

IgE mediated hypersensitivity in ageing

G. DELESSESSE,* J. DE MAUBEUGE,† B. KENNES,
R. NICAISE‡ and A. GOVAERTS*

*Departments of *Immunology and †Dermatology, and ‡Institute Pacheco
(Dr Kunstler), Hôpital Saint-Pierre, Free University of Brussels, B-1000 Brussels,
Belgium*

Summary

The serum IgE concentration is significantly lower in aged as compared with young people. This is more pronounced in males than in females ($P < 0.05$). In fifteen aged (> 70 years) compared with fifteen young subjects (< 40) the specific IgE antibody response to an injection of diphtheria toxoid was significantly reduced ($P < 0.01$). The minimum concentration of anti-IgE antibody able to induce a weal and flare reaction when injected intradermally, was comparable in the two age groups. However, the diameter of the weal reaction was significantly reduced in the aged. It is concluded that the reduced incidence of atopic symptoms in old people might be secondary to an anomaly of both the immune system and the mast cells.

Introduction

It is well documented that immediate hypersensitivity reactions are less frequent in old age (Barbee *et al.*, 1976; Palma-Carlos, 1976; Pruzansky, 1972). This might be secondary to an alteration with ageing of either IgE antibody production or mast cell function. An age-associated impairment of cell mediated immunity and IgG or IgM primary antibody response is well established in animals and in man (Roberts-Thomson *et al.*, 1974; Pisciotto *et al.*, 1967). However, little data is available concerning IgE antibody synthesis and mast cell function in ageing. The present report comparing old and young healthy subjects indicates a significant reduction in the former of both the serum IgE concentration and the specific IgE antibody response to a subcutaneous injection of diphtheria toxoid. Furthermore, there is a reduction of the skin response of the same subjects to the intradermal injection of purified anti-IgE antibody (reversed Prausnitz–Kuestner reaction).

Material and methods

Participants

The young subjects (Y.S.), less than 60 years (mean age 37.9) were blood donors and the others were members of the laboratory staff. The old subjects (O.S.), more than

Correspondence: Dr G. Delespesse, Service d'Immunologie, Hôpital Universitaire St Pierre, rue Haute 322, B-1000 Brussels, Belgium.

70 years (mean age 80.1), were living in an old-aged home. Subjects with actual or recent (in the last 2 years) symptoms of asthma, hay fever, chronic urticaria or atopic eczema were excluded from this study.

Total serum IgE concentration

This was determined using a solid phase sandwich radioimmunoassay (Ceska & Lundkvist, 1972) employing the Phadebas PRIST kits (Phadebas reagents, Pharmacia, Uppsala).

Specific IgE antibodies against diphtheria toxin (D.T.)

These were measured by the radioallergosorbent technique (RAST) employing the reagents provided with the Phadebas RAST kits, except that the paper discs were coated with D.T. Results are expressed on a 0–4 score system by referring to the standard sera included with the RAST kits. Antigen-coated discs were prepared by applying a solution of 100 µg/ml (30 Lf units/ml) purified D.T.* to CNBr activated paper discs, following the method of Ceska (Ceska, Eriksson & Varga, 1972). The specific IgE antibody response against D.T. was determined in fifteen young and fifteen old subjects. They received one subcutaneous injection of 0.25 ml of diphtheria-tetanus vaccine (Di-Te, Lab. Rit, Genval, Belgium). Blood was collected before the injection and then four times at weekly intervals thereafter. Sera were frozen at –40° C until use. The five bleedings of equal numbers of young and old subjects were processed simultaneously for antibody measurement.

Reversed Prausnitz-Kuestner (PK) reaction

Intradermal injections of 0.05 ml of various dilutions of purified rabbit anti-IgE antibody were made in the forearm. The initial antibody concentration measured by optical absorbance at 280 nm, was 1.7; dilutions of this stock solution were made in saline containing 0.2% human serum albumin. Twenty minutes after the injection, the lowest antibody concentration inducing a weal and flare reaction was noted, and the diameter of the wheal reaction was measured. Purified IgE myeloma protein (P.S.), kindly supplied by Dr K. Ishizaka, was used to immunize rabbits. These were injected three times, at 2-week intervals, with 200 µg IgE dispersed in complete Freund's adjuvant. The serum was absorbed on IgG covalently linked to Sepharose 4B (Porath, Axén & Ernbacks, 1967) and then applied on an IgE-Sepharose column. The latter was treated with glycine buffer (pH 3, 0.1 M) and the eluted antibody was concentrated under vacuum. After extensive dialysis against saline, the anti-IgE solution was filtered through a 0.2 µm Millipore filter.

The skin response to intradermal injection of 0.05 ml histamine (100 µg/ml) was determined in ten old and ten young subjects. The diameter of the weal reaction was measured after 20 min.

Statistical methods

The mean values of total serum IgE for the groups of young and old subjects were compared by Student's *t*-test after logarithmic conversion. Specific IgE antibody responses against D.T. were compared in the two groups by variance analysis after logarithmic conversion of the CPM. Reversed PK reactions were compared similarly

* The purified D.T. was a gift from Professor Raynaud, Institute Pasteur, Garches, France.

by variance analysis after logarithmic conversion of the inverse of the anti-IgE antibody dilution.

Results

Serum IgE concentration

The histograms representing the distribution of serum IgE concentrations in the groups of old and young subjects are shown in Fig. 1. There is a highly significant tendency ($P < 0.01$) for serum IgE to be lower in the old group. As indicated in Table 1, this parameter is strongly influenced by sex. Indeed, in the older subjects the females had significantly lower IgE concentration than males ($P < 0.05$). Further, there was no significant difference between the IgE levels observed in the young and old males.

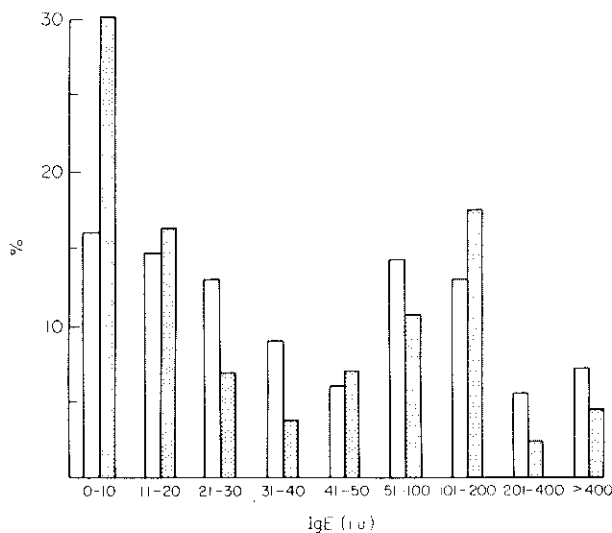


Fig. 1. Serum IgE concentration in the young (□) and the old subjects (■).

Table 1. Comparison of serum IgE concentration in the young and old subjects

Old subjects					Young subjects		
Sex	No. of cases	Age	IgE		No. of cases	Age	IgE
F	100	81 ± 6	20.4† (3.9-107)	P < 0.05	75	38 ± 9	34.7 (7.9-151)
M	35	76 ± 7*	36 (8.3-158.5)	N.S.	79	36 ± 12	49 (12-199.5)
M + F	135	80 ± 6	23.4 (4.7-114.8)	P < 0.01	154	37 ± 10	38.4 (10.2-141.2)

* Mean ± s.d.; † i.u./ml, geometric mean; the geometric mean ± 1 s.d. are indicated in parentheses.

Table 2. Comparison of the IgE antibody response to diphtheria toxoid in fifteen young and fifteen old subjects

	Old subjects					Young subjects				
	Bleeding number					Bleeding number				
	1	2	3	4	5	1	2	3	4	5
No. of positive reactions*	2	2	3	3	3	7	8	8	10	9
Total RAST score	2	2	5	5	4	9	10	12	16	15
Serum IgE† (i.u./ml)	82	82	82	92	106	55	67	61	82	75

* A reaction is considered to be positive when the RAST score is > 1 ; the score is given by referring to the standard sera provided with the Phadebas kits.

† Geometric mean.

Specific IgE antibody response to diphtheria toxin (Table 2)

In the two groups of subjects, the vaccination produced a low but highly significant rise of specific IgE antibodies against D.T. Note that the total serum IgE concentration was not significantly affected (analysis of variance). A significantly lower response was observed in the old subjects ($P < 0.01$). At the first bleeding, before the injection of diphtheria toxoid, IgE antibodies were detectable in two old and seven young subjects. After the vaccination an increase in IgE antibody was observed in two old as opposed to nine young subjects. It must be noted that the old subjects included in this study were selected on the basis of a normal or high total serum IgE.

Table 3. Reversed P-K reaction and response to histamine in young and old subjects

	Young subjects		Old subjects	
No. of cases	20		47	
Males/females	11/9		22/25	
Threshold concentration of anti-IgE	5.05 $\pm$ 1.2*	N.S.	5.49 $\pm$ 1.4	
Weal reaction	7.25 $\pm$ 1.41†	$P < 0.01$	5.64 $\pm$ 2.1	
Response to histamine	12.6 $\pm$ 3.5†	N.S.	12.3 $\pm$ 4.11	

* Log. of the inverse of the dilution, mean $\pm$ s.d.

† Mean diameter (mm) $\pm$ s.d.

N.S., Not significant.

Reversed PK reaction

Forty-seven old subjects, classified into four subgroups according to their serum IgE concentration, were compared to twenty young subjects (Tables 3 and 4). The lowest effective concentration of anti-IgE antibody was not different in the two groups. Old subjects with high serum IgE had a tendency to react to smaller amounts of anti-IgE than those with lower IgE concentration. However, this tendency was not statistically significant. The magnitude of the skin reaction to the threshold concentration of anti-IgE was significantly different in the old and in the young subjects, and this was independent of the serum IgE concentration. Comparison of the skin reactions to intradermal injections of histamine in ten young and ten old subjects revealed no

Table 4. Reversed PK reaction and serum IgE concentration in old subjects

	I	II	III	IV
No. of cases	11	9	10	7
Males/females	7/4	6/3	3/7	5/2
Threshold concentration of anti-IgE	5.36 ± 1.43	5.9 ± 1.3	6.3 ± 0.82	6.7 ± 0.76
Skin reaction (mm)	5.4 ± 1.7*	6.3 ± 1.41	6.7 ± 2.8	5.14 ± 2.48
IgE (i.u./ml)	3 ± 1.4	45.8 ± 19	136 ± 19	402 ± 155

The participants were classified into four groups according to their IgE concentration (i.u./ml): I < 10; II: 10–100; III: 100–200; IV > 200.

* Logarithm of the inverse of the dilution.

difference. This indicates that the lesser response of the old subjects to anti-IgE does not result from skin inability to react to inflammatory stimuli, but rather from an alteration of mast cell function.

Discussion

It is well known that ageing is associated with a reduction of the prevalence and the intensity of positive immediate skin reactions to common allergens (Barbee *et al.*, 1976; Palma-Carlos, 1976; Pruzansky, 1972; Gervais *et al.*, 1967). The present results strongly suggest that this decline is due partly to an impairment of IgE synthesis and partly to a decrease in the skin capacity to respond to an immunological challenge. Our observation of a reduced serum IgE concentration in old subjects is in keeping with previous reports (Johanson, 1968; Orren & Dowdle, 1975) in which the influence of sex is also noted. It might be argued that our finding of reduced serum IgE levels in old subjects results from their mode of living and not from an immunological defect. However, this interpretation can be ruled out by the observation in these subjects of a reduced specific IgE antibody response after challenge with diphtheria-tetanus vaccine. As this was noted in cases with normal or high total serum IgE concentration it can be concluded that by simply measuring the total serum IgE concentration we may overestimate the ability of old people to develop a reaginic antibody response. A similar dissociation between a normal or increased concentration of one immunoglobulin class and decreased specific antibody response of this Ig class has been described in various clinical conditions including ageing (Roberts-Thomson *et al.*, 1976). It seems possible that the age-associated reduction of IgE synthesis is secondary to an impairment of the T lymphocyte function. Indeed, T lymphocytes are involved in the control of IgE antibody synthesis and a decline of their function is well established during ageing (Roberts-Thomson *et al.*, 1974; Pisciotto *et al.*, 1967; Weksler & Hutteroth, 1974).

As the reversed PK reaction is largely independent of the serum IgE concentration (Schwartz & Buckley, 1971; Stenius *et al.*, 1971), this test can be used to evaluate the cutaneous mast cell function.

Thus, the intensity of the weal and flare reaction and the minimum effective concentration of anti-IgE antibody depend on four factors: (1) the number of mast cells available at the injection site; (2) the sensitivity of the mast cells, determined by the number of the IgE molecules present on their surface (Ishizaka *et al.*, 1974); (3) the

reactivity of the cells corresponding to the amount of mediators liberated upon immunological challenge (Ishizaka *et al.*, 1974); (4) the skin reactivity to the chemical mediators of the allergic reaction.

As we found a normal skin response to histamine, the observations with a comparable concentration of anti-IgE in old and young subjects shows a contrast with the difference in the magnitude of their weal reactions suggesting an impairment of the mast cell numbers or reactivity in old people. Our data thus suggest that the reduced prevalence of atopic symptoms in ageing partly results from an immunological defect and partly from an alteration of mast cell function. This implies the existence of an age-associated natural desensitization in atopic patients. In accord with this suggestion is the observation in atopic patients of a progressive reduction with ageing of the serum concentration in total IgE and in IgE specific antibodies (Hanneuse *et al.*, 1977). It is presently unknown whether this natural desensitization is associated with the appearance of IgG or IgA 'blocking' antibodies as observed during specific immunotherapy.

References

- BARBEE, R.A., LEBOWITZ, M.D., THOMPSON, H.C. & BURROWS, B. (1976) Immediate skin-test reactivity in a general population sample. *Annals of Internal Medicine*, **84**, 129.
- CESKA, M. & LUNDKVIST, U. (1972) A new and simple radioimmunoassay method for the determination of IgE. *Immunochemistry*, **9**, 1021.
- CESKA, M., ERIKSSON, R. & VARGA, S.M. (1972) Radioimmunosorbent assay of allergens. *Journal of Allergy and Clinical Immunology*, **49**, 1.
- GERVAIS, P., GERVAIS, A., MORAULT, S. & DAMON, H. (1967) Les réactions cutanées aux allergènes courants dans une population de sujets âgés. *Revue Française d'Allergie*, **7**, 161.
- HANNEUSE, Y., DELESPESE, G., DECOSTER, A. & GOVAERTS, A. (1977) In preparation.
- ISHIZAKA, K., ISHIZAKA, T., KISHIMOTO, T. & OKUDAIRI, H. (1974) Biosynthesis of IgE antibodies and mechanisms of sensitization. In: *Progress in Immunology* (Ed. by L. Brent and J. Holborow), Vol. 4, p. 7. Academic Press, London and New York.
- JOHANSON, S.G.O. (1968) Serum Ig ND levels in healthy children and adults. *Internal Archives of Allergy*, **34**, 1.
- ORREN, A. & DOWDLE, E.B. (1975) The effects of sex and age on serum IgE concentration in three ethnic groups. *Internal Archives of Allergy*, **48**, 824.
- PALMA-CARLOS, A.G. (1976) Allergic diseases in the aged. *Allergie und Immunologie*, **4**, 187.
- PISCIOTTA, A.V., WESTRING, D.W., DEPREY, C. & WALSH, B. (1967) Mitogenic effect of phytohemagglutinin at different ages. *Nature*, **215**, 193.
- PORATH, J., AXÉN, R. & ERNBACKS, S. (1967) Chemical coupling of protein to agarose. *Nature*, **215**, 1491.
- PRUZANSKY, J. (1972) Immunologic and cellular aspects of immediate hypersensitivity. In: *Allergic Diseases* (Ed. by R. Patterson), p. 31. Lippincot, Pennsylvania.
- ROBERTS-THOMSON, I.C., WITTINGHAM, S., YOUNGCHAIYUD, U. & MACKAY, I.R. (1974) Ageing, immune response and mortality. *Lancet*, **ii**, 368.
- SCHWARTZ, D.P. & BUCKLEY, R.H. (1971) Serum IgE concentration and skin reactivity to anti-IgE antibody in IgG deficient patients. *New England Journal of Medicine*, **284**, 513.
- SOMERS, H. & KUHING, W.J. (1972) Effects of aging on the differentiation and proliferation potentials of cells of the immune system. *Proceedings of the Society for Experimental Biology*, **141**, 1104.
- STENIUS, B., WIDE, K., SEYMOUR, W.M., HOLFORD-STREVEVS, V. & PEPYS, J. (1971) Clinical significance of specific IgE to common allergens. 1. Relationship of specific IgE against Dermatophagoides and grass pollen to skin and nasal tests and history. *Clinical Allergy*, **1**, 37.
- WEKSLER, M.E. & HUTTEROTH, T.H. (1974) Impaired lymphocyte function in aging. *Journal of Clinical Investigation*, **53**, 99.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.