

Local intranasal immunotherapy for ragweed allergic rhinitis

I. Clinical response

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Local nasal immunotherapy (LNIT) of ragweed allergic rhinitis was studied in a double-blind controlled trial. Sixty-seven subjects were divided into three groups. Twenty-one received unmodified ragweed extract (RW), 24 received a glutaraldehyde polymer of ragweed extract (PRW), and 22 received placebo. Mean symptom/medication scores during the season were 2.12, 2.76, and 3.93 for the RW, PRW, and placebo groups, respectively. Both the RW- and the PRW-treated group scores were significantly lower than those of the placebo group ($p < 0.01$, and $p < 0.025$, respectively). The results of the patients' self-evaluations indicated that therapy was effective in 71%, 59%, and 41% for the RW-, PRW-, and placebo-treated groups, respectively. Adverse reactions to treatment were limited to the upper respiratory tract and were noted by all patients. They were significantly more severe in the RW-treated patients than those in the PRW- or placebo-treated groups. We conclude that LNIT is an effective therapy for ragweed allergic rhinitis. The use of a PRW decreased adverse reactions significantly while slightly decreasing the therapeutic benefit. (J ALLERGY CLIN IMMUNOL 68:33, 1981.)

Parenteral immunotherapy for seasonal allergic rhinitis has not changed substantially since it was introduced by Noon¹ in 1911. This treatment has been proven effective in many controlled studies.² However, it is neither uniformly nor completely effective, and it also has several drawbacks, including cost, inconvenience, and the risk of serious anaphylactic reactions.

Parenteral immunotherapy regularly produces a systemic antibody response, but it does not produce a

local immune response.³⁻⁶ This may contribute to the incomplete efficacy of this mode of therapy. Studies with viral vaccines have shown that local immunization of the mucous membrane yields a distinct, protective local immune response that is not seen after parenteral immunization.⁷ It seems possible that topical immunization with allergens might also produce a protective local immune response.

Local immunotherapy for the treatment of respiratory allergies is not new. Herxheimer⁸ first described mucosal desensitization in 1951. Subsequently several investigators have reported uncontrolled studies that show good clinical efficacy of LNIT in allergic rhinitis.⁹⁻¹² More recently, controlled studies of LNIT have been performed¹³⁻¹⁷; three^{13, 15, 17} reported a significant beneficial clinical response. In most of the reports on LNIT, local adverse reactions have interfered with therapy. Therefore several of the more recent studies^{11, 16, 17} have used chemically modified allergens, which have a reduced allergenicity while still retaining immunogenicity.

In 1979 we described a pilot study that suggested the clinical efficacy of LNIT.¹² This report describes a double-blind, placebo-controlled study of LNIT in which an unmodified aqueous extract of short rag-

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Abbreviations used

LNIT:	Local nasal immunotherapy
RW:	Ragweed extract
PRW:	Glutaraldehyde polymer of ragweed extract
RAST:	Radioallergosorbent test
NPT:	Nasal provocation test

weed (RW) and a glutaraldehyde-polymerized short ragweed extract (PRW)¹⁸ were used. The clinical response to this treatment is reported here, and the immunologic response is reported in the accompanying paper.¹⁹

MATERIALS AND METHODS

Antigens

An unmodified crude RW (15% w/v) was prepared from defatted pollen of *Ambrosia elatior* (short ragweed; Greer Laboratories, Inc., lot No. 18N56-90). The antigen E concentration was 80 $\mu\text{g/ml}$. The extract was stored in a lyophilized state at 4° C until used. A PRW with a molecular-weight range of 200,000 to 20,000,000 Daltons was prepared by Dr. Roy Patterson, as previously described.¹⁸ The crude ragweed extract used to prepare the polymerized material contained 285 $\mu\text{g/ml}$ of antigen E. It was stored as a concentrate at 4° C until used. Treatment material was diluted in 0.9% saline containing 0.3% human serum albumin and 0.3% phenol. Histamine diphosphate (2.7 mg = 1 mg histamine base) in diluent and diluent alone were used as placebo treatment. The same ragweed extract was used for LNIT, serologic investigations, and nasal challenges in all patients.

Patient selection

Subjects were recruited through an advertising campaign. The history was recorded and a physical examination performed by one of the authors. Skin testing (prick) was carried out with extracts of short ragweed, *Hormodendrum*, *Alternaria*, and house pet epidermis (in patients with house pets).

Criteria for inclusion in the study were: (1) a history of seasonal allergic rhinitis coinciding with the ragweed pollen season and (2) a positive skin test to short ragweed extract.

Subjects were excluded from the study for the following reasons: (1) perennial rhinitis, (2) immunotherapy within the last 3 yr, (3) a strongly positive skin test to *Alternaria* or *Hormodendrum*, which may be present in high concentrations during the ragweed season, (4) a strongly positive skin test to house pet epidermis extract, or (5) the regular use of medications that might interfere with the study (local decongestants, steroids). Subjects who also had allergic rhinitis in another season or asthma were not excluded.

Of the 165 individuals who replied to the advertising campaign, 75 were selected for this study. These 75 subjects were further evaluated by the RAST and NPT with short ragweed. They were then matched into triplets on the

TABLE I. Treatment protocol

Week of therapy	Concentration of treatment solution			
	Active treatment		Placebo	
	RW ($\mu\text{g AgE/ml}$)	PRW ($\mu\text{g AgE/ml}$)	Histamine (mg/ml)*	Saline (%)
0	0.008	1	0.05	0.9
2	0.08	10	0.1	0.9
4	0.8	50	1	0.9
6	8	100	2	0.9
8	80	100	5	0.9
10	80	100	5	0.9

*Of histamine base.

basis of their NPT and RAST scores. Each member of the triplet was randomly allocated into one of three groups: placebo, RW, or PRW. To control for the difference in adverse reactions in the RW and PRW groups, the placebo group was randomly divided into two subgroups: one receiving histamine and the other receiving diluent alone.

Ragweed RAST values were performed as previously reported²⁰; total serum IgE levels were measured by a solid-phase radioimmunoassay.

NPT was done according to the method of Okuda.²¹ Paper discs measuring 3 mm in diameter were soaked in serial 10-fold dilutions of RW extract or diluent, lyophilized, and kept refrigerated until used. A diluent disc was placed under direct visualization on each inferior turbinate and left in place for 5 min. If no reaction occurred within this period the discs were removed and replaced with discs containing the 10⁵-fold dilution (0.0008 μg antigen E/ml) of the RW. This was repeated with increasing serial 10-fold concentrations until the endpoint was reached or until the patient tolerated a disc with undiluted (80 μg antigen E/ml) extract. The endpoint was defined as the dilution of extract that elicited at least three of the following five signs and symptoms: itching, sneezing, stuffiness, secretions, and edema or pallor. The endpoint was recorded as the log of the dilution that elicited the reaction. The most sensitive patients, those who reacted to the most dilute disc (10⁵), were assigned a value of 5; patients reacting to the concentrate were assigned a value of 0. The least sensitive patients, those who did not react at any concentration, were assigned a value of -1. Those who reacted to the control discs were not assigned a numerical value and were not included in the analysis of NPT data. NPT was not performed when the patient was symptomatic. Repeated NPTs resulted in a score of ± 1 of the original score in 18 of the 21 patients tested (86%), indicating an acceptable reproducibility of the procedure.

Study design

Therapy was preseasonal, beginning in mid-May and ending in the first week of August. Treatment solutions were dispensed in opaque plastic nasal spray bottles (kindly supplied by the Schering Corp.). Each squirt delivered ap-

TABLE II. Patient population

	Placebo (n = 22)	RW (n = 21)	PRW (n = 24)
Mean age in years (range)	34 (17-61)	38 (20-66)	35 (16-57)
Sex (M/F)	10/12	11/10	11/13
Previous immunotherapy	7	6	7
Mean total IgE (IU) (range)	102.5 (10-600)	101.4 (9.5-1200)	75.4 (<9.5-460)
Mean ragweed RAST (% standard) (range)	46.2 (8-276)	23.2 (2.5-204)	31.3 (<2.5-336)
NPT (mean $\pm$ SD)	2.23 $\pm$ 1.7	2.43 $\pm$ 2.06	2.33 $\pm$ 1.76

proximately 0.04 ml of a droplet mist. The initial treatment was given with one of the authors present. After that, the patients were instructed to use the spray once every other day at home. One squirt was applied to each nostril on days 1 and 3, two squirts were applied on days 5 and 7, and five squirts were applied on days 9, 11, and 13. The concentration was increased as tolerated every 2 wk according to the schedule in Table I. The maintenance dose was three squirts of the undiluted extract into each nostril every other day. Every attempt was made to reach maintenance by week 8. All medication was packaged and coded by one of the investigators who had no contact with the patients at any time. Neither the remaining investigators nor the patients knew the type of individual treatment they were receiving. The code was not broken until all of the clinical results had been collected and all decisions to drop patients because of their lack of compliance with the protocol had been made.

All patients were offered chlorpheniramine tablets (4 mg) to take as needed during the treatment period and season. Patients who wished to use another oral antihistamine and/or decongestant were allowed to do so. The use of topical decongestants was not allowed.

Evaluation

Patients were seen biweekly throughout the study. At each visit a brief history was reviewed and a physical examination was performed. During the treatment period, patients recorded daily on adverse reactions to the treatment by filling in a questionnaire. The actual amount of treatment solution delivered was determined by weighing the bottles before they were dispensed and after they were returned. During the season, patients kept a symptom/medication score card that was filled in twice daily, as described by Norman and Winkenwerder.²² Symptoms were rated by severity (0-4) and duration (0-3). The number of antihistamine/decongestant tablets was also recorded. There was no attempt to adjust the medication score to account for the different compositions or strengths of antihistamine/decongestant tablets used.

NPT was performed on four occasions: before treatment, after treatment (preseason), at midseason, and immediately after the season.

The patient self-evaluation was made at the end of the

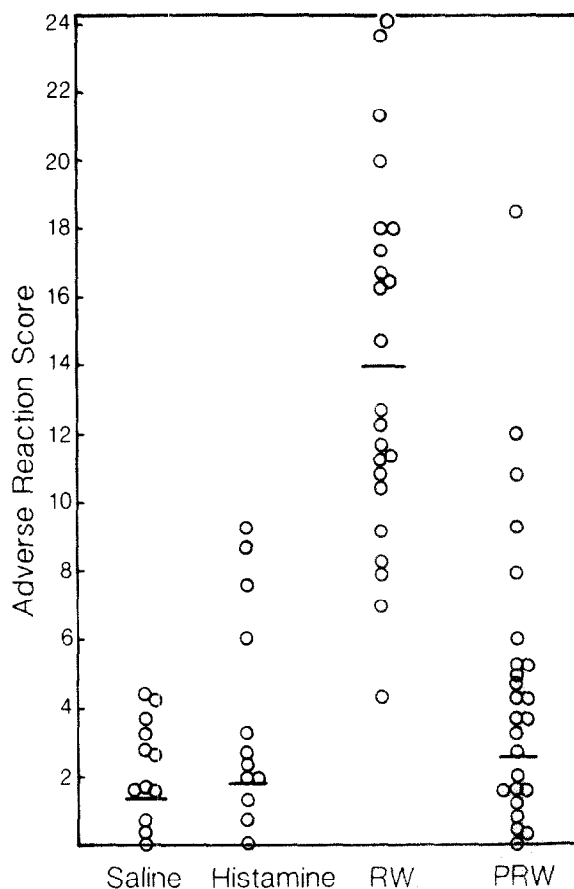


FIG. 1. Adverse reaction score by treatment group. Each circle represents an individual subject. Horizontal bars denote group means. RW vs PRW, RW vs histamine, RW vs saline: $p < 0.001$. PRW vs saline, PRW vs histamine, saline vs histamine: $p > 0.1$. (Mann-Whitney U Test.)

season before the code was broken. Each patient was asked for his/her overall evaluation of this season as compared to previous seasons, with categories of not improved, improved, or asymptomatic.

Patient acceptance of the treatment was evaluated by asking those who rated themselves as improved or asymptomatic

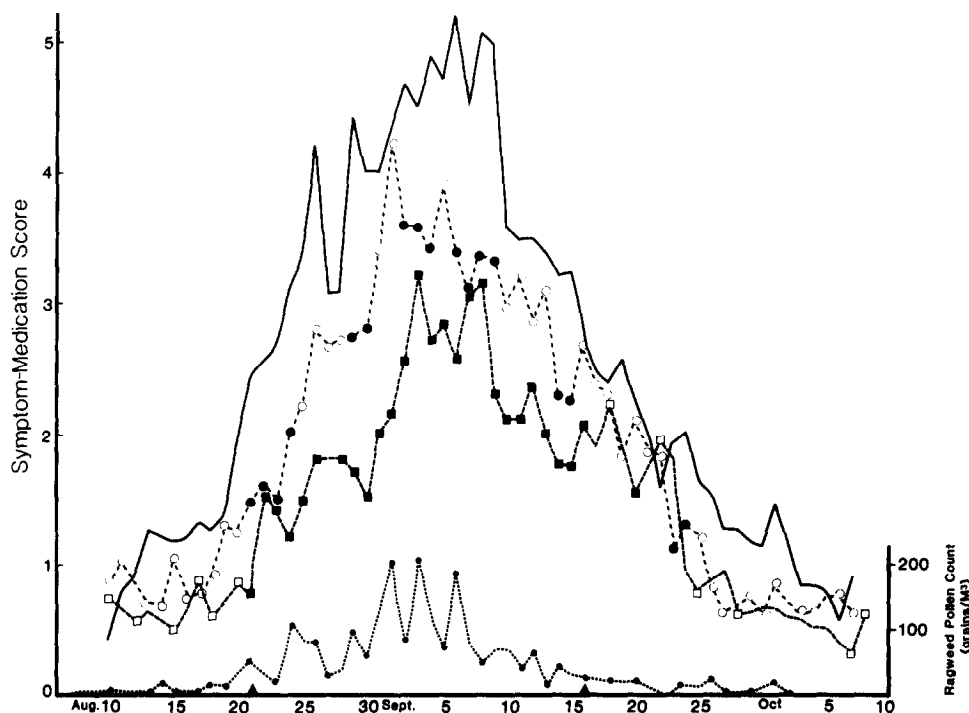


FIG. 2. Group mean daily symptom/medication score. Pollen counts are indicated at bottom (•---•). Solid line, Placebo; circles, RW; squares, PRW. Closed symbols indicate statistically significant differences from placebo.

matic whether the preseason adverse reactions and inconvenience were severe enough to counterbalance the seasonal benefit.

Pollen counts

Pollen counts were done daily with an intermittent rotorod sampler (Ted Brown Associates). Ragweed pollen counts were greater than 30 grains/m³ during the 27 days from 8/21/79 to 9/16/79 (Fig. 2). This period is called the peak pollen period.

Statistical analysis

Symptom/medication scores and adverse reaction scores were compared by nonparametric techniques (Mann-Whitney U test between groups, Wilcoxon's paired rank sum test within groups). Analysis of patients' self-evaluation was done with χ^2 analysis. NPT results were analyzed with either χ^2 or Wilcoxon's paired rank sum tests. Geometric means are reported for total IgE and IgE antibody levels.

RESULTS

Dropouts

Three patients withdrew from the study, one because of transportation problems and two because of adverse reactions to the treatment. Five patients were dropped from the analysis because of their failure to comply with the protocol (two because of inadequate records, one because of use of topical decongestant, and two because of leaving the area during the sea-

son). The 67 patients who completed the study are characterized in Table II. There are no statistically significant differences between the groups.

Therapy

RW and PRW patients complying with the protocol would have received 170 and 462 μ g of antigen E, respectively. The amount of antigen E actually delivered ranged between 3.9 to 109.4 μ g (59 ± 50) and 44 to 429 μ g (315 ± 110), respectively. There was no correlation between the amount of antigen E administered and the symptom/medication score in either group.

Seventeen patients were unable to reach the scheduled maintenance dose; 12 were in the RW group, three in the PRW group (RW vs PRW: $\chi^2 = 7.85$, $p = 0.005$), and two in the histamine group. Both patients who withdrew from the study because of adverse reactions were in the RW group.

All subjects experienced some adverse reactions, which were limited to the upper airways and conjunctivae. Sneezing, nasal itching, rhinorrhea, a burning sensation of the nose and throat, itchy throat, and watery eyes were reported. These reactions were usually brief but lasted up to 24 hr in some individuals. Two patients developed herpes labialis during the treatment period. When the severity of the adverse reactions is compared (Fig. 1), the saline, histamine,

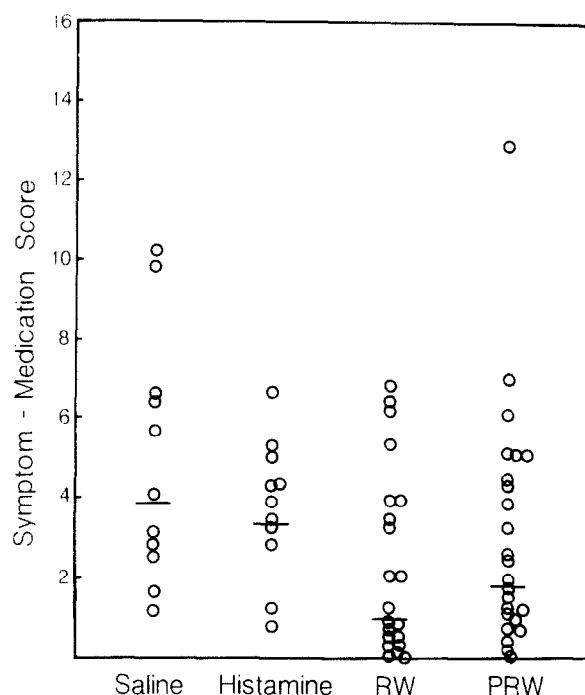


FIG. 3. Peak pollen period total symptom/medication score by treatment group. Each circle is an individual subject. Horizontal bars denote group means. RW vs placebo (saline + histamine), $p = <0.01$; PRW vs placebo, $p = <0.025$; RW vs PRW, $p > 0.1$. (Mann-Whitney U Test.)

and PRW groups do not differ statistically. The RW group had significantly higher adverse reaction scores than those of either of the other groups ($p < 0.001$).

Clinical response

Results for histamine- and saline-treated groups did not differ statistically in any of the parameters evaluated. Therefore they are considered together as a single placebo group in the following analysis.

The mean daily symptom/medication scores for each group are shown in Fig. 2. The placebo group had the highest daily score, the RW the lowest score, and the PRW group score was intermediate. When one compares the 27 consecutive days of peak pollen count (8/21 to 9/16), the mean daily symptom/medication score for the RW group was significantly lower than for placebo on 26 days. The PRW group differed significantly from placebo on 15 of 27 days. On only one day was there a significant difference between the RW and PRW groups.

Each patient's daily total symptom/medication score was averaged over the peak pollen period to obtain a 27-day mean symptom/medication score (Fig. 3). The ranges for each group were similar. The lower mean scores of the RW and PRW treatment group were caused by a clustering of symptom/

TABLE III. Group mean symptom/medication scores during 27 days of peak pollen count

	Symptom/medication score in treatment groups			Significance	
	P	RW	PRW	P vs RW	P vs PRW
Sneezing	2.16	1.25	1.94	<0.025	NS
Rhinorrhea	2.86	1.71	2.09	<0.01	0.05
Congestion	3.25	2.06	2.35	<0.025	NS
Eye symptoms	2.32	1.09	1.75	<0.005	NS
Overall severity	2.39	1.67	1.67	<0.025	<0.025
Medication	1.23	0.52	0.73	<0.01	<0.025
Average total score	3.93	2.12	2.76	<0.01	<0.025

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

medication scores in the low range in these groups. When group average symptom/medication scores are compared (Table III), the RW group differs significantly from placebo for sneezing, rhinorrhea, congestion, eye symptoms, overall severity, and medication, as well as for the average of all the scores (total score). The PRW group differs significantly from placebo in rhinorrhea, overall severity, medication, and total score.

The patient self-evaluation was as follows: In the placebo group 41% were classified as "improved." Seventy-one percent of the RW group were "improved" or "asymptomatic" (RW vs P: $\chi^2 = 4.06$, $p < 0.05$). Sixty-three percent of the PRW group were "improved" or "asymptomatic" (PRW vs P: $\chi^2 = 2.4$, $p < 0.1$).

Patient acceptance of the therapy was determined in the 49 subjects who had a good clinical response as indicated by a self-evaluation of "improved" or "asymptomatic." Six stated that the severity of the adverse reactions was such that they would not use this treatment on a yearly basis. Four of these were in the RW group, one in the PRW group, and one in the histamine placebo group. Two of these six had a self-evaluation of "asymptomatic."

NPT

Nasal sensitivity as measured by NPT is shown in Fig. 4. There were no statistically significant differences between the three groups at any time. In each group the pattern of NPT was similar. The lowest value was obtained before treatment, the highest value after treatment, and the postseason value was intermediate. In both actively treated groups (RW and PRW) the posttreatment value was significantly

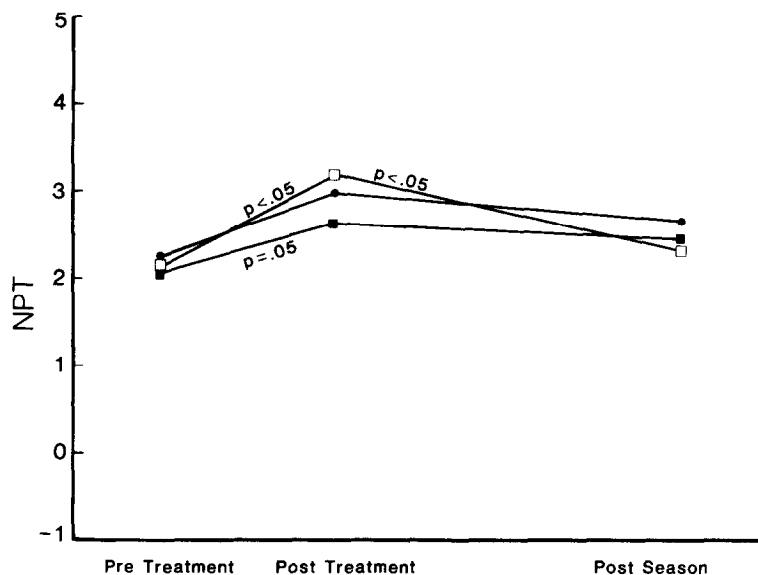


FIG. 4. Mean values of NPT scores by treatment group. ●, Placebo; ■, RW; □, PRW.

higher than the pretreatment value (Wilcoxon's paired sum test, $p < 0.05$). NPT at midseason is not shown because many patients were symptomatic at that time.

There is a positive correlation between a low pretreatment NPT (≤ 2) and a low seasonal symptom/medication score (≤ 3) (fourfold $\chi^2 = 9.09$, $p < 0.005$). The correlation between posttreatment NPT and symptom/medication score does not reach statistical significance ($\chi^2 = 1.48$, $p = 0.22$). When each treatment group was divided on the basis of NPT there was a trend for patients with a low NPT to have lower symptom/medication scores, but this did not reach statistical significance for any of the groups (Table IV). However, if one analyzes the differences between the daily symptom/medication score for each of the treatment groups, RW patients with a low NPT score (≤ 2) had a significantly lower symptom/medication score than that of the corresponding placebo patients on 24 of the 27 days of peak pollen count, and PRW patient scores were significantly lower than placebo on 22 of the 27 days. Patients with a high pretreatment NPT score (≥ 3) had a significantly lower symptom/medication score than that with placebo on 6 and 0 days for the RW and PRW group, respectively. These data are presented as group mean symptom/medication scores in Table IV.

There is also a statistically significant correlation between patient NPT and self-evaluation. When the entire study population is considered as a single group, a low pretreatment nasal sensitivity (NPT ≤ 2) correlates highly with an "improvement" on self-evaluation ($\chi^2 = 8.26$, $p < 0.005$). This correlation continues for the posttreatment NPT and postseason

NPT ($\chi^2 = 4.61$, $p < 0.05$; $\chi^2 = 13.72$, $p < 0.001$, respectively). This same trend is noted for each treatment group (placebo, RW, and PRW), although the numbers are small and do not reach the level of statistical significance.

DISCUSSION

This study demonstrates the efficacy of LNIT in the treatment of ragweed allergic rhinitis. Comparison of symptom/medication scores shows that RW and PRW are superior to placebo to a statistically significant degree, whereas only RW is significantly superior to placebo according to patient self-evaluation. RW appears more effective than PRW but this difference does not reach statistical significance.

This study is in mixed agreement with the previously reported blinded studies (Table V). Because the designs of these studies vary markedly, direct comparison is difficult. When one compares the studies that used unmodified extracts,¹³⁻¹⁵ the results have been generally favorable. Taylor and Shivalker¹³ and Welsh et al.¹⁵ showed statistically significant improvement in nasal symptoms. McLean et al.¹⁴ found a trend toward clinical improvement in the treated group, but this was not statistically significant and may have been caused by the low dose of antigen E used in that study.

Two other studies have used chemically modified allergens in LNIT.^{16, 17} In the study of Johansson et al.¹⁷ with glutaraldehyde-modified timothy grass extracts, the active treatment was superior to placebo. On the other hand, Mathews et al.,¹⁶ using the same glutaraldehyde-modified ragweed extract as that used

TABLE IV. Relationship of pretreatment nasal sensitivity (NPT) to seasonal symptom/medication scores

NPT score	Mean symptom/medication score in treatment groups			Significance	
	P	RW	PRW	P vs RW	P vs PRW
Low (≤ 2)	3.39	1.75	1.51	$p < 0.05$	$p < 0.001$
High (≥ 3)	4.58	2.46	4.02	$p = 0.05$	NS
Significance (high vs. low)	NS	NS	NS		

NS = not significant.

TABLE V. Controlled studies of local nasal immunotherapy

Study	Treatment	Amount	Symptom/medication score			
			Nasal	Eye	Med	NPT
Taylor and Shivalkar ¹³	Grass	NR	+	+	+	↓
Johansson et al. ¹⁷	Grass	280,000 PNU	+	—	—	↓
	Allergoid					
Welsh et al. ¹⁵	Ragweed	NR	+	+	NR	NR
McLean et al. ¹⁴	Ragweed	$< 7 \mu\text{g AgE}$	+ —	+ —	NR	NR
Mathews et al. ¹⁶	Polymerized ragweed	710 $\mu\text{g AgE}$	—	NR	—	↑
		63,000 PNU				
Present study	Ragweed	60 $\mu\text{g AgE}$	+	+	+	↑
	Polymerized ragweed	350 $\mu\text{g AgE}$	+	—	+	↑
		31,000 PNU				

+ = treatment benefit; — = no benefit; + — = beneficial but not statistically significant; ^ = increase after treatment; ↓ = decrease after treatment; NR = not reported.

in our study, found no difference between actively treated and placebo patients. Variations in the study design may be responsible for this disparity. Our patients were treated over a longer preseasonal period and were monitored at more frequent intervals during the treatment period. Differences in the degree of pollen exposure may also be of importance.

As in this study, reduction in nasal symptomatology has been reported after LNIT with both crude^{12–15} and chemically modified pollen extracts.¹⁷ Eye symptoms, however, improved only after treatment with crude extract^{13, 15} and not after LNIT with modified allergen.¹⁷ Our study is in agreement with these reports, showing a significant decrease in eye symptoms for the RW- but not for the PRW-treated groups. Differences in systemic availability of RW and PRW are thought to be responsible for this observation.

We used the NPT as an indicator of nasal sensitivity. If one compares nasal sensitivity to symptom/medication scores, the pretreatment NPT correlates roughly with seasonal symptom/medication scores (Table IV). There is a better clinical response to LNIT in patients with low nasal sensitivity than in those with a high sensitivity. Thus pretreatment NPT is both

a predictor of subsequent clinical severity and the clinical response to LNIT. This is in agreement with previous findings^{12, 23} and validates our use of the NPT as a main component in patient matching. The reason for the improved response to LNIT in patients with less nasal sensitivity to ragweed is not known. However, it does not seem to be a function of the amount of treatment extract that a patient could tolerate, since we found no correlation between the amount of extract actually administered to a patient and the clinical response.

Nasal sensitivity as measured by NPT did not decrease with treatment as predicted¹² but rather increased in all three treatment groups. This may be because of a "priming phenomenon."²⁴ We attempted to avoid this possibility by using every-other-day treatment but were without success. Because the increase in NPT score was also seen with placebo treatment, it is possible that priming can occur from nonimmunologic irritants. This phenomenon was recently tested by Bacon et al.,²⁵ who found that a nonspecific irritant, ammonia, would not prime the nasal mucosa. Another possible explanation is that the posttreatment NPT was done in the second

week of August. By that time the RW pollen was already present in low amounts (<6 grains/m³).

Adverse reactions, although localized to the upper airways, remain a significant problem. They interfered with the treatment in 14 of 24 RW patients and in three of 24 PRW patients. As expected, the PRW treatment resulted in markedly fewer adverse reactions. This is in accord with the study of Patterson et al.,²⁶ which demonstrated a 10⁵- to 10⁸-fold decrease in the antigenicity with endpoint skin titration. However, despite the sixfold higher amount of antigen E applied, the PRW group did not do as well clinically as did the RW group. Possible reasons for this are discussed in the accompanying paper.¹⁹

LNIT therapy is an effective treatment for ragweed allergic rhinitis. As with parenteral immunotherapy, it is neither uniformly nor completely effective. It does, however, have the advantage of being safe and can therefore be used at home. This increases the convenience and decreases the cost to the patient. Different treatment schedules must be studied in an effort to increase the efficacy of the treatment. Further studies are also needed to develop treatment strategies that will decrease the local side effects.

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