

Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma

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Experimental studies have demonstrated that induction of a nasal allergic reaction can lead to an increase in bronchial responsiveness (BR). To assess the clinical relevance of these experimental changes to chronic asthma, we sought to determine the effect of nasal beclomethasone dipropionate (Bdp) on BR in patients with seasonal allergic rhinitis and asthma. Eighteen subjects with histories of seasonal allergic rhinitis and asthma during the fall pollen season with positive skin tests to short ragweed and bronchial hyperresponsiveness to inhaled methacholine were assigned to receive either nasal Bdp (336 µg/day) or placebo for the entire ragweed season. Patients recorded daily nasal and chest symptoms, nasal blockage index, oral peak expiratory flow rates, and supplemental medication use. BR to methacholine was measured during the baseline period and 6 weeks into the ragweed season. Although the Bdp group did have a significant improvement in nasal blockage index, there was no improvement in daily asthma symptom scores, oral peak expiratory flow, or asthma medication use. However, subjects treated with Bdp were protected from the increase in BR seen in the placebo group (geometric mean PC₂₀ placebo group: baseline = 0.70, week 6 = 0.29; Bdp group: baseline = 0.80, week 6 = 0.93; intergroup difference, $p = 0.022$). We conclude that nasal corticosteroid therapy can prevent the increase in BR associated with seasonal pollen exposure in patients with allergic rhinitis and asthma. (J ALLERGY CLIN IMMUNOL 1992;90:250-6.)

Key words: Asthma, rhinitis, bronchial responsiveness, corticosteroids, ragweed allergy

Disorders of the upper respiratory tract, particularly allergic rhinitis, are commonly associated with asthma. Epidemiologic data indicate that allergic rhinitis often coexists with and may precede the development of reactive airways disease.¹⁻³ Welch et al.⁴ provided additional compelling evidence of an association between allergic rhinitis and asthma by demonstrating that nasal corticosteroids resulted in a significant improvement in seasonal asthma symptoms. Several investigators have sought to define the mechanism linking rhinitis to asthma by assessing lower

Abbreviations used

Bdp:	Beclomethasone dipropionate
BR:	Bronchial responsiveness
FEV ₁ :	Forced expiratory volume in one second
FVC:	Forced vital capacity
OPEF:	Oral peak expiratory flow rate
NBI:	Nasal blockage index
NPEF:	Nasal peak expiratory flow rate
PC ₂₀ :	Provocative concentration of methacholine causing a 20% drop in FEV ₁

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airway function after nasal challenge.⁵⁻¹¹ Although a variety of provocative substances have been shown to result in immediate bronchoconstriction,⁵⁻⁷ studies with use of allergen as the challenge material have failed to detect changes in pulmonary function.⁸⁻¹¹

More recent investigations have examined the effect of nasal allergen challenge on lower airway reactivity.^{12, 13} Although these studies again demonstrated that nasal allergen challenge did not alter airway caliber, they did show that induction of a nasal allergic reaction resulted in both immediate and late increases

in bronchial responsiveness (BR) and provided a link between allergic nasal disease and pulmonary physiology.^{12, 13} Although a single laboratory challenge has been shown to be capable of causing short-term increases in BR, it still remains uncertain whether nasal allergy plays a significant role in modulating BR during long-term allergen exposure. In the current study we therefore sought to investigate the effect of nasal corticosteroid therapy on lower airway responsiveness and clinical parameters of asthma after seasonal pollen exposure in patients with allergic rhinitis and asthma.

SUBJECTS

Patients with histories of mild seasonal rhinitis and asthma symptoms during August and September for at least 2 preceding years were selected for study. All subjects were required to have a positive skin prick test (≥ 3 mm wheal diameter¹⁴) to a full-strength extract of short ragweed pollen (100,000 allergy units per milliliter) and a heightened response to inhaled methacholine with $PC_{20} < 8$ mg/ml.¹⁵ Subjects were excluded from study if they had used nasal, pulmonary, or systemic corticosteroid preparations or cromolyn sodium within 3 months before beginning the study or if they had had an upper respiratory illness in the prior 6 weeks, had received allergy immunotherapy during the past 3 years, had any prior history of smoking during the year before entering the study, or were allergic to a pet that lived in their home. All subjects provided statements of informed consent, and the study protocol was approved by the Institutional Review Board of the National Jewish Center for Immunology and Respiratory Medicine.

STUDY DESIGN

We used a randomized, double-blind, placebo-controlled parallel study design. After a preliminary screening visit (history, physical examination, skin tests, and bronchial methacholine challenge) during the final 2 weeks of July 1990, patients were given a daily diary for recording hay fever and asthma symptoms, medication use, and oral peak expiratory flow rate (OPEF), and nasal peak expiratory flow rate (NPEF), to be started August 1. After the first (baseline) week of record-keeping, patients returned to the clinic to review their diaries and were randomized to receive either beclomethasone dipropionate (Bdp) nasal spray or placebo. They again returned 1 week later (week 2) to review their technique of medication use and 4 weeks later (week 6) to receive a fresh supply of study medication and perform their second methacholine challenge. Patients turned in all diaries and medication canisters at the final visit (week 8).

METHODS

Skin testing. Subjects had skin tests with full-strength extracts of short ragweed, Bermuda grass, timothy grass, *Alternaria tenuis*, and *Cladosporium herbarum* by use of the standard prick method.¹⁴ Histamine phosphate (1 mg/ml base) and glycerol saline were used as positive and negative controls, respectively. When indicated, skin

prick tests to animal danders were performed. Medications were withheld before skin testing according to standard guidelines.¹⁶

Methacholine challenge. BR was assessed by methacholine challenge testing, performed according to the guidelines of Chai et al.¹⁷ After establishing reproducible baseline forced expiratory volume in 1 second (FEV_1) values, subjects inhaled five inspiratory capacity breaths of normal saline followed by doubling concentrations of methacholine from 0.075 to a maximum of 25 mg/ml at 5-minute intervals, generated and delivered by a De Vilbiss 646 (De Vilbiss Health Care, Inc., Somerset, Pa.) nebulizer and Rosenthal-French (Laboratory for Applied Immunology, Baltimore, Md.) dosimeter. Measurements of FEV_1 and forced vital capacity (FVC) with use of a Collins' spirometer began 2 minutes after each dose, and forced expiratory maneuvers were performed twice. Percent change in FEV_1 was plotted against the log base 2 dose of methacholine, and PC_{20} was determined by linear interpolation. Pulmonary medications were withheld before all challenges according to ATS guidelines,¹⁸ and all challenges were performed at the same time of day in each patient.

Daily diaries. Evaluable nasal symptoms consisted of sneezing and/or pruritis, rhinorrhea, congestion, and ocular itching and chest symptoms of wheezing, chest tightness, and dyspnea. Both nasal and chest symptoms were scored as 0, none; 1, noticeable but intermittent; 2, mild; 3, mild to moderate; 4, moderate; 5, severe; and 6, very severe and were assessed during the evening.⁴ OPEF was measured each morning with use of a Mini-Wright (Clement Clarke International, Ltd., London, England) peak flow meter. The NPEF maneuver was conducted by having the patient expire maximally through the nose (with lips sealed) into a nasal adapter mask attached to a peak flow meter.¹⁹ Both maneuvers were performed in triplicate, with the highest value recorded. The nasal blockage index (NBI) was calculated as $NBI = (OPEF - NPEF)/OPEF$.²⁰

Study medications. Patients were randomized to receive either Bdp 0.042% nasal suspension (Vancenase AQ; Schering-Plough, Kenilworth, N.J.), two sprays (84 μ g) in each nostril twice daily or placebo nasal solution, two sprays twice daily, with use of an identical vehicle formulation and atomizer. Subjects were instructed to take their study medication after awakening and approximately 12 hours later. As a safeguard against aerosol delivery to the lower airways, the patients were instructed to inspire to total lung capacity before administering the nasal spray. Laser particle analysis of the aerosol demonstrated that the mass median particle diameter is 30 μ m, and that the percentage of particles in the easily-respirable range ($< 5 \mu m^2$) is $< 2.5\%$ (unpublished data).

Rescue medication for unrelieved nasal and chest symptoms consisted of dexbrompheniramine maleate with pseudoephedrine (Drixoral; Schering-Plough), one tablet twice daily, and albuterol metered-dose inhaler (Proventil MDI; Schering-Plough), two puffs every 4 hours, both medications taken as needed.

Pollen count

Airborne allergens were collected daily by use of an intermittent rotorod sampler (Ted Brown Associates, Los

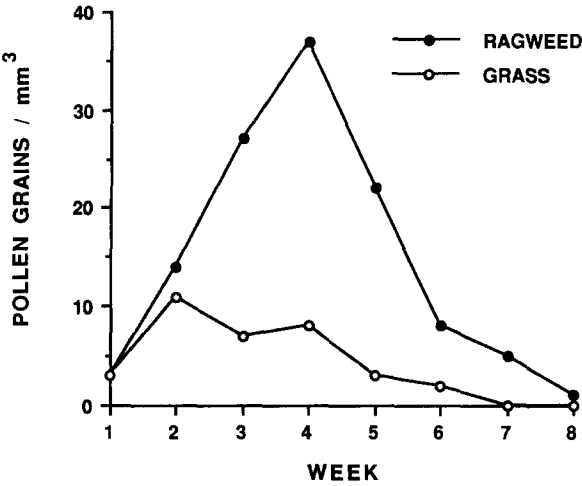


FIG. 1. Mean weekly pollen counts during 8 weeks of study expressed as grains per cubic meter (for the period of study from Aug. 1 to Sept. 26, 1990).

Altos Hills, Calif.). Pollen counts were performed daily and expressed as pollen grains per cubic meter.

Statistics

All data generated from the daily diaries (nasal symptoms, chest symptoms, OPEF, NPEF, and nasal and asthma medication use) were averaged on a weekly basis. Changes in these parameters were assessed between treatment groups by comparing the baseline week (week 1) with the peak of season (average of weeks 4 to 6) by use of the unpaired *t* test. Changes in FEV₁ and PC₂₀ were assessed between groups by comparing the baseline week with week 6 with use of the unpaired *t* test. All analyses of PC₂₀ were performed with logarithmically transformed data, and significant individual changes in BR were considered to be greater than one dilution of methacholine.¹⁵ Pearson correlations were performed between changes in PC₂₀ and changes in FEV₁, nasal symptoms, and NBI. All tests of hypotheses were two-tailed and performed at the 0.05 significance level.

RESULTS

Twenty-two patients were originally enrolled for study. Two of 10 patients started on placebo withdrew before study completion (one because of an upper respiratory infection and the other for uncontrolled rhinitis symptoms), and two of 12 subjects started on Bdp withdrew (one because of an upper respiratory infection, and the other was not able to be contacted). The characteristics of the remaining 18 patients who completed the trial are shown in Table I.

Mean weekly pollen counts are shown in Fig. 1. Ragweed pollen peaked during the fourth week of the study and then decreased. Grass pollen declined throughout the study, reaching very low levels by week 4.

TABLE I. Subject characteristics

Patient	Age (yr)	Sex	FEV ₁ (L)	FEV ₁ (%)	Atopic status	Meds
Placebo						
1	47	F	2.15	81	R,G	B
2	46	F	3.27	114	R	B
3	38	F	2.65	92	R,G	—
4	21	F	2.57	82	R,G	B,T
5	31	F	3.02	94	R,G,M	T
6	20	F	2.48	78	R,M	B
7	37	M	3.64	82	R,G,M	B
8	41	F	3.15	105	R,G,M	B
Mean	35.1		2.87	91.0		
(SEM)	(3.6)		(0.18)	(4.5)		
Nasal Bdp						
1	43	F	2.82	99	R	—
2	43	F	2.88	92	R	B
3	25	M	4.07	79	R,G,M	B
4	41	F	2.69	100	R,G,M	B
5	29	M	3.89	89	R,G,M	B,T
6	40	M	3.98	108	R	B
7	39	F	3.02	108	R,G	B,T
8	19	F	2.66	77	R,G,M	B
9	41	F	3.00	105	R	—
10	41	M	3.52	99	R,G,M	B
Mean	36.1		3.25	95.6		
(SEM)	(2.7)		(0.18)	(11.1)		

R, Short ragweed; G, grass; M, outdoor mold; B, inhaled beta-agonist; T, theophylline.

Data from the daily diaries were used to compute averages for nasal symptoms, chest symptoms, OPEF, NBI, and medication use at baseline and during the peak of the pollen season and are presented in Table II. All of these parameters were comparable between the two treatment groups during the baseline period. Although nasal symptoms appeared to worsen (increase) mildly in subjects receiving placebo and improve (decrease) in the Bdp group, differences between the two groups were not significant. Mean daily asthma symptoms also increased in the placebo group and decreased in the Bdp group, but were not significantly different between the two groups. Whereas morning NBI worsened in the placebo group, it improved in the group receiving Bdp (intergroup difference, *p* = 0.03). Morning OPEF values did not change in either treatment group, and there were no significant differences in the amount of supplemental medications required for rhinitis or asthma symptoms (data not shown).

FEV₁ was similar in the two groups at baseline and remained unchanged during week 6 (placebo: baseline 2.87 ± 0.18 L, peak 2.88 ± 0.16; Bdp: baseline 3.25 ± 0.18, peak 3.17 ± 0.21). Similarly, bron-

TABLE II. Daily diaries

Patient	Nasal symptoms		Chest symptoms		NBI		OPEF	
	Baseline	Peak	Baseline	Peak	Baseline	Peak	Baseline	Peak
Placebo								
1	1.71	1.29	0.43	1.52	0.38	0.39	505	487
2	7.67	5.04	2.83	3.09	0.56	0.86	447	502
3	7.00	11.95	1.00	6.52	0.68	0.59	330	239
4	3.57	1.90	1.86	0.05	0.58	0.49	323	319
5	7.57	10.38	3.86	5.00	0.27	0.63	451	442
6	2.43	1.81	2.71	0.52	0.66	0.58	450	455
7	5.67	6.86	2.00	2.81	0.57	0.69	563	585
8	2.43	4.19	1.57	1.62	0.55	0.44	385	430
Mean	4.76	5.43	2.02	2.64	0.53	0.58	432	433
(SEM)	(0.88)	(1.43)	(0.39)	(0.78)	(0.05)	(0.05)	(29)	(38)
Nasal Bdp								
1	2.14	0.74	0.43	0.31	0.28	0.22	486	475
2	7.00	4.57	3.86	3.62	0.49	0.28	418	455
3	4.56	0.86	1.29	1.38	0.37	0.28	495	550
4	5.43	8.33	6.57	9.18	0.47	0.23	392	366
5	1.00	0.28	7.15	4.85	0.34	0.28	520	520
6	8.57	6.48	3.86	3.19	0.31	0.24	582	602
7	3.57	9.24	1.0	2.64	0.18	0.21	479	481
8	7.33	6.51	4.67	2.88	0.52	0.32	300	282
9	9.60	12.00	0	0	0.54	0.57	406	408
10	2.60	0.43	0.80	0.52	0.40	0.29	557	549
Mean	5.18	4.94	2.96	2.78	0.41	0.29	464	467
(SEM)	(0.92)	(1.34)	(0.83)	(0.85)	(0.05)	(0.03)	(27)	(31)
p value*	NS		NS		P = 0.03		NS	

*Intergroup difference.

chial hyperresponsiveness to methacholine was comparable at baseline in the two treatment groups (Fig. 2). However, after 6 weeks of pollen exposure, the PC₂₀ of the placebo group decreased, whereas the PC₂₀ of the Bdp group remained relatively unchanged (geometric mean [95% confidence intervals] placebo; baseline = 0.70 mg/ml [0.30 to 1.63], peak = 0.29 mg/ml [0.12 to 0.73]; Bdp; baseline = 0.80 mg/ml [0.37 to 1.71], peak = 0.93 mg/ml [0.34 to 2.53]; intergroup difference, $p = 0.022$). Of note, seven of eight patients receiving placebo exhibited a significant (>one dilution) decrease in PC₂₀. Correlations between changes in FEV₁ and changes in PC₂₀ were not significant in either treatment group, nor were correlations between changes in nasal symptoms or NBI and changes in PC₂₀.

DISCUSSION

Many physicians note that there is a relationship between allergic rhinitis and bronchial asthma. Recent investigations have defined a possible pathogenetic link between these two disorders, showing that nasal allergen challenge leads to an increase in BR.^{12, 13} In

an attempt to demonstrate relevance of these experimental results to chronic asthma, the current study clearly demonstrated that nasal corticosteroid therapy prevented the increase in BR associated with seasonal allergen exposure in patients with mild asthma.

Although daily nasal symptom scores were moderately better in the group treated with nasal corticosteroids, these changes did not reach statistical significance. Nasal corticosteroid treatment did, however, provide a significant improvement in nasal patency as measured by NBI. Neither lower airway symptoms nor OPEF were improved in the group treated with nasal Bdp. This may in part reflect the type of subjects who were selected to participate in the study. To avoid the confounding effects of inhaled antiinflammatory medications on BR, we intentionally chose patients with histories of mild asthma who had not required cromolyn or corticosteroids during the preceding 3 months or during prior ragweed seasons. In addition, detection of significant changes in asthma symptom scores may have been made difficult by the small number of subjects enrolled in the study. A recent trial of inhaled cromolyn performed on a small

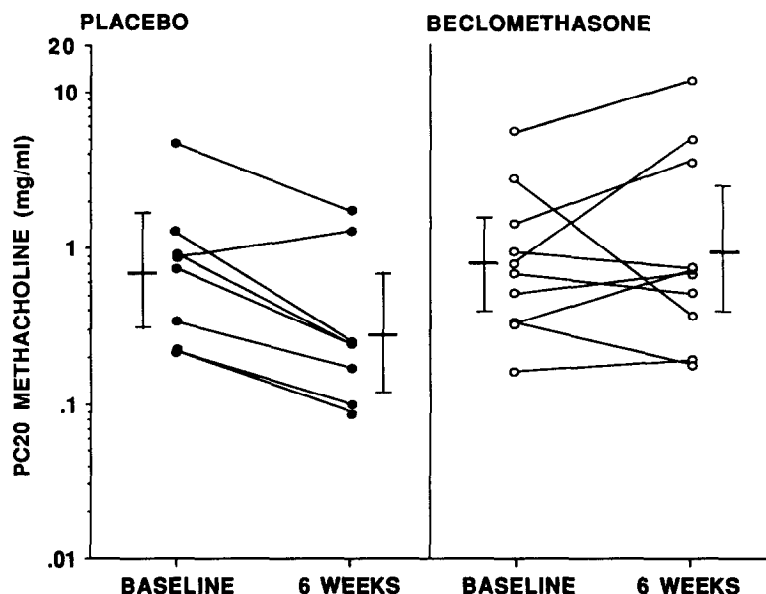


FIG. 2. PC₂₀ values expressed as milligrams per milliliter of methacholine for individual subjects at baseline and after 6 weeks of study. Geometric mean values denoted by horizontal bars with 95% confidence intervals. Intergroup difference comparing change from baseline, $p = 0.022$.

number of subjects with mild asthma was also unable to show improvement in asthma symptoms or OPEF despite demonstrating significant improvement in BR.²²

A primary goal of this investigation was to determine the effect of nasal Bdp on the development of BR after seasonal allergen exposure. Our results demonstrated a marked, statistically significant difference in BR between the two treatment groups (Fig. 2). The increase in airway reactivity in the placebo group after a single pollen season is consistent with changes reported from other studies, which have been on the order of one- to two-doubling dilutions of methacholine.^{22, 23} This increase in responsiveness was completely prevented by nasal corticosteroid treatment. It is important to note that the changes in BR occurred independently of any changes in baseline airway caliber.

We attempted to determine whether any aspect of the nasal allergic response was associated with the changes in BR. We correlated the changes in NBI, total nasal symptom score, and individual component nasal symptom scores with changes in responsiveness. None of these measures of rhinitis correlated with the changes in BR. Although our sample size is small, making such correlations difficult, the current results suggest that no specific alteration in nasal physiology can be used to predict changes in lower airways responsiveness.

A variety of mechanisms have been proposed to explain the link between upper and lower airways disease. These include (1) elicitation of a nasal-bronchial reflex; (2) increased oral inhalation of cold, dry

air or airborne allergen; (3) postnasal drainage of inflammatory material into the lower airways; (4) absorption of mediators or chemotactic factors; (5) diminished beta-adrenergic responsiveness.²⁴ Several of these mechanisms may have contributed to the results seen in our study.

As mentioned earlier, recent investigations suggest that BR to methacholine may occur immediately after nasal provocation without altering airway caliber.^{12, 13} It has been suggested that rapid changes in BR are likely to be a result of nasal reflexes, possibly acting through irritant receptors.²⁵ Corticosteroid therapy, which has been demonstrated to reduce mediator release from resident cells and retard influx of inflammatory cells into the nasal mucosa, would be expected to reduce the intensity of the stimulus triggering a neural reflex.

Previous work has shown that nasal breathing can reduce exercise-induced asthma,²⁶ most likely because of the warming and humidification of inspired air before it reaches the lower airways.²⁷ The upper airways also affect deposition of airborne allergens into the lower airways. Since the nose effectively filters a broad size range of airborne particles during normal function,²⁸ ragweed pollen allergens would be far less likely to penetrate into the lower airways during periods of normal nasal function than during periods of oral breathing. The improvement in NBI that we observed may be important in this regard, but the lack of correlation to improvement in PC₂₀ suggests other factors are important.

Postnasal drip of allergen-induced inflammatory products may also play an important role in increasing

BR. In an animal model of rhinosinusitis, induction of nasal inflammation resulted in increased BR to histamine without causing airflow limitation.²⁹ This increase in lower airway reactivity was prevented by strategies that blocked drainage of nasal secretions into the lower airways. A variety of mast cell and eosinophil-derived mediators released during allergic reactions may contribute to increases in BR after allergen exposure.^{30, 31} By reducing the release of mediators and influx of inflammatory cells that cause the nasal allergic response, topical nasal corticosteroids may help prevent subsequent changes in BR.

An alternative explanation for the success of nasal corticosteroids in protecting BR in this study is the possibility that corticosteroids may have reached the lower airways either directly through aerosolization and aspiration or by systemic absorption via the nasal or gastrointestinal mucosa. Several factors militate against these possibilities as explanations of the current results. Direct aerosolization of the medication into the lower airways was unlikely, since the particles generated by the atomizer were large (mass median diameter, 30 μ m). In addition, patients were carefully instructed to administer the nasal spray during breath-holding at total lung capacity, which would also help prevent aerosol deposition of the medication into the lungs. Aspiration of corticosteroid was also unlikely, since patients administered the spray during waking hours (7 AM and 7 PM) and aspiration of oropharyngeal contents in normal subjects is usually limited to periods of depressed consciousness.³² Finally, although nasal beclomethasone can be systemically absorbed from both nasal tissue and the gastrointestinal tract, first-pass hepatic degradation to inactive metabolites would be expected to minimize effects of the absorbed drug on lung physiology.^{33, 34}

This study provides additional evidence that allergic rhinitis may have a significant effect on lower airway reactivity. On the basis of these current results as well as prior studies, rhinitis should be considered and treated aggressively in all individuals with allergic asthma. Studies of larger groups of patients with more severe asthma will be important in demonstrating significant improvement in lower airway symptoms and peak flow rates.

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Treatment of peanut allergy with rush immunotherapy

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Peanut and peanut products are a common food in the diet. Peanuts are also one of the most common foods responsible for food-induced anaphylaxis. Patients rarely lose sensitivity to peanuts. Although the ideal treatment is avoidance, this is often not possible because of hidden exposures; therefore, a more effective treatment is needed. Subjects with confirmed peanut allergy were treated in a double-blind, placebo-controlled study with peanut immunotherapy or placebo. Objective measures of efficacy included changes in symptom score during double-blind placebo-controlled peanut challenge (DBPCPC) and titrated end point prick skin tests (PST). Three subjects treated with peanut immunotherapy completed the study. These subjects displayed a 67% to 100% decrease in symptoms induced by DBPCPC. Subjects also had a 2- to 5-log reduction in end point PST reactivity to peanut extract. One placebo-treated subject completed the study. This subject had essentially no change in DBPCPC symptom scores or PST sensitivity to peanut. Two other placebo-treated subjects underwent a second PST session. These subjects had a 1- to 2-log increase in skin test sensitivity to peanut. All peanut-treated subjects were able to reach maintenance dose, and in no case did an anaphylactic reaction occur secondary to the peanut immunotherapy. The current study provides preliminary data demonstrating the efficacy of injection therapy with peanut extract and provides a future line of clinical investigation for the treatment of this potentially lethal disease. It should be noted, however, that the rate of systemic reactions with rush immunotherapy was 13.3%. Thus, at the present time, this therapy should only be considered investigational and done only in research settings with intensive care unit support immediately available. (J ALLERGY CLIN IMMUNOL 1992;90:256-62.)

Key words: Peanut allergy, rush immunotherapy, allergy immunotherapy, anaphylaxis

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Although peanuts and peanut products are common foods in the diet, they are also a frequent cause of food allergy. In a review of fatalities from food-induced anaphylaxis, four of seven cases were due to peanut.¹ Sensitivity to peanuts appears early in life and, once established, persists indefinitely. In a study performed at National Jewish Center, none of the 32 patients with peanut allergy followed for up to 16 years had lost their clinical sensitivity, and despite attempts to avoid this allergen, 75% of patients had accidentally ingested peanuts during the 5 years pre-