

Serum total IgE in normal subjects and the influence of a family history of allergy

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Summary

The purpose of this study was to establish the range of serum total immunoglobulin E (IgE) in a healthy population free of personal and family history of allergy, and to determine whether a family history of allergy influenced serum IgE levels. Using commercially available Phadebas reagents, the mean serum IgE in eighty-four adults aged 17–30 years with no personal or family history of allergy was found to be 38.8 iu/ml. Seventy-five percent of subjects had a serum IgE below 50 iu/ml and in only one subject was serum IgE in excess of 150 iu/ml, which we suggest be taken as the upper limit of normal. When healthy subjects with no personal history but with a family history of allergy were included with this normal population, the mean serum IgE in 207 subjects was 95.4 iu/ml and the upper limit of the distribution curve over 200 iu/ml, suggesting an influence of genetic factors on IgE production.

Introduction

Since immunoglobulin E (IgE) was isolated (Ishizaka, Ishizaka & Hornbrook, 1966) numerous studies have been undertaken to determine the biological role of this antibody and the usefulness of total serum IgE estimation in the diagnosis and management of allergic diseases (Ishizaka & Ishizaka, 1976; Orgel *et al.*, 1975; Steinberg, Ishizaka & Norman, 1974; Havnen *et al.*, 1973; Orgel *et al.*, 1977). The diversity of opinion regarding the latter is at least partly attributable to the lack of precise definition of the level of serum total IgE in the healthy population, and the absence of reliable data with which to compare an abnormal sub-population. Preliminary observations suggested to us that apparently healthy siblings of atopic subjects might have higher serum IgE levels than subjects without a personal or family history of atopy, causing us to question the validity of some previous studies of 'normal' IgE (Johansson, 1967; Berg & Johansson, 1969; Rowe & Wood, 1970; Orren & Dowdle, 1975) in which subjects were not questioned about their family history. Recent studies in

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children (Kjellman, Johansson & Roth, 1976) and adults over a wide age range (Nye *et al.*, 1975), free of a history of allergy in first degree relatives, have found mean IgE levels lower than previously reported. We undertook the present study to establish the range of serum IgE in healthy young New Zealand adults with negative personal and family histories of allergic disease, and to determine whether serum IgE was influenced by a family history of allergy.

Methods

Selection of subjects

Students of three large science and medical classes of the University of Otago, were invited to complete a questionnaire and to provide a venous blood sample. Students of four other classes (medical, nursing, physiotherapy) and selected hospital staff were asked to complete the questionnaire but provided a blood sample only if they were free of a personal and family history of allergy.

Questionnaire

Subjects recorded age, sex, race, place of birth, recent travel outside New Zealand; personal history (past or present) of asthma including wheezing on exertion, hayfever, eczema, other allergies (including drug allergy, skin rashes, insect stings) and migraine; and a history of asthma and allergies in the immediate (parents, siblings, children) and distant family (grandparents, parents' siblings, cousins). On completion of the questionnaire the subject was interviewed by one of us (M.S.) to check and clarify if necessary the information recorded. The subjects were then classified as follows:

- (1) Current personal history of asthma (P1), hayfever (P2), eczema (P3), other allergies (P4), or migraine (P5), with symptoms within the previous year.
- (2) Past personal history of asthma (P6), hayfever (P7), eczema (P8), other allergies (P9), or migraine (P10), with no symptoms within the previous year.
- (3) Immediate family history of asthma (F1), or any other allergic disease (F2), with a negative personal history.
- (4) Distant family history of asthma (F3), or any other allergic disease (F4), with a negative personal and immediate family history.
- (5) Normal subjects (totally negative personal and family histories).

Each group was exclusive, there being no overlap. Personal (P) classifications took precedence over family (F) classifications, and lowered numbered categories over higher; i.e. a subject with both asthma and hayfever within the past year was classified P1. Present disease took precedence over past disease, so that a subject with current eczema and a past history of asthma, was classified P3.

IgE analysis

Within 2 hr of venepuncture the serum was separated by centrifugation and frozen in two aliquots at -20°C . No later than 1 month after collection, one aliquot from each student was thawed and duplicate measurements of serum IgE made by a standard technique (Johansson, Bennich & Wide, 1968), using a commercially available radio-immunosorbent test (RIST, Phadebas[®] IgE Test, Pharmacia Diagnostics, Uppsala, Sweden). ^{125}I -IgE was added to sera diluted 1:10 and incubated with Sephadex-conjugated anti-IgE with constant agitation at room temperature for 16 hr. Unbound

IgE was removed by centrifugation and the radioactivity of the Sephadex particles determined by counting for 2 min in polystyrene tubes (BSP 10015 CE, Keyline Plastics, S.A.) in a Packard Model 3002 Gamma Scintillation Counter with a 50% efficiency. If duplicate measurements varied by more than 10% the analyses were repeated. Serum IgE was determined by plotting the radioactivity of the Sephadex particles on the calibration curve, after correction for background counts obtained with an empty centrifuge tube. Serum IgE was expressed as international units (iu) per ml. Standard concentrations of IgE (2.5, 5, 25, 100, 200, 400 iu/ml) were measured in duplicate or triplicate, and the calibration curve drawn as a sigmoid curve of best fit through all points. The IgE standard supplied by Pharmacia (previously standardized against WHO standard 68/341) was calibrated against WHO standard 69/204 (WHO International Reference Centre for Immunoglobulins, Lausanne, Switzerland).

Results

From the classes where full participation was requested, questionnaires and blood samples were obtained from 472 subjects (75.9% of class rolls). Of these, thirty were non-European, two were over 30 years of age and one was adopted; these thirty-three were excluded from further analysis. A similar response was obtained from other classes but blood was drawn from only forty-two subjects with negative personal and family histories of asthma and allergy. The 439 unselected students were designated Group A, and the forty-two selected non-allergic subjects Group B.

Age and sex distribution

Group A varied in age from 17.0 to 29.7 years with a mean of 20.1 years while Group B ranged from 17.8 years to 28.6 years with a mean of 21.9 years (Fig. 1). Group A contained 256 males and 183 females, while Group B had twenty-one males and twenty-one females.

History of allergy

Of 439 Group A students, 274 (62.4%) had personal histories of possible allergic disease either current or past, the majority suffering from asthma or hayfever (Fig. 2). A further 123 students recorded only an immediate or distant family history of possible allergy. Forty-two students (9.6%) of Group A and all forty-two Group B subjects had entirely negative personal and family histories of allergic disease.

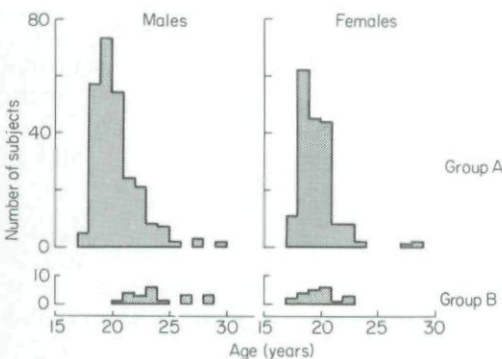


Fig. 1. Age and sex distribution of unselected (Group A) and selected (Group B) subjects.

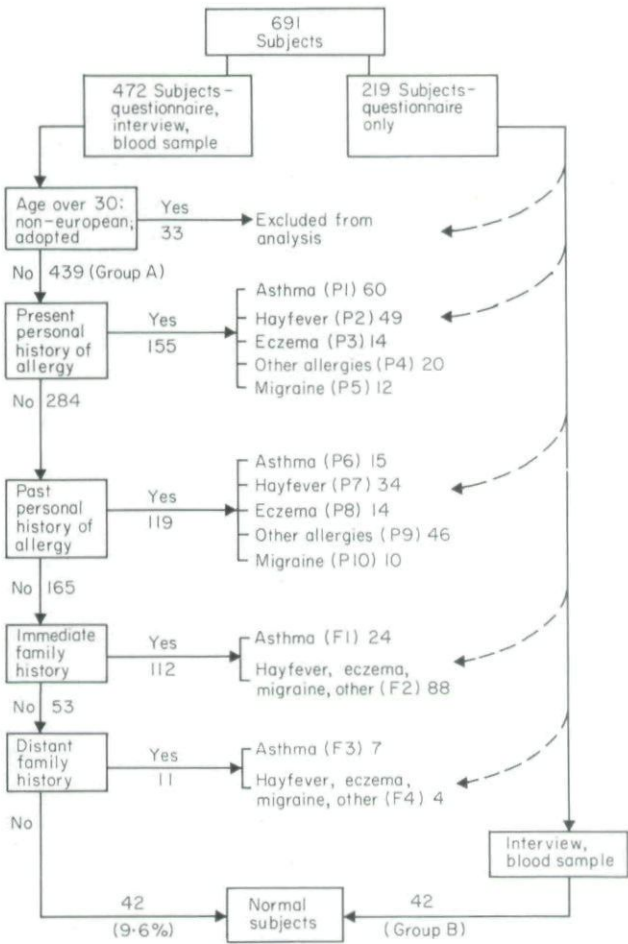


Fig. 2. Classification of subjects by questionnaire concerning personal and family history of allergic disease.

IgE analysis

Triplicate measurement of reference IgE concentrations yielded highly reproducible results enabling a smooth curve to be constructed for reading unknown IgE concentrations (Fig. 3). However, no advantage in accuracy was found in triplicate compared with duplicate measurement, and duplicate measurements only were performed on the unknown sera.

The Pharmacia standard IgE supplied was identical in activity with WHO standard 69/203 (Fig. 4).

IgE levels in normal subjects

The mean serum IgE in eight-four subjects (fifty males, thirty-four females, age range 17.5–28.6 years) with totally negative personal and family histories of allergy was 38.8 iu/ml with a skew distribution (Fig. 5). Seventy-five percent of these normal subjects had serum IgE levels below 50 iu/ml. Female subjects had a significantly higher mean

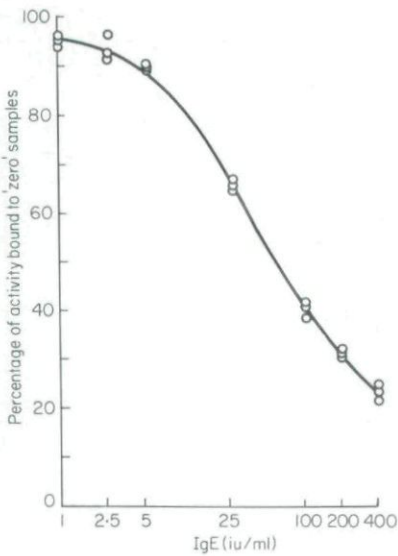


Fig. 3. Calibration curve constructed using triplicate measurements of reference IgE concentrations.

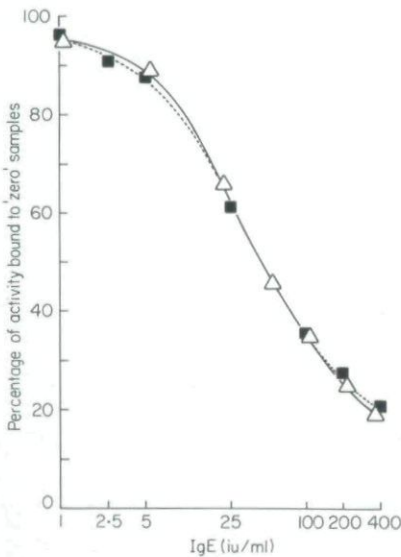


Fig. 4. Comparison of calibration curves of Phadebas IgE standard with WHO standard reference IgE. ■, Phadebas; Δ WHO 69/204.

serum IgE (54.5 iu/ml, s.d. 38.6) than males (28.0 iu/ml, s.d. 34.9), $P < 0.005$ (Student *t*-test).

IgE levels in 'allergic' diseases

Sera from all Group A students were analysed to obtain the spectrum of serum IgE levels in the various 'allergic' conditions specified on the questionnaire. Those with current asthma had the highest mean serum total IgE (529 iu/ml). Elevated mean IgE

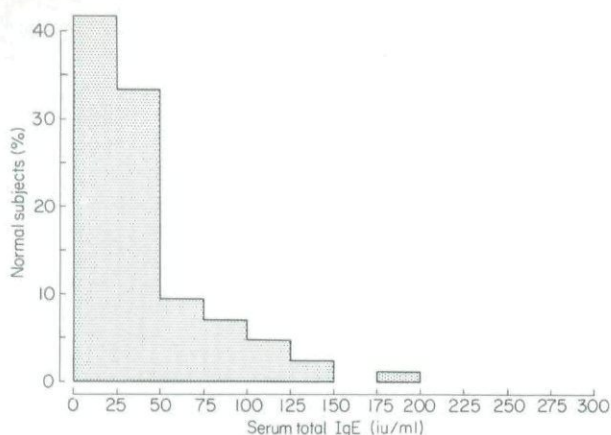


Fig. 5. Histogram of IgE levels in 84 normal subjects with no personal or family history of allergy.

Table 1. Serum IgE values in normal subjects and in allergic subgroups

Sub group	Classification	n	Serum Total IgE (iu/ml)		P < *
			Mean	Range	
N	NORMALS (Groups A & B)	84	38.8	5-180	
	Personal history				
P1	Current asthma	60	528.7	22-4450	0.001
P2	Current hayfever	49	306.5	13-1640	0.001
P3	Current eczema	14	96.1	20-450	0.001
P4	Current other allergies	20	179.6	5-795	0.001
P5	Current migraine	12	91.2	41-355	0.001
P6	Past asthma	15	412.1	23-1840	0.001
P7	Past hayfever	34	331.2	10-1960	0.001
P8	Past eczema	14	142.5	10-1250	0.01
P9	Past other allergies	46	311.5	5-6450	0.025
P10	Past migraine	10	99.2	16-378	0.005
	No personal history				
F1	Immediate family history asthma	24	122.2	17-780	0.001
F2	Immediate family history other	88	144.4	10-1520	0.001
F3	Distant family history asthma	7	75.3	36-157	0.05
F4	Distant family history other	4	80.3	49-151	0.05
	Combined groups N, F1-F4 inclusive	207	95.4	5-1520	0.01

* Compared to normals, Student *t*-test.

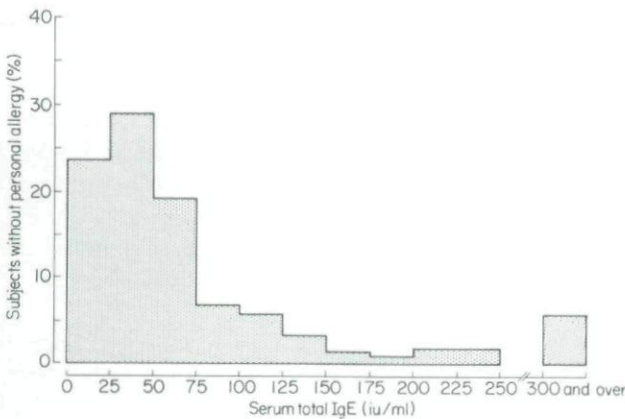


Fig. 6. Histogram of IgE levels in 207 subjects with no personal history of allergy but not excluding a positive family history.

levels were found in hayfever, eczema, miscellaneous other allergies and migraine. Those with no current disease but with a past history of allergy also had significantly higher IgE levels than the 'normal' group (Table 1).

Influence of family history on serum IgE levels

The mean serum total IgE level in 123 subjects with no personal history of allergic disease, but an immediate (112) or distant (eleven) family history suggesting allergy, was 134.1 iu/ml (range 10–1520, s.d. 233.1). Inclusion of these subjects into the previously described normal group gave a mean serum total IgE of 95.4 iu/ml (s.d. 187.0, $n=207$) and an upper limit of normal in excess of 200 iu/ml, as judged from the distribution curve (Fig. 6).

Discussion

A normal range for serum total IgE in subjects with no current or past history of any form of allergic disease, and with no immediate or distant family history of allergy, was established in young adults. Our results are comparable with those of Nye *et al.* (1975) who found a mean serum IgE of 36.3 iu/ml with a range of 1–178 units in 102 subjects ranging from 18 to 83 years, screened for personal and immediate family history of allergy in much the same manner as in the present study. It is of interest that our mean total serum IgE of 38.8 iu/ml was so close to that of Nye *et al.* as we used the Phadebas solid phase technique only, whereas they used more sensitive liquid phase estimations. The upper limit of normal in our study was considerably lower than that reported by Johansson (1967) Berg & Johansson (1969), Rowe & Wood (1970) and Orren & Dowdle (1975) where levels of up to 500 units were considered normal. Our data show that the inclusion of subjects with a past history of possible allergies, or even with only a family history suggestive of allergy, would account for this difference. Inclusion of subjects with no active present allergy but a past history of allergy (even excluding asthma) would give a much increased mean IgE of 155 iu/ml (range 5 to 6540); inclusion of those with only a positive family history of allergy would increase the mean IgE to 95.4 iu/ml with a range of 5 to 1520. The distribution curve of IgE in this latter group (Fig. 6) would suggest the upper limit of normal should be at least 200 iu/ml

whereas our data (Fig. 5) and the study of Nye *et al.* (1975) would suggest 150 iu/ml as the upper limit of normal.

The lower limit of normal has not been defined in our study, as the sensitivity of the method used precluded accurate analysis of IgE levels less than 10 iu/ml. For statistical purposes, all twenty-nine sera with less than 10 iu/ml IgE were recorded as 5 iu/ml. Measurements were not made on undiluted sera to overcome this lack of sensitivity at low range, as Johansson, Berglund & Kjellman (1976) have shown significant interference with the assay due to the presence of undiluted serum factors. Recently however, Gamo & Maruyama (1977) have reported a simple method for detecting low levels of serum IgE.

No reason can be proffered for the difference between normal male and female mean serum IgE found in this study. Nye *et al.* (1975), Berg & Johansson (1969) and Grundbacher (1975) all found no significant difference.

The major purpose of this study was to define the range of normal IgE and information was recorded on occurrence of allergic diseases primarily to exclude these subjects from the 'normal' population. Three factors may have influenced the mean IgE data in these allergic sub-groups. Firstly, where doubt existed as to the nature of any symptoms, they were classified as allergic rather than non-allergic e.g. skin rashes, rhinitis. Although a clear history was usually obtained on interview, some sub-groups may contain subjects whose symptoms do not fully meet strict criteria for the diagnosis given. Secondly, most of those with evidence of allergy were only mildly affected. Thirdly, this study was undertaken in late autumn and winter when pollen-specific IgE levels would be declining. Had the study been in spring or summer, higher IgE levels might have been found particularly in those with asthma and hayfever. The mean value of serum IgE recorded in each sub-group is therefore probably lower than that found in patients seeking medical advice for symptoms.

The finding of elevated serum total IgE in some subjects with only a family history of allergy raises interesting questions—have they forgotten, ignored, or been unaware of some personal manifestations of allergy, or are they genetically primed to be 'overproducers' of IgE and hence 'potentially allergic'? (Bazaral, Orgel & Hamburger, 1971; Bazaral, Orgel & Hamburger 1974; Kjellman, 1976; Turner, Rosman & O'Mahony, 1974).

The normal serum total IgE levels found in our non-allergic subjects are strictly valid only for the limited age range studied. Berg & Johansson (1969) found a progressive increase in serum IgE in children from 2 to 15 years of age with no personal history of allergy, while Delespesse *et al.* (1977) showed that serum IgE, at least in females, declined with advancing age. This study provides normal data for serum total IgE levels in young adults (17–30 years of age) and also documents the influence of a positive family history of allergy on IgE levels in otherwise normal subjects of this age group.

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