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Natural immunity to dust mites in patients with chronic rhinosinusitis

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Chronic rhinosinusitis is an extremely common clinical problem of which the etiology is poorly understood. To understand the role of common environmental antigens in this disease, natural immunity to antigens derived from the house dust mite was evaluated in 22 adults with chronic rhinosinusitis and compared to a carefully matched group of patients with chronic asthma or to a group of normal individuals. Allergic reactivity to dust mites was very common in patients with chronic rhinosinusitis, with 68% exhibiting a positive immediate skin test reaction and 41% exhibiting elevated levels of mite-specific serum IgE; 72% of patients with rhinosinusitis also exhibited markedly elevated levels of mite-specific serum IgG, which were present in both mite-allergic and nonallergic patients. IgG titers were much higher in the group with rhinosinusitis than in patients with asthma, whereas allergic reactivity to dust mites was significantly higher in the patients with asthma. Mite-specific immunity was low or absent in the group of normal individuals. These findings demonstrate that natural immunity to dust mites is very common in patients with chronic rhinosinusitis and suggest that immunity to mites may be involved in this syndrome. Furthermore, the data indicate that there may be significant differences in the ability of patients with rhinosinusitis or asthma to produce mite-specific antibodies of the IgG class. (J ALLERGY CLIN IMMUNOL 1988;82:855-62.)

Chronic rhinosinusitis is a clinical problem characterized by persistent mucus discharge from the paranasal sinuses (postnasal drip) and symptoms associated with low-grade sinus inflammation, such as pain and discomfort in areas overlying the maxillary, frontal, or ethmoidal sinuses.¹

Abbreviation used

PEFR: Peak expiratory flow rate

It can be distinguished from chronic allergic or seasonal rhinitis by the absence of anterior nasal symptoms, such as rhinorrhea or sneezing. In contrast, it is often differentiated from acute or chronic bacterial sinusitis, since sinus x-ray films in at least 50% of these patients reveal no obvious abnormalities or only minimal changes, such as mucoperiosteal thickening or low-grade opacification. Despite the difficulty in objectively diagnosing this syndrome, chronic rhinosinusitis appears to be an extremely common problem among most outpatient pop-

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ulations. Estimates of its prevalence vary from a low 1% to 2% in English and American populations^{2,3} to a number that is as high as the estimated 15% to 25% of the American population that has some sinus abnormality visible on x-ray film.⁴

The etiology of chronic rhinosinusitis remains poorly understood. The condition often develops after an upper respiratory tract viral infection, but the reasons it begins and persists are not clear. Some patients develop this problem after more typical allergic problems, such as seasonal rhinitis, whereas in a third, large group rhinosinusitis gradually develops without any obvious precipitating cause.

The chronic inhalation of allergens or antigens is known to be associated with a number of diseases at various sites of the respiratory tract, including asthma,⁵ rhinitis,⁶ and alveolitis.⁷ One of the most important inhaled antigens implicated in the cause of upper respiratory disease are those derived from the common and extremely ubiquitous house dust mite of the species *Dermatophagoides*.⁸⁻¹³

Immune reactivity to the antigens derived from the dust mite has not been carefully studied in patients whose major problem is chronic rhinosinusitis, although numerous studies have demonstrated mite allergy in subjects with chronic asthma.¹⁴⁻¹⁷ We have therefore analyzed natural immunity to dust mite antigens in such patients and compared this to normal individuals and to patients with chronic asthma. The findings of this study demonstrate that a large percentage of patients with chronic rhinosinusitis exhibit some form of immunity to dust mites, as demonstrated by elevated levels of mite-specific serum IgG or IgE, and that serum levels of mite-specific IgG are much higher in the patients with rhinosinusitis than in patients with asthma. These findings suggest that inflammation mediated by the interaction between specific antibody and dust mite antigens in the paranasal sinuses may play a role in the cause of chronic rhinosinusitis.

MATERIAL AND METHODS

Patient population

Patients were selected from allergy or asthma outpatient clinical facilities in the New York/New Jersey area. Racial and socioeconomic groupings were typical of this area and included male and female subjects ranging in ages from 20 to 73 years.

Patients were selected for the study based on an unequivocal history of never having any form of allergic immunotherapy at any time. This ensured that any measured immunologic alterations represented those arising as a result of natural exposure to dust mite antigens rather than from their deliberate or inadvertent medical administration.

After informed consent was obtained, all patients had a complete examination, including a detailed history and physical examination and measurement of PEFs. The diagnosis of chronic rhinosinusitis was based on clinical criteria, such as the presence of a postnasal drip and discomfort or pain localized to the area overlying the maxillary, ethmoid, or frontal sinuses.¹ Chronicity was determined by the presence of symptoms for a minimum of 3 months duration or symptoms that recurred at least four times a year for at least the 2 years up to the time of examination. All patients were symptomatic at the time of the initial examination.

Sinus x-rays were performed when it was clinically indicated to rule out any disease other than chronic rhinosinusitis. The x-ray films were read as within normal limits in 54%. In those patients with abnormal sinus x-ray films, pathologic changes were restricted to mucoperiosteal thickening in the maxillary sinuses or mild opacification of one or more sinuses. No patient had radiographic evidence of abnormal growths within the sinuses or changes consistent with acute or chronic bacterial sinusitis.

Patients with any evidence of airway obstruction were excluded from the group with rhinosinusitis. These included a PEF less than normal or a history of wheezing or chest tightness. Patients with symptoms that suggested only the presence of rhinitis (nasal congestion, rhinorrhea, or sneezing) without sinusitis were also excluded, as were patients whose symptoms only occurred during the warm months or after pet exposure. No study patients exhibited signs or symptoms of acute sinusitis such as fever, elevated white blood cell count, purulent nasal discharge, or marked pressure tenderness over the sinus regions.

Patients were assigned to the group with asthma if their symptoms were compatible with this diagnosis and if they manifested a PEF that was below the normal for their age, sex, and height, with at least a 20% increase after inhalation of a short-acting bronchodilator (isoproterenol). Any patients who had symptoms consistent with both asthma and a significant degree of chronic rhinosinusitis were also excluded to keep the two clinical groups as distinct as possible.

The group with rhinosinusitis consisted of 22 patients. They were age and sex matched with patients with asthma. A matched control group of normal individuals who were free of atopic disease or asthma based on careful historical assessment was also studied. Previous studies have demonstrated that <10% of individuals considered to be normal by these criteria had elevated levels of serum dust mite-specific IgE or IgG.¹⁴

Skin testing

Skin testing was performed by the intracutaneous injection of 0.02 ml of allergen to raise a 3 mm bleb in the upper arm. All patients were tested with a battery of antigens at a concentration of 100 PNU/ml in buffered saline containing 0.3% human serum albumin (Hollister-Stier Laboratories, Spokane, Wash.). Antigens included mixed tree pollens, mixed grass pollens, ragweed pollen, dust mite (*D. farinae*), cat and dog dander, mixed feathers, household insects, and

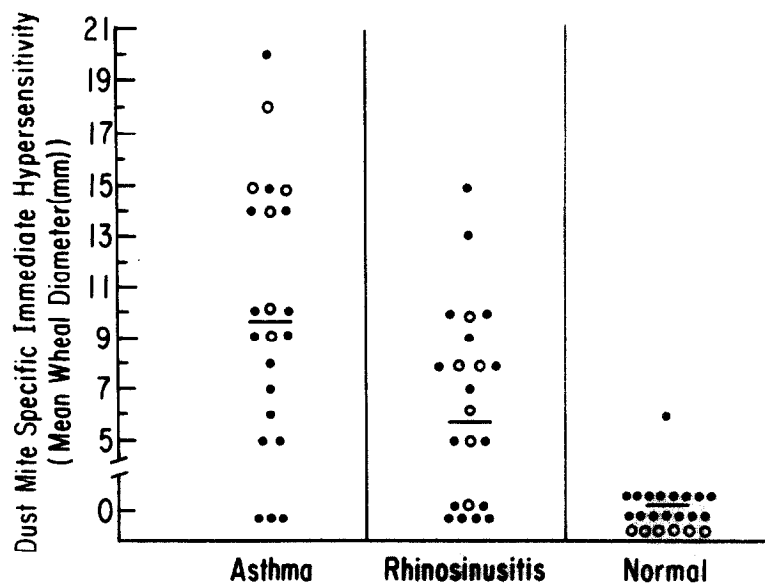


FIG. 1. Immediate hypersensitivity of dust mites in patients with rhinosinusitis and asthma was evaluated by intracutaneous skin testing. Results represent the mean diameter of the induced wheal where wheals less than 5 mm in diameter were considered to be negative. Symbols denote the presence (○) or the absence (●) of cats or dogs in the home environment.

several mixtures of mold-spore extracts. Skin testing was only performed on individuals who had not received anti-histamine medication for at least 48 hours. Reactions were read 20 minutes after injection, and the mean diameters of the wheal and erythema were measured and recorded. A positive reaction was considered to be a wheal of 5 mm or larger accompanied by erythema of at least 7 mm in diameter. Histamine at a concentration of 0.3 mg/ml and a buffer solution were included in each set as positive and negative controls.

Dust mite-specific serum IgG and IgG4

Blood was allowed to clot at room temperature, and the serum was separated within 1 hour after being drawn. Aliquots of serum were stored at -20°C in plastic tubes until testing was performed. Mite-specific serum IgG was measured by a double-antibody ELISA.

Dust mite extract (5000 PNU/ml in 50% glycerol, Hollister-Stier) was dialyzed twice against phosphate-buffered saline. The antigen solution was diluted to a concentration of 16 $\mu\text{g}/\text{ml}$ with coating buffer (sodium carbonate 0.085 mol/L, pH 9.6) and 100 μl was placed in wells of flat-bottom polystyrene microtrays (Linbro Plastics, Hamden, Conn.). The trays were incubated for 4 hours and then kept at 4°C . Before further processing, the antigen solution was removed, and 200 μl of 5% human serum albumin solution was added to each well. The trays were incubated again for 1 hour, followed by washing with washing buffer (phosphate-buffered saline containing 0.05% Tween 20, pH 7.2) with a modified, semiautomated apparatus (Titertek cell harvester, Flow Laboratories, Rockville, Md.).

One hundred microliters of tenfold dilutions of the sera then was added to each well, and the trays were incubated for 1 hour. After thorough washing, 100 μl of a 1/4000 dilution of monoclonal mouse antihuman IgG (Bethesda Research Laboratories, Bethesda, Md.) was added and incubated for 30 minutes, followed by an hour at room temperature. After washing, 100 μl of a 1/1000 dilution of alkaline phosphatase-labeled goat antimouse IgG (Kirkegaard and Perry Laboratories, Gaithersburg, Md.) was added. The trays were incubated for 1 hour, and after washing, the substrate (P-nitrophenyl phosphate disodium substrate; Sigma Chemical Co., St. Louis, Mo.) was added. Plates were read in an automated ELISA reader (Artek Industries, Farmingdale, N.Y.) at 405 nm after 5 minutes of incubation. For the measurement of IgG4, a monoclonal mouse antihuman IgG4 antibody (Bethesda Research Laboratories) and serum dilutions of 1/10, 1/30, and 1/90 were used.

Previous studies with an antigen-inhibition method demonstrated that this assay was specific for IgG against *D. farinae*.¹⁴ Each plate included positive and negative sera as controls. Units of mite-specific IgG were defined as the reciprocal of the highest dilution that produced an absorbance that was 0.02 units more than the highest absorbance produced by the negative control serum.

Dust mite-specific serum IgE levels

Mite-specific serum IgE was determined by a commercial RAST kit (Pharmacia, Piscataway, N.J.). As a positive reference, a pool of serum from a single, highly dust-mite allergic patient was prepared and tested for levels of mite-specific IgE by Dr. Thomas Platts-Mills (Charlottesville, Va.). Several negative control sera were included in each

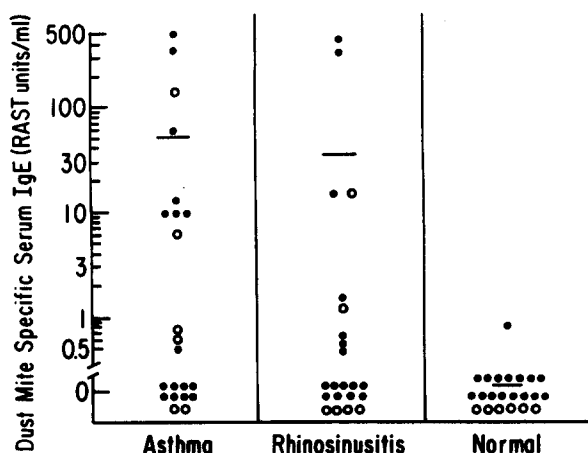


FIG. 2. Levels of dust mite-specific serum IgE in patients with rhinosinusitis and asthma were measured with a RAST immunoassay. Results were normalized to a known positive serum and are listed in terms of RAST units per milliliter. Symbols denote the presence (○) or the absence (●) of cats or dogs in the home environment.

RAST determination. In general, a RAST titer of 0.5 U/ml corresponded to binding ^{125}I that was at least three times higher than the negative control values, and titers above this level were therefore considered positive.

Total serum immunoglobulins levels

The serum levels of total IgG, IgM, and IgA were determined with a commercial radial immunodiffusion kit (Diffu-Gen, Tago, Inc., Burlingame, Calif.). The total IgE serum level was measured by a commercial PRIST kit (Pharmacia).

Statistical evaluation

Statistical calculations were performed with a statistical software package (BMPD Statistical Software, Inc., Los Angeles, Calif.) on a VAX 11/780 computer system with the Mann-Whitney U test for not normally distributed data.¹⁸

RESULTS

Dust mite-specific allergy

Mite-specific allergy was investigated in a group of patients with chronic rhinosinusitis with both skin testing and levels of mite-specific serum IgE and compared to a matched group of subjects with asthma and normal control subjects. Allergic reactivity was common in the patients with chronic rhinosinusitis with 68% of this group exhibiting a positive skin test to the mite antigen (Fig. 1). This degree of responsiveness was significantly different from that of the normal individuals in whom only 1/18 (6%) were skin test positive for dust mites.

As a group, the patients with asthma were signif-

icantly more allergic to dust mites than were patients with rhinosinusitis, with 86% of the patients with asthma exhibiting a positive skin test. This percentage is similar to previously reported data for adults with asthma.^{14, 17} In addition, the mean wheal size was also larger in the patients with asthma (9.8 mm versus 5.8 mm), and the difference between the two patient groups was statistically significant ($p < 0.02$).

Since home exposure to cats or dogs is a major cause of chronic upper respiratory disease in adults, the relationship of this variable to mite allergy was also analyzed. Mite-specific allergy in the group with rhinosinusitis was found to be unrelated to the presence (*open circles*) or absence (*closed circles*) of domestic pets (Fig. 1).

The existence of mite-specific allergy in the patients with rhinosinusitis was confirmed by measuring mite specific-serum IgE levels. With this assay, 41% of the patients with rhinosinusitis exhibited elevated levels of mite-specific IgE in contrast to only 1/22 (5%) of normal subjects (Fig. 2). Patients with asthma were also slightly more allergic to dust mites than patients with rhinosinusitis with this assay, with 55% exhibiting elevated titers. The mean titer in the patients with asthma (50 IU/ml) was also higher than in the patients with rhinosinusitis (34 IU/ml). However, the difference between the groups with asthma and rhinosinusitis in this assay did not reach statistical significance.

Dust mite-specific serum IgG antibodies

Serum levels of dust mite-specific IgG antibodies were also measured in each individual with a double-antibody ELISA. Interestingly, the patients with rhinosinusitis exhibited very high levels of mite-specific serum IgG (Fig 3); 72% of these individuals had positive titers, and the mean titer in this group was 1277 U/ml. Moreover, mite-specific IgG levels were much higher in the patients with rhinosinusitis than in the patients with asthma. Only 18% of this selected group of patients with asthma had elevated levels of mite-specific IgG, and the mean level was only 117 U/ml ($p < 0.0005$). None of the normal control subjects were positive in this assay. Chronic pet exposure did not appear to influence the levels of mite-specific IgG.

Because of proposed relationships between immunoglobulins of the IgG4 subclass and atopic disease,¹⁹ mite-specific serum IgG4 levels were also measured in these patients (Fig. 4). Only 9% (2/22) of the patients with asthma and only 13% (3/22) of the patients with rhinosinusitis exhibited elevated levels of mite-specific IgG4, suggesting that mite-specific IgG4 is not important in the cause of these diseases.

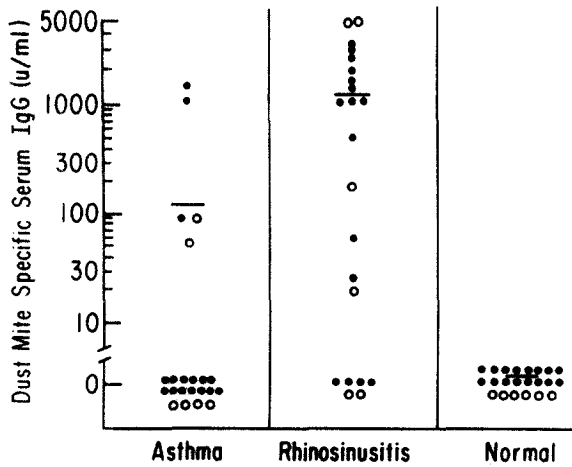


FIG. 3. Levels of dust mite-specific serum IgG in patients with rhinosinusitis and asthma were measured by a double-antibody ELISA. Results represent units of IgG per milliliter as defined in the Methods section. Symbols denote the presence (○) or the absence (●) of cats or dogs in the home environment.

There were no apparent clinical differences between patients with or without elevated levels of mite-specific IgG4.

Total serum immunoglobulin level

Total serum immunoglobulin levels were measured in the two groups to determine if the marked difference in mite-specific IgG levels between the patients with sinusitis and asthma was reflected in a difference in total serum immunoglobulin levels. Total levels of serum IgG, IgA, and IgM were measured by radial immunodiffusion, and levels of total serum IgE were measured by use of a radioimmunoassay. No differences were observed in the total levels of serum IgG, IgA, or IgM between the patients with asthma and sinusitis (Fig. 5). As a group, patients with asthma exhibited a slight increase in total levels of serum IgE, but this difference was not statistically significant. One patient with asthma was found to be IgA deficient. This finding is consistent with the estimated incidence of IgA deficiency in subjects with asthma.²⁰ One patient with sinusitis had an IgA level that was below normal.

Correlation between dust mite-specific IgG levels and mite-specific allergy

The relationship between mite-specific serum IgG and allergy to dust mites was investigated by comparing IgG levels to the degree of skin test reactivity or levels of mite-specific serum IgE.

Mite-specific serum IgG was evaluated in mite-

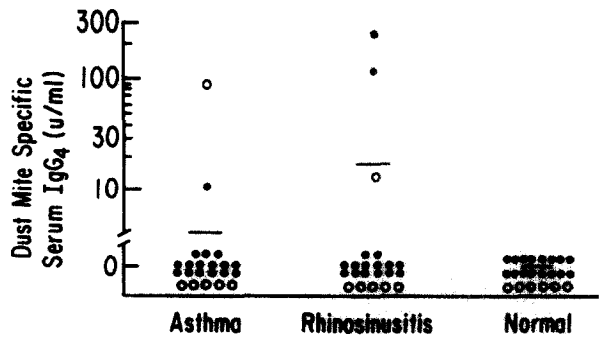


FIG. 4. Levels of dust mite-specific serum IgG4 in patients with rhinosinusitis and asthma were measured with a modification of the double-antibody ELISA outlined in the Methods section. Symbols denote the presence (○) or the absence (●) of cats or dogs in the home environment.

specific skin test positive or negative patients (Fig. 6). Negative mite-specific skin tests were common in the patients with rhinosinusitis with seven of these individuals being skin test negative to dust mites (32%). Of these patients, six (86%) exhibited elevated levels of mite-specific IgG; 10/15 (67%) of the patients with allergic rhinosinusitis had elevated dust mite-specific IgG levels. Mean levels in the allergic group (2116 U/ml) were significantly higher than in the nonallergic group (1150 U/ml) ($p < 0.02$). In the group with asthma, relatively few patients were skin test negative; however, one of these individuals did exhibit a high titer of mite-specific IgG. Among the allergic patients with asthma, four (22%) had elevated IgG levels, but the mean level (380 U/ml) was lower than levels in the group with rhinosinusitis.

The comparison between serum dust mite IgE-negative and positive individuals in both patient groups demonstrated similar results (Fig. 7). The difference in mite-specific IgG levels between allergic patients with asthma and patients with rhinosinusitis was even more striking in this analysis, with mean IgG levels of 77 U/ml in the former and 2317 U/ml in the latter.

Thus, these findings indicate that it is possible to develop immunity to dust mites (elevated levels of mite-specific IgG) in the absence of demonstrable allergic reactivity and that this immunologic state is relatively common in patients with chronic rhinosinusitis.

DISCUSSION

In the present investigation, we have analyzed the presence of immunity to antigens derived from house dust mites in a group of patients with symptoms consistent with a diagnosis of chronic rhinosinusitis and compared them to a matched group of patients with

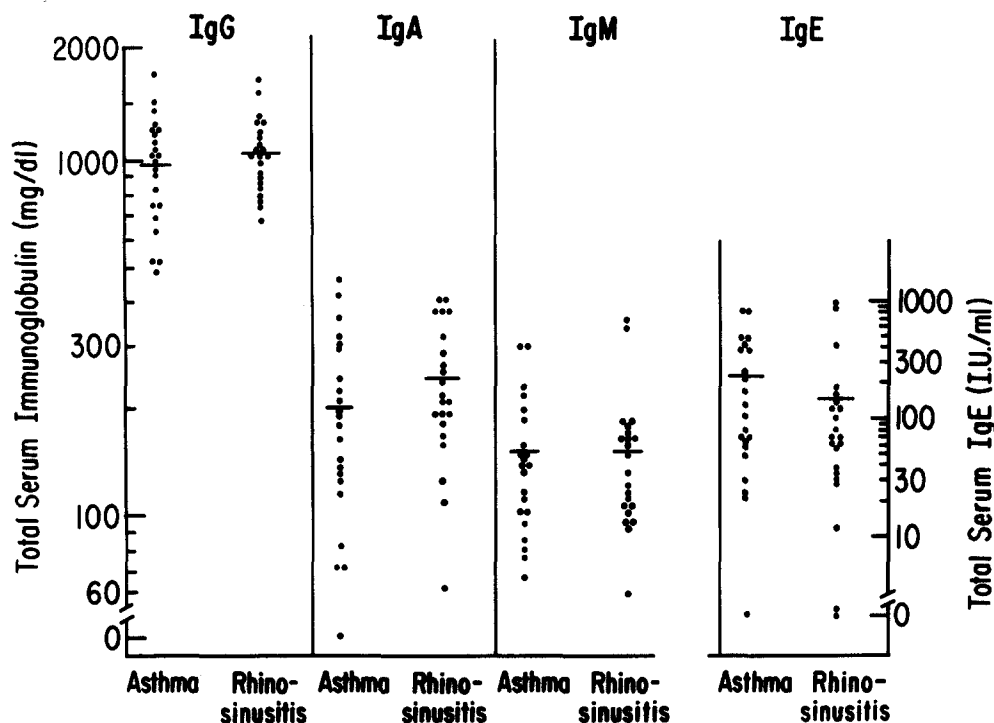


FIG. 5. Total serum immunoglobulin levels were measured in patients with rhinosinusitis and asthma. IgG, IgA, and IgM were quantified by radial immunodiffusion. Total IgE levels were measured with a commercial PRIST assay.

chronic asthma and a matched group of normal control subjects. No patient had ever received allergic immunotherapy; therefore, their immunity was due only to natural exposure to dust mites. The results demonstrate that two forms of immunity (elevated mite-specific serum IgE or IgG) to house dust mites are very common in patients with chronic rhinosinusitis. In total, 86% of patients with chronic rhinosinusitis exhibited some form of immunity to dust mites, suggesting that inhalation of this prevalent antigen may be involved in the pathogenesis of chronic rhinosinusitis.

A comparison of the patients with chronic rhinosinusitis with a matched group of patients whose major respiratory problem was chronic asthma, indicated some interesting differences. The patients with asthma as a group were more allergic to dust mite antigens than the patients with rhinosinusitis, whereas patients with chronic rhinosinusitis have much higher levels of mite-specific serum IgG than patients with asthma. Thus, it appears that patients with rhinosinusitis are characterized by the ability to produce high levels of mite-specific IgG in comparison both to normal control subjects and to patients with asthma. These findings are consistent with those of Platts-Mills et al.²¹

who found that rat allergen-specific serum IgG levels were higher in a group of rat-allergic patients with rhinitis than in a corresponding group of patients with asthma.

An interesting and important question is whether the elevated levels of mite-specific IgG observed in patients with chronic rhinosinusitis are related to the pathogenesis of this disease. One possibility is that patients with rhinosinusitis are those individuals who respond to the constant inhalation of dust mite antigen by producing large amounts of IgG antibodies. The interaction in the sinuses between inhaled dust mite antigens and IgG antibodies present in submucosal fluid could produce a chronic inflammatory reaction and result in chronic rhinosinusitis.

Alternatively, it is also possible that the elevated levels of IgG observed in patients with chronic rhinosinusitis are not the primary cause of their disease but only secondary to the presence of inflammation in the sinuses. Thus, patients with chronic rhinosinusitis may be characterized by some anatomic abnormality or exhibit inflammation secondary to some other cause, such as an upper respiratory tract viral infection. In this case, the inhalation of dust mite antigen into chronically inflamed sinuses might pre-

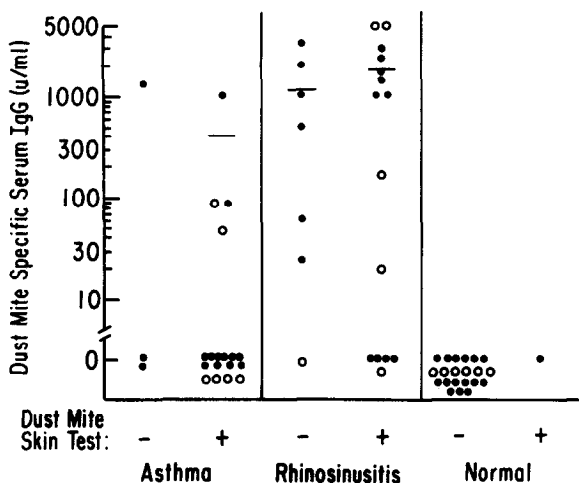


FIG. 6. Relationship between dust mite-specific serum IgG levels and immediate hypersensitivity skin test reactivity to dust mites in patients with rhinosinusitis and asthma. Patients were divided into skin test negative or positive subgroups based on the criteria for positive skin test reactivity outlined in the Methods section. *Horizontal bars* denote the arithmetic means of the positive titers in each group. *Symbols* denote the presence (○) or the absence (●) of cats or dogs in the home environment.

dispose the patient to the development of high levels of dust mite-IgG antibodies. The difference between patients with rhinosinusitis and asthma may therefore only reflect the difference between inhalation of antigen into a poorly drained space, such as the sinuses, in comparison to inhalation of the same antigen into an area that is constantly being cleared of mucus, the bronchial airways.

Finally, it should be noted that there is a close connection between asthma and rhinosinusitis. Previous studies have demonstrated that a high percentage of patients with asthma suffer from sinusitis and that asthma did not improve until the sinusitis was adequately treated.²²⁻²⁴ In this investigation we have not attempted to unequivocally document the presence of sinusitis in the group with asthma. Patients in the rhinosinusitis group generally had little or no problem with bronchoconstriction. The relative absence of asthma in the rhinosinusitis group could be established fairly easily because of the unambiguous nature of the clinical findings of asthma, as well as the ability to easily measure airway obstruction. In contrast, it is possible that a substantial number of the patients in the group with asthma did suffer from some degree of chronic rhinosinusitis, since the diagnosis of this condition is not based on objective measurements. It is therefore possible that the patients with asthma with high mite-specific IgG levels also had rhinosinusitis.

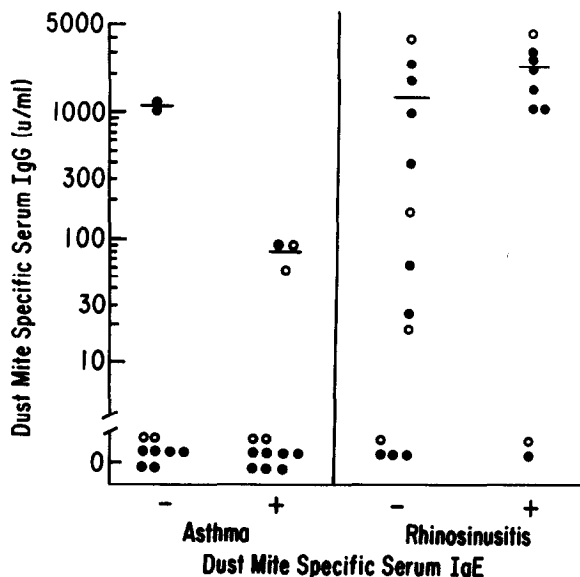


FIG. 7. Correlation between dust mite-specific serum IgG levels and mite-specific serum IgE levels in patients with rhinosinusitis and asthma. Patients were divided into groups positive (≥ 0.5 RAST units per milliliter) or negative (< 0.5 RAST units per milliliter) for dust mite IgE. *Horizontal bars* denote the arithmetic means of the positive titers in each group. *Symbols* denote the presence (○) or the absence (●) of cats or dogs in the home environment.

This is an important point that deserves further investigation.

The exact significance of the elevated levels of mite-specific serum IgG antibodies in patients with chronic rhinosinusitis remains to be established. As mentioned earlier, such antibodies may either be primarily involved in the pathogenesis of the disease or may be produced as a result of the disease and may therefore only be a marker for this condition. If the antibodies are only present secondarily, a measurement of dust mite IgG may prove to be useful in the diagnosis of chronic rhinosinusitis. In contrast, if the antibody levels are related to the pathogenesis of the disease, it would suggest that methods directed against the elimination of dust mite exposure, or treatment directed toward removal of dust mite-specific or dust mite-generated chronic inflammation might be useful. The finding that 86% of patients with chronic rhinosinusitis exhibit some form of immunity to dust mites suggests that simple measures directed toward their removal from the sleep environment of the patient with chronic rhinosinusitis might prove useful.²⁵⁻²⁷

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