

Age-related serum immunoglobulin E levels in healthy subjects and in patients with allergic disease

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Serum IgE levels were measured by a paper-disc radioimmunoassay technique (PRIST) in 425 nonallergic subjects and in 570 patients with asthma, 244 with allergic rhinitis, 48 with asthma and eczema (atopic dermatitis), 49 with eczema but without asthma, and 57 with chronic urticaria. The data are presented for age groups in geometric means and standard deviations and by modal distribution. Normal mean IgE levels for the total sample were 32 IU/ml with highest levels (mean of 51 IU/ml) in school-age children. The highest IgE levels were found in patients with both asthma and eczema (mean of 985 IU/ml), followed by asthma alone (305 IU/ml), eczema alone (273 IU/ml), and allergic rhinitis (171 IU/ml). The values for our United States population were higher than those reported from Scandinavian countries but lower than those reported from Canada. The geometric mean plus 1 SD (64 IU/ml for infants, 150 IU/ml for schoolchildren, and 100 to 120 IU/ml for all other age groups) appears to be the most useful limit of normalcy. Overlaps with normal values are largest for urticaria, eczema, and allergic rhinitis and least for patients with allergic asthma.

Estimates of serum IgE levels have become part of the diagnostic assessment of the patients with established or suspected allergic disease. The interpretation of such estimates must, however, depend on the availability of standards of normalcy for given populations. Reports in the literature provide such information, but many are based on population studies outside the United States.¹⁻⁸ Some are limited to pediatric⁹ or to adult populations,¹⁰ and others do not furnish readily accessible tabulations of normal values for different age groups.¹¹ Stiehm and Rachelefsky¹² tried to solve the problem of disparate population reports by combining data from different sources. The information they used, however, was gathered from Scandinavia and England and therefore does not necessarily reflect normalcy for a United States population.

The purpose of this study was to gather information on serum IgE levels in healthy Americans of different

age groups and to compare these levels with those found in patients of similar ethnic backgrounds who had asthma, allergic rhinitis, atopic dermatitis, or urticaria.

METHODS

Populations studied

Subjects selected for study were healthy children and adults predominantly of white heritage from three southern states (Florida, Georgia, and Alabama) and persons of similar background with allergic disease. Sera from healthy (nonallergic) children were obtained in child health care clinics, crippled children's clinics, and postoperative clinics at a university hospital. Some sera from healthy adults (taken in routine examinations, birth control clinics, and from premarital blood tests) were obtained from patients at a university student health clinic, some from noninfected patients of the orthopedic services of Veterans Administration and university hospitals, and some from healthy hospital employees. All subjects completed a questionnaire concerning personal or family history of allergy. Only sera from subjects with negative history were accepted. Sera from patients with doubtful history were subjected to radioallergen sorbent testing (RAST) (as was a random sample) and were rejected if test results were positive.

Sera from allergic patients were obtained in the inpatient and outpatient services of a university clinic and a Veterans Administration hospital. During the period 1973 to 1978 all

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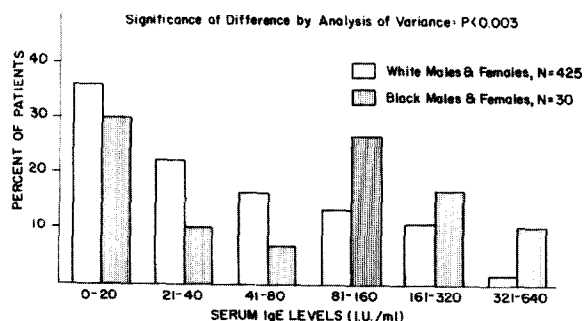


FIG. 1. Frequency distribution of serum IgE levels in a normal United States population by race.

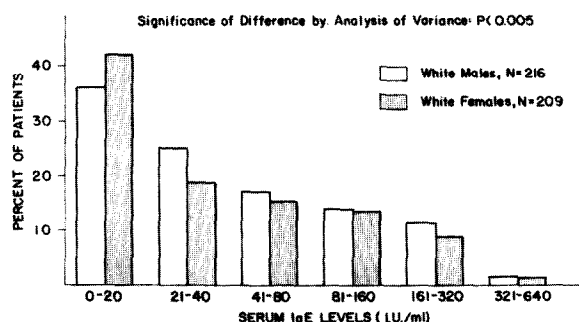


FIG. 2. Frequency distribution of serum IgE levels in a normal United States population by sex.

patients who attended these clinics had blood drawn for serum IgE measurements.

For the purpose of this study asthma was defined as recurrent paroxysmal dyspnea with wheezing, responsive to bronchodilator treatment, irrespective of the presence or absence of allergic phenomena. Allergic rhinitis was defined as sneezing, rhinorrhea, or nasal obstruction associated with at least three definitely positive (3+ or 4+) intradermal skin tests with inhalant antigens of 100 or 1,000 PNU/ml. The diagnosis of atopic dermatitis and urticaria was made strictly on clinical grounds, usually in consultation with the dermatology service physicians of the university hospital.

IgE measurements

All measurements were done with the Phadebas IgE PRIST radioimmunoassay (Pharmacia Diagnostics Inc., Piscataway, N. J.), using fresh or recently frozen sera. Radioactive measurements were performed with a Model 600 Gamma Tec Instrument (The Nucleus, Inc., Oak Ridge, Tenn.). Allergen-specific IgE antibody measurements were performed by Pharmacia with the Phadebas RAST test.

Statistics

Measurements of serum IgE were tabulated for diseases and for age groups (1 to 2, 3 to 5, 6 to 15, 16 to 20, 21 to 30, 31 to 40, and over 40 yr of age). The rationale for this type of grouping was based partly on the observed differences of serum IgE levels for different ages and partly on the availability of adequate sample sizes for statistical

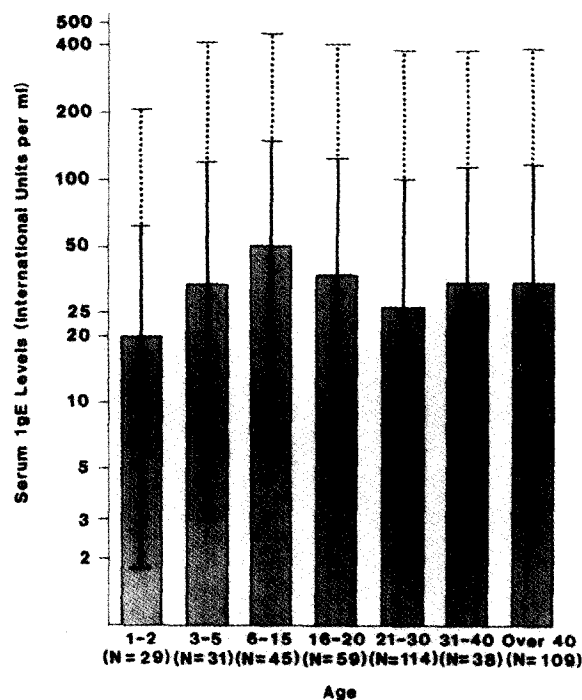


FIG. 3. Serum IgE levels in 425 normal white subjects. Geometric means plus and minus SD.

evaluation. Comparison of results was done by use of the unpaired Student *t* test with the aid of a Monroe 1930 calculator.

RESULTS

Normal serum IgE levels

Differences by race. Serum IgE levels are higher in blacks than in whites (Fig. 1). In whites distribution is unimodal, with 37% having levels between 0 and 20 IU/ml. In blacks there are two peaks: one between 0 and 20 and another between 81 and 160 IU/ml. Levels above 321 IU/ml (approximately 2 SD above mean) are noted in 2% of whites and 10% of blacks. However, because the black population ($N = 30$) is too small for meaningful tabulation of data with regard to age groups and diseases, the information given in subsequent tables and figures is limited to the white population. A somewhat larger sample of IgE levels in black subjects (113 children, 59 adults) has been described by Grundbacher.¹⁰

Differences by sex. Comparison of serum IgE levels in 216 males and 209 females showed the differences between sexes to be much less striking than those between races (Fig. 2). Although slightly more males than females had high levels >20 IU/ml ($p < 0.005$), the distribution of values within the various orders of magnitude was such that we felt justified in treating males and females as one group in further tabulations.

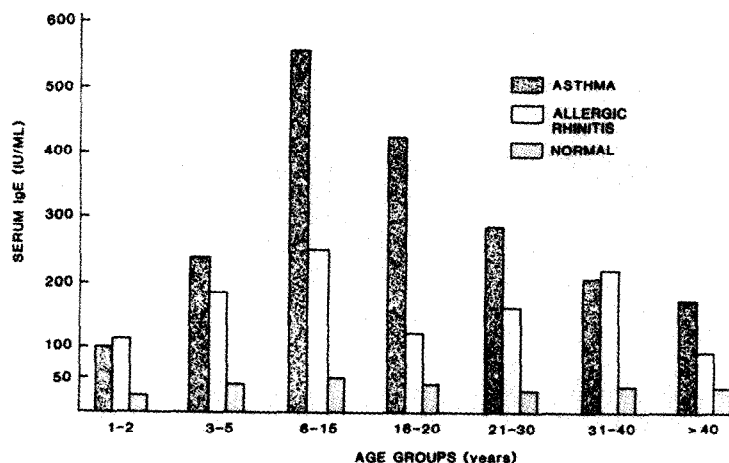


FIG. 4. Mean serum IgE levels for patients with asthma or allergic rhinitis and for control subjects (all white).

TABLE I. Serum IgE levels in 425 healthy white subjects by age groups

Age (yr)	N	Natural log means	Natural log SD	Antilog means (IU/ml)	Antilog means + 1 SD (IU/ml)	Antilog means + 2 SD (IU/ml)
1 to 2	29	2.98	1.18	20	64	208
3 to 5	31	3.55	1.23	35	119	405
6 to 15	45	3.92	1.09	51	150	446
16 to 20	59	3.63	1.18	38	123	401
21 to 30	114	3.29	1.32	27	100	376
31 to 40	38	3.53	1.19	34	113	372
Over 40	109	3.52	1.21	34	114	382
Total	425	3.47	1.21	32	108	386

Geometric means and standard deviations. Natural log and antilog IgE means for age groups as well as antilog means + 1 and + 2 SD are given in Table I and Fig. 3. Geometric means suggest a bimodal distribution of serum IgE levels for age groups, with lowest levels (20 IU/ml) in the 1- to 2-yr-olds, a peak in the 6- to 15-yr-olds (51 IU/ml), another low in the 21- to 30-yr-olds (27 IU/ml), and another rise for all subjects older than 30 yr (34 IU/ml). The relatively large sample sizes in these adult groups (114 subjects 21 to 30 yr old and 109 subjects over 40) make it unlikely that this bimodality was an accidental finding.

The standard deviations from the means are relatively widespread in all age groups: the 2 SD above mean level lies near 400 IU/ml for all groups except the infants.

Serum IgE levels in patients with asthma but without atopic dermatitis (eczema)

Table II and Fig. 4 show that geometric means of serum IgE levels in 570 patients with asthma were lowest in infants (94 IU/ml), peaked in the 6- to 15-yr-old group (548 IU/ml), and then declined

TABLE II. Serum IgE levels in 570 white patients with asthma without atopic dermatitis

Age (yr)	N	Log means	Log SD	Antilog means (IU/ml)
1 to 2	52	4.545	1.408	94
3 to 5	97	5.425	1.474	227
6 to 15	206	6.305	1.319	548
16 to 20	57	6.056	1.139	427
21 to 30	73	5.650	1.331	284
31 to 40	34	5.245	1.366	190
Over 40	51	5.146	1.235	172
Total	570	5.719	1.444	305

steadily and reached another low in the over-40-yr-old group (172 IU/ml). As in healthy subjects, somewhat higher IgE levels are found in male than in female asthmatics (Fig. 5).

Comparison of the frequency distribution of serum IgE levels of healthy subjects with that of asthmatic patients (Fig. 6) shows that 73% of healthy and 18% of asthmatic subjects have serum IgE levels below 80

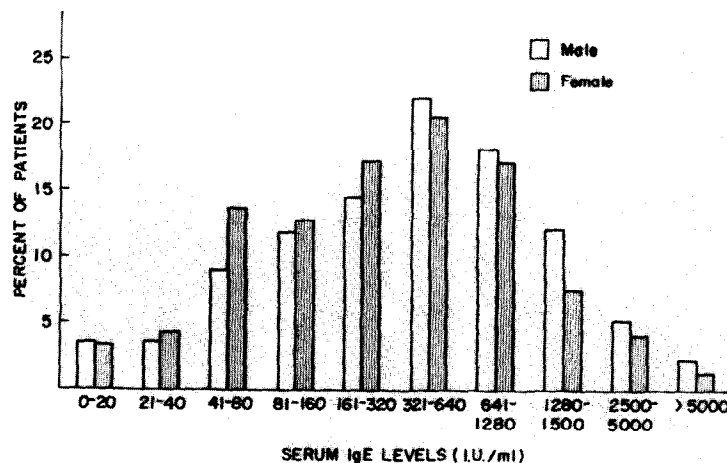


FIG. 5. Frequency distribution of serum IgE levels in an asthmatic population by sex.

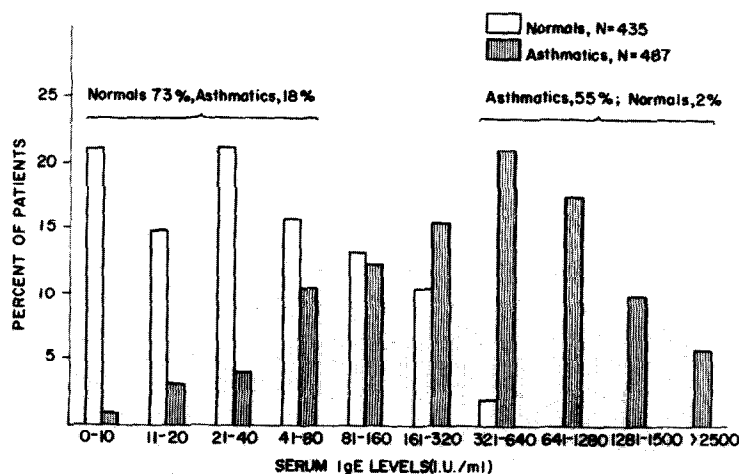


FIG. 6. Frequency distribution of normal subjects and asthmatics by serum IgE levels.

IU/ml, whereas 55% of asthmatic and only 2% of healthy subjects have levels above 320 IU/ml. IgE levels are between 81 and 320 IU/ml in 25% of healthy subjects and in 22% of asthmatics.

If a level of 100 IU/ml (about 1 SD) of IgE were to be adopted as the upper limit of normal, it appears that at least 20% of the asthmatic patients have "normal" IgE levels (<100 IU/ml) and 24% of normal subjects have "elevated" IgE values (>100 IU/ml).

Fig. 7 shows that in healthy subjects serum IgE levels are below 100 IU/ml in all infants and in 75% to 85% of the other subjects. In asthmatic patients IgE levels were less than 100 IU/ml in 60% of infants, but this percentage declined to only 2% in the 16- to 20-yr-olds and then rose gradually to about 30% in patients over 40. In Fig. 8 an attempt is made to differentiate patients with allergic asthma from those with nonallergic asthma by age groups. The criteria for labeling patients as "allergic" were (1) a serum

IgE level that was at least 1 SD above the geometric mean for the age group and (2) the presence of at least three markedly positive skin tests. "Nonallergic" asthmatics were those patients who had (1) IgE levels below 1 SD from geometric mean and (2) either negative skin tests or only one or two reactions. Skin tests were done by the intradermal method. The few positive test results were usually reactions to one or two house dust antigens. Patients who had more than two positive skin tests but low IgE levels or elevated IgE levels and negative tests were omitted from this tabulation. Evidence of atopy is found in most asthmatic patients between 6 and 40 yr of age but in only 20% of the infants and about 50% of the patients over 40.

Serum IgE levels in patients with allergic rhinitis

Table III and Fig. 9 describe serum IgE levels in patients with allergic rhinitis. As with asthmatics, IgE

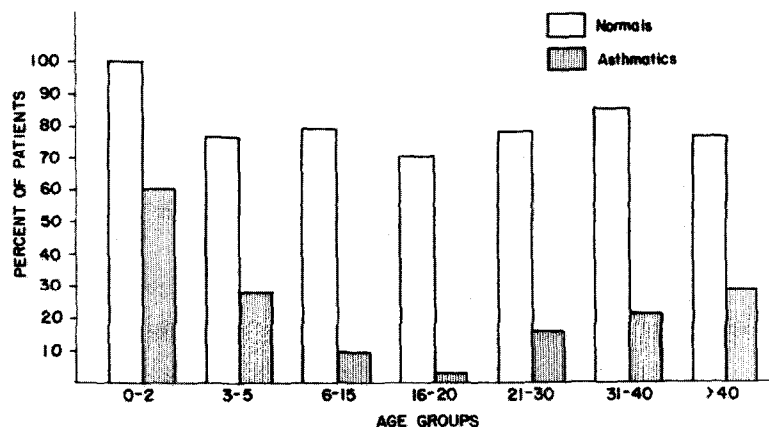


FIG. 7. Frequency distribution of normal subjects and asthmatics with serum IgE levels <100 IU/ml by age (all white).

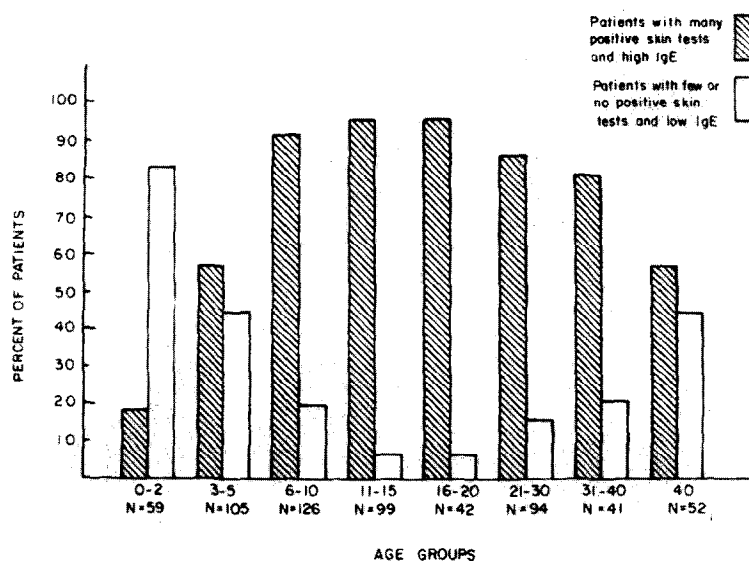


FIG. 8. Comparison of patients with asthma with elevated serum IgE levels (greater than 1 SD above geometric mean) and with three or more positive skin tests versus asthmatics with lower serum IgE levels and less than three positive skin tests ("allergic" versus "nonallergic" asthma).

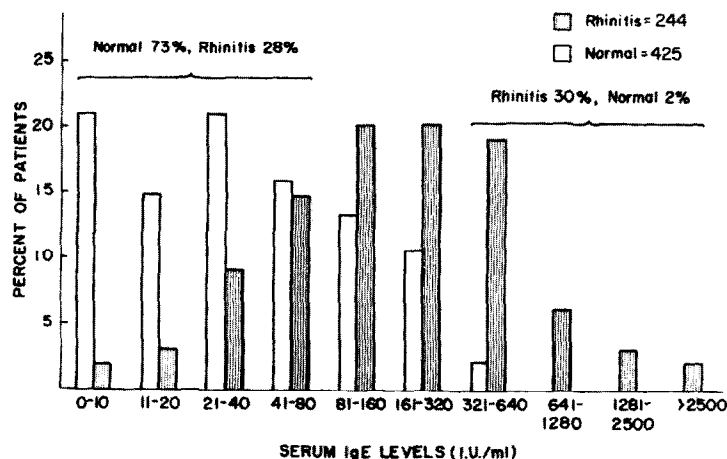


FIG. 9. Comparison of serum IgE levels of normal subjects and patients with allergic rhinitis.

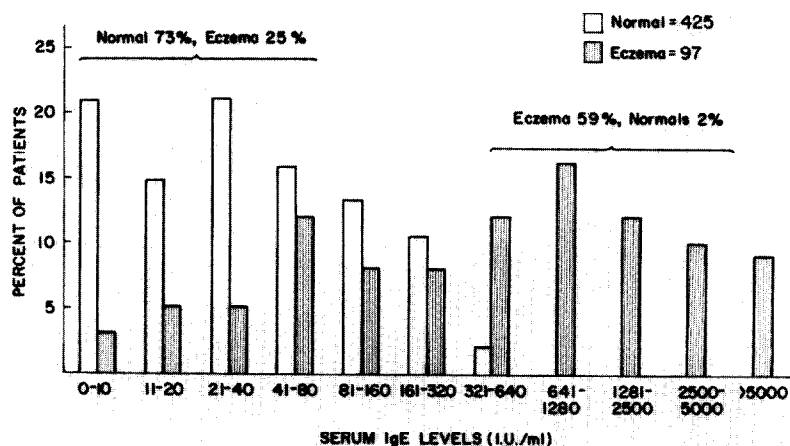


FIG. 10. Comparison of serum IgE levels of normal subjects and patients with eczema.

TABLE III. Serum IgE levels in 244 patients with allergic rhinitis without asthma or atopic dermatitis

Age (yr)	N	Log means	Log SD	Antilog means (IU/ml)
1 to 2	13	4.811	0.945	123
3 to 5	23	5.199	1.244	181
6 to 15	61	5.547	1.238	256
16 to 20	20	4.916	1.651	136
21 to 30	86	4.995	1.087	148
31 to 40	20	5.551	1.241	257
Over 40	21	4.596	1.295	99
Total	244	5.143	1.260	171

TABLE IV. Serum IgE levels in 48 white patients with atopic dermatitis and asthma

Age (yr)	N	Log means	Log SD	Antilog means (IU/ml)
1 to 2	5	5.253	2.439	191
3 to 5	7	6.744	1.972	849
6 to 15	23	7.232	1.168	1,383
16 to 20	4	7.814	1.378	2,475
21 to 30	6	6.787	1.552	887
31 to 40	2	5.727	2.685	307
Over 40	1	7.601	—	2,000
Total	48	6.892	1.631	985

levels are lowest in infants, and only modest peaks are noted in the 6- to 15-yr-old and the 31- to 40-yr-old patients. Comparison of frequency distribution of serum IgE levels of healthy individuals with that of patients with allergic rhinitis shows that 73% of healthy subjects and 28% of those with allergic rhinitis have IgE levels below 80 IU/ml, whereas 2% of healthy subjects and 30% of those with allergic rhinitis have levels above 320 IU/ml. Finally, 25% of normal subjects and 42% of patients with allergic rhinitis have IgE levels falling between 81 and 320 IU/ml.

Serum IgE levels in patients with atopic dermatitis

Serum IgE levels were evaluated in patients with atopic dermatitis (eczema) with or without asthma. Fig. 10 shows the overlap of IgE levels in healthy subjects and in patients with eczema. Of our relatively small sample of patients with eczema (97) 59% have IgE levels above 320 IU/ml, whereas 25% of such patients have IgE values of less than 80 IU/ml. In

16% of patients with eczema and 25% of normal subjects IgE levels fall in the gray zone between 81 and 320 IU/ml. When patients with eczema were segregated into two groups, one with and one without concomitant asthma, it was noted that the IgE mean values for the respective age groups are consistently higher for the group of patients with eczema and asthma than for the alternate group (Tables IV and V).

Not included in the above tabulations are the findings in three black children with eczema who had extremely high levels of serum IgE: 38,000, 77,000, and 79,000 IU/ml (the last two patients were 4-yr-old twins who also had asthma). Parasites were not found in the twins, but the other child had ascaris and hookworm infection.

Serum IgE levels in patients with urticaria

Fig. 11 compares serum IgE levels of healthy subjects with those of patients with urticaria. In this disease category 23% of patients with urticaria have IgE levels higher than 320 IU/ml. Half (46%) of the IgE

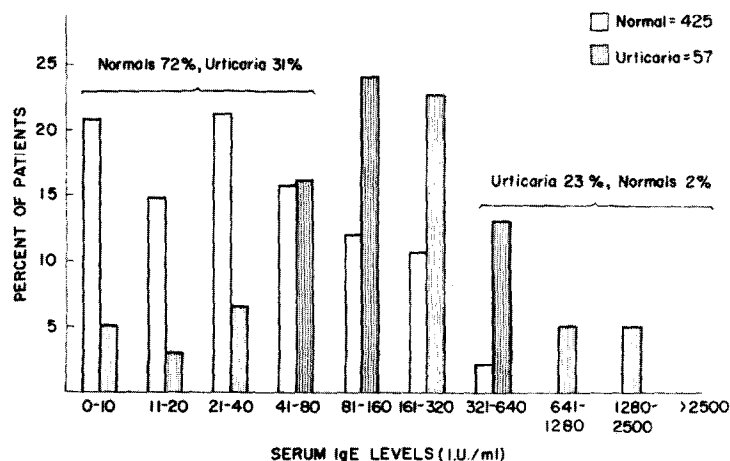


FIG. 11. Comparison of serum IgE levels of normal subjects and patients with urticaria.

TABLE V. Serum IgE levels in 49 white patients with atopic dermatitis without asthma

Age (yr)	N	Log means	Log SD	Antilog means (IU/ml)
1 to 2	16	4.615	1.323	101
3 to 5	12	6.272	1.426	530
6 to 15	12	6.000	1.817	402
16 to 20	5	5.671	0.699	290
21 to 30	3	5.811	3.012	334
31 to 40	0	—	—	—
Over 40	1	8.071	—	320
Total	49	5.610	1.672	273

levels in patients with urticaria fall between 81 and 320 IU/ml.

Comparison of IgE levels among patient groups with asthma, allergic rhinitis, and eczema against normal subjects

Fig. 4 compares geometric means of serum IgE levels by age groups for patients with asthma or with allergic rhinitis with levels in normal subjects. This histogram shows a striking difference in IgE levels between healthy and asthmatic subjects of all age groups. In all age groups a relatively small difference is noted between IgE levels of healthy subjects and of patients with allergic rhinitis. Also in all age groups except infants (1- to 2-yr-olds) and, surprisingly, in the 31- to 40-yr-old group, the IgE geometric mean of the allergic rhinitis groups are lower than those of corresponding asthmatic groups.

A statistical comparison of serum IgE levels in patients with asthma without eczema, with eczema with or without asthma, and with allergic rhinitis (Table VI) shows highest IgE levels in the patient group with

TABLE VI. Differences in serum IgE levels and significance of difference in different disease categories (geometric means in IU/ml)

Eczema with asthma (N = 48)	Asthma without eczema (N = 570)	Eczema without asthma (n = 49)	Allergic rhinitis (N = 244)	p value by t test
985	305			<0.0001
985		273		<0.001
	305	273		NS
985			171	<0.0001
	305		171	<0.0001
		273	171	<0.01

both asthma and eczema. Progressively lower IgE levels are noted in patients with asthma but without eczema, with eczema without asthma, and with allergic rhinitis in such rank order.

Diagnostic utility of IgE determinations

To investigate the differentiation between healthy and allergic individuals by determination of IgE levels, we compared using as indicators of upper limits of normalcy (1) 80 IU/ml IgE (mean + about 1 SD for all age groups), (2) 320 IU/ml IgE (mean + about 2 SD for all age groups), and (3) 100 IU/ml IgE (average customary IgE cutoff for using PRIST assay). Table VII lists the diagnostic sensitivity (i.e., percent diseased patients correctly identified) and specificity (i.e., percent nondiseased individuals correctly identified) of IgE test at the three possible upper levels of normal values evaluated in four atopic conditions. Use of either the mean + 1 SD (80 IU/ml) or the 100 IU/ml upper limit cutoff affords the best combination of diagnostic sensitivity and specificity for all groups; with such cutoffs 82% or 78% of indi-

TABLE VII. Diagnostic sensitivity and specificity of IgE test at three cutoff levels

Patient groups	Upper limit of normalcy (IU/ml)	Sensitivity*	Specificity†
Asthma	80	82	73
	320	55	98
	100	78	80
Allergic rhinitis	80	72	73
	320	30	98
	100	60	80
Eczema with or without asthma	80	75	73
	320	59	98
	100	70	80
Urticaria	80	68	73
	320	23	98
	100	NA	80

*Sensitivity = percent positive in disease.

†Specificity = percent negative in health.

viduals with atopic asthma are detected, respectively. On the average, 70% of other atopic conditions are detected with either cutoff. Using the traditional 2 SD from mean as the upper limit of normal (about 230 IU/ml), only 55% of asthmatics, 30% of patients with allergic rhinitis, 59% of patients with eczema plus asthma, and 23% of those with urticaria are identified as diseased.

DISCUSSION

Early studies of normal serum IgE levels were done in Scandinavia. Johansson¹ reported IgE findings in 49 children and 125 adults as early as 1968, based on the examination of sera from subjects determined to be "nonallergic" by RAST. These data show four values over 1,000 ng/ml (about 500 IU/ml) in 20- to 30-yr-old subjects and a gradual decline of normal values from 15 to 70 years of age. More recently Kjellman² reported that in 207 healthy Swedish children aged 0 to 14 yr tabulation of IgE levels showed the geometric mean to be the highest in the 10- to 14-yr-olds (20 to 23 IU/ml). In the United States Gleich et al.¹⁰ reported that IgE levels in 96 healthy adults varied from 1 to 2,700 ng/ml, with a mean of 179 and a median of 80 ng/ml. Gerrard⁴ compared serum IgE levels in 819 apparently healthy white Canadians between 1 and 70 yr of age with those of an Indian community (275 measurements). The Indians had significantly higher IgE levels than the white population. Grundbacher¹¹ found differences between nonwhite and white populations to be similar to those reported by Gerrard.⁴

In our study the universal mean IgE level of the normal population (32 IU/ml) compares well with the

median value reported by Gleich et al.¹⁰ (33 IU/ml). Like Kjellman, we also noted a peak in IgE levels in young teenagers; however, our mean IgE levels for this group were significantly higher than Kjellman's (50 IU/ml versus 20 to 23 IU/ml). Our higher values may be a result of less stringent criteria for normalcy or geographic difference. Finally, our mean IgE values were much lower than those of the white or Indian populations reported by Gerrard. This discrepancy may be due, at least in part, to the different methods used for determination of IgE protein. Gerrard used the competitive IgE RIST test, whereas, we used the newer, noncompetitive IgE PRIST test. The latter test reportedly yields more precise and specific measurements, especially in the lower IgE range.

We found no significant difference between IgE levels between male and female subjects. Our black population was too small for comparison between races.

Of the three IgE levels used to investigate the differentiation between allergic and healthy individuals (mean plus about 1 SD, mean plus about 2 SD, and 100 IU/ml) the mean plus 1 SD was the preferable indicator of upper limit of normalcy. Use of the 100 IU/ml IgE cutoff was acceptable for all acceptable age groups except infants.

Use of the traditional mean plus 2 SD as upper limit of normal for IgE affords poor diagnostic sensitivity. The diagnostic reliability of IgE determinations is most pronounced in the differentiation of asthmatic from healthy subjects. Differentiation of patients with allergic rhinitis and those with eczema or urticaria from healthy individuals is less clear cut. Average IgE levels in the asthmatic patients were higher than those in patients with hay fever, although many of the latter patients had a larger number of positive skin tests. This relatively lesser association between nasal allergy and serum IgE levels is further confirmed by reports on patients with hay fever whose skin tests and serum RAST test results were negative but who had reaginic antibodies in nasal secretions.¹³⁻¹⁵ Whether secretory specific IgE antibodies may be found in bronchial secretions of asthmatics with negative serum antibodies has, to our knowledge, not been reported.

CONCLUSIONS

1. Routine measurements of serum IgE levels in allergic patients or patients suspected of having allergic disease are helpful in assessing presence and severity of atopic sensitization.

2. Serum IgE level determination is particularly valuable in differentiating allergic from nonallergic asthma, because the atopic process in asthma appears

to produce high IgE levels, particularly in young patients between 6 and 30 yr of age.

3. The separation of allergic from nonallergic rhinitis, eczema, or urticaria is less easily accomplished by determining serum IgE levels, because of the greater overlap of average serum IgE levels in these conditions and in normal individuals. However, high levels are significantly more common in all allergic conditions than in normal populations.

4. For patients over 5 yr of age it seems useful to consider 100 IU/ml serum IgE the upper limit of normal for discriminating atopic from nonatopic conditions, although 25% to 30% of patients with allergic rhinitis, as manifested by several markedly positive skin tests, may have normal levels.

5. The extent of tissue involvement appears to have a determining effect on serum IgE levels, with greatest involvement and highest levels (mean of almost 1,000 IU/ml) in patients with both asthma and eczema, somewhat lesser involvement and lower but still significantly elevated levels in patients with asthma without eczema or eczema without asthma (mean near 300 IU/ml), and significantly less tissue involvement and lower levels in patients with allergic rhinitis without other complicating organ participation (mean of 171 IU/ml).

From the aforementioned information it appears that the expense and time lag involved in determining a serum IgE level may be justified for the clinician attempting to classify asthma as atopic or nonatopic (extrinsic or intrinsic). However, this laboratory test is not always reliable in distinguishing allergic from nonallergic rhinitis.

In summary, this study represents an attempt to define normal and abnormal serum IgE levels in a United States population for different age groups. Determinations of serum IgE levels by the Phadebas PRIST method has, in our hands, proved to be a relatively simple, reliable, and valuable laboratory test in the assessment and management of suspected or established allergic disease.

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