

Nasal provocation with allergen induces a secondary serum IgE antibody response

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The study of the IgE response to seasonal antigen exposure is limited by its occurrence once a year and by the variability of patient exposure to pollens. To overcome these problems, we investigated whether nasal challenge with antigen causes an increase in serum anti-ragweed IgE levels. We challenged individuals with ragweed allergy intranasally with nanogram quantities of ragweed antigen extract and measured their serum anti-ragweed IgE levels before and at weekly intervals after challenge. In a series of studies we found that there was a reproducible rise in antigen-specific serum IgE levels beginning the first week after challenge that plateaued at about 180% of baseline levels during the fourth week and remained elevated for 8 weeks. Not all individuals showed this response. The magnitude of the allergen-specific IgE response to nasal challenge appeared to be greater than the response to seasonal exposure. Treatment with intranasal beclomethasone before challenge did not affect the response. The results demonstrate a human *in vivo* model for the study of the antigen-specific secondary IgE response to allergen. (*J Allergy Clin Immunol* 1997;100:505-10.)

Key words: IgE, nasal challenge, beclomethasone, human, antigen, allergic rhinitis

The development of specific IgE antibodies against aeroallergens is essential to the sensitization phase of allergic rhinitis and is a hallmark of the disease. Once sensitized, the serum levels of specific IgE antibodies increase with seasonal exposure and decline slowly in the months after the season.^{1,2} The significance of this secondary immune response in maintaining inflammation or in perpetuating the allergic condition is unknown. Both topical steroids and immunotherapy affect this response.¹⁻³ It is conceivable that without seasonal stimulation, the level of IgE would fall, and the natural history of the disease might be altered.

Seasonal increases in allergen-specific IgE antibody levels provide a starting point for studying the influence of drugs and immunotherapy on the secondary humoral response but are limited by yearly occurrence and variable antigenic exposure. To circumvent these problems,

Abbreviation used

TAME: N- α -tosyl-L-arginine methyl ester

we investigated whether nasal antigen challenge causes a rise in allergen-specific IgE antibody responses. This model would allow us to control the dose of antigen used, while maintaining the natural route of exposure. Furthermore, it would help in elucidating the mechanism of the secondary humoral response, which might provide insight into the control of primary IgE synthesis. Better knowledge of the mechanism of IgE antibody production may also lead to novel ways to improve the therapy of allergic respiratory conditions.

METHODS

Study design

A series of studies was performed. First, we measured allergen-specific serum IgE levels before challenge and then weekly, for 4 weeks, after challenge with ragweed antigen extract on 3 consecutive days. The decision to challenge for 3 days was made arbitrarily with the idea that this would mimic repeated seasonal exposure and maximize the effects of antigen on the nasal mucosa. Second, to assess the reproducibility of the response we repeated the experiment in a subset of the original patients. Third, a group of patients with ragweed-induced allergic rhinitis was followed up through a season and then challenged with ragweed extract 3 months after the season and followed up for 8 weeks. Serum IgE antibody levels were obtained before, in the middle, and after the season and again before and at weekly intervals after the allergen challenges. Finally, a double-blind, placebo-controlled, parallel study was performed to examine the effect of treatment with aqueous beclomethasone dipropionate on the allergen-induced IgE antibody response.

Subjects

Volunteers who were in good health, other than having a history of allergic rhinitis or mild asthma, were selected. Seasonal allergic rhinitis was defined by a history of symptoms of rhinorrhea, nasal congestion, or sneezing during seasonal exposure and a positive skin test response to ragweed antigen extract.

Nasal challenge

Standardized ragweed extract, and the diluent for the extract (phenol-buffered saline), were purchased from Greer Laboratories (Lenoir, N.C.). The extracts were delivered by spraying 0.12 ml from a metered-dose bottle. Challenges follow our previously published protocol.⁴ After a series of lavages to bring

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Supported in part by National Institutes of Health grant RO1 DC 02714 and Allen & Hanburys.

Received for publication July 6, 1995; revised May 12, 1997; accepted for publication May 19, 1997.

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0091-6749/97 \$5.00 + 0 1/1/83342

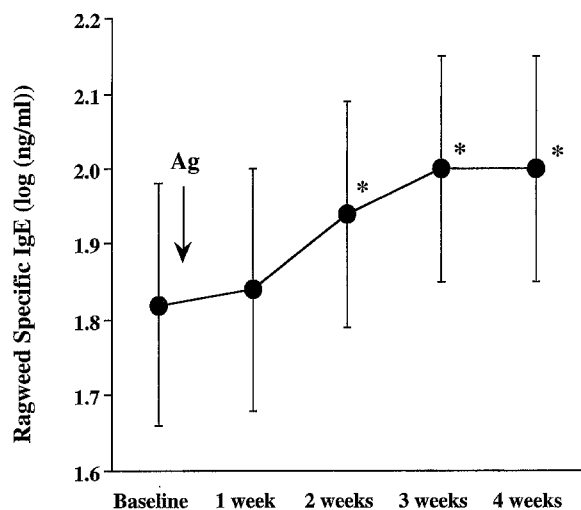


FIG. 1. Serum anti-ragweed IgE response to nasal challenge. Patients were challenged intranasally with ragweed antigen, and their serum was analyzed for ragweed-specific IgE antibodies before and weekly for 4 weeks after challenge ($n = 17$). $*p < 0.05$ compared with baseline. Values are geometric mean $\pm$ SD. Ag, Antigen.

the concentration of nasal mediators to baseline, oxymetazoline hydrochloride was applied topically to the nasal mucosa to prevent mucosal congestion, which interferes with lavage. Prior experiments have shown that oxymetazoline does not interfere with sneezing or histamine release.⁴⁻⁷ After two control challenges with diluent, increasing doses of ragweed (10, 100, and 1000 AU) were instilled into the nose. The dose of antigen delivered per challenge was approximately 4 μ g of Amb a 1. Ten minutes after each administration of diluent or antigen, a 5 ml nasal lavage was performed. During the experiment, subjects evaluated symptoms and recorded the number of sneezes. The nasal lavages were processed for the measurement of histamine and N- α -tosyl-L-arginine methyl ester (TAME) esterase activity.

Histamine was assayed by an automated fluorometric method capable of detecting as little as 1 ng/ml with an accuracy of $\pm 5\%$.⁸ The assay for TAME esterase activity measures proteases with arginine esterase activity and is essentially that of Imanari et al.,⁹ with tritiated TAME (Amersham). Proteases possessing arginine esterolytic activity hydrolyze the TAME, liberating tritiated methanol. In the immediate response to antigen, approximately 75% of the activity represents plasma kallikrein complexed to α_2 -macroglobulin, 20% represents mast cell tryptase, and less than 5% represents glandular kallikrein.^{10, 11}

Measurement of allergen-specific IgE in serum

The RAST used in this study has been previously described.¹² Briefly, ragweed was insolubilized onto CNBr-activated Sepharose CL-4B particles (Pharmacia) and then sequentially incubated with either a reference serum or unknown sera and iodine 125-labeled rabbit anti-human IgE. Bound radioactivity was quantified in a multi-well by using gamma counter and bound counts per minute were interpolated from a reference serum dilution curve into nanograms per milliliter of IgE anti-ragweed. The IgE anti-ragweed content of the reference serum was calibrated with depletion analysis.¹³ The analytical sensitivity of this RAST is 1 ng/ml.¹² All sera were coded and analyzed in a

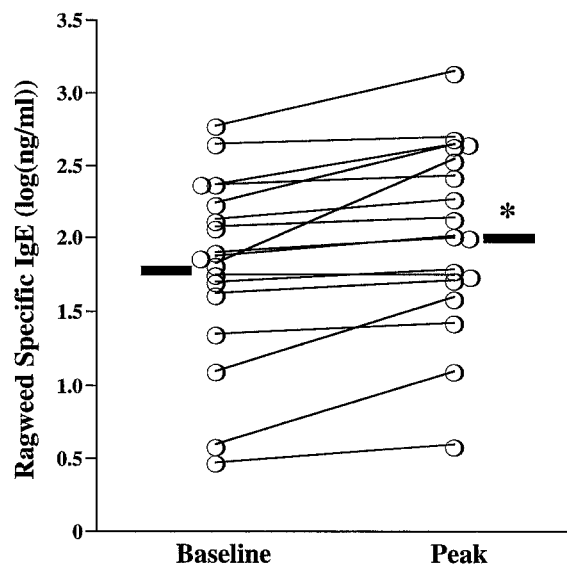


FIG. 2. Individual responses to nasal challenge. Initial level of ragweed-specific IgE antibodies for each individual is paired with peak IgE antibody responses after challenge ($n = 17$). $*p < 0.05$ compared with baseline. Solid bars indicate geometric mean levels.

blinded manner by laboratory personnel. All sera from a given individual were stored frozen and run in the same assay to minimize random error relating to inherent assay variation.

Statistical methods

Parametric and nonparametric statistical methods were used to analyze results. For evaluation of the changes in both mediator levels and symptom scores after the nasal challenge, differences from baseline were analyzed nonparametrically. The log of serum IgE levels is normally distributed.¹³ Thus IgE levels were log-transformed and analyzed with parametric statistics. The Wilcoxon matched-pairs signed-rank test (nonparametric analysis) and Student's paired t test (parametric analysis) were applied for paired data analysis. The unpaired Student's t test was used for the comparisons between the groups treated with either placebo or intranasal steroids. We used the Spearman rank correlation coefficient to compare changes in the nasal response with changes in the level of allergen-specific IgE antibody. Routine statistical tests were performed with the Statview II (Abacus Concepts, Inc.) software package for the Macintosh computer (Apple Computer, Cupertino, Calif.).

RESULTS

Seventeen individuals allergic to ragweed had blood collected and were then challenged intranasally with ragweed antigen extract on 3 consecutive days. The levels of serum anti-ragweed IgE antibodies remained relatively unchanged 1 week after the first challenge (Fig. 1). These levels increased significantly at 2 weeks and remained significantly elevated at weeks 3 and 4. On examining the data for each subject, 16 of 17 patients showed an increase in serum antibody when levels were compared before the challenge with peak values after the challenge (Fig. 2). The mean values increased from 1.73 ± 0.14 to 1.97 ± 0.15 (log [ng/ml]). Many of these

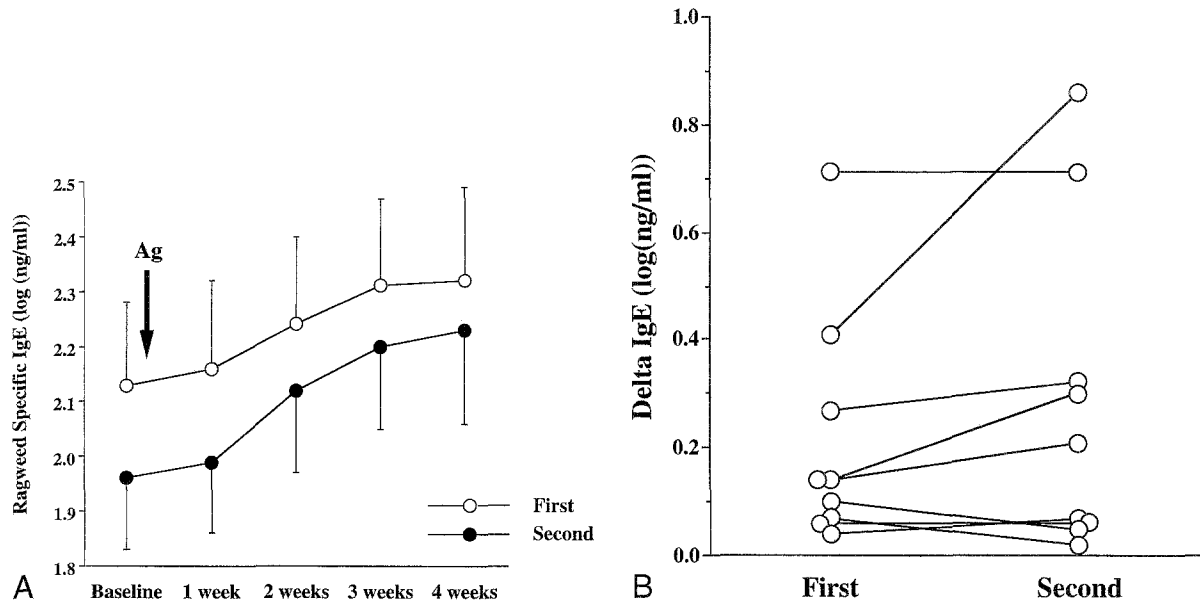


FIG. 3. Reproducibility of the IgE antibody response to antigen challenge. **A**, Individuals were challenged with ragweed on two different occasions, and their serum anti-ragweed IgE antibody response followed. The IgE antibody levels at baseline were significantly different. On both occasions, ragweed challenge induced a significant increase in ragweed-specific IgE antibodies. Ag, Antigen. **B**, Changes from baseline to peak were not different after the two challenges ($n = 9$).

changes are modest. We do not have data on the subjects followed up over the same period without challenge to assess the spontaneous variability of the measurement to provide a reference for the magnitude of a "meaningful change." In two subjects allergic to both ragweed and grass who were challenged with ragweed, the mean maximum increase in the amount of IgE antibodies to grass was 7%, compared with the 100% increase for ragweed. If a 7% increase is considered to be a meaningful change, 16 subjects showed an increase. If a 15% increase, a high estimate of the intraassay variability, is considered to be meaningful, then 13 of 17 subjects showed a meaningful increase. If a 0.17 log change is assumed, the difference between the levels after 1 year (see below) showed a meaningful increase in six patients after challenge.

In 13 of the 17 subjects, the relationship between the nasal and humoral responses to antigen challenge was examined. The correlations between the initial nasal response (as assessed by sneezing, the levels of histamine, or TAME esterase activity) and the initial serum ragweed IgE level were $r_s = 0.31, 0.45,$ and 0.48 , respectively. These values did not reach statistical significance. They are, however, similar to those we previously reported in a larger patient group in which significance was obtained.¹⁴ Priming, as defined by the change in responsiveness to nasal challenge for each response between the first and subsequent antigen challenges, showed no correlations with the IgE antibody responses.

To evaluate the reproducibility of the response, we repeated the nasal challenge protocol in nine of the original 17 volunteers approximately 1 year later. All

nine individuals who responded after the first challenge responded to the second challenge. The prechallenge anti-ragweed IgE levels, however, were significantly different (2.13 ± 0.15 vs 1.96 ± 0.13 log [ng/ml], $p < 0.02$) (Fig. 3, A) between the two studies, with the second year being less than the first. Despite this, the antibody levels increased significantly after challenge in both studies. The total change over baseline (the sum of the differences from the baseline IgE antibody level for the subsequent 4 weeks) was not different for the two challenges (0.51 ± 0.19 vs 0.69 ± 0.26 log [ng/ml], $p = 0.4$), and neither was the change from baseline to peak (Fig. 3, B).

In the third set of experiments, eight subjects allergic to ragweed had blood drawn for serum before, during, and 1 month after ragweed season. Six of the eight subjects showed an increase in serum-specific IgE after seasonal exposure. The levels of anti-ragweed antibody increased from 1.50 ± 0.12 to 1.52 ± 0.13 and 1.57 ± 0.11 log (ng/ml) ($p = 0.13$) (Fig. 4). Three months after the season, the specific antibody level decreased to 1.46 log (ng/ml). Nasal antigen challenge for 3 days induced increases in serum-specific IgE in all eight subjects. The specific antibody levels were significantly elevated, including 1 week after challenge. Eight weeks after challenge, the levels of ragweed-specific IgE antibodies remained significantly elevated and did not show evidence of declining. The peak increase in ragweed-specific IgE levels that occurred after antigen challenge was greater than that induced during ragweed season.

Finally, we studied the effect of treatment with 168 μ g of aqueous beclomethasone dipropionate, taken twice a

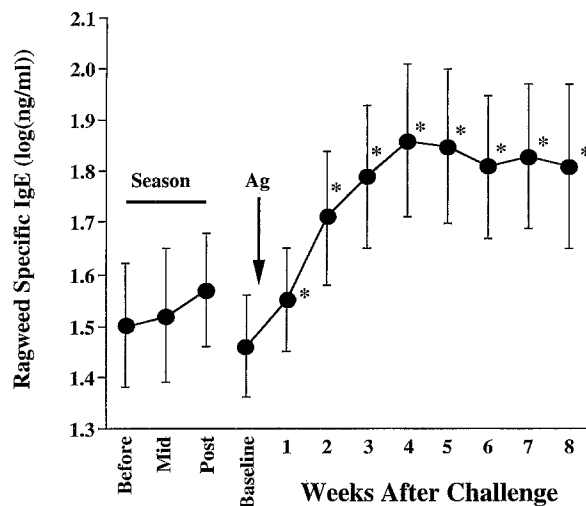


FIG. 4. Comparison of the IgE antibody response to season and challenge. Subjects had blood drawn for serum before, during, and immediately after the ragweed pollen season. Three months after the pollen season, blood was again drawn for serum, and the subjects were challenged with ragweed allergen. Their serum IgE antibody levels were monitored weekly for the next 8 weeks ($n = 8$). * $p < 0.05$ compared with baseline. Ag, Antigen.

day for 7 days before the intranasal challenges and continued throughout the challenges, on the specific IgE antibody response. Twenty-six subjects allergic to ragweed were randomized to receive treatment with aqueous beclomethasone or placebo. The levels of ragweed-specific IgE found at the initiation of this study were not significantly different between the two groups (Fig. 5). Nasal challenge with ragweed antigen produced a significant increase in the level of ragweed-specific serum IgE in both groups ($p < 0.05$), with no significant difference detected between treatment protocols. In the placebo group 11 of 13 responded to challenge by increasing their serum-specific IgE, whereas 10 of 13 undergoing topical steroid treatment responded.

DISCUSSION

Our results clearly demonstrate that nasal provocation with ragweed antigen induces a secondary, antigen-specific IgE antibody response that has not been previously shown. This result is not surprising because local, intranasal, ragweed immunotherapy can cause a rise in ragweed-specific IgE¹⁵ and seasonal exposure causes a rise in specific IgE antibody levels.

Studying the disease in our *in vivo* model allowed investigation of the kinetics of the response. The IgE antibody response caused by nasal provocation plateaus approximately 4 weeks after challenge and remains elevated for at least 8 weeks. Because the serum half-life of IgE antibody is approximately 2½ days, the ragweed-specific IgE antibody must be continually produced throughout this period. Whether the production occurs locally in the nose or in distant lymphatic tissue is unknown. The response occurs in essentially all individ-

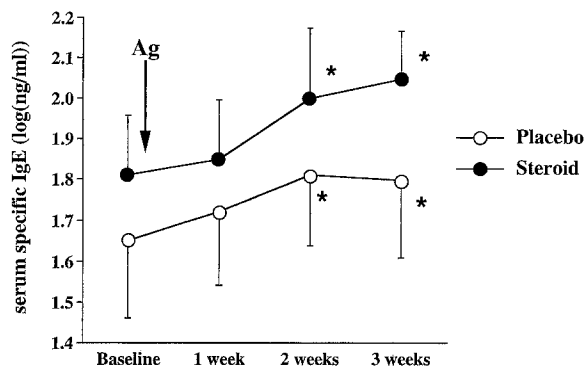


FIG. 5. Effect of intranasal beclomethasone on the secondary IgE antibody response. A double-blind, placebo-controlled, parallel study was conducted with 168 μ g of beclomethasone dipropionate aqueous twice per day, beginning before challenge and continuing throughout the nasal challenge protocol ($n = 13$ for each group). No significant differences were found between treatments at any point ($p > 0.1$). However, both groups demonstrated significant rises in ragweed IgE over baseline at 2 and 3 weeks. * $p < 0.05$. Ag, Antigen.

uals regardless of their initial level of anti-ragweed IgE antibodies.

The relatively poor correlation between the immediate response to nasal challenge and the serum IgE antibody response suggests that these two components of the immune system are independent. This observation is not unexpected, considering the multiplicity of nasal events associated with mast cell degranulation and the end-organ responses to released mediators.

Individuals responding to natural ragweed exposure with increases in their levels of ragweed IgE antibodies also had an increased IgE antibody response after nasal challenge with ragweed, with the response to ragweed challenge being greater than that after seasonal exposure. Furthermore, some individuals who did not respond with increases in IgE antibodies after natural exposure did respond to challenge. These comparisons suggest that the dose of ragweed arbitrarily chosen for the 3 days of nasal challenges exceeded the subjects' seasonal antigen exposure.¹⁶ With air-conditioned cars and homes and the tendency for more individuals to work in modern, climate-controlled buildings, the level of exposure to allergens can be quite small and can vary greatly between individuals living in the same locale. This idea is supported by epidemiologic studies showing greater symptoms on weekends compared with weekdays in patients working Monday through Friday in an air-conditioned building.¹⁷ Unfortunately, there is no way to directly measure the quantity of pollen an individual inhales to directly compare an individual's responses to nasal provocation and any natural exposure. Because seasonal exposure is so varied, the use of a model that allows exact measurements of the doses of allergen delivered would be expected to yield useful and relevant data. Future studies with reduced doses of antigen would be interesting.

On the basis of studies of nasal immunotherapy, a total dose of 4.8 μ g of antigen E given every other day over 7 weeks induced no change in serum-specific IgE. Doses of 59 μ g and 139 μ g of antigen E produced significant changes.^{15, 18} Our total dose of antigen E (Amb a 1) (approximately 12 μ g) produced consistent changes. Direct comparison of these results is difficult because we do not know whether the total dose or the interval during which that dose is delivered is the important variable.

The IgE antibody serum response to antigen provocation was not affected by 10 days of treatment with intranasal beclomethasone given before and during antigen stimulation. We previously performed two seasonal studies to evaluate the effect of continuous treatment with intranasal steroids, beginning slightly before the appearance of ragweed pollen, on serum levels of ragweed-specific IgE antibodies.³ In both studies the control groups showed the anticipated rise in ragweed-specific IgE levels. In the first study, in which aqueous beclomethasone dipropionate was used (168 μ g twice per day), no rise occurred in serum IgE anti-ragweed antibodies after seasonal exposure, and the levels actually decreased in eight of 12 subjects. In the second study, in which triamcinolone was used (220 μ g twice per day), the rise in ragweed-specific IgE antibodies was also reduced, although less dramatically, probably related to the relative potency of the dose of steroid delivered. The reduction in the rise in specific IgE levels may be due to a direct effect of steroids on humoral immunity or a simple barrier effect whereby intranasal steroids prevented the access of antigen to the nasal mucosa. Our current observation appears to contradict our previously published data. However, differences between the two studies need to be considered. Our data comparing serum IgE antibody changes after both seasonal exposure and antigen challenge, combined with the knowledge that the daily dose of beclomethasone was the same, suggest that the amount of antigen used in this study may have exceeded the protective effect of the topical steroid (i.e., a dose-response effect). This would correspond to the difference between seasonal exposure and provocation. In addition to the difference in the dose of antigen delivered to the subjects, the timing of treatment might also play a role. The current regimen was chosen because previous studies with the challenge model have shown that 1 week of pretreatment with topical steroids inhibits the early- and late-phase responses. The intranasal steroid treatment was started before antigen stimulation and continued throughout the antigen challenges. Chronic inflammatory changes occurring after antigen challenge may have proceeded after the discontinuation of the intranasal steroid. These inflammatory responses might occur during the season and be responsive to steroids, thus explaining the difference between our studies.

During seasonal exposure, the rise in specific IgE antibody levels occurs about midseason, increases later in the allergy season, and peaks 1 to 2 months later. In

contrast, the response to challenge clearly does not occur until 2 weeks after antigen exposure. Intranasal steroids given during the season might have affected some processes related to IgE synthesis that occurred during the season but did not occur until after the challenge, thus potentially explaining the discrepancy between the studies.

The mechanism responsible for the observed action of intranasal steroids given during the allergy season is unknown. Oral steroids have modest effects on total IgG antibody levels, with large doses causing a slight decrease in IgG and IgM and no change or a slight increase in total serum IgE.¹⁹ Intranasal steroids may have simply reduced nasal inflammation during the season and thereby altered the amount of allergen penetrating the mucosa. Alternatively, the timing of the dose may have different effects on T_{H1} and T_{H2} cytokine production.²⁰

Observations on IgE production can be studied in our in vivo model. Using this model, we can control the amount of antigen given to the patient and do not have to wait 1 year hoping for a "good" pollen season to experimentally examine human IgE synthesis in vivo. This experimental model may not reflect naturally occurring disease, but it does provide a means to address questions about the secondary humoral response caused by ragweed such as its kinetics and the association of the serum response with cellular changes in the nose and the blood.

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Corrections

In the June 1997, Part 3, issue of the Journal (*J Allergy Clin Immunol* 1997;99:S829-S848), reference 82 (page S847) contains a typographic error. The reference should read as follows:

82. Wawrose SF, Tami TA, Amoils CP. The role of guaifenesin in the treatment of sinonasal disease in patients infected with human immunodeficiency virus (HIV). *Laryngoscope* 1992;102:1225-8.

In the same issue of the Journal, the references cited in Table I (page S831) are incorrect. Here is the revised table:

TABLE I. Costs of sinusitis

People with sinusitis	14.7% of population ³
Sinus surgeries, 1994	170,000 to 200,000 ⁸²
Restricted activity days per year, 1986-88	50 million ⁴
Restricted activity days per year, 1990-92	73 million ⁴
1993 U.S. hospital discharges, acute sinusitis*	16,000 ⁵
1993 U.S. hospital discharges, chronic sinusitis*	29,000 ⁵
1991 physician office visits for sinusitis	11.6 million ⁶
1985 antibiotic prescriptions for sinusitis	5.8 million ⁶
1992 antibiotic prescriptions for sinusitis	13 million ⁶
1992 direct medical costs of sinusitis	\$2.4 billion ^{5†}

*Does not include admissions for inpatient or outpatient sinus surgery.

†Does not include cost of surgery. The direct medical costs for sinusitis can be calculated by using data from 1992, the latest year with complete data. The direct medical costs include hospitalizations for acute and chronic sinusitis ambulatory care visits to both private physician's offices and hospital outpatient departments for chronic sinusitis and prescriptions written for antimicrobials during the visits for acute and chronic sinusitis. The cost estimates were derived from the 1987 Health Care Expenditure Survey and have been adjusted for inflation (Hahn). The direct medical cost of sinusitis during 1992 was approximately \$2,378,023,000. This estimate is conservative because no data are available for a number of important components, including outpatient surgery and diagnostic imaging.