

IgE synthesis in man

II. Comparison of tetanus and diphtheria IgE antibody in allergic and nonallergic children

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Specific IgE and IgG antibodies were quantitated in 91 allergic and 80 nonallergic age- and sex-matched children between 4 and 17 yr of age. Statistically significant increased antidiphtheria and antitetanus IgE antibodies ($p < 0.01$) measured by the radioallergosorbent test (RAST) were noted in allergic compared with nonallergic subjects. Of the allergic children with total serum IgE >500 U/ml, 19 of 52 (37%) and 25 of 52 (48%) had elevations (>2 SD above nonallergic control mean) of serum antitetanus or antidiphtheria IgE antibody, respectively, whereas only 2 of 35 allergic children with serum IgE <500 U/ml had elevation (>2 SD) of these antibodies. Antitetanus and antidiphtheria IgG antibodies were measured by passive sheep red blood cell (SRBC) hemagglutination. Geometric mean antitetanus IgG antibodies were higher in allergic (4.9 AU/ml) as compared to nonallergic (1.7 AU/ml) children ($p < 0.001$). Geometric mean antidiphtheria IgG antibodies were higher (0.31 AU/ml) in nonallergic and lower in allergic (0.10 AU/ml) subjects ($p < 0.01$). These data suggest that allergic individuals with markedly elevated total serum IgE have unique antibody responses following routine immunization with tetanus-diphtheria (Td) toxoids and tetanus-pertussis-diphtheria (DPT) which are manifest by enhanced specific IgE synthesis.

Our prior documentation of specific diphtheria and tetanus IgE antibody synthesis following booster immunization with tetanus-diphtheria (Td) toxoids has provided a means of exploring factors important in the regulation of specific IgE antibody production in man. In our initial communication, no statistically significant differences in antidiphtheria or antitetanus IgE antibody synthesis were noted between a group composed of 18 allergic and a group of 21 nonallergic adults and adolescents following booster immunization with alum-precipitated Td toxoid.¹ From the allergic group, 2 individuals with total serum IgE values of 3,300 and 5,000 U/ml sera demonstrated ex-

ceptionally large rises (up to 35% counts bound) in anti-diphtheria and/or antitetanus IgE antibody which have persisted for up to 36 months. Since all subjects in our initial study had been selected for booster Td immunization on the basis of low (>0.125 antitoxin units [AU]/ml) serum tetanus hemagglutinating (IgG) antibody, regardless of their immunization history, the possibility was raised that this pre-selection had influenced the previous study by selecting only individuals who synthesized less antibody, received less antigen, or had not received antigen for a prolonged time interval. Therefore, the present study was carried out to measure serum antidiphtheria and antitetanus IgE antibodies in age- and sex-matched allergic and nonallergic children who were known to have received at least four prior immunizations with diphtheria and tetanus toxoid antigens and had higher antitoxin values. The results have shown that allergic children with increased total serum IgE may produce increased antidiphtheria and/or antitetanus IgE antibodies without demonstrating a clinical hypersensitivity reaction following the immunization. Values of antitoxoid IgE antibody were not related to concurrent levels of antitetanus or antidiphtheria IgG antibody.

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Supported by United States Public Health Service Grants HD 02662, HD 07850, and a grant from Southwestern Pennsylvania Chapter, Allergy Foundation of America.

Received for publication April 3, 1978.

Accepted for publication Nov. 7, 1978.

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*Supported by United States Public Health Service Training Grant HD 00062.

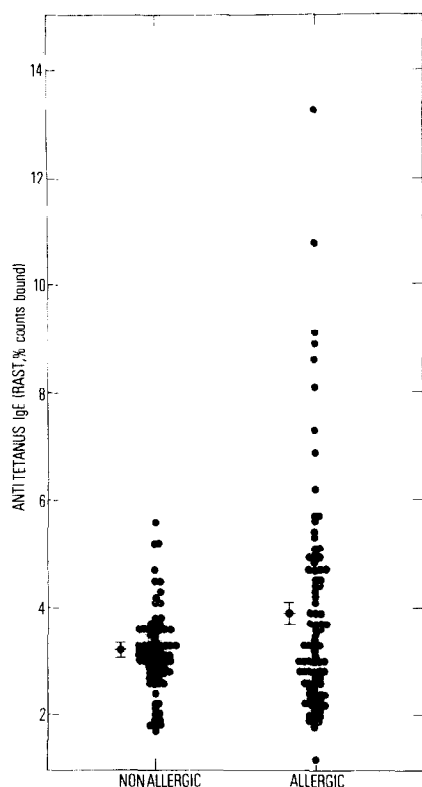


FIG. 1. Antitetanus IgE antibody values expressed as percentage of counts bound in allergic and nonallergic groups. Mean $\pm$ SEM are indicated by the bar and the bracket, respectively.

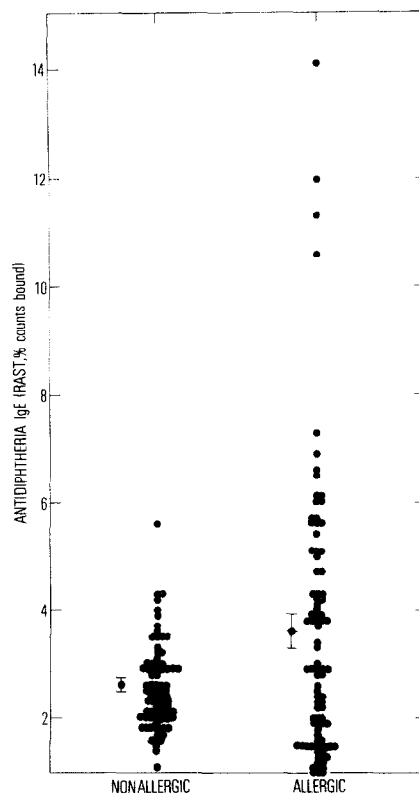


FIG. 2. Antidiphtheria IgE antibody values expressed as a percentage of counts bound in allergic and nonallergic groups. Mean $\pm$ SEM are indicated by the bar and the bracket, respectively.

MATERIALS AND METHODS

Study population

Two groups of patients were compared. The allergic group was composed of 91 patients from the Allergy Clinics of the Children's Hospital of Pittsburgh whose parents provided informed consent. All of these patients had a documented history of recurrent asthma (83/91), seasonal/perennial rhinitis (52/91), or eczema (14/91) present either individually or in combination. Age range of this allergic group was 4 to 17 yr (mean, 10.2 yr). There were 39 females and 52 males. The patients from this allergic group were subdivided on the basis of clinical history and previous skin tests. Fifty-two of the patients had allergic asthma or rhinitis precipitated by recognized inhalant and/or food allergens and positive immediate hypersensitivity skin tests which agreed with their clinical history. Subsequent determinations of serum IgE values for this group ranged from 500 to 5,000 U/ml (geometric mean, 1,287 U/ml). Members of this group were labeled AHE for "allergic high IgE." Ages ranged from 4 to 16 yrs (mean, 11.1 yr) and included 23 females and 29 males. Fourteen of these patients (27%) regularly used alternate-day oral or daily aerosol corticosteroids along with oral bronchodilators to control wheezing. Most (37/39) of the remaining allergic individuals also had recurrent wheezing and rhinitis (19/39); however, most had histories which implicated no spe-

cific inhalant or food as causing or worsening their symptoms, and all had negative or a few very slightly reactive immediate hypersensitivity skin tests to common foods and inhalant allergens. Twelve of these patients (31%) had severe intractable asthma with daily wheezing and were receiving oral or aerosol corticosteroids. Total serum IgE levels of these 39 individuals ranged from 10 to 430 U/ml (geometric mean, 72 U/ml), and this group was labeled ANE for "allergic normal IgE."

The nonallergic comparison group consisted of 80 children who were patients in a private pediatric practice and whose parents gave informed consent. All individuals had been followed for several years and were considered to be "healthy," i.e., having no known chronic or recurrent acute illnesses and no personal history of allergic disease. Age range of this comparison population was 4 to 17 yrs (mean, 9.6 yr). There were 31 females and 48 males.

Hemagglutination (IgG) antibody assay

Serum tetanus and diphtheria IgG antibodies were estimated by passive SRBC hemagglutination by a previously described method.¹ Antibody titers were converted to AU/ml of sera by comparison of the unknowns with simultaneous titrations of U. S. Standard tetanus (5 AU/ml) or diphtheria (6 AU/ml) antitoxin (Bureau of Biologics, Food and Drug Administration, Rockville, Md.). It was estab-

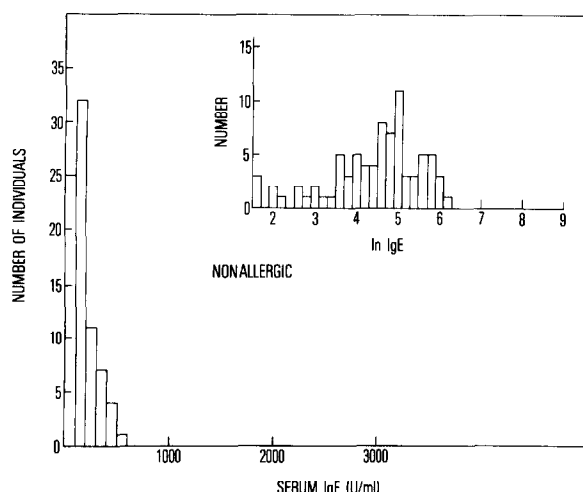


FIG. 3. Frequency distribution of the total serum IgE values (U/ml serum) for nonallergic children expressed in raw numbers and as $\ln(x)$ transformation.

lished by heat inactivation and mercaptoethanol (ME) treatment using the method of Levine and co-workers² on representative sera that essentially all of the tetanus and diphtheria hemagglutinating antibody was of the IgG class.

Total serum IgE

Total serum IgE was quantified using a commercial radioimmunosorbent (RIST) test (Phadebas IgE test, Pharmacia Diagnostics, Piscataway, N. J.). In this test, 1 U/ml is approximately 2 ng/ml of IgE.

Specific IgE antibodies

Antitetanus and antidiphtheria IgE antibodies were measured by the radioallergosorbent (RAST) method. Paper discs were activated by a modification of the method of Ceska, Eriksson, and Varga.³ Two grams of activated discs were coupled to fluid tetanus toxoid (procured from the Massachusetts Department of Public Health, Jamaica Plain, Mass. containing 1,200 Lf (purity, 2,140 Lf/mgPN) of tetanus toxoid and 0.005% thimerosal in borate saline, pH 8.0. The discs were then washed, using constant agitation, twice with 0.1 M NaHCO_3 , once with 0.05 M monoethanolamine in 0.1 M NaHCO_3 , to remove any binding sites not coupled with antigen, three times with 0.1 M acetate buffer, pH 4.0, and, finally, in two changes of incubation buffer containing 0.9% NaCl, 0.05 M phosphate buffer, 0.3% bovine serum albumin (BSA), and 0.05% sodium azide. The same procedures were followed for coupling the diphtheria toxoid. The diphtheria toxoid (Massachusetts Department of Public Health) contained 1,075 Lf (purity, 1,500 Lf/mgPN) of diphtheria toxoid and 0.005% thimerosal. The tetanus and diphtheria discs were stored at 4° C under commercial RAST buffer (Pharmacia Diagnostics). Single tetanus or diphtheria-activated and -sensitized disc preparations were used for all of the RAST tests.

Antigen-coupled discs were incubated at room temperature with 50 μl of sera for 3 hr and then washed three times

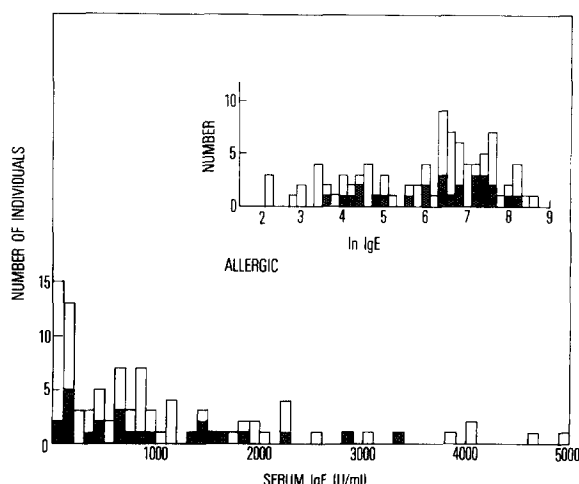


FIG. 4. Frequency distribution of the total serum IgE values (U/ml serum) for allergic children expressed in raw numbers and as $\ln(x)$ transformation. Black individuals are shown by cross-hatching.

with 3 ml of 0.9% saline. Fifty μl of ^{125}I -labeled rabbit antihuman IgE (Pharmacia Diagnostics) was then added to each sample and incubated for 18 hr. Total radioactivity added was determined by counting each sample prior to washing in a gamma counter (Nuclear-Chicago, Des Plaines, Ill.). The radiolabeled discs were then washed three times with 3 ml of 0.9% saline, dried, placed in clean tubes, and the specific radioactivity bound to each disc determined. This procedure allowed background counts to be kept below 0.8% of the total counts added. All RAST results are expressed as the number of counts bound to the antigen-coupled disc divided by total counts added $\times 100$. RAST tests were performed in duplicate and the results expressed as the mean.

RESULTS

The 91 allergic individuals had a mean antitetanus IgE antibody value of $3.9 \pm 0.2\%$ counts bound (Fig. 1), while the nonallergic comparison children had a significantly lower ($p < 0.01$) mean of $3.2 \pm 0.1\%$ counts bound.

The mean antidiphtheria IgE antibody of the allergic group was $3.6 \pm 0.3\%$ counts bound (Fig. 2), which was also significantly higher ($p < 0.001$) than the mean value of $2.6 \pm 0.1\%$ counts bound for the nonallergic comparison group.

The frequency distribution of the total serum IgE values (Figs. 3 and 4) was strongly skewed to the left. Transformation of this data to the natural logarithm ($\log_e$, $\ln[x]$) yielded a more normal distribution for statistical analysis. Geometric mean total serum IgE for the nonallergic group was 87 U/ml and for the allergic group, 374 U/ml ($p < 0.001$).

The 52 individuals comprising the AHE group (+ history and skin tests, IgE > 500 U/ml) had a mean

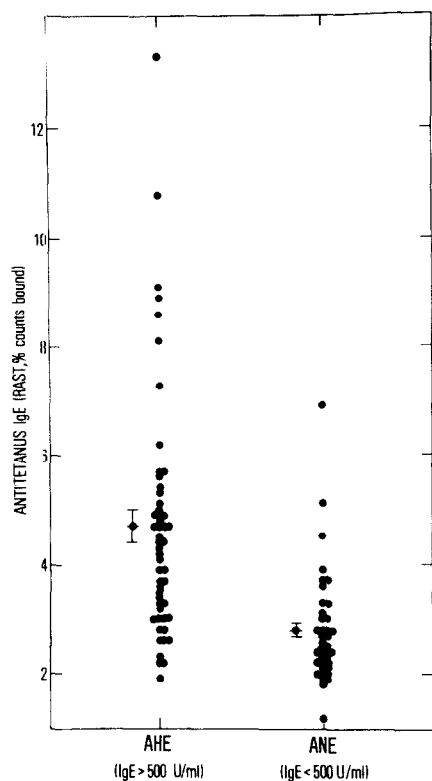


FIG. 5. Antitetanus IgE antibody values expressed as percentage of counts bound for the allergic group with serum IgE greater than 500 U/ml (AHE) and less than 500 U/ml (ANE). Mean $\pm$ SEM are indicated by the bar and the bracket, respectively.

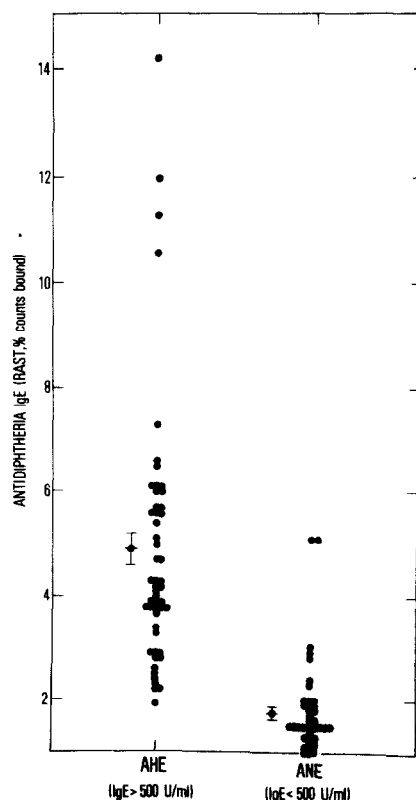


FIG. 6. Antidiphtheria IgE antibody values expressed as percentage of counts bound for the allergic group with serum IgE greater than 500 U/ml (AHE) and less than 500 U/ml (ANE). Mean $\pm$ SEM are shown by the bar and the bracket, respectively.

antitetanus IgE antibody value of $4.7 \pm 0.3\%$ counts bound (Fig. 5) and a mean antidiphtheria IgE antibody value of $4.9 \pm 0.3\%$ counts bound (Fig. 6). Antitetanus and antidiphtheria IgE antibodies were both significantly higher ($p < 0.001$) in the AHE group than in the nonallergic comparison group. The geometric mean total serum IgE of the AHE group was 1,287 U/ml.

In contrast, the 39 individuals of the ANE group ($\text{IgE} < 500 \text{ U/ml}$) had an antitetanus IgE antibody value of $2.8 \pm 0.1\%$ counts bound (Fig. 5) and an antidiphtheria IgE antibody value of $1.8 \pm 0.1\%$ counts bound (Fig. 6). Both of these parameters were significantly lower ($p < 0.05$ and $p < 0.001$) than the nonallergic group and contrasted with the higher values of the AHE group. Geometric mean total serum IgE of the ANE group was 72 U/ml and not statistically different from the nonallergic group.

Nineteen of 52 (37%) of the AHE individuals had antitetanus IgE and 25 of 52 (48%) had diphtheria IgE antibody values greater than 2 SD above the respective means of the nonallergic group. Only 5 of 119 (4.2%) ANE and nonallergic individuals had an-

titetanus IgE and 3 of 119 (2.5%) had antidiphtheria IgE antibody values greater than 2 SD above the mean of the nonallergic group.

Geometric mean antitetanus IgG antibody was 1.7 AU/ml sera (Fig. 7) in the nonallergic children compared with a value of 4.9 AU/ml sera in the allergic group ($p < 0.001$). Antidiphtheria IgG antibody was 0.31 AU/ml in the nonallergic group and 0.10 AU/ml in the 91-member allergic group ($p < 0.01$). Mean antitetanus IgG antibody was significantly higher ($p < 0.01$) in both the AHE (3.4 AU/ml) and ANE (8.1 AU/ml) groups. This contrasts with the geometric mean antidiphtheria IgG of 0.11 (Fig. 8) in the AHE group, which was significantly lower ($p < 0.05$) than in the nonallergic comparison group. A significantly lower ($p < 0.01$) value of 0.08 AU/ml was also found for antidiphtheria IgG antibody in the ANE group. A positive correlation coefficient (Kendall tau test) of 0.32 was found between total serum IgE and specific tetanus IgE in the AHE group. Specific diphtheria IgE and total serum IgE had a coefficient of 0.15 in this same group. Correlation coefficients for these same parameters in the ANE and

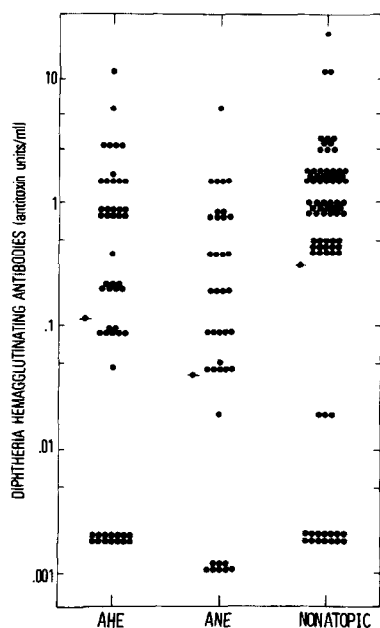


FIG. 7. Tetanus hemagglutinating antibody levels expressed in antitoxin U/ml serum for nonallergic, allergic IgE > 500 U/ml serum (AHE), and allergic IgE < 500 U/ml serum (ANE) groups. Geometric mean for each group is shown by the bar.

nonallergic groups were between ± 0.1 . Correlation coefficients between specific IgE and hemagglutinating (IgG) antibody values were between ± 0.1 for all groups.

To assess the potential presence of spurious differences created by uncontrolled variables, the 80-member nonallergic comparison group was subjected to an analysis of variance test by considering the first and last 40 individuals as separate treatment groups and comparing the differences between the population means for antitetanus and antidiphtheria IgE antibody, total serum IgE, antitetanus and antidiphtheria hemagglutinating antibody values, age, and sex. The F values for these intragroup comparisons were between 0.13 and 1.03 ($p > 0.5$) and therefore not statistically significant.

DISCUSSION

In a prior communication we documented that antitetanus and antidiphtheria IgE antibody is synthesized by some adolescents and adults following booster immunization with Td toxoids; however, no statistical difference in the incidence of this response was found between atopic and nonatopic individuals.¹ Since the number of participants in our initial study was relatively small (39 individuals) and the grouping into atopic and nonatopic was done only on the basis of historical information, we felt it necessary to re-

examine in a larger, more extensively characterized population the relationship between antitetanus and antidiphtheria IgE antibody synthesis and clinical allergy. The children included in the present study were grouped by both laboratory and historical criteria rather than by only historical data as was done in our previous report. Their tetanus-diphtheria immunization status is, we felt, representative of pediatric and adolescent patients since by history all individuals received at least 4 or 5 injections of commercial alum-precipitated Td or DPT toxoids in the preceding 17 yr. Individuals were not pre-selected by antitoxin levels and, except for 2 male/female sibling pairs in the allergic groups, all of the children were unrelated, so that possible genetic influences on IgG and IgE antibody synthesis would be left uncontrolled.

All children came from similar socioeconomic backgrounds; however, the nonallergic and allergic groups were not equally distributed by race. The 91-member allergic group was composed of 26 blacks and 65 Caucasians. Grundbacher^{4, 5} previously reported finding higher total serum IgE values in blacks compared to Caucasians, which he attributed to social-genetic differences. The approximately 350 individuals in each of his studies were drawn from the same population of only 64 families, this fact possibly creating a profound influence on serum IgE levels since other investigators have documented elevations of serum IgE in asymptomatic members of atopic families.^{6, 7} Although several reports have documented elevated serum IgE values in Filipino children,⁸ Grundbacher's papers are the only ones to our knowledge that report elevated total serum IgE values in "normal" black children in the United States. Several reports have documented elevated serum IgG levels in blacks when compared with Caucasians.^{9, 10} Analysis of variance of our data demonstrated no statistically significant differences between blacks and Caucasians in antitetanus and antidiphtheria IgE antibody, total serum IgE, and antitetanus and antidiphtheria hemagglutinating antibody values within the allergic groups.

None of the children with greatly elevated antitetanus or antidiphtheria IgE antibody had a history of a systemic immediate hypersensitivity reaction following prior tetanus, DPT, or Td immunization, although several recalled local tenderness and induration at the injection site. Three patients (not included in this study) were referred to us for evaluation of what was clinically diagnosed as a systemic immediate hypersensitivity reaction following immunization with tetanus or DPT toxoid(s), and we were unable to document elevated antitetanus or antidiphtheria IgE antibody. Several patients with ele-

TABLE I. Serum IgE antibodies

Subjects	Diphtheria IgE (% counts bound)	Tetanus IgE (% counts bound)
Nonallergic (80)*	2.6 ± 0.1	3.2 ± 0.1†
Allergic (91)	3.6 ± 0.3	3.9 ± 0.2
AHE (52)	4.9 ± 0.3	4.7 ± 0.3
ANE (39)	1.8 ± 0.1	2.8 ± 0.1

*Number of subjects in parentheses.

†Mean % counts bound ± SEM.

TABLE II. Hemagglutinating (IgG) antibodies

Subjects	Tetanus (AU/ml)	Diphtheria* (AU/ml)
Nonallergic (80)†	1.7	0.31
Allergic (91)	4.9	0.10
AHE (52)	3.4	0.11
ANE (39)	8.1	0.08

*Geometric mean.

†Number of subjects in parentheses.

vated antitetanus IgE antibody by RAST were skin-tested with tetanus toxoid and demonstrated a positive immediate wheal-and-flare reaction. Several weeks after skin testing, 3 of these individuals had increased their serum antitetanus IgE and IgG antibodies, although without any apparent adverse systemic symptoms. Because of these findings we have been hesitant to recommend the administration of additional tetanus toxoid to these children, although booster immunization may historically be indicated. It should be noted, however, as shown in Fig. 7, that all children had tetanus antibody values at least one log above recommended protective levels (>0.1 AU/ml).

Statistical analysis of the serum IgE values of our nonallergic comparison group and published reports of serum IgE levels in nonallergic children¹¹⁻¹³ led us to select a value of 500 U/ml as one which would be approximately 3 SD above the mean serum IgE values of nonallergic children. Subdivision of the allergic children on the basis of this number (< or >500 U/ml) served in effect to confirm the earlier grouping of the allergic individuals into those whose symptoms were precipitated by specific allergens (AHE group) and those individuals with few identifiable factors precipitating their "allergic" symptoms (ANE group).

The total serum IgE values in this study were determined by the Phadebas IgE test (Pharmacia Diagnostics). Several recent studies have indicated that an inhibition test such as the RIST used in this study tends to overestimate IgE concentrations in sera containing less than approximately 50 to 60 U/ml of IgE.

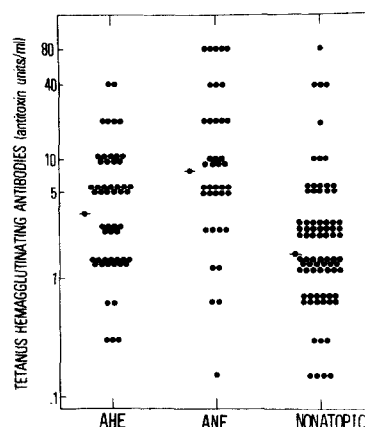


FIG. 8. Diphtheria hemagglutinating antibody levels expressed in antitoxin U/ml serum for nonallergic, allergic IgE > 500 U/ml serum (AHE), and allergic IgE < 500 U/ml serum (ANE) groups. Geometric mean for each group is shown by the bar.

This is reportedly due to a nonspecific factor present in some sera.¹⁴ This methodologic problem may have selectively elevated the total serum IgE value of some sera included in the nonallergic and ANE groups as indicated by the nonallergic group in our study having a mean serum IgE value of 87 U/ml (range, <10 to 475 U/ml), which is slightly higher than levels reported in a recent study of European children using the direct sandwich radioimmunoassay (PRIST).¹⁵

There has been disagreement over the existence in man of an IgG bioregulatory mechanism on specific IgE synthesis, although ample data exist in animal models.¹⁶⁻¹⁸ Secondary IgE antibody responses may be suppressed and high titers of IgG "blocking antibody" produced clinically by multidose immunotherapy for pollen allergies; however, there has not been direct evidence that the elevation of specific IgG antibody is directly responsible for the suppression of IgE antibody synthesis. We were not able in this study to document an inverse relationship between antitoxoid IgG and specific IgE values, although the possibility exists that the antigenic determinants for the IgE antibody response to tetanus and diphtheria toxoids may not be the same as those for the IgG antitoxin response. Antitetanus and antidiphtheria IgE antibody values were independent of concurrent IgE antitoxin levels, and in a few patients longitudinally studied they decreased apparently independently of the antitoxin values. A correlation coefficient of ± 0.10 (Kendall tau test) between diphtheria and tetanus IgE antibodies and their respective hemagglutinating IgG antibodies was found in the nonallergic as well as in both the AHE and ANE groups (Table I). Tetanus IgG antitoxin values were higher and diphtheria values lower in allergic subjects, yet specific IgE antibody

was higher in the AHE than in the nonallergic or ANE groups (Table II).

Two allergic individuals who were immunized with Td and who had substantial rises in both IgE and IgG antidiphtheria and antitetanus antibody have maintained greatly elevated (>10% counts bound) antitetanus and antidiphtheria IgE antibodies for over 18 and 36 months. Several other patients included in this study were by history immunized several years prior to our documenting their elevated antitoxoid IgE values. In contrast, 2 nonallergic adults who participated in our initial study and who had rises in antidiphtheria IgE antibody to 11.3% and 12.5% counts bound following booster immunization had rapid decreases in specific IgE antibody by 3 months postimmunization. Although supported by data from only a small number of patients, this difference in the persistence of specific IgE antibody synthesis in atopic and nonatopic individuals with similar IgG antitoxin levels suggests the possibility that IgE antibody production in these allergic patients may not be controlled by levels of IgG antibody, but rather by cellular events which control the initiation and memory for an enhanced IgE antibody response. In animal models, IgE synthesis has been shown to be regulated by subpopulations of thymus-derived lymphocytes which control the class, magnitude, and duration of antibody production.¹⁹⁻²³

Because the receipt of tetanus and diphtheria toxoid is almost universal, the measurement of antitetanus and antidiphtheria IgE antibodies by the RAST method has provided a useful investigative tool for the study of the mechanisms of IgE synthesis in man. Even though immunization with these products has as yet not been directly associated with proved serious IgE-mediated clinical hypersensitivity, allergic children with increased total serum IgE synthesized increased antidiphtheria and anti-tetanus IgE antibodies.

We are grateful to Dr. Floyd Taylor for his statistical consultations and to Dr. Ralph LaNeve for allowing us to study his patients. We also thank Sylvia Cirotta and Eleanor Wielechowski for assistance in the preparation of this manuscript.

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