind controlled manner. Patients treated with specific injection therapy were found to have significantly fewer symptoms than those who received placebo injections. Specific serum IgE antimountain cedar antibody decreased during the pollen season in the treated group and increased in the placebo group.

Pollen from the tree, *Juniper sabinoides*, commonly called mountain cedar, is a very important cause of respiratory allergy in San Antonio and other areas of Texas, New Mexico, and Northern Mexico.¹ This tree pollinates heavily during the months of December, January, and February and less so in November and March. During the three-month period of heaviest pollination, the pollen from this tree is the only one present in significant amounts in the atmosphere around San Antonio.² This period of time, therefore, offers a unique opportunity to study clinical response to a specific pollen without significant interference from other pollinating species.

During the past two decades there have been a number of controlled studies which have evaluated effectiveness of specific allergy injection therapy or "immunotherapy" on symptoms of allergic rhinitis and asthma caused by exposure to inhalant allergens. These studies have concluded that immunotherapy with extracts of ragweed pollen,³⁻⁵ purified antigen E,⁶⁻⁷ grass pollen,⁸ and house dust⁹ may suppress symptoms of rhinitis and asthma due to exposure to these antigens. The fact that injection therapy has been shown to reduce symptoms from these inhalants does not guarantee similar results for other inhalant allergens and further studies with other antigens should be useful until our knowledge of this form

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TABLE I. Clinical data of treatment group before immunotherapy started (positive test is wheal > 5 mm with erythema)

Patient	Age	Sex	Treatment group (17 subjects)				
			Skin reactivity*	RAST†	Serum IgE‡	Last year of previous immunotherapy	Other allergens
S. A.	38	F	10 ⁻⁵	22	160	None	0
P. D.	38	M	10 ⁻⁸	43	360	None	0
M. D.	27	M	10 ⁻⁷	4	110	1973	+
J. G.	33	F	10 ⁻⁷	27	140	None	+
S. G.	20	F	10 ⁻⁷	44	580	None	+
H. H.	78	M	10 ⁻⁵	5		1955	+
G. H.	37	F	10 ⁻⁵	8	360	None	+
G. L.	52	F	10 ⁻⁸	32	90	1969	+
D. O.	77	F	10 ⁻⁶	15	550	None	0
E. S.	33	F	10 ⁻⁵	28	58	None	+
P. A.	36	F	10 ⁻⁷	51	190	1970	+
S. H.	15	M	10 ⁻⁸			1965	+
J. M.	34	F	10 ⁻⁷	21	65	None	0
E. O.	34	F	10 ⁻⁸	44	180	None	0
P. P.	24	M	10 ⁻⁷	16	27	None	+
K. P.	30	M	10 ⁻⁸	31	50	None	0
P. S.	26	M	10 ⁻⁶	6	38	1959	+
Mean	37	10 (F) 7 (M)	10 ^{-6.7}	25	182	11 (0) 6 (+)	6 (0) 11 (+)

*Skin reactivity expressed as lowest w/v dilution which gave positive skin test.

†Radioallergosorbent test expressed as percent of control serum.

‡Expressed in international units/ml.

of treatment is more complete. The availability of a large population of patients in San Antonio with symptoms due to mountain cedar pollen provides a good opportunity to study effectiveness of specific immunotherapy on respiratory symptoms due to yet another inhalant allergen and to add more information to our growing knowledge on the role of immunotherapy for allergic disease.

During the past year, 40 patients with mountain cedar pollinosis seen at Brooke Army Medical Center and Wilford Hall Medical Center were studied in a double-blind controlled manner to evaluate effectiveness of specific high-dose injection therapy. The patients were active duty or retired military personnel and family dependents.

MATERIALS AND METHODS

Selection of patients

Prior to the recently completed mountain cedar pollen season (1974-1975), 40 patients were selected on the basis of: (1) history of seasonal hay fever or asthma during the months of November through March; (2) strongly positive intradermal skin test (wheal and flare) to aqueous extract of mountain cedar pollen at 1:500 weight/volume (w/v) concentration; and (3) not currently taking injection therapy.

Six patients in the treatment group and 2 in the placebo group had been on immunotherapy in the past. Of these, 1 patient in the placebo group had received immunotherapy to allergens other than mountain cedar within 1 yr of the beginning of the study and 1 patient in the treatment group had terminated immunotherapy 2 yr before the study. The other patients previously on immunotherapy had all terminated such therapy over 4 yr prior to this study (see Tables I and II). None of the patients in this study had previously received immunotherapy with mountain cedar extract.

The patients were divided on a random basis into two equal groups of 20. A *treatment*

TABLE II. Clinical data of control group before starting placebo injections

Patient	Age	Sex	Placebo group (15 subjects)				
			Skin reactivity	RAST (%)	Total IgE	Last year of previous immunotherapy	Other allergens
D. N.	46	F	10^{-7}	34	150	None	0
M. H.	44	F	10^{-5}	25	50	None	0
N. E.	43	F	10^{-8}	49	280	None	0
R. A.	29	M	10^{-4}	5	100	None	+
A. T.	62	M	10^{-7}	25	95	None	+
B. M.	53	M	10^{-9}			None	+
E. M.	50	F	10^{-8}		20	None	0
A. D.	28	F	10^{-7}	40	130	None	0
V. A.	27	M	10^{-8}	26	128	1970	+
A. D.	31	F	10^{-8}	36	400	1974	+
O. W.	51	M	10^{-8}	23	85	None	+
L. W.	55	M	10^{-7}	70	210	None	+
G. W.	52	F	10^{-7}	69	250	None	0
E. M.	33	F	10^{-8}	22		None	+
F. J.	52	F		29	51	None	+
Mean	44	9 (F) 6 (M)	$10^{-7.2}$	35	150	13 (0) 2 (+)	6 (0) 9 (+)
	*p < 0.5		p < 0.5	p < 0.8	p < 0.5		

*Student t test comparing treated group (Table I) with untreated group.

group received aqueous extract of mountain cedar pollen subcutaneously as tolerated to a maintenance dose of 0.3 cc of a 1:50 w/v concentration. The extract was obtained from Greer Laboratories, Lenoir, N. C., and all extract used was from the same lot. The second group, or placebo group, received injections of caramelized glucose with histamine added to simulate the appearance and local reactions caused by the true extract. Informed consent was obtained from each patient and they were assigned to either of the two groups in such a manner that neither the physicians nor the patients knew who was in which group until the study was completed in March, 1975. Although a few of the patients had mild wheezing recorded, rhinitis symptoms and not asthma were the main problem in all the patients.

Injection therapy

The patients from both groups were placed on the same injection schedule which started injections at a thousand-fold dilution of the full strength concentration (1:50 w/v). The injections were given preseasonally, starting in the spring of 1974. Injections were given twice weekly in gradually increasing doses until maintenance dose was reached, at which point injections were given at weekly intervals. For the purpose of comparing the dose of extract used in this study to that used in previous studies, it would be convenient to convert these doses to protein nitrogen unit equivalents (PNU). Conversion of these doses to PNU equivalents with mountain cedar, however, is misleading due to the relatively very low protein nitrogen content of this pollen. But, for comparison purposes, if the same dose and concentrations of ragweed pollen extract were used, the maintenance dose would be approximately 3,000 PNU. For purposes of calculation and comparison of doses used for the patients in this study, the w/v solution received was converted to milligrams of extracted pollen actually given in treatment. Using this conversion, the maintenance dose was 6 mg of extracted pollen per dose. The total dose given to individuals in the treated group varied from 1 mg to 157 mg of extracted pollen with a mean dose of 58 mg. Again, for comparison only, this amount of extracted ragweed pollen would be approximately 315 PNU to 78,500 PNU with a mean dose of 29,025 PNU.

Skin sensitivity

The skin sensitivity of each person in the study was quantitated by testing at serial dilutions of extract ranging from 1:1,000 w/v dilution (10^{-3}) to a 1:1 billion w/v dilution (10^{-9}).

The weakest concentration to give a positive response, indicated by a 5-mm wheal with erythema, was recorded as a measure of skin sensitivity.

Specific serum IgE antibody (RAST)

Specific antimountain cedar IgE antibody levels in the sera of the patients were measured by means of the radioallergosorbent test (RAST) originally described by Wide, Bennich, and Johansson.¹⁰ Mountain cedar antigen-coupled paper discs were obtained commercially (Pharmacia Laboratories, Piscataway, N. J.). Fifty microliters of undiluted serum was incubated with one disc for 2 hr. Each serum was run in duplicate. The discs were then washed three times with normal saline. Fifty microliters of ¹²⁵I-labeled rabbit antihuman IgE (obtained from Pharmacia Laboratories, Piscataway, N. J.) containing 160,000 counts per minute (cpm) activity were then added to each disc and incubated overnight. The discs were again washed three times with normal saline, and the amount of radioactivity remaining on the discs was determined in a well-type scintillation counter for gamma counting. The results were obtained initially as cpm and the background count was subtracted. A known positive serum with very high antibody levels (as determined by RAST and serial dilution skin testing) was included as a reference standard, and the results for each patient were expressed as a percent of the reference standard. The tests were performed in 12 × 75 mm capped plastic tubes (Falcon, Oxnard, Calif.) at 20° C. When the reference serum and study sera were tested on different days with different lots of reagents, there was less than 7% variation in the final RAST value obtained for each sample.

Sera were collected at the time treatment was started in June, 1974, just prior to the pollen season (November, 1974), and at the conclusion of the pollen season (March, 1975). Sera were stored at -20° C. All the sera collected as well as sera from 26 nonatopic individuals were run at the same time in one determination in an effort to eliminate as many variables as possible so that RAST titers could be compared.

Symptom scores

Evaluation of the patients' clinical course throughout the season of 1974-1975 was performed by having patients record symptoms on a daily basis. A format was used which was very similar to that used by Norman¹¹ in evaluating ragweed hay fever. The patients were asked to report separately: (1) stuffy, runny nose, (2) sneezing, (3) itchy, watery eyes, (4) cough, (5) shortness of breath or wheezing, and (6) medication taken to relieve these symptoms. Medications used to treat the patients were antihistamines or antihistamine-decongestant combinations and were dispensed by the investigators. The patients were instructed to take the medication only as needed. The particular preparation used for each patient was dependent upon which preparation, by history, worked best for the patient with the fewest side effects. Steroid preparations were not used.

The patients were asked to check whether each symptom persisted for ½ hr, ½ to 2 hr, or over 2 hr for each of the 12-hr periods in a day. Symptoms and medications were recorded each day and the results were mailed to the physicians at the end of each week. The scores for each day were tabulated consisting of the number of symptoms, duration of each symptom, and medication taken. An average daily symptom score for each patient was then calculated, as well as average daily symptom scores for the two groups. Symptoms were tabulated for the period from December 1, 1974 through February 28, 1975.

At the end of the season the treatment code was broken and the symptom scores for each patient were placed into either placebo or treatment group and the average symptom score for each group was calculated for the season and compared in a statistical manner as described below.

Pollen counts

Daily pollen counts were done during the season at three different locations in San Antonio: (1) Brooke Army Medical Center in the Northeast section of the city; (2) Wilford Hall Medical Center on the far west side of the city; and (3) in the downtown business district, courtesy of Boen Swinney, Jr., M.D. Counts were performed using Durham gravitational slide

counters and results were reported as pollen grains per square centimeter of slide per 24-hr period. When possible, the results from the three locations were averaged. The pollen counts at the different locations varied considerably on a day-to-day basis, but there was no consistent pattern established in which one area had consistently higher counts than the other areas. The residences of the patients were distributed throughout the San Antonio area and neither study group was selectively sequestered in any one area of the city or near any one of the counting sites.

Serum IgE levels

Serum samples were obtained from patients at the time of the initial evaluation and IgE levels were determined by use of the Phadebas kit purchased from Pharmacia Laboratories (Piscataway, N. J.).

Statistics

The Student *t* test was used for determining significance of differences observed between the two groups. The paired *t* test was used to determine significance of observed changes in RAST values within each group. Correlations between various parameters were determined with the Pearson product-moment correlation coefficient.¹²

RESULTS

At the end of the 1974-1975 season, the data from the patients in each group were analyzed and compared. Thirty-two patients completed the study with 17 in the treated group and 15 in the placebo group. Table I is a summary of the clinical and laboratory findings of the treated group before starting injection therapy. Table II summarizes the clinical findings in the control group. When the two groups were compared, they were found to be closely matched for age, sex, skin reactivity, RAST titers, and total IgE. There was no significant difference between the groups when compared for skin reactivity ($p < 0.5$), age ($p < 0.5$), RAST ($p < 0.8$), or total IgE ($p < 0.5$). The incidence of clinically significant inhalant allergies other than mountain cedar, as determined by history and skin tests, is about the same for both groups, also.

Perennial inhalant allergens, such as house dust, mold, and animal danders, could conceivably cause significant symptoms during the time period of this study and cause errors in interpretation of symptom scores. Danders and other more unusual causes of perennial allergy (feathers, kapok, etc.) were not identified as causative factors for the patients in this study. Mold and/or house dust sensitivity, however, was present in 4 of 17 patients in the treatment group (24%) and in 4 of 15 patients in the placebo group (27%) as determined by positive skin tests and histories. Fig. 2 shows that each study group had measurable symptoms at the time the pollen season started. These symptoms were presumably from the small number of patients in each group with mold and house dust sensitivity. The fact that the symptom scores for each group were very close at the beginning of the study and the incidence of sensitivity to these allergens was very similar for each group would suggest that these allergens were not a cause for any significant difference in symptoms observed between the groups during the mountain cedar pollen season.

Table III lists the average daily symptom scores for treated patients along with their total immunotherapy doses and RAST titers. Table IV does the same for the control group. When the average daily symptom scores for the two groups

TABLE III. Effect of immunotherapy on treatment group. Symptom scores are the average daily symptom scores during mountain cedar season

Patient	Treatment dose*	Treatment group				
		Symptom scores	Pretreatment RAST	Preseasonal RAST	Postseasonal RAST	Δ † RAST
S. A.		2.19	22	8	6	2
P. D.	56	4.13	43	78	57	21
M. D.	53	0.50	4	5	4	1
J. G.	5	9.54	27	26	34	-8
S. G.	62	4.75	44	20	13	7
H. H.	101	2.82	5	5		
G. H.	157	8.09	8	12	6	6
G. L.	137	7.30	32	36	17	19
D. O.	141	7.42	15	11	11	0
E. S.	69	3.35	28	15	11	4
P. A.	1	7.02	51		42	
S. H.	3	3.23				
J. M.	21	13.31	21	14	13	1
E. O.	13	3.67	44	40		
P. P.	36	4.29	16	10	8	2
K. P.	17	8.11	31		29	
P. S.		3.11	6		5	
Mean	58	5.46	25	22	18	5
Student's t test‡		p < 0.01	p = NS	p = NS	p < 0.002	p < 0.01

NS: not significant ($p > 0.05$).

*Treatment dose expressed as milligrams of extracted pollen given to each patient over entire course of therapy.

† Δ RAST is difference of preseasonal RAST minus postseasonal RAST values.

‡Student t test comparing treated group with untreated group (Table IV).

are compared, there is a statistically significant difference between the two groups ($p < 0.01$ with Student's t test). Fig. 1 charts the average daily symptom score of each patient and compares the two groups. This shows that there was a considerable amount of overlap in the symptoms of the patients in both groups, but the mean symptom score for the treated group was significantly lower than for the untreated group ($p < 0.01$).

Fig. 2 charts the average daily symptom scores for each group as a whole and compares them to the pollen counts throughout the course of the season. There was good correlation between pollen count and symptom scores reported in each group throughout the weeks of the pollen season ($r = 0.71$, $p < 0.01$ for placebo group and $r = 0.65$, $p < 0.01$ for treatment group). At the beginning of the season, the symptom scores for both groups were very close. As the pollen counts increased, the difference between the groups became apparent. This difference was greatest when pollen counts were highest and became less as the pollen counts dropped at the end of the season. It is apparent from this chart that the treated patients, as a group, had fewer symptoms throughout the season than did the placebo group.

The RAST test appeared to be a reliable indicator of clinical sensitivity as shown in Fig. 3. This figure shows pretreatment RAST values for 29 of the 32 patients who completed the study and RAST values for 26 nonallergic individuals. The 26 nonallergic patients tested had a mean value of 8.82% with standard deviation (SD) of 1.13%. Values above 11% were more than two standard

TABLE IV. Placebo group during same time interval as treated group in Table III

Patient	Placebo group				
	Symptom scores	Pretreatment RAST	Preseasonal RAST	Postseasonal RAST	Δ^* RAST
A. D.	10.52	36	56	61	- 5
N. E.	8.33	49	74	51	22
M. H.	8.20	25	25	42	-17
F. J.	7.72	29	28	27	1
E. M.	8.61	22	18	24	- 6
G. W.	4.24	69	55	73	-17
L. W.	9.91	70	63	63	0
O. W.	16.36	23	30	52	-22
A. T.	14.40	25	20	23	- 3
R. A.	8.74	5	6	5	1
V. A.	7.37	26	43	78	-35
A. D.	7.01	40		73	
E. M.	6.18			50	
B. M.	9.30				
D. N.	5.50	34	36	43	- 8
Mean	8.83	35	38	48	- 8

*Difference between preseasonal RAST and postseasonal RAST.

deviations from the mean for the nonallergic group and were considered positive. Using this criteria, all those in the study who were tested before treatment were positive except for 5 patients. There was a wide range in RAST levels among the allergic patients and there was not a good correlation between pretreatment RAST level and skin sensitivity or symptom scores ($r = 0.12$, $p > 0.10$). In this study, neither the RAST nor skin sensitivity were good indicators of severity of symptoms but both were good qualitative tests for clinical sensitivity.

The effect of immunotherapy on specific IgE antimountain cedar antibody was measured by the RAST technique on the sera collected before treatment, before the pollen season, and after the pollen season. The results are listed in Tables III and IV. The mean values for the untreated group showed a definite increase during the pollen season (35 to 48). The treated group, on the other hand, had a gradual decrease in mean values (25 to 18) which carried through to the end of the season. The mean values for the two groups were close at the beginning of immunotherapy with the mean values for the untreated group being slightly higher (35 vs 25). By the end of the season the mean values had separated widely and the difference between the two groups was highly significant (48 vs 18, $p < 0.002$). The changes in RAST values within each group, however, were not statistically significant when analyzed with the paired t test with $p > 0.10$ for the increase in RAST for the control group and $p > 0.10$ for the decrease in RAST for the treated group. This progression of the RAST values for the two groups is charted in Fig. 4. The change in RAST values (Δ RAST) which occurred during the pollen season was very different for the two groups. Comparisons of the mean change (untreated = -8, treated = 5) in RAST titers for the groups reveals a significant difference ($p < 0.01$). There was not a good correlation between the amount of change in RAST and the dose of immunotherapy given ($r = 0.14$, $p > 0.10$) or in the average daily symptoms scores ($r = 0.06$, $p > 0.10$) during the season.

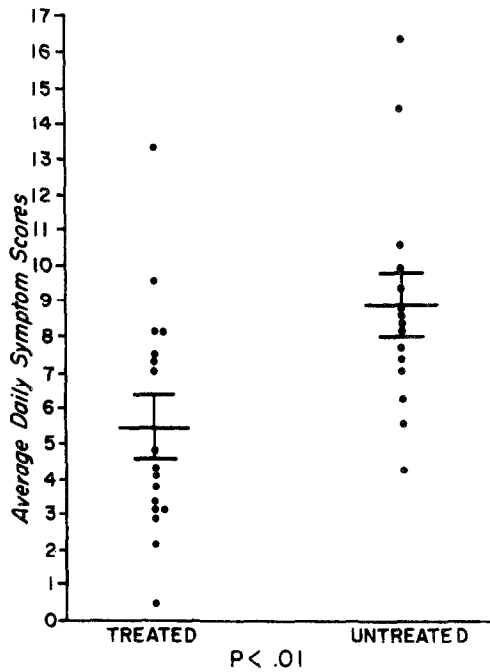


FIG. 1. Average daily symptom scores for treated and control subjects showing the mean $\pm$ standard error of the mean (SEM) for each group. The difference between the groups is significant at the $p < 0.01$ level.

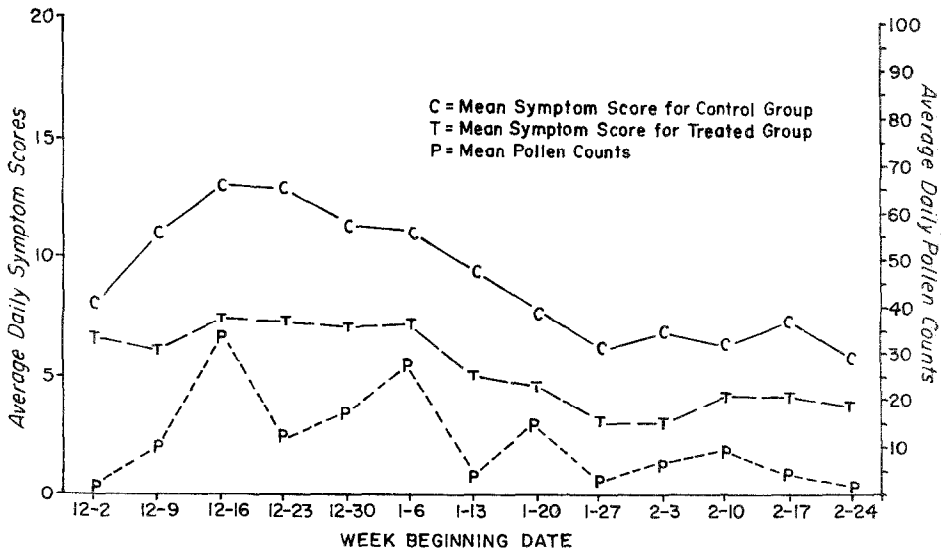


FIG. 2. Mean daily symptoms scores for treated and placebo groups charted for each week of pollen season (December, 1974, through February, 1975) plotted with average daily pollen counts for each week. Pollen count reported as pollen grains per square centimeter of slide per 24 hr.

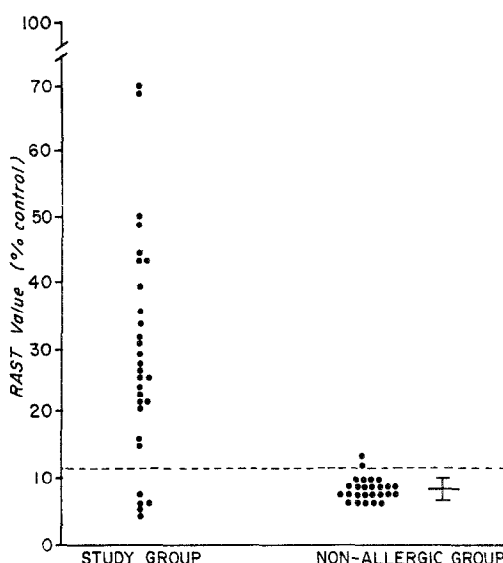


FIG. 3. Pretreatment RAST for 29 of the 32 patients who completed the study compared to 26 nonallergic individuals. Dashed line presents a value 2 standard deviations (SD) above mean for nonallergic individuals. Values above this line were considered positive and those below the line negative. Nonallergic group shown with mean RAST value $\pm$ SD.

DISCUSSION

In 1964, Miller, Smith, and Lawson¹³ reported a controlled study with mountain cedar extract in repository form with mineral oil used as the repository agent. They reported no significant difference in symptoms between treated and untreated patients. They felt the lack of clinical response to treatment may have been due to relatively low doses of extract given. Patients in their treatment group received a total of 1,000 PNU of mountain cedar extract. Their conclusions are consistent with those of Johnstone,¹⁴ Franklin and Lowell,¹⁵ Norman,¹¹ and Pruzansky and Patterson,¹⁶ who have shown that patients show best clinical response to high dose therapy and do little better than placebo groups when given very low dose therapy. This study was done with relatively high dose therapy using aqueous extract. The treated group had demonstrably fewer symptoms than the placebo group. This study would seem to add a new allergen to the growing list of those which have been shown, by controlled studies, to be effective in reducing symptoms of inhalant allergy with immunotherapy.

The mountain cedar tree, *Juniper sabinoides*, is a conifer which differs phylogenetically from most pollen-producing allergenic plants in that it is in the Gymnosperm class of plants which have naked seeds with no proper ovaries. Almost all pollen-producing allergenic plants are in the Angiosperm class which have their seeds in an ovary. This tree is one of many species in the family Cupressaceae which Yoo, Spitz, and McGerity¹⁷ recently demonstrated to be immunogenic in man with a marked cross-reactivity between members of the family. This is the first controlled study to demonstrate effectiveness of immunotherapy in plants of this family and class.

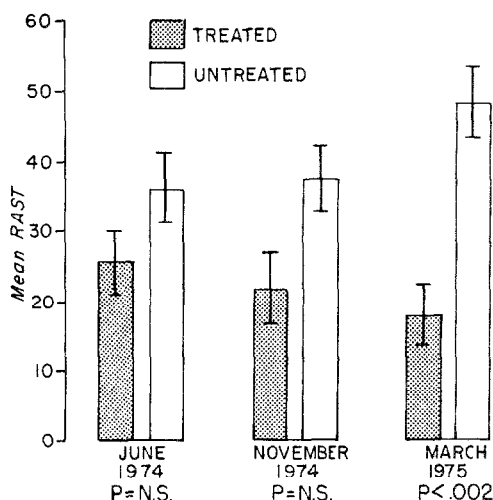


FIG. 4. Mean RAST values $\pm$ SEM for 17 treated and 15 untreated patients showing decrease in mean RAST for the treated patients and increased mean RAST for untreated. NS = not significant = $p > 0.05$.

A number of immunologic changes have been noted to occur with allergy injection therapy which include: (1) a rise in antigen-specific IgG (blocking) antibody in sera¹⁸⁻²⁴; (2) a decrease in sensitivity of circulating leukocytes as measured by leukocyte histamine release^{5, 16, 18, 22, 24}; and (3) a decrease in lymphocyte blastogenic response and lymphokine production.²⁴ In this study, we investigated only one immunologic parameter, RAST titer or specific IgE antimountain cedar antibody levels. The decrease in RAST titer which continued through the pollen season in the treated group is consistent with other reports for different allergens.^{18, 19-22} However, some studies have shown an initial rise in specific IgE levels followed by suppression with more prolonged immunotherapy.^{19-21, 25} We did not see an initial rise in specific IgE antibody in the treated group but there was a 5-mo period between initial RAST and preseasonal RAST during which an early rise in value may have been missed. It is generally accepted that a rise in specific IgE occurs with seasonal allergen exposure in untreated patients, and our study confirmed this for mountain cedar pollen exposure.¹⁸⁻²⁴

It has recently been demonstrated that nonreaginic antibody and other undefined serum factors may have an inhibitory effect on RAST determinations.^{26, 27} It has been suggested that some patients receiving immunotherapy have sufficient nonreaginic antibody to cause suppression of RAST values, particularly in undiluted serum.²⁶ These factors could possibly have contributed to the decrease in RAST values seen in the treated group of this study. This possibility is now being investigated.

Ideally, we would have liked to monitor symptoms and immunologic parameters of the patients of both groups through one pollen season without immunotherapy to establish good baseline values. This was not possible because of the short duration of military assignment and the need to use one pollen season to collect enough patients to do the study. As discussed previously, however, the pa-

tients were assigned to the two groups in random fashion and the groups were very similar in skin reactivity, age, sex, RAST titers, and total serum IgE before immunotherapy. We feel, therefore, that it is not unreasonable to assume they were also similar in clinical sensitivity before immunotherapy was initiated.

CONCLUSIONS

Specific high dose allergy injection therapy with aqueous extract has been shown to suppress symptoms of respiratory allergy due to pollen from the conifer, mountain cedar. This study would seem to add this allergen to the expanding group of inhalant allergens for which controlled studies have demonstrated effectiveness of immunotherapy in suppressing symptoms of respiratory allergy. The injection therapy was accompanied by a drop in specific IgE antimountain cedar antibody during the pollen season while untreated patients had an increase in specific IgE levels. This study suggests that immunotherapy can be a helpful addition in treating those patients with mountain cedar pollinosis whose symptoms cannot be controlled with pollen avoidance and symptomatic therapy.

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