

Development of IgE and allergy in infancy

H. A. Orgel, M.D., Ph.D., R. N. Hamburger, M.D., M. Bazaral, Ph.D.,
H. Gorrin, M.D., T. Groshong, M.D., M. Lenoir, M.D., J. R. Miller, M.D.,
and W. Wallace, M.D. La Jolla, Calif.

Serum IgE levels were followed throughout the first year of life in a sample of 34 infants from atopic and nonatopic families. Their parents' serum IgE levels were also measured. Neonatal levels ranged from 0 to 10 U/ml. Half of the study group, which included a high proportion of infants from atopic families, maintained serum IgE levels below 10 U/ml until 1 yr of age. In the remainder, the serum IgE exceeded 10 U/ml before 1 yr of age, but the time of increase and the rate of increase varied from infant to infant; the sooner the IgE started to increase, the higher was the serum IgE level at 1 yr of age. The relationship of serum IgE level to the development of atopic disease and to other parameters was analyzed. Elevation of serum IgE level at or before 1 yr of age was highly correlated with atopic disease in the first 2 yr of life. The elevation preceded the manifestation of atopy.

The mean levels of IgE in cord serum and in the serum of infants at specified ages have been reported.¹ However, no study of the IgE levels of individual children as a function of age or of the relationship between the time of increase of serum IgE and the time of onset of atopic disease has been published.

We present here the results of sequential measurements of serum IgE during the first year of life and at 2 yr of age in a sample of infants from atopic and nonatopic families. These IgE levels are discussed in relation to the individual and family histories of atopic disease, the serum IgE levels of the parents, and the incidence of infectious diseases. Serum IgA levels at 3 and 12 mo of age were also assayed and their correlation with eczema, serum IgE, and other parameters is analyzed.

MATERIALS AND METHODS

Study population and clinical procedures

More than 150 women who had uncomplicated deliveries at Balboa Naval Hospital, San Diego, Calif., were interviewed by a physician within 2 days of delivery and invited to participate in a prospective study of allergy in infants. Forty-four families entered the study initially; of these, 42 were Caucasian, 1 was Negro, and 1 was Filipino. Visits were scheduled at a special clinic at 2 wk, 1, 2, 3, 4, 6, 9, and 12 mo of age. Comprehensive well-baby care was offered to all participants. This paper is based principally on data from the 34 families who completed 1 yr in the study; each of their infants attended the clinic at least 6 times.

From the Pediatric Immunology and Allergy Division, Pediatric Department, School of Medicine University of California, San Diego.

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Reprint requests to: Dr. H. A. Orgel, Pediatric Department, School of Medicine, University of California, San Diego, La Jolla, Calif. 92037.

At each visit the baby was examined and the mother was questioned regarding the baby's diet and health since the previous visit, with special reference to gastrointestinal and respiratory symptoms and skin rashes. A venous blood sample was obtained. All babies received DPT immunizations and polyvalent oral polio vaccine at 2, 4, and 6 mo of age, except in 2 cases in which the 4-mo immunizations were delayed by 1 mo on account of febrile illness at the scheduled clinic visit. A venous blood sample was taken from the parents and their allergy history was obtained. In each case informed consent was given by the parents for all of the procedures performed during the course of the study.

Twenty-eight of the 34 infants who completed 1 yr in the study were located when they were 2 yr of age. Of these, 17 attended the clinic again; follow-up information about the remaining 11 children was obtained by telephone or by letter. At the 2-yr clinic attendance, the procedures described previously were carried out, and in addition the children were skin-tested by the prick-puncture method with selected allergens. The testing solutions used were *Alternaria*, *Hormodendrum*, Bermuda grass, mugwort-sage, wheat, milk, egg, and house dust (Berkeley Biologicals, Berkeley, Calif.), and house dust (Hollister-Stier Laboratories, Spokane, Wash.). A wheal exceeding the control wheals by 4 mm and accompanied by erythema constituted a positive skin test reaction.

Diagnostic criteria

In some cases, particularly in those patients with chronic or recurrent rhinorrhea, no firm diagnosis was possible on clinical grounds. Infants were, therefore, divided into 3 categories for analysis: definitely atopic, possibly atopic, and nonatopic. We have defined definite atopy as eczema or asthma, diagnosed by clinical criteria, or the presence of other atopic symptoms or signs together with positive skin tests to allergens consistent with the history. Thus, 1 subject with hypersensitivity to milk and positive skin tests to whole milk and milk whey protein is classified as definitely atopic. Infants with chronic rhinorrhea have been classified as possibly atopic in the absence of positive skin tests. One subject with diarrhea following ingestion of specific foods but with negative skin tests has also been placed in the possibly atopic category.

The physicians who examined and diagnosed the infants did not know the results of the laboratory procedures.

LABORATORY PROCEDURES

Serum from venous blood was separated within 24 hr of venipuncture and stored at -10° . Serum IgE was measured by a radioimmunoassay described previously¹ and expressed as U/ml relative to WHO IgE standard 68-341.2.³

Unless special precautions are taken, this radioimmunoassay may overestimate the IgE level in some but not all samples due to the nonspecific blocking phenomenon noted previously.¹ This error, which is less than 10 U/ml in most sera, may be minimized by absorbing an aliquot of serum with high-capacity insolubilized anti-IgE, and expressing the IgE level as the difference between the value obtained for unabsorbed serum and the postabsorption value (after suitable correction for the dilution factor introduced by the immunosorbent). In measurements of infants' sera we used an immunosorbent that had the capacity to remove essentially all IgE from sera containing up to 130 U/ml. In order to obtain the 2 ml volume required for duplicate assays of 0.4 ml unabsorbed serum and 0.4 ml postabsorption serum, some sera were diluted up to 1:3. Sera of all babies were measured in this way until an IgE level of 50 U/ml was attained. Subsequent IgE levels of babies' serum, and adult IgE levels, were determined by duplicate assay of 0.1 ml serum samples, without absorption.

In order to verify the efficiency of the absorption procedure, serum of known IgE content was assayed, pre- and postabsorption, at 3 dilutions with almost all assay runs. In every case we confirmed that all IgE (up to 100 U/ml) was removed by the anti-IgE immunosorbent.

To check the reproducibility of the procedure, a sample of pooled cord serum was "spiked" with a known amount of IgE. Three aliquots each of pooled spiked and of pooled unspiked serum were assayed in duplicate with and without absorption in 3 separate assays. (These

TABLE I. Median serum IgE and range at each age

Age (mo)	n	Median IgE (U/ml)	Range IgE (U/ml)
0.5	20	2.2	0-10.8
1	26	2.65	0-26.0
2	31	1.7	0-44.0
3	28	3.1*	0-59.5
4	26	3.9	0-53.5
6	32	3.9	0-97.3
9	31	9.8†	0-480
12	34	10.4	0.1-525

*Significantly different from 2-mo median ($p < 0.05$).†Significantly different from 6-mo median ($p < 0.025$) (Mann-Whitney U test).

were carried out at 1-mo intervals.) The results, calculated as the corrected difference between absorbed and unabsorbed sera, were as follows:

	Mean (U/ml)	SD	n*
Pooled cord serum IgE	0.21	0.35	9
"Spiked" pooled cord serum IgE	3.70	1.18	9

The results show that assays of sera with less than 1 U/ml of IgE are unreliable, while repeat assays of sera containing 1 to 10 U/ml of IgE have a substantial standard deviation. Repeat assays of sera with IgE levels in the range of 10-15 U/ml differ on average by $\pm 10\%$. Sera containing more than 50 U/ml were assayed without absorption; the standard deviation of repeat assays on different days is then $\pm 6\%$.¹

Serum IgA levels were measured using low-level radial immunodiffusion plates purchased from Meloy Laboratories, Springfield, Va. Levels are expressed as $\log_{10}$ mg/100 ml relative to Meloy Laboratories standard serum Lot D 701-5. According to the manufacturer, 291 mg/100 ml IgA is equal to 191 IU/ml IgA.

Statistical analyses

Since serum IgE levels do not have a Gaussian distribution in the population, nonparametric statistical methods are used in all analyses in which IgE is a variable. The Spearman rank-order correlation test was used for correlations and the Mann-Whitney U test for analysis of differences between medians. Other statistical tests were used as indicated in the text.

RESULTS

Serum IgE levels in babies in the first year

The serum IgE levels at each clinic visit of the 34 babies who completed 1 yr in the study are presented in Fig. 1. The serum IgE level of 50% of the infants remained in the neonatal range, defined as 0-10 U/ml, throughout the first year of life. IgE levels in sequential determinations of serum samples containing less than 10 U/ml increased in 69 instances ($\bar{x} = 2.25$ U/ml ± 1.81 SD) and decreased in 49 instances ($\bar{x} = 2.19$ U/ml ± 1.82 SD). In 12 instances no IgE was detected in either of two sequential determinations. Since the difference in most cases is small and since experimental error in the low range can be large, we do not ascribe any significance to these fluctuations, but note the slight tendency to increasing serum IgE concentration in these measurements.

*Number of duplicate assays.

TABLE II. Correlation coefficients (r_s) of serum IgE levels at different ages with the serum IgE level at 12 mo of age and correlation coefficients for IgE levels measured at selected 3-mo intervals in individual infants

Age (mo)	n	r_s at 12 mo of age	r_s at 3-mo intervals
0.5	20	0.4406*	
1	26	0.7120	
2	31	0.6042	
3	28	0.5680	0.7393 (n = 21)
4	26	0.8070	0.6108 (n = 27)
6	32	0.8689	0.9166 (n = 30)
9	31	0.9026	

* $p < 0.05$; all other correlations, $p < 0.01$.

The serum IgE levels of the 17 infants whose concentrations exceeded 10 U/ml by 1 yr of age rarely showed a decline once the level rose above the neonatal range, as shown in Fig. 1. The age at which the serum IgE level increased most rapidly and the rate of increase varied from individual to individual. By 12 mo of age, a wide distribution of values for serum IgE is seen ($\log_{10}$ mean 1.0253 U/ml $\pm$ 0.8513 SD).

The median IgE levels and the range observed in each age group are summarized in Table I. The median level increases with age except between 1 and 2 mo of age. The decrease that occurs in this interval is not statistically significant. A large and statistically significant change in the median level occurs between the ages of 6 and 9 mo. The change in the median level that is observed between 2 and 3 mo of age also appears to be statistically significant; however, to some extent this may reflect the downward fluctuation at the age of 2 mo. The general trend of the median levels is undoubtedly upwards with age.

The rank order correlation coefficients (r_s) for IgE levels at different ages in the individual infants are shown in Table II. The correlations show clearly that those babies who have unusually high levels at 1 yr of age are, in general, those who had unusually high IgE levels at earlier ages. The correlation coefficients observed between the levels at 3 and 6 mo of age were lower than those observed for other 3-mo intervals. This is consistent with our observation that, although there is no statistically significant change in median IgE levels until 9 mo of age, a rapid increase of serum IgE in some infants occurred between 2 and 6 mo of age, with consequent transient changes of rank order.

Correlation of serum IgE levels with atopic disease in the first two years

Clinical data for each baby and IgE levels at 1 and 2 yr of age are presented in Table III. By 1 yr of age, 5 male infants had developed eczema and 1 female infant (No. 8) demonstrated an immediate hypersensitivity reaction on contact with whole milk and was scratch test-positive on testing with whole milk and milk whey protein. These 6 infants, who were considered to have definite atopic disease, are identified in Fig. 1 and Table III. They had serum IgE levels that rose above 20 U/ml prior to 1 yr of age, although in 1 (No. 13) the serum IgE level had declined from 21.6 U/ml at 9 mo to 16.9 U/ml at 12 mo of age. (An additional infant developed severe eczema at the age of 2½

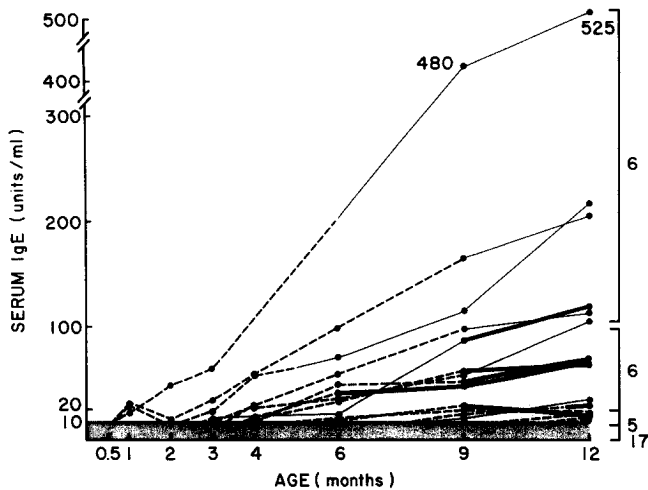


FIG. 1. Serum IgE levels of 34 infants from 2 wk to 1 yr of age. The shaded area represents 17 babies whose serum IgE level remained under 10 U/ml throughout their first year. (—, Definite atopy; — — —, possible atopy; ·····, normal.)

mo but was lost to follow-up after the 6-mo clinic visit. The serum IgE levels of this infant were 11.8, 47.6, and 73 U/ml at 3, 4, and 6 mo of age, respectively.) A further 4 infants with serum IgE levels above 20 U/ml by 1 yr had possible atopy; 1 of these (No. 1) developed definite atopy during the second year. Another infant who had been free of symptoms during the first year (No. 6), but who had an elevated serum IgE level by 1 yr of age, developed eczema during the second year. Thus, of 12 infants whose serum IgE level exceeded 20 U/ml by 1 yr, 8 infants developed definite atopic disease and 4 had possible atopic disease by 2 yr of age. The elevated serum levels preceded the manifestations of disease in 11 of the 12 infants (as shown in Fig. 1).

By contrast, of the 17 children whose serum IgE level did not exceed 10 U/ml by 1 yr of age, only 2 developed definite atopic disease and 4 developed possible atopic disease by 2 yr of age. Of the 5 infants with serum IgE levels 10-20 U/ml by 1 yr of age, 1 had definite and 1 had possible atopic disease by 2 yr of age. These data are presented in Table IV. They demonstrate that infants with serum IgE levels above 20 U/ml before 1 yr of age are at increased risk of developing atopic disease.

The 17 sera available from 2-year-old children (Table III) do not constitute a large enough sample for the statistical analysis of the correlation between serum IgE levels and atopy. The 5 children with serum IgE levels above 20 U/ml before 1 yr of age and with possible or definite atopy at that time had unchanged or increased serum IgE levels at 2 yr of age; all children still had symptoms. One of these children (No. 11) who had a serum IgE level of 25.6 U/ml at 1 yr of age had a serum level of 7,000 U/ml at 2 yr of age. The child was recalled and the level was found to have fallen to 560 U/ml 3 mo later. This child had had mild eczema since 1 yr of age. Stool examinations for ova and parasites and skin tests with *Trichinella* and *Ascaris* extracts were

TABLE III. Rank order of serum IgE level of 34 babies at 1 yr of age, allergy problems, skin test results, parental IgE levels, and family history of atopy

Rank order	Serum IgE (U/ml)		Clinical history, symptoms, or signs of atopy by 2 yr	Age of onset (mo)	History of atopy and IgE				
	1 yr	2 yr			Father		Mother		Sibling
					H _x	IgE	H _x	IgE	H _x
1	525	700	Rhinorrhea†	6	—	80	+	291	
			Asthma	20 (+)§					
2	216		Chronic rhinorrhea	5	+	137	+	40	
3	204		Chronic rhinorrhea, Wheezing with URI	9	—	84	+	475	
4	118*		Chronic rhinorrhea‡	22					
			Eczema	3	—	157	—	122	
				9					
5	113	93	Diarrhea with specific foods	9 (—)§	+	83	—	30	+
6	104	209	Eczema†	18 (—)§	+	790	+	76	
7	69*		Eczema†	9	—	148	—	130	+
8	69*		Milk hypersensitivity†	6 (+)§	—	505	—	37	
9	65*		Eczema†	9	+	118	—	170	
10	28.1		Recurrent rhinorrhea	1	—	54	—	43	
11	25.6*	7,000	Eczema, recurrent infections†	12 (—)§	—	57	—	62	×
12	19.5	60	0	— (—)§	+	324	—	140	
13	16.9*	16.7	Eczema, chronic rhinorrhea†	9 (+)§	+	20	+	82	+
14	16.9	11.2	Eczema†	24 (—)§	+	275	—	125	
15	16.6		0	—	+	960	—	278	
16	12.6		0‡	—			+	105	
17	11.0	268	Recurrent rhinorrhea	4-12	—	162	+	870	+
			Itchy eyes, shiners	24 (—)§					
18	9.8	17.8	Chronic rhinorrhea†	Since birth	+	275	+	310	+
			Eczema	18 (+)§					
19	8.9		0‡	—	—	34	—	43	
20	8.7	1.8	0	—	—	100	—	35	
21	6.3	319	Dry, scaling skin on cheeks, forehead	18 (—)§	+	119	+	116	+
			Rhinorrhea	18					
22	5.1		0‡	—	—	975	—	15	
23	3.9		Chronic rhinorrhea‡	1	—	362	—	31	
24	3.0	16.5	Eczema†	20 (±)§	+	45	+	282	+
25	2.6		0	—	—	423	—	45	
26	2.6		0	—	+	60	—	32	
27	2.4	0	0	—	—	32	—	35	
28	2.2	43	Recurrent nasal congestion	12 (—)§	—	31	—	50	
29	1.7	4.1	Recurrent URIs and otitis media, seborrhea	9 (—)§			+	200	2+
30	1.5	20	0	— (+)§	—	24	—	45	
31	1.1		0	—	—	25	—	270	
32	0.9		0	—	—	118	—	25	
33	0.3	8.7	0	— (—)§	+	740	—	43	
34	0.1		0‡	—	—	39	—	20	

URI: upper respiratory infection.

*Definite atopy by 1 yr of age.

†Definite atopy by 2 yr of age.

‡No 2-yr follow-up.

§Skin test result at 2 yr of age.

||Seen but permission to take blood sample refused by mother.

negative. Similarly high IgE values have been found in association with eczema in older children.^{4, 5}

Two children (Nos. 17 and 21) whose serum IgE levels increased greatly between 1 and 2 yr of age developed symptoms and signs suggestive of atopic disease in that interval; however, both of these infants had negative prick-punc-

TABLE IV. Correlation between serum IgE level at 1 yr of age and symptoms and signs of atopic disease manifested by 2 yr of age

Serum IgE (U/ml) by 1 yr of age	n	Symptoms or signs of atopic disease by 2 yr of age		
		Definite	Possible	Definite and possible
<10	17	2 (12%)	4	6 (35%)
10-20	5	1 (20%)	1	2 (40%)
20.1-100	6	5 (83%)	1	6 (100%)
>100	6	3 (50%)	3	6 (100%)
Total	34	11	9	20

ture skin tests at 2 yr of age. Four infants with serum IgE levels of 10-20 U/ml at 2 yr of age had eczema. The remaining 7 infants had IgE levels ranging from 0 to 60 U/ml; 5 of these were asymptomatic (serum IgE: 0, 1.8, 8.7, 20, and 60 U/ml) and 2 had recurrent rhinorrhea (serum IgE: 4.1 and 43 U/ml).

Skin tests did not contribute significantly to the classification of children into definitely or possibly atopic categories, since most of the positive skin tests were obtained in children already classified as definitely atopic by clinical criteria. Of the 4 children with serum IgE levels of 10-20 U/ml who had eczema (Nos. 13, 14, 18, and 24), Nos. 13 and 18 had positive skin tests to house dust and to *Hormodendrum*, Bermuda grass, mugwort-sage and milk, respectively; infant No. 24 had an equivocal skin test to house dust and infant No. 14 had negative skin tests. Infant No. 1 also had positive skin tests to *Alternaria*, *Hormodendrum*, house dust, and egg. One asymptomatic child had a positive skin test to egg (No. 30). The remaining 8 children tested had negative skin tests. Thus, only for the child with milk hypersensitivity did the skin test data result in a change in classification from possible to definite atopy.

In 2 infants, Nos. 1 and 4, chronic rhinorrhea and elevated serum IgE levels preceded the development of definite atopic disease by 14 and 6 mo, respectively. On the other hand, 1 child (No. 18) with chronic rhinorrhea since birth developed eczema at 18 mo, although his IgE level at 1 yr was only 9.8 U/ml and at 2 yr, 17.8 U/ml.

Serum IgE and history of atopy of the parents

An allergy history and a blood sample for IgE assay were obtained from 66 of the 68 parents whose infants completed 1 yr in the study. The data are presented in Table III. Thirteen fathers and 11 mothers (36%) gave a history of eczema, hay fever, asthma, or urticaria; in 6 families both parents were affected. Thus, 53% of these families may be considered atopic on the basis of parental history. In 7 of these atopic families and in 2 additional families without parental atopy, a sibling of the index case was affected by atopic disease.

The geometric mean serum IgE level of the 66 parents was 99.5 U/ml ($\log_{10}$ mean = 1.9980 ± 0.4706 SE). The geometric mean serum IgE level of the 24 parents with a history of atopy was 166.5 U/ml ($\log_{10}$ mean = $2.2214 \pm$

0.4770 SD), predictably, higher than that of the 42 nonatopic parents, which was 72.0 U/ml ($\log_{10}$ mean = 1.8569 ± 0.4247 SD). This difference is highly significant ($p < 0.005$). Mean maternal and paternal serum IgE levels did not differ significantly.

In 7 families that failed to complete 1 yr in the study, but attended 4 or more clinics, a history of atopy was obtained in 6 families; in 1 of these there was bilateral atopy. Thus, lack of interest in allergic disease was probably not a factor in their failure to remain in the study.

Family history, serum IgE levels, and atopic disease in the infant

Of the 11 infants who developed definite atopic disease by 2 yr of age, 8 (73%) had a history of atopic disease in a parent or sibling; in 4 of these, both parents had a history of atopy. The other 2 infants with both parents atopic were possibly atopic. Three of the 4 infants with eczema, but whose serum IgE levels were between 10 and 20 U/ml at 2 yr of age, had bilaterally positive family histories.

There was a positive family history in 14 of the 17 families with infants whose serum IgE level was above the median level at 1 yr of age and in 6 of 17 families with infants whose serum IgE level was below the median at that age. There is a significant correlation between infants' serum IgE level at 1 yr and mean $\log_{10}$ parental serum IgE level ($r_s = 0.4206$, $p < 0.05$). A genetic effect on serum IgE levels was therefore apparent at 1 yr of age.

Incidence of respiratory tract infections in the first year of life

During the first year all except one child (No. 12) had at least one "cold" (range = 0-8, $\bar{x} = 3.24 \pm 1.71$ SD). Nonatopic children had fewest complaints, $\bar{x} = 2.43 \pm 0.94$ SD, while children with a diagnosis of definite and possible atopy had mean frequencies of 3.00 ± 1.34 SD and 4.78 ± 2.11 SD, respectively.

The incidence of upper respiratory tract infections was not significantly different in males ($\bar{x} = 2.93 \pm 1.79$ SD, $n = 15$) and females ($\bar{x} = 3.47 \pm 1.65$ SD, $n = 19$), and there was no apparent sex difference in the frequency of otitis media or in pulmonary infections.

There was no apparent difference in the incidence of illnesses requiring a physician's visit in relation to the diagnosis of atopy. Fourteen infants developed otitis media; 4 infants had 2 attacks and 1 infant 3 attacks in the first year. Three infants had pneumonia (at 1, 2, and 3 mo of age). Four infants had bronchiolitis (2 at 6 mo and 2 at 8 mo of age); each of them had a serum IgE level below 10 U/ml at 1 yr of age.

Serum IgA levels

Both 3-mo and 12-mo serum samples of 31 infants were available and were assayed for serum IgA levels. At 3 mo of age the serum IgA levels of those infants who developed definite atopic disease by 1 yr of age were lower ($\log_{10}$ mean, 0.9836 mg/100 ml ± 0.1630 SD, $n = 6$) than those of infants who did not ($\log_{10}$ mean, 1.3340 mg/100 ml ± 0.1979 SD, $n = 25$). The difference is

significant ($p < 0.05$) and confirms a previous report.⁶ There was no significant difference in serum IgA levels between atopic and nonatopic infants at 1 yr of age.

There was no significant correlation between serum IgE and IgA levels in the individual infant at 3 mo of age ($r_s = 0.1872$) or at 12 mo of age ($r_s = 0.1326$).

The serum IgA levels at 1 yr of age were inversely correlated with the frequency of infectious illness during the first year ($r_s = -0.42$, $p < 0.05$). No correlation between serum IgA level at 3 mo of age and the number of infections in the first year was seen.

DISCUSSION

The 36% parental incidence of atopy in our study group is significantly higher ($p < 0.005^*$) than the 16.7% incidence of atopy reported in an unselected group of college students.⁷ The geometric mean serum IgE level of 99.5 U/ml is significantly higher ($p < 0.005$) than the 46 U/ml previously reported for a group of male veterans⁸ and higher also ($p < 0.05$) than the 73 U/ml observed in a group of unselected adults 31-40 yr of age.⁹ This high incidence of atopy relative to that of unselected populations supports the view that a high proportion of the study population was motivated to participate by an interest in atopic disease resulting from personal or family experience. It is probable, therefore, that the median values and the distribution of IgE levels of the infants are not characteristic of an unselected group.

Geometric mean IgE levels of children of about 160 unselected families have been reported to reach adult levels by 4 yr of age, and then to increase gradually to a maximum at about 12 yr of age.⁹ Our data show that by 1 yr of age different children have very different IgE levels. In some infants whose IgE increases rapidly in the first year of life, the changes in IgE level during the second year are no greater than the short-term fluctuations that occur in adults.^{8, 10} In other children whose IgE level remained in the neonatal range throughout the first year of life, a rapid increase occurred during the second year. It is clear, therefore, that measurements of population means fail to reveal many interesting details about the way that IgE levels develop in the individual.

It is not clear to what extent the differences between infants reflect genetically determined capacity to produce IgE, differential exposure to environmental antigens, or other, as yet unknown, factors. Genetic effects are presumably of major importance since, by 1 yr of age, a correlation is seen between infant and mean parental IgE levels. Moreover, the intrapair variance in the IgE level of twin children aged 3 to 9½ yr is smaller than that of adult twins, indicating that nongenetic effects on IgE levels become increasingly important with time.⁸

We found the mean incidence of respiratory illness in the first year to be lower than that reported in the Tecumseh study¹¹ in which families were contacted weekly in order to ascertain the occurrence of short-term illness.

*Test for significance of difference of two proportions, normal approximation to binomial.

The retrospective ascertainment of respiratory illness in our study may have resulted in underreporting of the true incidence. However, climatic differences, low prevalence of respiratory viruses in the community, or other factors may have contributed to the observed difference in frequency.

The high frequency of minor respiratory illness that we found in the infants classified as possibly atopic is at least in part a consequence of our definition, since we classified children with chronic rhinorrhea without positive skin tests as possibly atopic. It is not clear whether or not our results reflect a genuine increase in susceptibility of children with allergy to respiratory infections as has been reported.¹² On one hand, the correlation of low serum IgA levels with a high frequency of respiratory illness suggests that these children may have had diminished resistance to virus infection as previously reported.¹³ On the other hand the low serum IgA levels at 1 yr of age may presage development of definite atopic disease, since transiently low levels of serum IgA in the first year of life were found to precede the development of eczema in this and in another study.⁶

It is frequently difficult to diagnose atopic disease in infants. Minor infections of the upper respiratory tract, which occur with high frequency in the first year of life,¹¹ are often indistinguishable on clinical grounds from allergic rhinitis. Skin tests with environmental and food antigens are often inconclusive in this age group. Any contribution that measurements of serum IgE might make in such situations would be valuable since the onset of atopic disease before 3 yr of age carries a poor prognosis.¹⁴ The early identification of children at risk is desirable so that appropriate management can be instituted.

Unfortunately, elevated serum IgE levels and atopic disease are not invariably associated. Previous work has shown that many adults and older children with low serum IgE levels are atopic.¹⁵⁻¹⁹ The same is true for some of these infants. Thus, while there is no doubt that serum IgE levels above 20 U/ml in the first year of life are associated with a very high incidence of possible or definite atopic disease, the value of IgE measurements in differentiating atopic disease from other conditions with a similar symptomatology requires further study.

Our sample included 8 children with chronic or recurrent rhinorrhea of possibly atopic etiology for whom appropriate follow-up data was available. Two of these children had high IgE levels at the time that chronic rhinorrhea was diagnosed; in both of these, atopic disease was subsequently confirmed. An additional child with an elevated IgE level developed rhinorrhea and eczema at about the same time. Five children classified as possibly atopic had low serum IgE levels. One of these was subsequently confirmed as atopic and 4 were still equivocal at the end of the study. In 2 of these 4, the serum IgE became elevated during the second year of life and the symptoms and signs became more suggestive of atopy. These results, while not dramatic, suggest that IgE measurements may be of some use in the differential diagnosis of allergic rhinitis.

IgE measurements might also be useful for the prediction of atopic disease in asymptomatic infants, since the rise in IgE levels almost always precedes

the manifestations of atopy. Systematic IgE measurements in random populations are impractical. In the infants of bilaterally atopic families, the probability of developing atopic disease is already so high (66% by the age of 10 yr,²⁰ 58% by college age⁷) that insofar as prophylactic measures are ever indicated, they are indicated independently of IgE levels. This is emphasized by our finding that 3 children of bilaterally positive families developed eczema although their serum IgE levels were low. Thus, the use of IgE measurements as a predictive tool seems, in practice, to be limited to children who have either one atopic parent, or atopic siblings without parental atopy. Our results suggest that for such infants an IgE level above 20 U/ml at, or before, 1 yr of age is a sign that the child is at substantially increased risk of developing atopic disease than might have been predicted by family history alone.

The work described in this paper was designed to investigate the development of IgE levels and the correlation of IgE levels with atopy in infants. A different approach is needed to establish the value of IgE measurements as a diagnostic and predictive tool in clinical medicine. Our current prospective studies are designed to provide such data.

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