

A year-round study of serum IgE levels in asthmatic children

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Among 26 children with asthma whose serum levels of immunoglobulin E were measured monthly for a year, significant fluctuations were found, especially when initial values were high. These changes related directly to changing severity of atopic dermatitis and exposure to allergens but failed to relate to variations in severity of asthma or rhinitis. Evidence was also gathered supporting the possibility that systemic corticosteroid therapy may suppress formation of newly stimulated IgE.

In the course of a previous study¹ of serum concentrations of immunoglobulin E in asthmatic children, variations of these values were found in serum samples obtained serially from some children. In an attempt to define some determinants of such fluctuations, we have carried on a year-round prospective survey. The results reported here indicate that IgE concentrations are most subject to change when they are elevated, when there is prolonged exposure to clinically relevant allergens, either naturally or by injection, or when the severity of atopic dermatitis fluctuates. In addition, the profound fall of serum IgE concentrations in 2 children treated with systemic corticosteroids over many months lends support to the notion that such therapy may depress serum IgE levels.

SUBJECTS AND METHODS

Twenty-six children with asthma, 14 boys and 12 girls aged 8 to 16 years, were selected for this study because they had been recently admitted to the Children's Asthma Research Institute and Hospital (CARIH) and would therefore be available for study for at least the next 12 months. The study period extended from July, 1969, through June, 1970, for some children and from January, 1970, through December, 1970, for the others.

Clinical data were obtained as reported previously¹ except that such data, as well as serum specimens, were collected each month. Criteria used for judging whether asthma was "allergic" or "nonallergic" and for grading severity of asthma, rhinitis, and atopic dermatitis have also been described. Seasonal variation of the frequency of airborne pollens and mold spores was estimated from information collected routinely at CARIH using the intermittent roto-slide pollen sampler.²

Serum IgE levels were estimated by an adaptation of the radioimmunoassay³ of Rowe which, in our hands, can measure IgE concentrations at or above 125 ng. per milliliter. Concentrations of IgG, IgA, and IgM were measured in selected sera using commercially

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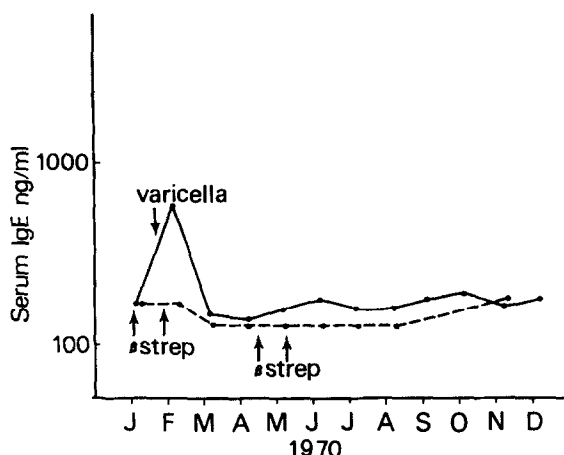


FIG. 1. Levels of serum IgE over a year's period are shown for 2 of the 8 children whose initial values were < 200 ng. per milliliter. No changes occurred following pharyngitis, often caused by streptococci (arrows). The only significant change was seen in one patient (solid line) after varicella.

TABLE I. Initial serum IgE concentrations in 26 children with asthma

	Allergic asthma				Nonallergic asthma		
Atopic dermatitis	-	-	+	+	-	-	+
Systemic steroids	-	+	-	+	-	+	+
No.	5	6	8	1	2	4	1
Mean IgE conc. (ng/ml)	932	390	2,350	550	165	< 125	125

available radial immunodiffusion plates (Melpar Labs., Falls Church, Va.). Whenever inspection of the raw data suggested concordance of a clinical variable with IgE levels, correlation coefficients (r) were calculated by standard methods⁴ after conversion of IgE values to natural logarithms. Group averages were also calculated from the logarithms.

RESULTS

Clinical correlates of initial values

Higher initial serum IgE levels were associated with "allergic" asthma, active atopic dermatitis and absence of long-term, systemic corticosteroid therapy in the present group (Table I), as in the former sample.¹

Variation of IgE values with time

After preliminary studies showed that there were no appreciable differences in levels of IgE in serum specimens drawn at different times of the same day or on sequential days, determinations were performed on sera drawn at monthly intervals.

When initial serum IgE concentrations were < 200 ng. per milliliter, values during the subsequent year changed only slightly. In only one girl was there a significant but short-lived rise to an IgE of 550 ng. per milliliter (Fig. 1) occurring in a serum drawn 16 days after the onset of chickenpox. Other forms of

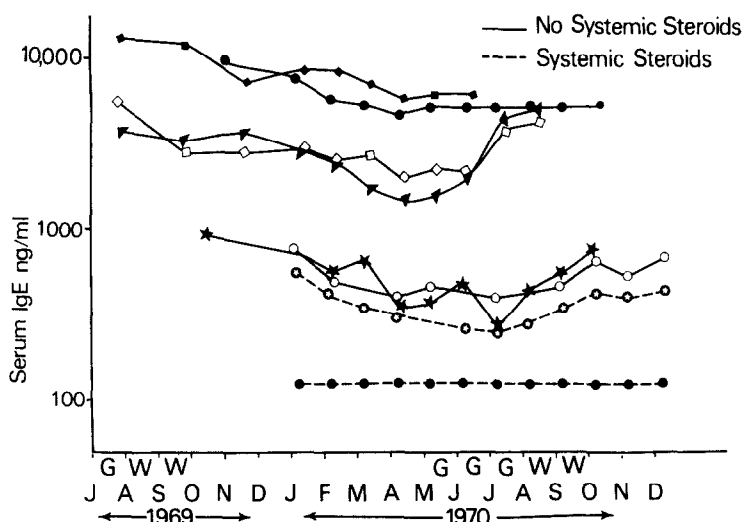


FIG. 2. Variations in serum IgE levels among patients with atopic dermatitis. Each line represents IgE values in a single child. Interrupted lines represent children receiving systemic corticosteroid therapy and solid lines indicate children not on such therapy. Peak pollinating season for grasses (G) and weeds (W) are also shown.

TABLE II. Correlation of changing serum IgE concentrations with certain variables

No.	Clinical factors	Correlation coefficient (r)
1	Severity of atopic dermatitis	0.75
2	Hyposensitization therapy	0.43
3	Severity of asthma	0.01 (N.S.)
4	Severity of rhinitis	0.02 (N.S.)

infection, mostly upper respiratory tract infections associated with β -hemolytic streptococci or presumed to be viral, did not have similar effects on IgE values. Since our technique does not measure IgE concentrations < 125 ng. per milliliter, it is possible that some of the initially low values did fluctuate but at levels lower than 125 ng. per milliliter.

Among the patients with high serum levels of IgE, the most striking changes occurred in 8 of the 10 who had active atopic dermatitis (Fig. 2) whose levels were closely correlated with changing severity of dermatitis (mean $r = 0.75$, range 0.3 to 0.9, Table II). Such correlation was not necessarily a direct one, for the dermatitis often flared up coincidentally with seasonal exposure to allergens to which these children responded with positive wheal and flare skin tests and bronchial inhalation challenges. It was remarkable, however, that their asthma was not generally worse at these times of seasonal exposure. Indeed, for the whole group of 26 children, there was no significant correlation between serum IgE concentrations and severity of asthma or allergic rhinitis (Table II). The 2 children with active atopic dermatitis who were receiving systemic steroids had low and relatively unchanging IgE levels, and their dermatitis also showed little or no seasonal change.

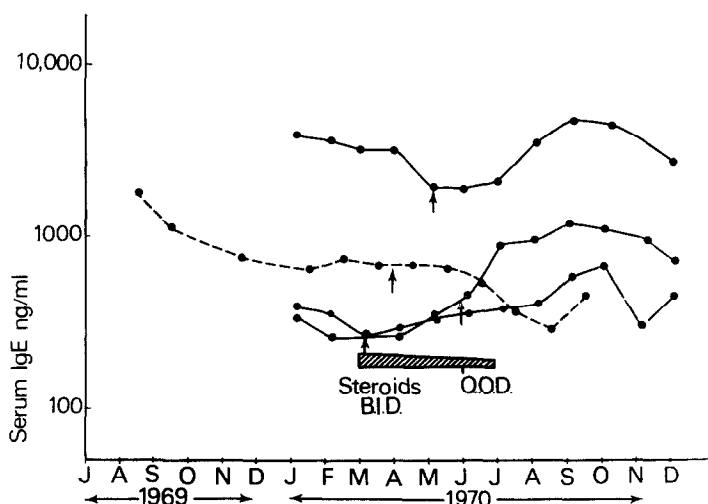


FIG. 3. Serial IgE levels in sera of patients started on injection therapy with allergen extracts (arrows). Each line represents IgE values in a single child. The interrupted line represents a child receiving systemic steroid therapy, first on a twice daily (B.I.D.) then on an alternate-day (Q.O.D.) schedule.

The effect of allergen exposure on serum IgE values was studied in two additional ways. No changes followed the brief exposures to allergens incurred with skin testing or inhalation challenges, but hyposensitization therapy appeared to change the levels in 3 of 4 children so treated (Fig. 3). One to 3 allergen preparations, including *Alternaria*, house dust, or rye grass, selected according to clinical reactions of each child, were injected subcutaneously at weekly and later at biweekly intervals. Doses were begun at 5 protein nitrogen units (PNU), and the total cumulative dose was increased to 30,000 to 33,500 PNU in each of these 3 children over a 4 to 6 month period. During this time the serum levels of IgE in the 3 patients rose in a way that correlated with the monthly increases in antigen doses ($r = 0.43$). Thereafter, however, IgE levels declined, despite increasing doses. The fourth child experienced no elevation in IgE levels after receiving a total dose of only 1710 PNU of *Alternaria* extract. He alone was receiving systemic corticosteroids (usually 5 mg. of prednisone on alternate days) during this period. As the serum IgE levels in 3 of these children rose during the summer, it is not possible to separate the effects of hyposensitization and natural exposure to allergens pollinating and sporulating at that time.

In this study, as in our previous series,¹ children receiving long-term systemic corticosteroid therapy had significantly lower serum IgE levels than children not so treated. Since most children who require such treatment at CARIH have received it for years before admission, it has been difficult to collect data bearing on the question of whether the steroids actually lower serum IgE levels or merely are used more frequently in children whose levels are already low. Experience with 2 asthmatic girls suggests that the former alternative may occur. In one, a serum specimen had been obtained

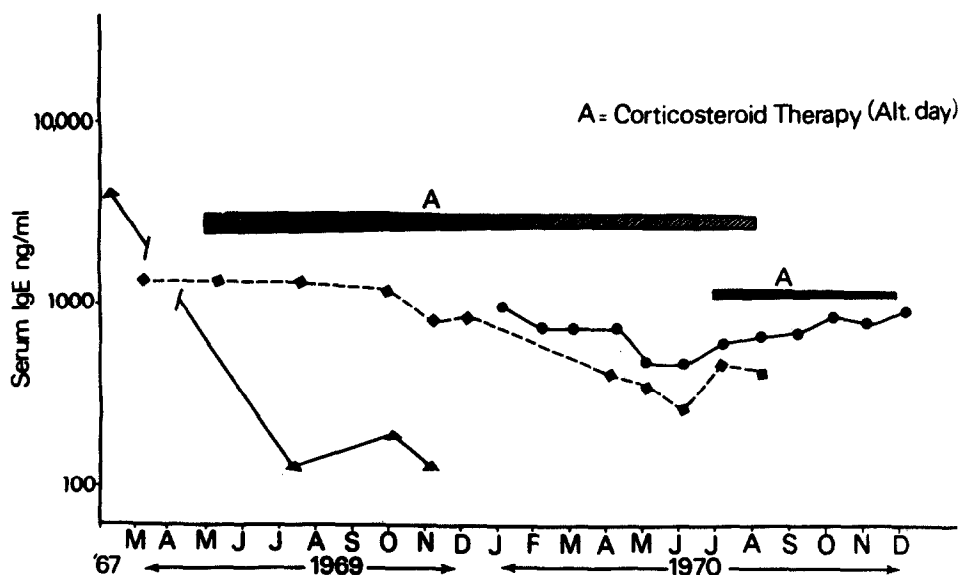


FIG. 4. Serial serum IgE levels in 2 children treated with long-term systemic steroid therapy, showing progressively diminishing IgE levels. The absence of significant depression after relatively brief treatment is also illustrated for one patient by solid line and circles. Thickness of bars indicate dosage of prednisone, given on alternate days. (Not shown for the girl given prednisone continuously since 1967.)

TABLE III. Rising serum IgE levels at times of corticosteroid administration

Steroids	Patient-months during which IgE rose	Total	%
Given	12	125	9.6
Not given	52	187	27.7
Total	64	312	20.5

$p < 0.001$

and stored frozen in 1967 after only 2 months of continuous prednisone administration. Sera collected in 1969, after 2 years of continuous therapy, had less than 10 per cent of the IgE concentrations of the original specimen (Fig. 4). The severity of asthma in another girl required that prednisone be initiated and continued after her arrival at CARH. Her initial serum IgE level of 1,285 ng. per milliliter was almost unchanged for 5 months, then declined to 670 ng. per milliliter at 8 months and 345 ng. per milliliter at 12 months after the start of treatment. By contrast, the IgE levels failed to change in 5 children given systemic steroids for up to 5 months (on an alternate-day schedule after the first week or two).

In considering the entire study experience, there were 125 patient-months during which systemic maintenance steroids were given; IgE levels rose at least 20 per cent over the prior month during only 12 of such patient-months. A similar rise was seen in 52 of 187 patient-months during which steroids were not administered (Table III).

The changes in serum IgE levels were not reflected in changes in the serum

concentrations of the major immunoglobulins, IgG, IgA, and IgM. Values for these proteins were determined for 8 pairs of serum specimens, both members of each pair drawn from a single patient when his IgE levels were maximally different. Although some technically significant differences were found (in one case the IgA decreased from 2.0 to 1.4 mg. per milliliter), these changes showed no relation to the changes in IgE levels.

DISCUSSION

The significance of the data reported here is limited by several factors. The technique used for measuring IgE concentrations is unreliable at values < 125 ng. per milliliter, so any fluctuations that may have occurred at lower levels would not have been detected. Although more sensitive methods are available,⁵ they are more costly and time consuming. Considerably more restrictive are the limitations inherent in correlative studies of a variable that can be influenced by several uncontrolled factors. For this reason the present results do not indicate, for example, whether the serum IgE levels in children with active atopic dermatitis rose and fell (Fig. 2) because the skin lesions worsened and healed, or possibly because IgE antibody-forming cells were being variably stimulated with allergens absorbed through respiratory mucosal surfaces or through the skin.

Nevertheless, it appears that an important relationship does exist between atopic dermatitis and serum IgE concentrations^{5, 7} that varies with the degree of disease activity.^{1, 6} It is not clear why this should be, in view of the dissimilarity between the chronic, eczematous nature of the skin lesions and the acute, wheal and flare skin reactions known to be mediated by IgE. It is perplexing that patients with urticarial disorders have less frequent and less impressive elevation of the serum IgE levels than patients with atopic dermatitis.⁷

It seems easier to understand the effects of substantial allergen exposure on total serum IgE levels. Titers of reaginic antibodies, a measure of specific IgE antibodies, have been shown to rise both after natural exposure and after injection therapy.⁸ While prolonged, high-dose therapy may depress reaginic antibody titers,⁹⁻¹¹ it may not prevent subsequent IgE rises occurring in response to seasonal allergen exposure.¹² The fact that levels of total IgE fluctuate in the same way as reaginic antibody titers has been shown by other investigators⁵ also. It seems doubtful, however, whether all the IgE increment can be attributed to IgE antibodies specific for such allergens. Definitive evidence bearing on this question must await techniques for quantitating specific IgE antibody changes after exposure to a homogeneous antigen.

The relatively low average serum IgE values among steroid-treated asthmatic children and the profound depression of these levels in 2 girls after long-term steroid therapy (Fig. 4) both suggest that steroids may depress the intravascular content of IgE. While it is possible that decreased disease activity may account for the diminution of serum IgE levels toward normal with prolonged steroid therapy, almost all children so treated have continued to have significant asthma. It is in fact a therapeutic rule at CARIH to reduce or eliminate steroids unless

significant asthma persists that cannot be otherwise controlled. If, therefore, chronic steroid administration decreased the portion of disease activity responsible for elevated serum IgE levels, such decrease was not obviously reflected in the severity or frequency of asthma.

If the factors controlling the metabolism of IgE were known, it would be easier to assess whether the effects of drugs like steroids on serum levels were related to altered tissue distribution, increased catabolism, or decreased IgE synthesis. Some data suggest that synthesis may be decreased.

Under some circumstances, corticosteroids can depress production of an IgE-like antibody in rats without affecting synthesis of other classes of antibody.¹³ The rarity of rising IgE levels in any children during administration of systemic steroid therapy (Table III), including one given injection therapy (Fig. 3), suggests that inhibition of IgE synthesis may occur in human beings. Moreover, in patients receiving high doses of corticosteroids, IgE-forming cells have been reported to be rare or absent in bronchial tissues studied by immunofluorescent techniques.¹⁴

Until more basic information is available, it seems likely that many of the questions raised by this study will not be answered. From a practical, clinical standpoint, the measurement of serum IgE concentrations may occasionally be useful in the diagnosis of obscure skin, asthma-like respiratory, or possibly parasitic diseases. It also is possible that the patterns of change in serum IgE levels over a year's period could provide a clue to clinically significant allergen exposure. Nevertheless, in most cases the information supplied by such determinations appears to be slight relative to that obtained with careful clinical techniques.

ADDENDUM

Since these studies were completed, serial IgE levels have been measured in 7 children with varicella and 2 children with mild infectious mononucleosis. No variations of IgE values have been found that could be attributed to these infections, although the IgA and IgG levels did increase temporarily in one child after mononucleosis.

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