

Serum IgE in atopic dermatitis

Relationship to severity of cutaneous involvement and course of disease as well as coexistence of atopic respiratory diseases

B. WÜTHRICH

Department of Dermatology, Allergy Station, University Hospital, Zurich, Switzerland

(Received 22 December 1977; accepted for publication 13 January 1978)

Summary

Serum IgE concentrations were determined according to the radioimmunosorbent technique (RIST, Phadebas) on 116 adult patients with atopic dermatitis of varying severity and activity. Geometric mean IgE levels of patients with atopic dermatitis were significantly higher compared with the mean level of ninety-three non-atopic adult subjects without parasitic infestation. Severity of the atopic dermatitis was highly correlated to the levels of serum IgE. Severe chronic cases with ever-recurrent exacerbations show the most extreme values. In the moderate forms of atopic dermatitis, coexistent bronchial asthma causes a greater increase in the IgE values. Among the mild or abortive forms, higher IgE levels were found in cases with allergic rhinitis than in the cases with 'pure' atopic dermatitis. Other findings in connection with IgE in atopic dermatitis are summarized. The pathogenetic significance of IgE in the cutaneous changes is briefly discussed.

Introduction

Since the first publications of Juhlin *et al.* (1969), Ogawa *et al.* (1971) and our own (Wüthrich *et al.*, 1972; Wüthrich, Kopper & Virchow, 1973) there is no doubt that serum IgE levels in atopic dermatitis are increased on average. Among the different atopic diseases, patients with this type of eczematous dermatitis have the highest mean serum IgE level (Berg & Johansson, 1969a; Virchow, Möller & Debelic, 1971; Leonardy & Peacock, 1972; Spitz *et al.*, 1972; Wüthrich & Kopper, 1974). Similar high values are otherwise only found in parasitic infestations (Hogarth-Scott, Johansson & Bennich, 1967; Johansson, Mellbin & Vahlquist, 1968; Heiner & Rose, 1970; Rosenberg, Polmar & Whalen, 1970; Ezeoke, Perera & Hobbs, 1973). However, it is still questionable whether the increase in IgE levels in atopic dermatitis is the result of

Correspondence: Dr B. Wüthrich, Department of Dermatology (Allergy Station), University Hospital, Gloriastrasse 31, CH-8091 Zürich, Switzerland.

0009-9090/78/0500-0241\$02.00 ©1978 Blackwell Scientific Publications

coexistent respiratory disorders, or whether the respiratory allergies in atopic dermatitis increase the IgE level even more (Öhman & Johansson, 1974a; Johnson *et al.*, 1974). The severe forms, with extensive skin involvement, also show the highest values (Clendenning *et al.*, 1973; Gurevitch, Heiner & Reisner, 1973; Stone, Gleich & Muller, 1976; Wüthrich, 1975).

If the different publications are compared there are, however, some difficulties, for the following reasons: (a) the use of different test techniques for IgE determination (radioimmunosorbent test, RIST, radioactive single radial immunodiffusion, RID, double-antibody radioimmunoassay, RIA, or paper disc immunosorbent test, PRIST); (b) different standardization and reference values (ng/ml); (c) different groups (children, adults) and races; (d) different patient populations (mild, moderate and severe forms, coexistence or not of atopic respiratory disease); and (e) the earlier publications in particular have not taken into consideration the fact that due to the extremely wide range of values the frequency of the IgE distribution is not normal. Therefore arithmetic values cannot be used.

In view of these different findings, the following report was designed to re-evaluate the relationship between the serum IgE levels and the severity, course of disease and coexistence of respiratory allergy in our patients with previously studied atopic dermatitis (Wüthrich, 1975). Only patients above 15 years of age were taken into consideration. Therefore the age-dependent distribution of the IgE values (Berg & Johansson, 1969b; Johansson, 1968; Bazaral, Orgel & Hamburger, 1971; Dessaint, Wattre & Lelong, 1974; Öhman & Johansson, 1974a; Kjellman, Hansson & Ludvigsson, 1977) did not have to be considered.

Materials and methods

Patients

116 patients with a diagnosis of atopic dermatitis of varying severity and activity, as observed in the Department of Dermatology, University Hospital, Zürich, were evaluated. A detailed case history was obtained from all the patients, in which special attention was given to allergic respiratory diseases such as asthma, hay fever or perennial rhinitis. The patients were also subdivided into three groups with mild, moderate and severe involvement of the skin (present condition) and into three similar groups according to the degree of the severity of the course of the disease (for more details see Wüthrich, 1975).

Normal controls

Ninety-three adult subjects without allergic or pruritic dermatological disease, and without parasitic infestation, comprised the control group.

Measurement of serum IgE levels

The IgE concentrations were estimated according to the radioimmunosorbent technique (RIST), performed as recommended by Pharmacia Company, Uppsala.

Statistical calculations

The statistical analyses were made on the logarithmic ($\log_{10}$) transformation of the IgE values (u/ml). In this way a more normal distribution is reached and the Student's *t*-test can be used to compare each group. In addition, a variance analysis of the

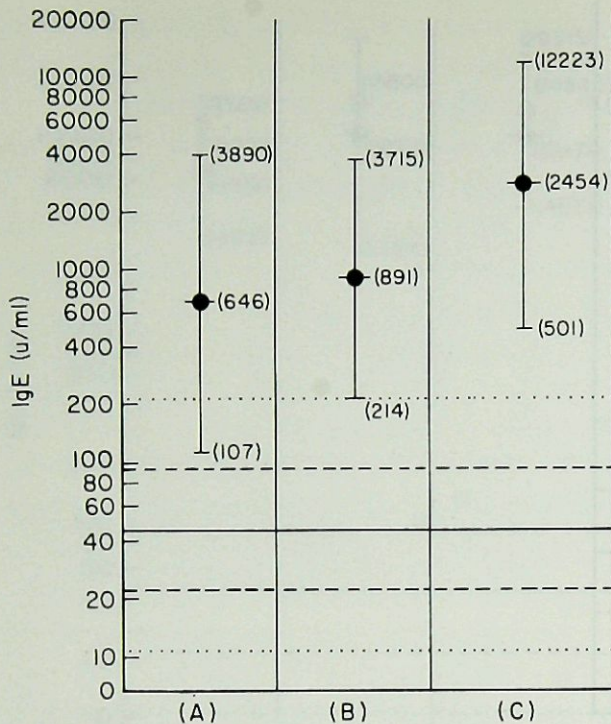


Fig. 1. Geometric mean values ($\pm$ s.d.) of serum IgE in adults with atopic dermatitis with or without respiratory allergy. Significances (t -test): (A) *vs* (B) $t = 0.82$, n.s.; (A) *vs* (C) $t = 3.64$, $P < 0.001$; (B) *vs* (C) $t = 2.73$, $P < 0.01$. Variance analysis: $F = 17.99$, $P < 0.001$. (A) Atopic dermatitis only ($n = 47$); (B) atopic dermatitis plus allergic rhinitis ($n = 29$); (C) atopic dermatitis plus asthma (with or without rhinitis) ($n = 40$). The solid horizontal line shows the mean for the controls, the dashed lines ± 1 s.d. and the dotted lines ± 2 s.d.

transformed data was performed with the use of a Hewlett-Packard calculator printer (9100), with a programme from the Biostatistical Center, University, Zürich.

Results

Fig. 1 shows the geometrical mean values of serum IgE with the corresponding standard deviation ($\pm$ s.d.) in patients with 'pure' atopic dermatitis ($n = 47$), with dermatitis and allergic rhinitis ($n = 29$) and with dermatitis and allergic asthma (with or without rhinitis) ($n = 40$) in relation to the non-atopic control group ($n = 93$). Here we see that if asthma coexists with dermatitis, the IgE values are the most elevated. However, this fact must be considered with certain restrictions (see below). The geometric mean serum IgE level of the ninety-three non-atopic patients was 47 u/ml ($\bar{x}$), with an upper confidence limit ($+2$ s.d.) of 222 u/ml.

Fig. 2 shows the serum IgE values in relation to the degree of severity and extent of the cutaneous alterations. There is a highly significant difference ($P < 0.001$) within the group with mild ($n = 39$), moderate ($n = 47$) and severe forms ($n = 30$). The situation is similar if instead of the severity of the present skin condition, the degree of severity of the course of the disease is taken into consideration (Table 1). The difference between the control group and both mild groups is highly significant ($t = 10.09$, respectively $t = 12.99$; $P < 0.001$).

With a view to an even more differentiated evaluation, the patients within these severity groups (mild, moderate and severe form of skin involvement) were divided further, into cases of pure and cases of mixed forms of atopic dermatitis (with additional rhinitis or asthma) (Figs 3 to 5). As regards the severe forms (Fig. 3), there is no

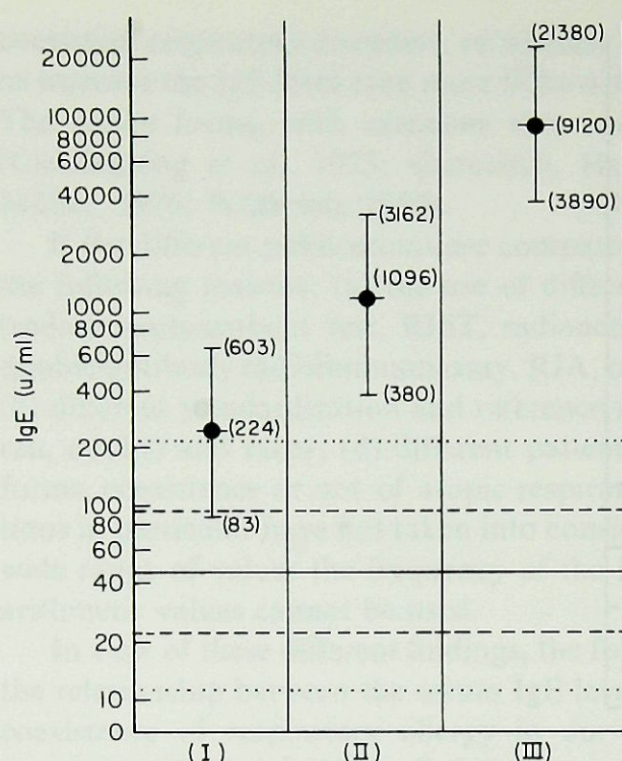


Fig. 2. Correlation of serum IgE levels (geometric means $\pm$ s.d.) with the extent of the atopic dermatitis. Significances (*t*-test): (I) vs (II) $t = 7.13$, $P < 0.001$; (I) vs (III) $t = 16.36$, $P < 0.001$; (II) vs (III) $t = 9.21$, $P < 0.001$. (I) Mild ($n = 39$); (II) moderate ($n = 47$); (III) severe ($n = 30$). The horizontal lines as for Fig. 1.

Table 1. Comparison between serum levels of IgE in patients with mild, moderate and severe degree of the course of the atopic dermatitis

Degree	<i>n</i>	Mean IgE (u/ml)	Range $\pm$ s.d.)
(1) Mild	62	302	120-759
(2) Moderate	40	3548	1318-9550
(3) Severe	14	13489	6166-29512

Significances (*t*-test): (1) vs (2) $t = 12.81$, $P < 0.001$; (1) vs (3) $t = 14.29$, $P < 0.001$; (2) vs (3) $t = 4.56$, $P < 0.001$.

significant statistical difference within these three subgroups. Among the moderate forms (Fig. 4), only in cases of bronchial asthma were higher IgE levels found. In the mild or abortive forms, however, the accompanying respiratory allergies resulted in a greater increase in the IgE values (Fig. 5). The variance analysis also showed a statistical difference ($F = 5.9$, $P < 0.01$).

Discussion

The present study confirmed the presence of significantly elevated levels of IgE in the sera of patients with atopic dermatitis as compared with the non-atopic control group. Severe chronic cases with recurrent exacerbations showed the most extreme values. In the moderate or abortive forms of atopic dermatitis, coexistent bronchial asthma caused a greater increase in the IgE values. These facts represent, however,

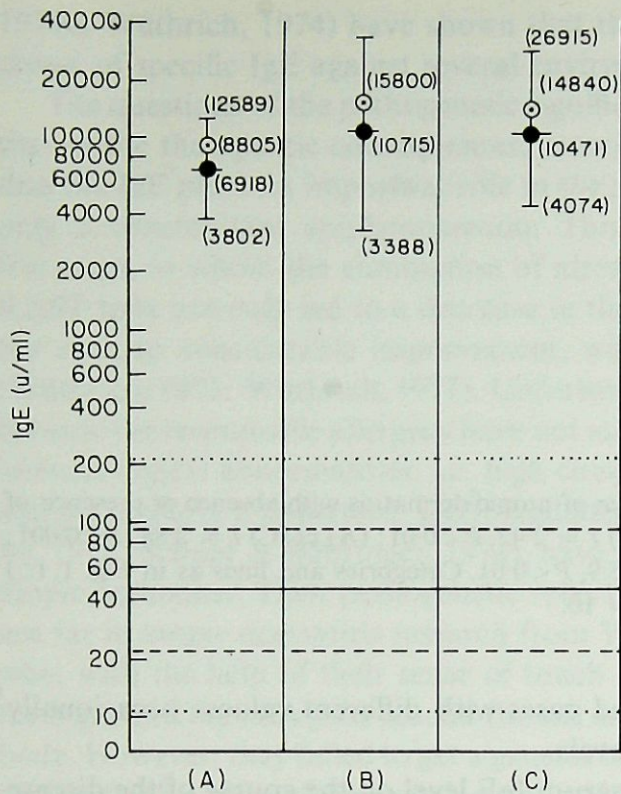


Fig. 3. Correlation of serum IgE levels in severe forms of atopic dermatitis with absence or presence of respiratory allergy. Significance (*t*-test): (A) *vs* (B) $t = 1.96$, n.s.; (A) *vs* (C) $t = 1.24$, n.s.; (B) *vs* (C) $t = 0.96$, n.s. Variance analysis: $F = 0.77$, n.s. Categories and lines as in Fig. 1, (○) arithmetic mean. (A) $n = 10$; (B) $n = 4$; (C) $n = 16$.

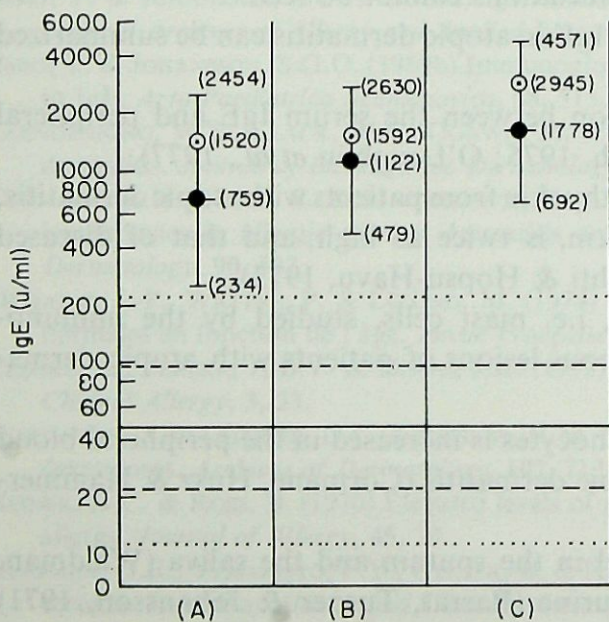


Fig. 4. Correlation of serum IgE levels in moderate form of atopic dermatitis with absence or presence of respiratory allergy. Significances (*t*-test): (A) *vs* (B) $t = 1.04$; n.s.; (A) *vs* (C) $t = 2.25$, $P < 0.01$; (B) *vs* (C) $t = 1.04$; n.s. Variance analysis: $F = 2.84$, n.s. Categories and lines as in Fig. 1, (○) arithmetic mean. (A) $n = 20$; (B) $n = 13$; (C) $n = 14$.

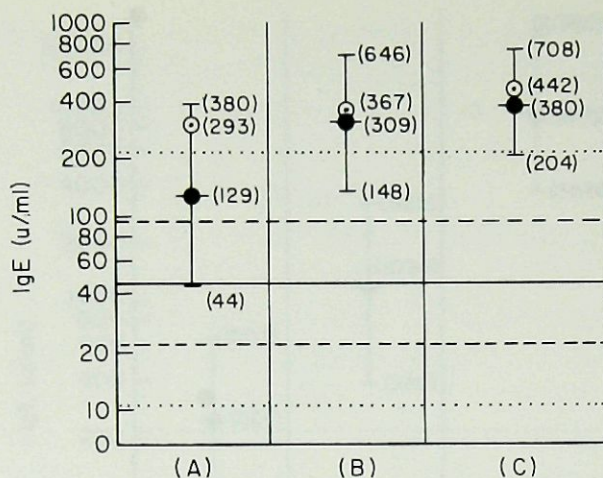


Fig. 5. Correlation of serum IgE levels in mild form of atopic dermatitis with absence or presence of respiratory allergy. Significances (*t*-test): (A) vs (B) $t = 2.43$, $P < 0.01$; (A) vs (C) $t = 2.88$, $P < 0.001$; (B) vs (C) $t = 0.704$, n.s. Variance analysis: $F = 5.9$, $P < 0.01$. Categories and lines as in Fig. 1, (○) arithmetic mean. (A) $n = 17$; (B) $n = 12$; (C) $n = 10$.

only an average; in practice we always find cases with different values: occasionally even severe forms may have normal IgE levels.

The question of the dependence of the serum IgE level on the course of the disease arises. Johansson & Juhlin (1970) proved that long, and not short, treatment with corticosteroids and immunosuppressives, as well as normalization of the state of the skin, lead to a decrease in the IgE values. If, over a period of several years, the cases are individually followed, it can be found that the state of the skin and the IgE level are roughly parallel (Wüthrich, 1975). As a rule, exacerbations of dermatitis result in an increase in the IgE values. Contrary to our observations, Öhman & Johansson (1974a) did not find, on average, any extensive fluctuations in serum IgE during the course of the disease. In fact, their period of observation only extended over just 1 year. Therefore, in calculating the means, individual variations cannot be seen.

The further findings in connection with IgE in atopic dermatitis can be summarized as follows:

(a) There is a rough positive correlation between the serum IgE and peripheral blood absolute eosinophil count (Wüthrich, 1975; O'Loughlin *et al.*, 1977).

(b) The IgE level in skin biopsies of healthy skin from patients with atopic dermatitis, in comparison with normal, non-atopic skin, is twice as high, and that of diseased skin three times as high (Jansen, Haapalahti & Hopsu-Havu, 1973).

(c) The number of IgE-staining cells, i.e. mast cells, studied by the immunofluorescent technique is increased in cutaneous lesions of patients with atopic dermatitis (Anan, 1976).

(d) The number of IgE-bearing B lymphocytes is increased in the peripheral blood and dermal infiltrates of patients with atopic dermatitis (Cormane, Husz & Hammerlinck, 1974).

(e) There is also an increased IgE level in the sputum and the saliva (Waldman, Virchow & Rowe, 1973), as well as the urine (Barrat, Turner & Johansson, 1971) (secretory IgE?) of patients with atopic dermatitis.

There is therefore, no doubt that the immune status of atopic dermatitis patients is characterized by an overall increase of IgE. Moreover, with the help of the radioallergosorbent test (RAST), several authors (Hoffmann *et al.*, 1974; Öhman & Johansson,

1974b, Wüthrich, 1974) have shown that the serum IgE increase is related to the increase of specific IgE against several environmental allergens.

The questions of the pathogenetic significance of IgE in atopic dermatitis, as well as that of the therapeutic consequences, remains to be established. Personally, I believe that the IgE plays an important role in the genesis of the cutaneous changes and is not only a concomitant epiphenomenon. This is based on clinical observations on a few cases, in whom the elimination of already detected allergic foodstuffs by skin or RAST tests not only led to a decrease in the total and the RAST-specific IgE values, but even to considerable improvement, with a normalization of the skin condition (Wüthrich, 1975; Wüthrich, 1977). Unfortunately, such cases are an exception, perhaps because the responsible allergens have not as yet been found. On the other hand, further immunological abnormalities, i.e. high circulating levels of IgG4 (Shakib *et al.*, 1977) and particularly a depressed T cell-mediated immunity (Lobitz, Honeyman & Winkler, 1972; Schöpf & Böhringer, 1974), have been demonstrated in some patients with atopic dermatitis. Their pathogenetic roles have not, as yet, been assessed. We are still not far in atopic dermatitis research from William's (1951) fable of the blind Hindus, who, with the help of their sense of touch only, had to examine an elephant. One of them grasped the snout, the second the tail and the remaining Hindus other parts of the body. However, they failed to get a general impression of the elephant. It is to be hoped that with the help of dermatologists, pediatricians, immunologists, geneticists and psychiatrists we shall nevertheless make further progress in this field.

References

- ANAN, S. (1976) Cellules porteuses d'immunoglobulines au niveau de la peau. *Revue Française d'Allergie*, **16**, 65.
- BARRATT, T.M., TURNER, M.W. & JOHANSSON, S.G.O. (1971) Urinary excretion of immunoglobulin E in the nephrotic syndrome and atopic eczema. *Lancet*, **ii**, 402.
- BAZARAL, M., ORGEL, H.A. & HAMBURGER, R.N. (1971) IgE levels in normal infants and mothers and an inheritance hypothesis. *Journal of Immunology*, **107**, 794.
- BERG, T. & JOHANSSON, S.G.O. (1969a) IgE concentrations in children with atopic diseases. *International Archives of Allergy and Applied Immunology*, **36**, 219.
- BERG, T. & JOHANSSON, S.G.O. (1969b) Immunoglobulin levels during childhood, with special regard to IgE. *Acta Paediatrica Scandinavica*, **58**, 513.
- CLENDENNING, W.E., CLACK, W.E., OGAWA, M. & ISHIZAKA, K. (1973) Serum IgE studies in atopic dermatitis. *Journal of Investigative Dermatology*, **61**, 233.
- CORMANE, R.H., HUSZ, S. & HAMERLINCK, F. (1974) Immunoglobulin- and complement-bearing lymphocytes in allergic contact dermatitis and atopic dermatitis (eczema). *British Journal of Dermatology*, **90**, 597.
- DESSAINT, J.-P., WATTRE, P. & LELONG, M. (1974) Dosage des IgE sériques chez l'enfant. Valeurs normales en fonction de l'âge. *Revue Française d'Allergie*, **14**, 189.
- EZEKE, A., PERERA, A.B.V. & HOBBS, J.R. (1973) Serum IgE elevation with tropical eosinophilia. *Clinical Allergy*, **3**, 33.
- GUREVITCH, A.W., HEINER, D.C. & REISNER, R.M. (1973) IgE in atopic dermatitis and other common dermatoses. *Archives of Dermatology*, **107**, 712.
- HEINER, D.C. & ROSE, B. (1970) Elevated levels of gamma E (IgE) in conditions other than classical allergy. *Journal of Allergy*, **45**, 30.
- HOFFMAN, D.R., YAMAMOTO, F.Y., GELLER, B. & HADDID, Z. (1974) Specific IgE antibodies in atopic eczema. *Journal of Allergy and Clinical Immunology*, **55**, 256.
- HOGARTH-SCOTT, R.S., JOHANSSON, S.G.O. & BENNICH, H. (1969) Antibodies to toxocara in the sera of visceral larva migrans patients: the significance of raised levels of IgE. *Clinical and Experimental Immunology*, **5**, 619.
- JANSEN, C.T., HAAPALAHTI, J. & HOPUSU-HAVU, V.K. (1973) Immunoglobulin E in the human atopic skin. *Archiv für Dermatologische Forschung*, **246**, 299.

- JOHANSSON, S.G.O. (1968) Serum IgND levels in healthy children and adults. *International Archives of Allergy and Applied Immunology*, **34**, 1.
- JOHANSSON, S.G.O. & JUHLIN, L. (1970) Immunoglobulin E in 'healed' atopic dermatitis and after treatment with corticosteroids and azathioprine. *British Journal of Dermatology*, **82**, 10.
- JOHANSSON, S.G.O., MELLBIN, T. & VAHLQUIST, B.O. (1968) Immunoglobulin levels in Ethiopian pre-school children with special reference to high concentrations of immunoglobulin E (IgND). *Lancet*, **i**, 1118.
- JOHNSON, E.E., IRONS, J.S., PATTERSON, R. & ROBERTS, M. (1974) Serum IgE concentration in atopic dermatitis. *Journal of Allergy and Clinical Immunology*, **54**, 94.
- JUHLIN, L., JOHANSSON, S.G.O., BENNICH, H., HÖGMAN, C. & THRESON, N. (1969) Immunoglobulin E in dermatoses. *Archives of Dermatology*, **100**, 12.
- KJELLMAN, N.-I.M., HANSSON, L.-O. & LUDVIGSSON, J. (1977) Atopic allergy and serum IgE in randomly selected 8 year old children. *Acta Allergologica*, **32**, 91.
- LEONARDY, J.G. & PEACOCK, L.B. (1972) An evaluation of quantitative serum immunoglobulin determinations in clinical practice. *Annals of Allergy*, **30**, 378.
- LOBITZ, W.C., HONEYMAN, J.F. & WINKLER, N.W. (1972) Suppressed cell-mediated immunity in two adults with atopic dermatitis. *British Journal of Dermatology*, **86**, 317.
- ÖHMAN, S. & JOHANSSON, S.G.O. (1974a) Immunoglobulins in atopic dermatitis. *Acta Dermatovenereologica (Stockholm)*, **54**, 193.
- ÖHMANN, S. & JOHANSSON, S.G.O. (1974b) Allergen-specific IgE in atopic dermatitis. *Acta Dermatovenereologica (Stockholm)*, **54**, 283.
- OGAWA, M., BERGER, P.A., MCINTYRE, O.R. & CLENDENNING, W.E. (1971) IgE in atopic dermatitis. *Archives of Dermatology*, **103**, 575.
- O'LOUGHLIN, S., DIAZ-PEREZ, J.L., GLEICH, G.J. & WINKELMANN, R.K. (1977) Serum IgE in dermatitis and dermatosis. *Archives of Dermatology*, **113**, 309.
- ROSENBERG, E.B., POLMAR, S.T.H. & WHALEN, G.E. (1971) Increased circulating IgE in trichinosis. *Annals of Internal Medicine*, **75**, 575.
- SCHÖPF, E. & BOEHRINGER, D. (1974) IgE and cell-mediated immunity in atopic dermatitis. *Journal of Dermatology*, **1**, 133.
- SHAKIB, F., McLAUGHLAN, P., STANWORTH, D.R., SMITH, E. & FAIRBURN, E. (1977) Elevated serum IgE and IgG4 in patients with atopic dermatitis. *British Journal of Dermatology*, **97**, 59.
- SPITZ, E., GELFAND, E.W., SHEFFER, A.L. & AUSTEN, F. (1972) Serum IgE in clinical immunology and allergy. *Journal of Allergy and Clinical Immunology*, **49**, 337.
- STONE, S.T.P., GLEICH, G.J. & MULLER, S.A. (1976) Atopic dermatitis and IgE. *Archives of Dermatology*, **112**, 1254.
- VIRCHOW, CHR., MÖLLER, E. & DEBELIC, M. (1971) IgE-Serumspiegel-bestimmungen bei chronisch-obstruktiven Atemwegsleiden. *Pneumologie-Pneumology*, **145**, 428.
- WALDMAN, R.H., VIRCHOW, C. & ROWE, D.S. (1973) IgE levels in external secretions. *International Archives of Allergy and Applied Immunology*, **44**, 242.
- WILLIAMS, D.H. (1951) Management of atopic dermatitis in children control of the maternal rejection factor. *Archives of Dermatology and Syphilology*, **63**, 545.
- WÜTHRICH, B. (1974) Allergen-spezifische IgE im Radio-Allergo-Sorbens-Test bei Neurodermitis. *Hautarzt*, **25**, 603.
- WÜTHRICH, B. (1975) *Zur Immunopathologie der Neurodermitis Constitutionalis*, p. 47. Hans Huber, Bern, Stuttgart, Wien.
- WÜTHRICH, B. (1977) Zur Klinik, Pathogenese und Therapie der Neurodermitis constitutionalis. *Therapiewoche*, **27**, 4288.
- WÜTHRICH, B. & KOPPER, E. (1974) Ergebnisse der IgE-Serum-spiegel-Bestimmung und ihre klinische Bedeutung. *Schweizerische medizinische Wochenschrift*, **104**, 1437.
- WÜTHRICH, B., KOPPER, E. & VIRCHOW, CHR. (1973) IgE-Bestimmung bei Neurodermitis und anderen Dermatosen. *Der Hautarzt*, **24**, 381.
- WÜTHRICH, B., STORCK, H., GROB, P. & SCHWARZ-SPECK, M. (1972). Zur Immunpathologie der Neurodermitis. *Archiv für Dermatologische Forschung*, **244**, 327.

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.