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ASSOCIATION OF ASTHMA WITH SERUM IgE LEVELS AND SKIN-TEST REACTIVITY TO ALLERGENS

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Abstract We investigated the association of self-reported asthma or allergic rhinitis with serum IgE levels and skin-test reactivity to allergens in 2657 subjects in a general-population study. Regardless of the subjects' status with respect to atopy or their age group, the prevalence of asthma was closely related to the serum IgE level standardized for age and sex ($P < 0.0001$), and no asthma was present in the 177 subjects with the lowest IgE levels for their age and sex (> 1.46 SD below the mean). The log odds ratio increased linearly with the serum IgE level after we controlled for possible confounders and the degree of reactivity to skin tests. In contrast, aller-

gic rhinitis appeared to be associated primarily with skin-test reactions to common aeroallergens, independently of the serum IgE level.

We conclude that asthma is almost always associated with some type of IgE-related reaction and therefore has an allergic basis, although not all the allergic stimuli that cause asthma appear to have been included in the battery of common aeroallergens we used to assess atopic status. These findings challenge the concept that there are basic differences between so-called allergic ("extrinsic") and nonallergic ("intrinsic") forms of asthma. (*N Engl J Med* 1989; 320:271-7.)

It is generally accepted that there are both allergic and nonallergic forms of asthma, and the distinction is usually based on the presence or absence of allergy skin-test reactivity to one or more aeroallergens considered capable of inducing the disease. Since Rackemann introduced the terms in 1918,¹ asthma that can be shown to be related to hypersensitivity to a foreign substance has been described as "extrinsic"; otherwise, the disease has been classified as "intrinsic."

After Ishizaka² and Johansson³ and their colleagues

identified immunoglobulin E (IgE) as the antibody responsible for the immediate type of immune response, a number of authors noted marked elevations of IgE in young patients with asthma,^{4,5} and some have attempted to distinguish extrinsic from intrinsic disease on the basis of the presence or absence of an elevated serum concentration of IgE.⁶ Regardless of the specific criteria, however, extrinsic asthma appears to be the predominant form of the disease among children and young adults, and intrinsic asthma is considered to be more common among older subjects.

These widely accepted concepts, based largely on clinical observations, fail to take into account the relations of both allergy skin-test reactivity (hereafter called atopy) and serum IgE levels to age in the general population. Both tend to decrease with advancing

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Supported by a Specialized Center of Research Grant (HL-14136) from the National Heart, Lung, and Blood Institute.

age. Although serum IgE reaches its peak level during childhood, atopy continues to develop up to the third decade.⁷⁻¹² In addition, serum IgE levels have been shown to be affected by sex and by smoking habits,^{13,14} and there is no agreement about the level of serum IgE that exceeds the normal limit.

In the present report, we consider the relation of reported "asthma" to both atopy and the serum IgE level, taking into account their close interrelation as well as their variations with age and sex. Findings for asthma are contrasted with those for reported "allergic rhinitis" among 2657 subjects 6 to 95 years old who were enrolled in an epidemiologic study of a sample from the general population.

METHODS

The details of the methods of selection and study of the population have been previously reported.¹⁵ The subjects were selected from a random stratified cluster sample of white non-Mexican-American households in Tucson, Arizona, in 1971. The sampling frame consisted of square blocks stratified on the basis of ethnic group, age of the head of the household, and socioeconomic status. The members of one of each six households in these square blocks were asked to participate. Blood samples were obtained from the subjects at least six years old, and serum IgE levels were measured. The present analyses were limited to the 2657 subjects in whom serum for measurement of IgE had been obtained and allergy skin tests had been performed at the time of enrollment. The average age ($\pm$ SD) was 44.1 ± 21.9 years, and 54.5 percent of the sample were female subjects. Nonsmokers, exsmokers, and current smokers made up 48.5, 21.5, and 30.0 percent, respectively, of the study group.

The presence of disease was determined by responses to a standardized self-completed questionnaire. "Allergic rhinitis," hereafter referred to simply as rhinitis, was indicated by a response of "Yes, I still have it" to the question, "Have you ever had hay fever or any other allergy that makes your nose runny or stuffy, apart from colds?" The presence of asthma was indicated by an affirmative response to the question, "Have you ever had asthma?" in a subject who claimed to "still have it," admitted to "wheezing or whistling in the chest" that occurred "apart from colds," or had more than rare "attacks of shortness of breath with wheezing."

Allergy skin tests were carried out according to the prick technique,¹⁶ using five tests that included a variety of allergens common to the Tucson area, plus a control. Commercially available skin-test materials were used (supplied by Hollister-Stier Laboratories). The allergens used in the five tests included (1) house dust, 1:10; (2) Bermuda grass, 1:20; (3) tree mix, 1:20 (olive, mulberry, mesquite, and cottonwood); (4) weed mix, 1:20 (rabbit bush, saltbush, careless weed, Russian thistle, desert ragweed, and slender ragweed); and (5) Dematiaceae mold mix, 1:100 (alternaria, helminthosporium, cladosporium, curvularia, spondylocladium, and stemphylium species). After subtraction of the size of the control, each test was graded on a scale (0 to 4) based on the frequency of a reaction of its size in the total population, as previously described.⁷ An overall allergy skin-test index was calculated for each subject by summing the individual test scores. The use of this method reduced the possibility that a reaction to any one of the allergens would have an overwhelming influence on the overall test result. A skin-test index of 0 represented completely negative responses to all five tests; the maximum score could reach 20 only if unusually large reactions occurred to all the allergens applied.

Measurement of serum IgE was carried out according to the paper radioimmunosorbent test (PRIST) (Pharmacia Diagnostics, Piscataway, N.J.) method. The reported values represent the mean of duplicate tests and are expressed in international units per milliliter. (It is conventional to express IgE concentrations in this manner, but their value in Système International units — micrograms per liter — can be approximated by multiplying the number of international units by 2.4.¹⁷) IgE values show a log normal distribution in the general population.¹¹ For this reason, log IgE was used in all

statistical analyses, and average values were reported as geometric means. Serum IgE shows a marked decrease with age and is significantly lower in women than in men. To standardize for age and sex, IgE values were transformed into Z scores, according to sex and the age groups 6 to 14, 15 to 34, 35 to 54, 55 to 74, and 75+ years of age. Age-sex-standardized IgE Z scores indicated the number of standard deviations by which individual subjects differed from the mean for their age-sex-specific group.

To test for the independent effects of IgE level, skin-test reactivity, and smoking habits, as well as their possible interactive effect on the prevalence of asthma and rhinitis, we used two types of logistic models. The first was a qualitative (or categorical) model, in which all relevant independent variables were stratified.^{18,19} This technique, in which each stratum is introduced as an independent regression variable, provides maximal flexibility to the multivariate analyses, avoiding a priori assumptions concerning the form of the relation between the independent and dependent variables. Relevant variables were stratified as follows: log IgE — <0.5 , $0.5 < 1$, $1 < 1.5$, $1.5 < 2$, $2 < 2.5$, $2.5 < 3$, and $3+$; skin-test index — 0, 1 to 3, 4 to 6, 7 to 9, and $10+$; and smoking — nonsmokers, current smokers and exsmokers. Age was stratified as described for the derivation of IgE Z scores. In these analyses, the risk of disease in each stratum was compared with that in the lowest stratum; this base-line stratum was assigned an odds ratio of unity. For skin-test index and smoking, the definitions of these base-line strata were straightforward; they consisted of negative skin test and nonsmoking status respectively. For serum IgE, the choice of the base-line stratum was dictated by the finding that subjects with log IgE values <0.32 did not have asthma. The predictive value of a given risk factor was assessed by determining the difference in the goodness-of-fit chi-square between models including and excluding the risk factor of interest.¹⁶ The regression coefficient for each level of a particular risk factor was an estimate of the logarithm of the odds ratio that a subject had the disease, as compared with the base-line group.

The second type of logistic analysis that we used was a quantitative linear model.¹⁸ This method was used to test the hypothesis that the log odds ratio of having disease was linearly related to the level of the apparent risk factor. Interactions between different risk factors and between risk factors and potential confounders were also tested. In these analyses, the mean value for the variable in each stratum was attributed to that group after weighting by the number of subjects in each stratum. Data were then standardized, and the Z scores obtained were introduced into the model. This type of analysis yielded a logistic regression coefficient that represents the change in the log odds ratio per unit change in the Z score after adjustment for confounders. Deviation from linearity was tested by determining the difference in goodness-of-fit chi-square between this model and the qualitative one described above. Confidence intervals around the regression of log odds ratios and levels of IgE and the skin-test index were calculated with the use of the weighted analysis proposed by Kleinbaum and Kupper,²⁰ as modified by Rothman.¹⁹

Reported probability values are two-tailed. For continuous variables, these values were calculated by analysis of variance, and for discrete variables by chi-square or trend chi-square techniques.

RESULTS

As expected, asthma rates showed highly significant progressive increases with increases in both the skin-test index and serum IgE level ($P < 0.0001$). The relation of asthma to IgE was especially close when the latter was expressed as an age-sex-standardized IgE Z score. Regardless of age, none of the 177 subjects with the lowest Z scores (< -1.46) had asthma, whereas 9.6 percent of the remaining 2480 subjects did ($P < 0.0001$). The prevalence increased to 37.3 percent among the 67 subjects with IgE Z scores of 2.0 or more.

The overall rates of asthma and rhinitis in three broad age groups are shown in Table 1. The table also shows the frequencies of skin-test reactivity and of

Table 1. Disease Prevalence, IgE Levels, and Skin-Test Index, According to Age Groups.

SUBJECTS	AGE 6 TO 34	AGE 35 TO 54	AGE 55+
All subjects			
Number	1083	545	1029
Percent with asthma	8.2	8.6	9.8
Percent with rhinitis	42.7	47.3	37.8
Subjects without asthma			
Number	994	498	928
Percent with positive skin test	44.3	40.0	22.8
Percent with IgE >100 IU/ml	30.2	18.1	13.0
Geometric mean IgE (IU/ml)	43	26	18
Mean IgE Z score $\pm$ SD*	-0.08 $\pm$ 0.97	-0.08 $\pm$ 0.96	-0.07 $\pm$ 0.98
Subjects with asthma			
Number	89	47	101
Percent with positive skin test	78.7	72.3	39.6
Percent with IgE >100 IU/ml	73.0	57.4	33.7
Geometric mean IgE (IU/ml)	224	117	56
Mean IgE Z score $\pm$ SD*	0.90 $\pm$ 0.87	0.86 $\pm$ 1.00	0.60 $\pm$ 1.00

*The differences between the age groups are not significant, but the differences between the subjects with and without asthma in each age group are significant ($P < 0.0001$).

"elevated" IgE concentrations, as well as the geometric mean serum IgE levels and mean IgE Z scores in subjects with and without asthma. The cutoff point for a high IgE level — 100 IU per milliliter — was roughly equivalent to the upper limit of normal recommended in a popular textbook of medicine.²¹ These indexes of allergy declined markedly in subjects with asthma who were older than 55, but so did the rates of atopy and the levels of IgE in subjects without asthma.

Although the serum IgE levels in subjects with asthma showed a significant decline with age ($P < 0.0001$), the IgE Z scores showed only a slight and statistically insignificant difference with age. In all age groups, however, both geometric mean IgE levels and IgE Z scores in subjects with asthma were significantly higher than in subjects without asthma ($P < 0.0001$). Figure 1 shows the prevalence of asthma in the three age groups in relation to their age-sex-standardized IgE Z scores. When IgE levels were examined in relation to the overall distribution of IgE values according to age and sex, the relations of the rates of disease to IgE were remarkably similar in all age groups.

A close examination of the overall relations of rhinitis and asthma to the skin-test index and the serum IgE level suggested that the prevalence of asthma seemed to follow the serum level of IgE more closely than the degree of atopy, whereas the opposite appeared to be true of rhinitis. To test the hypothesis that asthma, in contrast to rhinitis, was primarily related to serum IgE and that its relation to the skin-test index might in large part be dependent on the close interrelation between IgE and skin-test reactivity, we performed the logistic analyses described in the Methods section.

After we controlled for age and sex, both the IgE level and the skin-test index were significant predictors of the disease. Both remained significant after adjustment for the effect of the other variable ($P < 0.0001$), but the goodness-of-fit chi-square for IgE

(179.9) was higher than that for the skin-test index (53.3). Furthermore, after adjustment for age, sex, and skin-test index, the use of a linear model for the IgE effect did not significantly change the goodness-of-fit of the relation of asthma to IgE levels that was found with the qualitative analysis using seven categories of IgE concentrations. This indicates that asthma rates increase linearly with log IgE values. In this analysis, the logistic regression coefficient ($\pm$ SE) for the prevalence of asthma in relation to the IgE Z score was 0.76 ± 0.08 . This linear relation did not apply, however, to the relation of asthma to the skin-test index. In this case, after adjustment for IgE, the linear model gave significantly worse results than the qualitative model.

A history of smoking did not add to the ability to predict the prevalence of asthma in the logistic analyses when age, sex, serum IgE level, and skin-test index were controlled for, and no significant interactions were noted between smoking and any of the other predictor variables. Also, there were no significant interactions between age or sex and the skin-test index or serum IgE level in determining disease frequencies, or between the skin-test index and serum IgE level.

The relative relations of the skin-test index and IgE level to rhinitis were quite different from their relations to asthma. After we controlled for age and sex, both the skin-test index and the IgE level did remain statistically significant predictors of rhinitis after adjustment for the other ($P < 0.0001$ for skin-test index and $P < 0.005$ for IgE), but the goodness-of-fit chi-square for the skin-test index (158.0) was higher than that for the serum IgE level (20.3). Also, unlike the results of the analysis for asthma, those of the quantitative linear logistic regression model indicated that the relation of the rhinitis rate to the skin-test index was essentially linear; the logistic regression coefficient ($\pm$ SE) was 0.62 ± 0.05 in this analysis.

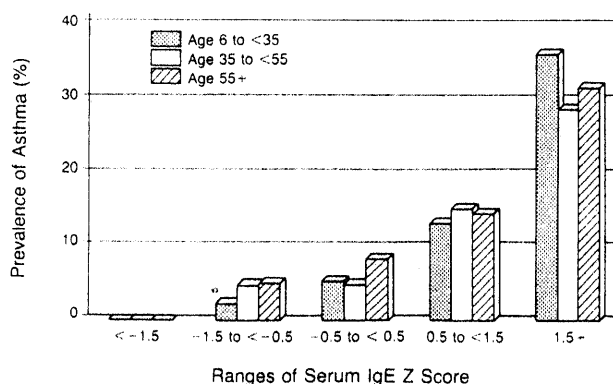


Figure 1. Prevalence of Asthma in Relation to IgE Z Scores Standardized for Age and Sex.

In all age groups, the trend for prevalence to increase with increasing Z scores had a high level of significance ($P < 0.0001$). The following numbers of subjects (according to age group) were at risk in the five ranges of scores: age 6 < 35 — 73, 248, 435, 252, and 75; age 35 < 55 — 43, 123, 205, 139, and 35; and age 55+ — 50, 255, 431, 236, and 57.

Figure 2 shows the relation of the odds ratio (on a log scale) of having asthma and rhinitis to the serum level of IgE. For this purpose, we used the regression coefficients obtained from the qualitative logistic analysis of IgE (see Methods) after correction for age, sex, skin-test index, and smoking status. Although there was evidence of colinearity among the regression variables entered into the model and the base-line level for IgE was chosen arbitrarily, the relative position of the increasing levels was still representative of the independent relation between the log odds ratio and risk-factor level. Figure 2 also demonstrates a remarkably linear relation between the log odds ratio of having asthma and increasing levels of IgE, as shown in the statistical analysis. In contrast, the relatively slight independent relation of rhinitis to IgE appeared to be present primarily at higher levels of IgE.

Figure 3 shows an identical type of analysis relating the log odds ratios for both diseases to levels of skin-test reactivity after adjustment for age, sex, serum IgE level, and smoking status. It is obvious that the relative relations of asthma and rhinitis to the skin-test index are reversed from their relative relations to serum IgE. The essentially linear relation of rhinitis to the skin-test index is evident. The independent association of asthma with the skin-test index appears to be related primarily to the presence or absence of a positive test; it shows little progressive increase with higher degrees of skin-test reactivity.

From a clinical viewpoint, it seemed relevant to demonstrate these same relations separately in the subjects who appeared least allergic according to the allergy skin test or the serum IgE level. The relation of asthma rates to the age-sex-standardized IgE Z scores in the 1662 subjects with completely negative

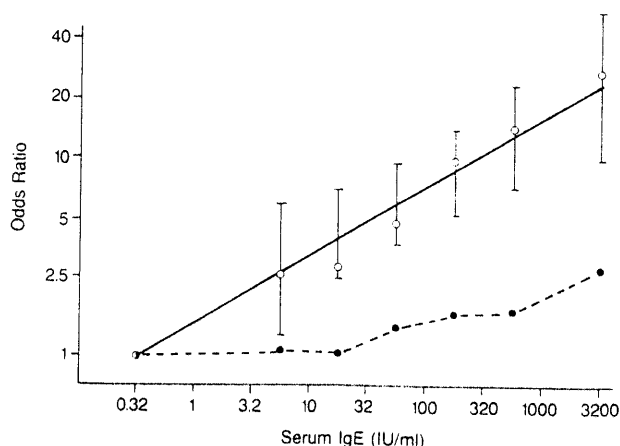


Figure 2. Odds Ratio (Log Scale) of Having Asthma (Open Circles) at Seven Levels of the Total Serum IgE Concentration, after Correction for Age, Sex, Smoking Habits, and Skin-Test Index in a Logistic Analysis.

The solid line, representing the risk of asthma, is a weighted, least-squares linear regression model fitted to the odds ratios at each log IgE level. The vertical lines are 95 percent confidence intervals around the regression for each odds ratio corresponding to a given log IgE level. The dashed line represents the odds ratios of having rhinitis at the same seven levels of serum IgE, after correction for the same confounders.

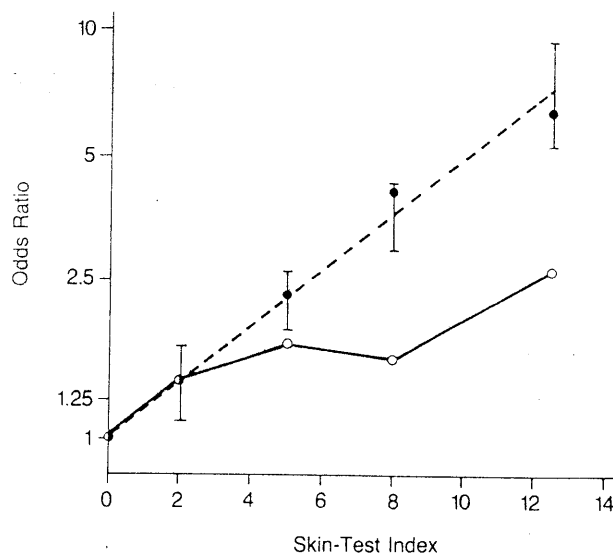


Figure 3. Odds Ratio (Log Scale) of Having Rhinitis (Solid Circles) at Five Levels of the Skin-Test Index after Correction for Age, Sex, Smoking Habits, and Serum IgE in a Logistic Analysis.

The dashed line, representing rhinitis, is a weighted least-squares linear regression model fitted to the odds ratios at each level of the skin-test index. The vertical lines are 95 percent confidence intervals around the regression for each odds ratio corresponding to a given value for the skin-test index. The solid line represents the odds ratio of having asthma at the same five levels of the skin-test index, after correction for the same confounders.

allergy skin tests is shown in Figure 4. If a lack of reactivity to our battery of common aeroallergens is accepted as indicative of an "intrinsic" form of the disease, this graph shows the relation of seemingly intrinsic asthma to the age-sex-standardized IgE level ($P < 0.0001$ by trend chi-square). If the findings in an equal number of subjects with the lowest serum IgE levels (the 1662 subjects with IgE Z scores < 0.32) are examined, no consistent relation is seen between asthma rates and the degree of allergy skin-test reactivity (Fig. 5), but a significant relation is evident between rhinitis rates and the skin-test index ($P < 0.0001$).

DISCUSSION

Our findings in regard to reported "allergic rhinitis" are relatively straightforward. In the Tucson area, 31.2 percent of subjects who have completely negative responses to skin tests of a battery of common aeroallergens report symptoms of rhinitis due to "hay fever or any other allergy," and the rate of reported disease is near 30 percent even in nonatopic subjects who have very low serum IgE levels. We presume that many of these cases represent nonspecific nasal reactions to our dry and somewhat dusty environment. It might be argued that the apparent frequency of atopy (as defined above) in subjects who report that they have rhinitis would be increased if more invasive methods of skin testing were employed. However, it has been shown that reactions to intradermal tests only, and not prick tests, are frequently unassociated with the presence of allergen-specific IgE in the serum.^{22,23}

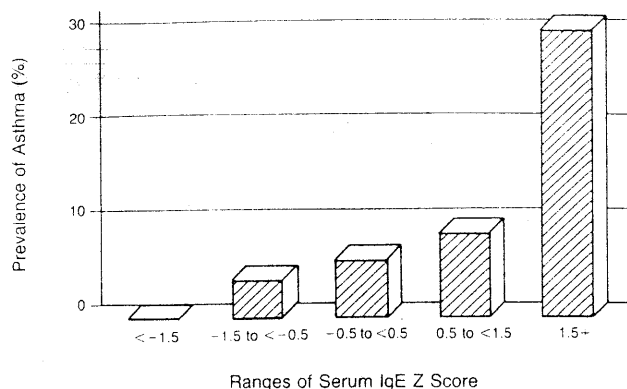


Figure 4. Prevalence of Asthma in Relation to IgE Z Scores, Standardized for Age and Sex, in the 1662 Subjects with Completely Negative Allergy Skin Tests.

The trend for prevalence to increase with increasing Z scores had a high level of significance ($P < 0.0001$). The following numbers of subjects were at risk in the five ranges of scores: 150, 521, 689, 259, and 43.

Nonetheless, the rate of reported rhinitis increased markedly with the degree of allergy skin-test reactivity to the antigens applied in this study, exceeding 85 percent among subjects with the most strongly positive tests (skin-test indexes of 16+). The finding that serum IgE levels added relatively little to the predictability of the symptoms of rhinitis after the degree of atopy was taken into account suggests that the battery of skin tests applied adequately represented the local aeroallergens most likely to induce a nasal reaction.

The situation with respect to asthma is much more complex. The clear-cut differences between asthma and rhinitis in their relations to atopy and serum IgE were unexpected, since not only are IgE and atopy closely interrelated but allergic rhinitis and asthma tend to be concordant. Nevertheless, although rhinitis had little relation to serum IgE levels after atopy was accounted for, the opposite was noted in regard to asthma. Asthma rates were closely related to serum IgE levels even in nonatopic subjects, and in all subjects they remained related to IgE after we accounted for the degree of atopy. The consistency of the relations at all ages became clear, however, only after serum IgE levels were considered in relation to the age and sex of the subjects.

Were it not for the findings about rhinitis, one would suspect that the relations to asthma might have reflected only a gross inadequacy of the skin tests used to assess atopy. But if this were the case, the rate of rhinitis should also have been closely related to serum IgE as well as to the skin-test index. It might also be argued that the high IgE Z scores of elderly subjects, which were associated with elevated asthma rates, represented relatively low actual serum levels of IgE and therefore were unlikely to be associated with a significant allergic response. However, the tendency to form IgE is an inherited trait,^{24,25} and the serum IgE level has a marked tendency to "track" with age. Even serum IgE levels present at nine months of age are

correlated with those found in cord blood at the time of birth.²⁶ Among the subjects who were entered in the present study before the age of 35, there was a marked and significant decline in the serum IgE level over the ensuing eight years¹⁰; nevertheless, IgE values recorded during follow-up strongly correlated with those recorded at entry ($r = 0.827$). An almost identical correlation was found in our subjects 35 years old or older at entry ($r = 0.822$), in whom the mean change in IgE level during the eight-year period was insignificant. Thus, high IgE Z scores among elderly subjects were likely to identify those who had much higher levels of IgE earlier in life, when their problems with asthma probably began. In addition, we have found that the presence of as little as 1 IU of Bermuda grass-specific IgE per milliliter of serum is almost always associated with a positive skin-test reaction to this antigen (Hälonen M: unpublished data). Large amounts of antigen-specific serum IgE are not necessary for an allergic response.

The most obvious question raised by the present findings is related to the nature of the allergic stimulus that leads to the type of IgE associated with asthma. Comparisons with rhinitis suggest that atopy to the common aeroallergens used in this study is not the essential factor, although one cannot deny that such aeroallergens may induce asthma, and they certainly appear to aggravate the symptoms of existing disease in some patients. Rackemann suggested many years ago that "intrinsic" asthma represented an allergic reaction to bacteria within the respiratory tract.¹ Although pneumococcal-specific IgE can sometimes be demonstrated,²⁷ there is no firm evidence that allergy to bacteria in the airway is of importance in the pathogenesis of asthma. A number of well-recognized allergens shown to be involved in asthma were not included in our skin-test battery, including dermatophagoides (the house-dust mite) and animal danders. However, dermatophagoides is uncommon in our locale, and when we applied an extract of it to subjects in our population sample on repeat skin test-

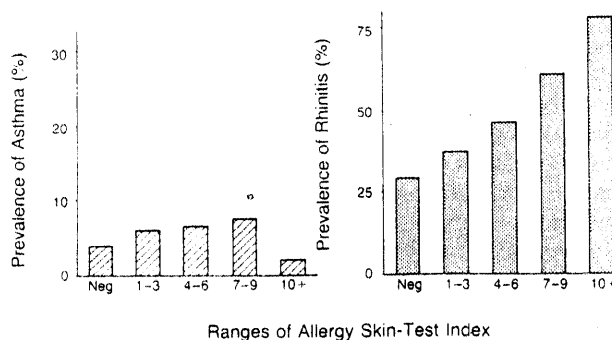


Figure 5. Prevalence of Asthma and Rhinitis in Relation to the Allergy Skin-Test Index in the 1662 Subjects with the Lowest IgE Z Scores (< 0.32).

There was no statistically significant trend for asthma rates to increase with the values for the skin-test index in these subjects, but the increase in rhinitis rates had a high level of significance ($P < 0.0001$). The following numbers of subjects were at risk in the five ranges for the skin-test index: 1253, 161, 137, 66, and 45.

ing several years after enrollment, it produced even fewer positive reactions than our crude house-dust antigen. In fact, only 2 percent of the retested population reacted to this antigen²⁸ but not to any of the allergens used in the present study. Also, very low rates of reactions to cat, dog, and horse danders were found in a subset of our population who underwent quite extensive allergy skin testing,²² especially among subjects who had completely negative reactions to the antigens used in the present study. However, additional organic antigens with possible relevance to asthma are being recognized and reported, such as airborne particles of insect origin.²⁹ It is also clear from studies of occupational asthma that a wide variety of relatively simple compounds, such as plicatic acid (in workers handling red cedar) and platinum salts,^{30,31} are capable of inducing IgE-mediated asthma and that this may occur in otherwise nonatopic subjects. The range of possible allergic stimuli other than commonly recognized aeroallergens is almost limitless. If it were not for the clusters of cases of asthma within occupational groups, many substances now recognized as causes of asthma³² would never have been identified.

None of the above is meant to imply that a complete evaluation by a trained allergist in a clinical setting might not have detected specific allergens in many of the subjects with asthma who appeared nonatopic on the basis of prick-test reactivity to the aeroallergens used in the present study. On the contrary, the relations to serum IgE suggest that our battery of allergy skin tests was inadequate to detect the wide range of allergens that may be of importance in asthma. We also recognize that our determination of the presence or absence of disease was relatively crude and was based entirely on information from questionnaires. More refined criteria for the diagnosis of asthma and allergic rhinitis in epidemiologic studies would be highly desirable, but any misclassification of cases in the present study would have served only to confound rather than to exaggerate the demonstrated relations to serum IgE and allergy skin-test reactivity.

Regardless of the specific allergic stimulus involved, since no asthma at all was found in subjects with extremely low IgE levels, virtually all the observed cases might be considered to be related to this evidence of "allergy." Indeed, the present data do not support the division of asthma into the extrinsic or allergic type and the intrinsic or nonallergic type. The difference in the course of asthma between older subjects and younger subjects may be the result of many factors wholly unrelated to the allergic origins of their disorder. However, regardless of the level of serum IgE, a minority of subjects have asthma, suggesting that some other factor in host susceptibility may have a critical role in the disease. Inherent hyperresponsiveness of the airways could well represent this essential risk factor,³³ but the present data suggest that some IgE-related reaction is required to induce overt asthma even in susceptible persons. The mechanism for

this relation cannot be determined from this type of study. Also, we cannot deny the possibility that there may be unusual forms of asthma that are not associated with IgE, but such cases must be so uncommon that they have not influenced the relations noted in the present report.

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ABNORMALITIES IN PARATHYROID HORMONE SECRETION AND 1,25-DIHYDROXYVITAMIN D₃ FORMATION IN WOMEN WITH OSTEOPOROSIS

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Abstract We investigated the parathyroid hormone-1,25-dihydroxyvitamin D₃ (1,25(OH)₂D) axis in osteoporosis by administering phosphate to 8 postmenopausal women with osteoporosis (49 to 78 years old) and to 10 normal women matched for age (50 to 74 years). All subjects responded with a similar increase in the serum phosphorus concentration (women with osteoporosis, 1.15 ± 0.06 to 1.79 ± 0.09 mmol per liter; controls, 1.14 ± 0.05 to 1.73 ± 0.08 mmol per liter) and a fall in the ionized calcium concentration (women with osteoporosis, 1.12 ± 0.03 to 1.06 ± 0.03 mmol per liter; controls, 1.17 ± 0.01 to 1.11 ± 0.02 mmol per liter).

Parathyroid hormone levels rose 2.5-fold in the control group (15.4 ± 2.2 to 37.9 ± 6.1 pg per milliliter) but increased by only 43 percent in the group with osteoporosis (14.8 ± 2.8 to 21.2 ± 4.1 pg per milliliter), an increase simi-

lar to that previously reported in young normal subjects (53 percent). In healthy older and younger subjects, the levels of 1,25(OH)₂D did not change; in the subjects with osteoporosis, however, they decreased significantly (50 percent).

We conclude that older women require a greater parathyroid hormone stimulus than younger women to maintain vitamin D homeostasis, because of an age-related decline in the formation of 1,25(OH)₂D in response to parathyroid hormone, and that in osteoporosis the age-appropriate parathyroid hormone response to the same hypocalcemic signal is diminished. Our results are consistent with the presence of an abnormality in parathyroid hormone secretory function in osteoporosis in addition to the universal decline in 1,25(OH)₂D responsiveness associated with aging. (*N Engl J Med* 1989; 320:277-81.)

IT is now well established that parathyroid hormone is a key regulator of the renal production of 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D).¹⁻³ Parathyroid hormone stimulates the renal 1- α -hydroxylase enzyme, leading to increased conversion of 25-hydroxyvitamin D to the active form of the hormone, 1,25(OH)₂D. Responsiveness to this regulatory pathway appears to become impaired in osteoporosis and aging, resulting in reduced formation of the active vitamin D metabolite.⁴⁻⁷ A possible mechanism of altered 1,25(OH)₂D formation in osteoporosis is a primary defect in the renal 1- α -hydroxylase or, alternatively, a defect in factors that stimulate the enzyme. These potential abnormalities in 1,25(OH)₂D formation in osteoporosis, however, have not been distinguished from the alteration in 1,25(OH)₂D production that is known to be a feature of the process of aging.

To address these issues, we studied the parathyroid

hormone-1,25(OH)₂D axis in women with osteoporosis, using a challenge with oral phosphate. There has been considerable interest recently in the use of phosphate as part of sequential-treatment protocols in the therapy of osteoporosis.^{8,9} For the purpose of this study, however, the use of phosphate allowed us to assess the effect of opposing stimuli to 1,25(OH)₂D production: the direct effect of phosphate in suppressing 1,25(OH)₂D levels, and an indirect effect of phosphate through elevation of parathyroid hormone levels in stimulating the formation of 1,25(OH)₂D.^{10,11} With the use of age-matched control women without osteoporosis, the protocol permitted an examination of both endogenous parathyroid hormone responsiveness and 1,25(OH)₂D production in women with osteoporosis. Data on a group of young normal subjects who were studied according to an identical protocol¹² enabled us also to evaluate aging as a factor independent of osteoporosis. The results support the existence of a distinct abnormality in the parathyroid hormone-1,25(OH)₂D axis in osteoporosis.

METHODS

We studied 8 women with osteoporosis (mean age, 63 years; range, 49 to 78) and 10 age-matched controls (mean age, 61; range 50 to 74). All subjects were postmenopausal white women. Those with osteoporosis had at least two nontraumatic vertebral compression fractures, and their bone mineral density as measured by dual-photon absorptiometry of the lumbar spine was more than 2 SD below the mean expected for their age. In five of

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Supported in part by grants (DK-01836, AR-39191, DK-32333, and RR-00645) from the National Institutes of Health. Dr. Silverberg is the recipient of a Clinical Investigator Award from the National Institutes of Diabetes, Digestive and Kidney Diseases.

Presented in part at the Tenth Annual Meeting of the American Society of Bone and Mineral Research, New Orleans, June 1988.