

Anti-IgE autoantibody in patients with bronchial asthma

Y. NAWATA, T. KOIKE, T. YANAGISAWA, I. IWAMOTO, T. ITAYA,
S. YOSHIDA & H. TOMIOKA *Second Department of Internal Medicine, School of Medicine,
Chiba University, Chiba, Japan*

(Accepted for publication 26 June 1984)

SUMMARY

The anti-IgE autoantibody in the IgG class was detected in 95.5% of patients with atopic asthma, and in 72.2% of those with non-atopic asthma, using a newly established solid phase enzyme immunoassay (EIA). The specificity of anti-IgE autoantibody was confirmed by both competitive inhibition and absorption experiments, using human IgG, IgA, IgM, IgD, IgE and rabbit anti-human IgG. Significant correlations were observed between the levels of the anti-IgE autoantibody and the serum IgE. Gel filtration studies indicated that the anti-IgE autoantibody in sera from asthmatic patients was present in the immune complex form with self-IgE, in addition to the monomeric antibody. Furthermore, this anti-IgE autoantibody has the ability to induce the reversed type immediate skin reaction, in asthma free individuals. These observations strongly suggest the putative role of the anti-IgE autoantibody in the modulation of IgE-mediated immune systems and the pathogenesis of bronchial asthma.

Keywords bronchial asthma anti-IgE autoantibodies immune complexes

INTRODUCTION

Ishizaka, Ishizaka & Hornbrook (1966) found that the IgE antibody is a prime immunoglobulin which mediates immediate hypersensitivity reactions. Considerable attention has been focused on the pathological significance of this IgE antibody, and it is now generally accepted that this antibody plays a crucial role in allergic disorders (Ishizaka & Ishizaka, 1978).

Bronchial asthma is one of the representative allergic disorders mediated by the IgE antibody. Although many advances have been achieved in the pathophysiology of bronchial asthma, the detailed mechanism for the development of this disease remains still unsettled.

We now report that significant amounts of anti-IgE autoantibody in the IgG class and the immune complex with self-IgE are present in sera from patients with bronchial asthma, and that this autoantibody has the ability to induce reversed type immediate skin reactions. On the basis of these findings, the pathological significance of the anti-IgE autoantibody and the autoimmune characteristics related to the pathogenesis of bronchial asthma are discussed.

MATERIALS AND METHODS

Patients and sera. Two groups of asthmatic patients, classified according to their past histories of allergy, the skin test by antigens, the total serum IgE levels, the specific IgE antibody levels and the bronchial provocation test, were studied. Included were: (1) 43 Japanese with atopic bronchial

Correspondence: Dr Yasushi Nawata, 2nd Department of Internal Medicine; School of Medicine, Chiba University, 1-8-1 Inohana, Chiba 280, Japan.

asthma sensitized by mite antigens, high total and specific IgE levels and histories of allergy and (2) 18 others with non-atopic bronchial asthma with a negative skin test with 30 common antigens, low serum total IgE levels and no history of allergy. Fifteen disease free individuals with no symptoms and history of allergy and serum total IgE levels less than 100 iu/ml served as the controls. All patients were followed in the Allergy Clinics at the Second Department of Internal Medicine in Chiba University Hospital. Half the number of atopic asthma patients are undergoing hyposensitization therapy using mite or house dust antigen. None of asthmatic patients were on corticosteroids. Sera from asthmatic patients were obtained during remission of asthmatic attacks. All sera were stored at -20°C until use and were centrifuged at 30,000g for 30 min at 4°C just before the application.

Preparation of immunoglobulins. IgE myeloma protein used as an antigen of EIA was isolated from the sera of three patients with IgE myeloma (IgE[NS] κ , Kimura *et al.*, 1981; IgE[TF] κ , Okumura, Okumura & Okumura, 1980 and IgE[KZ] λ). After salt fractionation with 50% saturated ammonium sulphate, IgE protein was isolated by diethylaminoethyl (DEAE)-cellulose (Whatman Inc., Clifton, New Jersey, USA) column chromatography followed by gel filtration with Sephadex G-200 (Pharmacia Fine Chemicals, Uppsala, Sweden) as described by Ishizaka, Ishizaka & Lee (1970). The purity of isolated IgE was confirmed by EIA using monospecific antibodies, and immunoglobulins other than IgE were not contained in this preparation. IgA and IgD myeloma proteins were also isolated using the same procedures. IgM was obtained from Cappel Laboratories, Inc. (Cochranville, Pennsylvania, USA). IgG was purified from normal human pooled sera by salt fractionation with 33% saturated ammonium sulphate followed by DEAE-cellulose column chromatography.

Enzyme immunoassay. Antibody against IgE was measured by a solid phase enzyme immunoassay (EIA). Each well of polyvinylchloride microtitre plates (Dynatech Laboratories, Alexandria, Virginia, USA) was first coated with 50 μl of purified IgE, 20 $\mu\text{g}/\text{ml}$ in 0.01 M phosphate-buffered saline (PBS), pH 7.4, by incubation overnight at 4°C . After three washes in PBS, 200 μl of 10% fetal calf serum (FCS) solution was added to each well and the preparations then incubated for 1 h at room temperature to block non-specific binding of immunoglobulin to the well surfaces. After five washes in PBS, 50 μl of serum to be tested (diluted 1:10–1:50 with PBS containing 0.05% Tween 20 [PBS-Tween] and 10% FCS) was added to each well in triplicate, and the preparations were incubated overnight at 22°C . After 10 washes in PBS-Tween, 50 μl of alkaline phosphatase (Sigma Chemical Co., St Louis, Missouri, USA) labelled mouse monoclonal anti-human IgG (Wako Chemical Co., Tokyo, Japan) was added to each well, and the plate was incubated for 1 h, after which 100 μl of *p*-nitrophenyl phosphate (Sigma Chemical Co.) in 1 M diethanolamine buffer, pH 9.0, was added to each well. After 1 h incubation, the optical density (OD) was measured at 405 nm by Microelisa Auto Reader, MR 580 (Dynatech Laboratories). The IgE binding activity of each serum was presented as OD counts after subtracting background which is the count in wells without IgE myeloma protein, as an antigen. The values of anti-IgE antibody of the IgG class were expressed as a unit of the standard serum containing 100 units per ml of antibody which correspond to 50 ng per ml of IgG amount measured by a solid phase EIA.

Inhibition study. The specificity of anti-IgE antibody was determined by a competitive inhibition EIA. A mixture of 100 μl each of the inhibitors (IgG, IgA, IgM, IgD and IgE) at varying dilutions and the samples to be tested were incubated overnight at 22°C . Prior to inhibition, the test samples were diluted to 50% of the maximum IgE binding. The results of inhibition were expressed as percent inhibition of IgE binding activity, calculated as follows:

$$\% \text{ inhibition} = \left(1 - \frac{\text{OD 405 nm count in the presence of inhibitor} - \text{background}}{\text{OD 405 nm count in the absence of inhibitor} - \text{background}} \right) \times 100$$

The background represents the count in wells without IgE myeloma protein as an antigen.

Absorption study. Immunoabsorbents were prepared using CNBr activated Sepharose 4B (Pharmacia Fine Chemicals) conjugated with human IgE myeloma protein, human pooled IgG or rabbit anti-human IgG (Cappel Laboratories, Inc.), as described by Fuchs & Sela (1978). Equal volumes of serum diluted with PBS and protein conjugated with Sepharose 4B were rotated

overnight at room temperature. After centrifugation at 250g for 3 min, the supernatant was used for experiments.

Gel filtration. Six millilitres of the diluted serum were chromatographed at 4°C on a 2.6 × 100 cm Sephacryl S-300 (Pharmacia Fine Chemicals) column developed with 0.01 M PBS, pH 7.4, at 10.7 ml/h, and 3 ml fractions were collected. Eluates were monitored by OD measurement at 280 nm. The value of anti-IgE autoantibody and the total IgE level were examined in each fraction.

Reversed type skin reactions. Serum to be tested was previously heated at 56°C for 4 h in order to inactivate the skin sensitizing activity of IgE antibody, and was dialysed against saline. After the centrifugation at 30,000g for 30 min at 4°C and passing through a Millipore filter (Millipore Co., Bedford, Massachusetts, USA), 0.02 ml of appropriate dilutions of the serum was intracutaneously injected into healthy subjects. Erythema wheal skin reactions appearing 10–15 min after the injection were traced on transparent paper and the diameters of the erythema and the wheal were measured.

Serum IgE. Total serum IgE levels were determined using the paper radioimmunosorbent test (PRIST, Pharmacia Diagnostics).

Statistical analysis. Statistical analysis was performed using Student's *t*-test.

RESULTS

Anti-IgE antibody in bronchial asthma

Fig. 1 illustrates the representative IgE binding of one asthma serum by means of a solid phase EIA. It is apparent that this serum has the antibody reacting with IgE. We employed it as a standard in a solid phase EIA. We examined 43 sera from atopic asthma patients, 18 sera from non-atopic asthma patients and 15 sera from normal individuals for their ability to bind to IgE proteins. The values of anti-IgE antibody for each group are presented in Fig. 2. Forty of 43 sera (95.5%) from atopic asthma patients and 13 of 18 sera (72.2%) from non-atopic asthma patients showed a positive IgE binding. The magnitude of the anti-IgE antibody is significant between normal controls and patients with atopic asthma (20.0 ± 28.4 units, $P < 0.005$) and in non-atopic asthma (3.95 ± 3.03 units, $P < 0.05$).

Specificity of anti-IgE antibody

Competitive inhibition studies were done to confirm the specificity of this anti-IgE antibody, using human immunoglobulins of each isotype (IgG, IgA, IgM, IgD and IgE) as inhibitors. Representative inhibition curves using the serum of an atopic patient are illustrated in Fig. 3. The IgE binding of this serum was inhibited by two IgE myeloma proteins of different origins (IgE[NS] and IgE[KZ]). On the contrary, the other immunoglobulins (IgG, IgA, IgM and IgD) showed no

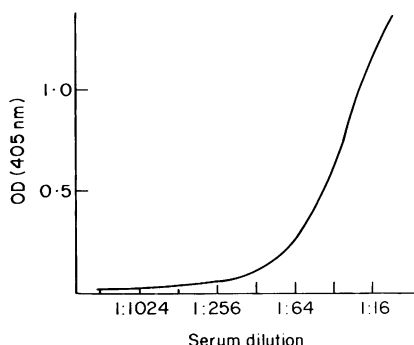


Fig. 1. Standard curve of a solid phase EIA for the detection of anti-IgE antibody.

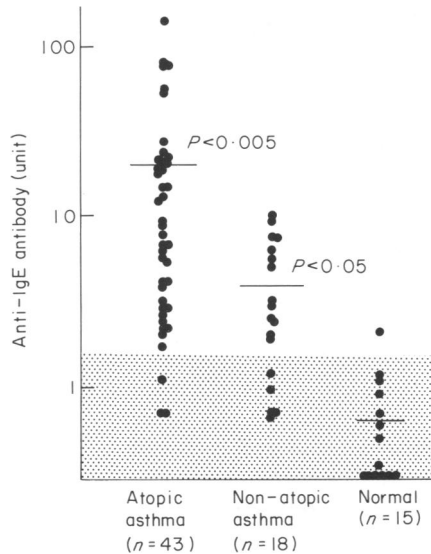


Fig. 2. Levels of anti-IgE autoantibody in sera from 43 atopic asthma, 18 non-atopic asthma and healthy individuals. The results are expressed as a unit of the standard serum. The shaded area represents the mean $\pm$ s.d. for the control group. The horizontal bars indicate the means.

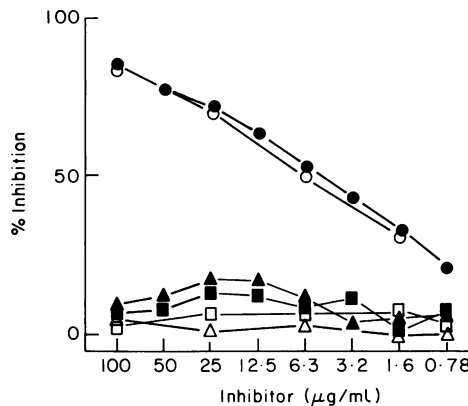


Fig. 3. Representative competitive inhibition EIA with one asthma serum. The values represent the mean percent inhibition of serum IgE binding activity in the presence of indicated inhibitors [IgE(NS) (○); IgE(KZ) (●); IgG (△); IgA (▲); IgM (□); IgD (■)].

inhibitory effects on the IgE binding of this serum. Similar results were observed by using sera from other asthmatic patients (data not shown).

To further clarify the IgE binding property of this antibody, we used immunoabsorbents conjugated with human IgE myeloma protein, pooled human IgG, and rabbit anti-human IgG antibody. Fig. 4 shows a representative result of the experiments. The IgE binding activity of this serum was completely absorbed with human IgE myeloma protein and rabbit anti-human IgG antibody, but not with human IgG purified from pooled normal human sera. These results support the idea of the IgE binding specificity of this antibody in the IgG class (anti-IgE autoantibody), in patients with bronchial asthma.

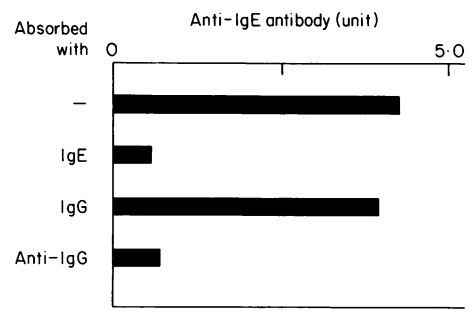


Fig. 4. Absorption study of the IgE binding activity of serum from one asthma patient. Horizontal bars represent levels of anti-IgE antibody after the absorption with indicated immunoadsorbents.

Relation of anti-IgE autoantibody to serum IgE levels

The relation of the values of anti-IgE autoantibody to the total IgE levels of the sera was examined. As illustrated in Fig. 5, significant correlations were noted between the values of anti-IgE autoantibody and the serum total IgE levels ($n = 76$, $r = 0.476$, $P < 0.01$).

IgE-anti-IgE immune complex

Gel filtration analyses by Sephacryl S-300 were carried out using sera from asthmatic patients which revealed high values of the anti-IgE autoantibody and the total IgE antibody. Representative

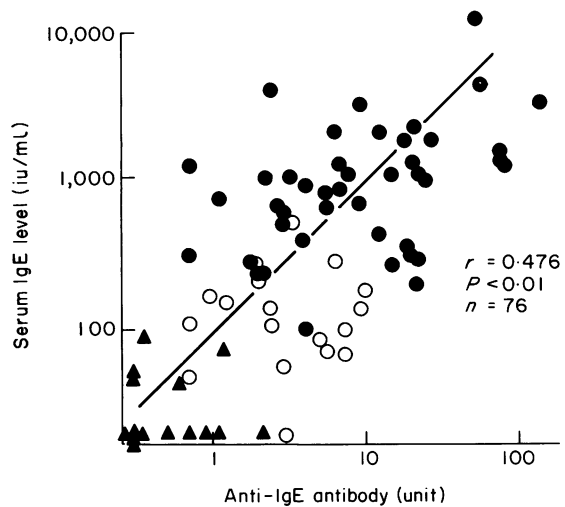


Fig. 5. Correlation between total serum IgE levels and the anti-IgE autoantibody. ● = atopic asthma; ○ = non-atopic asthma; ▲ = normal.

results are shown in Fig. 6. The anti-IgE autoantibody showed two distinct peaks, the smaller, anti-IgE autoantibody peak corresponded to the IgG peak, as observed in Fig. 6c. The other peak was considered to be a complexed form. As shown in Fig. 6b total IgE protein was also composed of two peaks. The IgE peak with a smaller molecular weight was observed at the position of the IgE (Fig. 6c). The other peak with a higher molecular weight corresponded to the anti-IgE autoantibody peak which is the complexed form. These results strongly suggested that the anti-IgE autoantibody in sera from asthmatic patients was present in the immune complex form with self-IgE, in addition to the monomeric antibody.

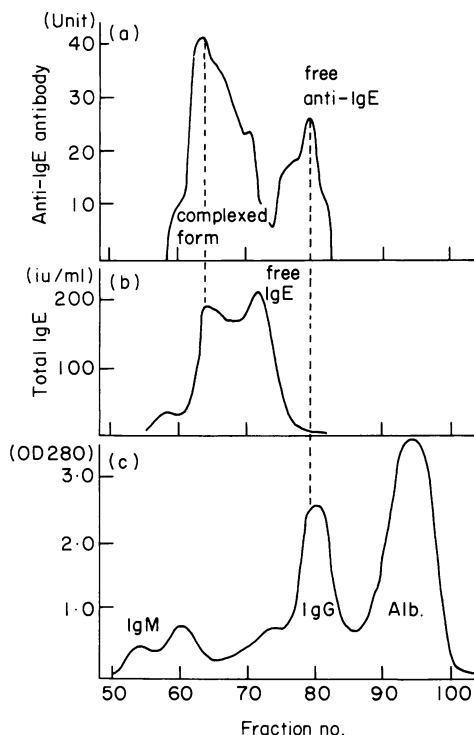


Fig. 6. Gel filtration analysis by Sephacryl S-300 using serum from an asthmatic patient with high IgE and high anti-IgE autoantibody level. (a) Represents the levels of anti-IgE antibody and (b) the total IgE. Protein distribution of this serum is shown in (c).

Reversed type skin hypersensitivity reactions

Heterologous anti-IgE antibody is known to induce the reversed type immediate skin reactions in human skin (Ishizaka & Ishizaka, 1968). To investigate the biological significance of the anti-IgE autoantibody *in vivo*, we performed the reversed type skin hypersensitivity reactions using asthmatic patients' sera with high values of anti-IgE autoantibody. After heat inactivation of the IgE antibody to destroy the skin sensitizing activity, the serum was intracutaneously injected into healthy individuals. Sera from asthmatic patients with high values of anti-IgE autoantibody gave a strong positive immediate type erythema wheal skin reaction and 6–12 h later, late phase skin reactions occurred.

To confirm that these skin reactions were caused by the anti-IgE autoantibody, we used the absorption study involving immunoadsorbents conjugated with human IgE myeloma protein, pooled human IgG and rabbit anti-human IgG. Representative skin reactions are shown in Fig. 7. The skin sensitizing activity of patients sera was eliminated by the absorption with IgE and anti-human IgG, but not with IgG. This skin sensitizing activity was not eliminated by 2-mercaptoethanol treatment (data not shown). These results strongly suggest that the anti-IgE autoantibody detected, *in vitro* by a solid phase EIA is a biologically active autoantibody, *in vivo*.

DISCUSSION

We obtained definite evidence for the presence of autoantibody which reacts exclusively with human IgE in the sera from patients with bronchial asthma.

Using a newly developed solid phase enzyme immunoassay (EIA), the anti-IgE autoantibody was detected in patients with either atopic (95.5%) or non-atopic (72.2%) asthma in significant

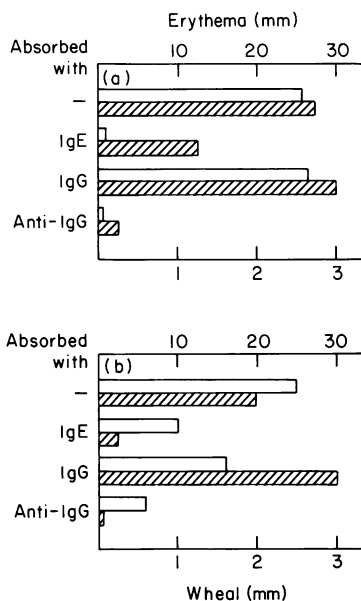


Fig. 7. Absorption of the immediate type erythema wheal skin reactions with sera from asthma patients. Horizontal bars indicate the diameter of erythema (□) and wheal (▨) after the absorption with indicated immunoadsorbents. The diameter of wheal is the value obtained by subtracting the control wheal which was induced by injection of saline in the same individuals. Two representative results are shown in (a) and (b).

quantities. The ϵ chain specificity of the anti-IgE autoantibody was confirmed in two experiments, competitive inhibition and absorption studies. This anti-IgE antibody bound to three different human IgE myeloma proteins, hence it is quite unlikely that this antibody is characteristic of an anti-idiotypic antibody or an anti-light chain antibody.

According to the gel filtration experiments, we also found that the anti-IgE autoantibody is present in the immune complex formed with self-IgE, in addition to the free antibody.

There are reports concerning the presence of immune complexes in sera from individuals with atopic and non-atopic diseases (Cano *et al.*, 1977; Stendardi, Delespesse & Debisschop, 1980). These are predominantly IgE antibodies and corresponding antigens (Brostoff, Johns & Stanworth, 1977; Brostoff *et al.*, 1979; Stevens *et al.*, 1983) and the rheumatoid factor of IgE class (Meretey *et al.*, 1979, 1982). Although we cannot completely exclude the possibility that the major IgE peak of large molecular weight (detected by gel filtration analysis) may be composed of these kinds of immune complexes, it is clear that the anti-IgE autoantibody corresponding to the large molecular weight of IgE in the immune complex form is also present.

Williams *et al.* (1972) reported the presence of a naturally occurring IgM class anti-IgE antibody in the sera from miscellaneous patients, using the tanned cell haemagglutination technique. But, the IgG class antibody was not detected, and no correlation was observed between the IgM class anti-IgE antibody and the serum IgE levels. As far as examined by EIA, we found no evidence of the IgM class anti-IgE antibody. Inganäs, Johansson & Bennich (1981) reported the presence of an antibody which could bind to both Staphylococcal protein A and IgE in 35% of 79 sera from non-atopic normal individuals and in 71% of 31 sera from atopic asthma patients. They found that the detection of this antibody was facilitated by heating the serum to 56°C, due to the disruption of IgE containing immune complexes, and that the antibody was directed against the heat labile D2 antigen. We found much the same evidence, but whether there are other factors present, which could bind to both Staphylococcal protein A and IgE remain to be determined.

Although the biological significance of anti-IgE autoantibody in the allergic reactions of bronchial asthma has not been clarified, it is assumed that this autoantibody, *per se*, can bind to IgE

molecules on mast cells and basophils, and which in turn would result in the cross-linking of IgE molecules and the release of chemical mediators of allergy. Thus, allergic reactions can be triggered without the corresponding antigens.

Factors which have an affinity for IgE and which regulate IgE production in animals and humans, include the IgE binding factor (Yodoi & Ishizaka, 1980; Ishizaka & Sandberg, 1981), the IgE potentiating factor (Suemura *et al.*, 1980), the IgE suppressive factor (Hirashima, Yodoi & Ishizaka, 1980), the suppressor factor of allergy (SFA) (Katz *et al.*, 1979; Zuraw *et al.*, 1981) and the enhancing factor of allergy (EFA) (Katz *et al.*, 1979). Antigen specific IgE regulation mechanisms by the anti-idiotypic antibody have also been reported (Blaser, Nakagawa & de Weck, 1980; Geha & Comunale, 1983). As well as these factors, the anti-IgE autoantibody may participate in the regulatory mechanisms of IgE production by reacting with surface IgE molecules on B cells, which are precursors of the IgE producing plasma cells.

We found that the anti-IgE autoantibody in asthmatic patients is present in the immune complex form with self IgE, in addition to the free antibody. Brostoff *et al.* (1979) reported that IgE containing immune complexes can fix complement. Rouzer *et al.* (1982) noted that mouse peritoneal macrophages responded to the immune complexes of IgE and antigen, and are capable of releasing arachidonic acid. Ito, Shinomiya & Mikawa (1983) found that the soluble immune complexes made of human IgE and goat anti-IgE antibody, *in vitro* could inhibit the chemotaxis of human neutrophils. All these findings taken together, suggest that the IgE-anti-IgE immune complex as well as the anti-IgE autoantibody may play some role in the pathogenesis of bronchial asthma.

Very recently we also found the same anti-IgE autoantibodies in patients with atopic dermatitis and other allergic disorders. The precise characteristics including the diversity of these autoantibodies in allergic patients are the subject of ongoing studies in our laboratory.

This work was supported by grants from the Ministry of Health and Welfare, Science and Culture, Japan, and from the Japan Medical Research Foundation. We are grateful for the support and advice of Professors A. Kumagai, Department of Internal Medicine, Toyama Medical-Pharmaceutical University and M. Taniguchi, Department of Immunology, School of Medicine, Chiba University. M. Ohara provided valuable comments on the manuscript and H. Fukuda secretarial services.

REFERENCES

- BLASER, K., NAKAGAWA, T. & DE WECK, A.L. (1980) Suppression of the BPO-specific IgE formation with isologous anti-idiotypic antibodies in BALB/c mice. *J. Immunol.* **125**, 24.
- BROSTOFF, J., CARINI, C., WRAITH, D.G. & JOHNS, P. (1979) Production of IgE complexes by allergen challenge in atopic patients and the effect of sodium cromoglycate. *Lancet*, **ii**, 1268.
- BROSTOFF, J., JOHNS, P. & STANWORTH, D.R. (1977) Complexed IgE in atopy. *Lancet*, **ii**, 741.
- CANO, P.O., CHOW, M., JERRY, L.M. & SLADOWSKI, J.P. (1977) Circulating immune complexes in patients with atopic allergy. *Clin. Allergy*, **7**, 167.
- FUCHS, S. & SERA, M. (1978) Immunoabsorbents. In *Handbook of Experimental Immunology* (ed. by D.M. Weir) 3rd edn. Chap. 10. Blackwell Scientific Publications, Oxford.
- Geha, R.S. & Comunale, M. (1983) Regulation of Immunoglobulin E antibody synthesis in man by antiidiotypic antibodies. *J. clin. Invest.* **71**, 46.
- HIRASHIMA, M., YODOI, J. & ISHIZAKA, K. (1980) Regulatory role of IgE binding factors from rat T lymphocytes. III. IgE-specific suppressive factor with IgE binding activity. *J. Immunol.* **125**, 1442.
- INGANÄS, M., JOHANSSON, S.G.O. & BENNICHT, H. (1981) Anti-IgE antibodies in human serum: occurrence and specificity. *Int. Arch. Allergy Appl. Immunol.* **65**, 51.
- ISHIZAKA, K. & ISHIZAKA, T. (1968) Reversed type allergic skin reactions by anti- γ E-globulin antibodies in human and monkeys. *J. Immunol.* **100**, 554.
- ISHIZAKA, K., ISHIZAKA, T. & HORN BROOK, M.M. (1966) Physicochemical properties of human reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity. *J. Immunol.* **97**, 75.
- ISHIZAKA, K., ISHIZAKA, T. & LEE, E.H. (1970) Biologic function of the Fc fragments of E myeloma protein. *Immunochemistry*, **7**, 687.
- ISHIZAKA, K. & SANDBERG, K. (1981) Formation of IgE binding factors by human T lymphocytes. *J. Immunol.* **126**, 1692.
- ISHIZAKA, T. & ISHIZAKA, K. (1978) A new concept of triggering mechanisms of IgE-mediated histamine release. *J. Allergy clin. Immunol.* **61**, 320.
- ITO, S., SHINOMIYA, K. & MIKAWA, H. (1983) Suppressive effect of IgE soluble immune complex on neutrophil chemotaxis. *Clin. exp. Immunol.* **51**, 407.
- KATZ, D.H., BARGATZE, R.F., BOGOWITZ, C.A. &

- KATZ, L.R. (1979) Regulation of IgE antibody production by serum molecules. IV. Complete Freund's adjuvant induces both enhancing and suppressive activities detectable in the serum of low and high responder mice. *J. Immunol.* **122**, 2184.
- KIMURA, J., SUZUKI, N., TOMIOKA, H. & TAKAHASHI, H. (1981) A case of IgE myeloma. *Japan J. Clin. Hemat.* **22**, 1469.
- MERETÉY, K., BOHM, U., FALUS, A. & BOZSOKY, S. (1979) Radioimmune double PEG precipitation technique for detecting complexed IgE. *J. Immunol. Meth.* **26**, 223.
- MERETÉY, K., FALUS, A., ERHARDT, C.C. & MAINI, R.N. (1982) IgE and IgE-rheumatoid factors in circulating immune-complexes in rheumatoid-arthritis. *Ann. Rheum. Dis.* **41**, 405.
- OKUMURA, T., OKUMURA, T. & OKUMURA, K. (1980) A case of IgE myeloma. *Clin. Immunol.* **12**, 221.
- ROUZER, C.A., SCOTT, W.A., HAMILL, A.L., LIU, F.T., KATZ, D.H. & COHN, Z.A. (1982) IgE immune complexes stimulate arachidonic acid release by mouse peritoneal macrophages. *Proc. Natl. Acad. Sci. USA* **79**, 5656.
- STENDARDI, L., DELESSESSE, G. & DEBISSCHOP, M.J. (1980) Circulating immune complexes in bronchial asthma. *Clin. Allergy*, **10**, 405.
- STEVENS, W.J., FELDMEIR, H., BRIDT, C.H. & DAFALLA, A.A. (1983) IgG and IgE circulating immune complexes, total serum IgE and parasite related IgE in patients with mono- or mixed infection with *Schistosoma mansoni* and/or *S. haematobium*. Influence of therapy. *Clin. exp. Immunol.* **52**, 142.
- SUEMURA, M., YODOI, J., HIRASHIMA, M. & ISHIZAKA, K. (1980) Regulatory role of IgE-binding factors from rat T lymphocytes. I. Mechanism of enhancement of IgE response by IgE potentiating factor. *J. Immunol.* **125**, 148.
- WILLIAMS, R.C., GRIFFITHS, R.W., EMMONS, J.D. & FIELD, R.C. (1972) Naturally occurring human antiglobulins with specificity for γ E. *J. clin. Invest.* **51**, 955.
- YODOI, J. & ISHIZAKA, K. (1980) Lymphocytes bearing Fc receptors for IgE. IV. Formation of IgE-binding factor by rat T lymphocytes. *J. Immunol.* **124**, 1322.
- ZURAW, B.L., NONAKA, M., O'HAIR, C.H. & KATZ, D.H. (1981) Human IgE antibody synthesis *in vitro*: stimulation of IgE responses by pokeweed mitogen and selective inhibition of such responses by human suppressive factor of allergy (SFA). *J. Immunol.* **127**, 1169.