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EDITORIAL

IgE Regulation and the Control of Allergic Diseases

The term "atopy" was initially coined by Coca and Cooke[1] in 1923 to donote a group of diseases characterized by heightened sensitivities to the external milieu such as in asthma, atopic eczema and hay fever. Several postulations were forwarded to explain the pathogenesis of these phenomena, most of which speculated the presence of an antibody, i.e. the reaginic antibody[2] capable of mediating hypersensitivity reactions. It was not until 1966 when the Ishizakas identified this reaginic antibody to be an isotype of immunoglobulin which they named immunoglobulin E (IgE).[3] Since then, evidence has accumulated to implicate the role of IgE in the pathogenesis of allergic diseases, mainly by its ability to initiate mediator release from the granules of mast cells and basophils[4] through its interaction with IgE receptors currently known to exist in both low and high affinity states.[5]

A relationship between the extent of atopic diseases and IgE levels has been demonstrated. Total IgE was frequently found to be significantly elevated in allergic asthmatics (such as in mite sensitive asthma), while commonly, only elevation of specific IgE was observed in patients with allergic rhinitis.[6] Nevertheless, a minority of atopic patients remained nonallergic when tested by immediate skin testing or by RAST (radioallergosorbent testing) for specific IgE. The existence of this group of patients has led to continuing efforts to delineate mechanisms other than IgE-mediated ones that could be responsible for the development of hypersensitivity. However, studies such as that of Burrow *et al*[7] have finally demonstrated that the prevalence of asthma, irrespective the patients' atopic status, did indeed correlate with the presence of IgE for the entire age range of the patients studied (age 6 on up). Apparently, a significant amount of IgE (specific IgE or total IgE) in atopic patients is produced against known allergens in the majority of cases and against unknown allergens in the minority. More importantly, the production of significant amounts of allergen-specific IgE (particularly mite-specific) has been shown to be associated with high levels of allergen-exposure[8] along with a risk of developing acute asthmatic attacks.[9] From these important findings it can concluded that (a) excessive IgE production is indeed associated with the development of atopic diseases with asthma being associated with an increase in total IgE and (b) the development of a significant amount of specific IgE is associated with high levels of allergen exposure.

Since hyperproduction of IgE leads to the development of atopy, it would be desirable to curb or to regulate the production of IgE in individuals at high risk for developing atopic diseases such as in infants born to atopic parents. The regulation of IgE production is complex and is thought to be (a) under genetic influences and (b) related to individual exposure to antigens to which they are capable of mounting an IgE response. Marsh *et al*[10] postulated two-allele autosomal system [a dominant allele (R) and a recessive allele (r) controlling basal IgE levels in which low IgE level production is inherited as a dominant trait and high IgE as a recessive one]. More recently, the production of specific IgE was found to be under HLA-linked genetic control; for instance, HLA DW2 is associated with hyperresponsiveness to ragweed antigen 5 and HLA A9 with hyporesponsiveness to timothy antigen T13.[11] The different frequency of HLA antigens among various ethnic groups could explain the high inci-

dence of atopy observed among Asian descendents as compared to their caucasian counterparts. [12]

For allergen sensitization to develop, exposure to antigens can occur either prenatally or postnatally. Allergens such as penicillin, milk, egg and wheat have been shown to stimulate IgE response in the fetus, prenatally. [13] This would have to be due to placental transfer of antigens since arterial cord blood consistently failed to contain (maternal) IgE. [14] Postnatal sensitization, on the other hand, is considered more important and could be due to food antigens or to inhalant allergens. Sensitization with food antigens in infants can be made possible through consumption of breast milk (maternally-ingested food antigens can be excreted into breast milk) or via an early introduction of allergenic diets such as eggs, milk, nuts, soy and wheat to infants during the critical period for sensitization. Since the rate of increase of IgE during the first five years of life is high as compared to that at later age, and since the peak rate occurs during the first two to three years of life, [15] the critical period for IgE sensitization would have to be at the very early stage of life, particularly during the first two years after birth. Rowntree *et al* followed infants who were born to atopic mothers for at least 18 months and have documented the rise in the level of specific IgE to food antigens, such as to egg, as early as 6 months of age; this specific IgE peaked at around one year of age during which the incidence of food allergy can be increasingly observed. [16] In contrast, the development of specific IgE to inhalants such as to antigen P1 of dust mites and to antigen Rye 1 of rye grass occurred later in life (around two years of age and peaked at around 4-5 years of age). The appearance of specific IgE to inhalants in this age group from this study coincided with the mean age for the development of respiratory tract allergy which has been observed to be at around 36 months of age. [17] An increase in the incidence of viral upper respiratory tract infections in this age group could also potentially lead to an increase in production of viral-specific IgE, such as that observed with respiratory syncytial virus infections. [18]

Thus, it is apparent that, for the regulation of IgE response in atopy prone infants to be effectively implemented, the control measures would have to be initiated very early in life. Methods for IgE regulation could potentially be (a) a hypothetical genetic alteration (b) the use of immunomodulators to decrease IgE production and (c) the reduction of allergenic load to infants prone to develop atopy. Our current knowledge only permits the last measure to be a realistic possibility. Breast feeding with a delay in the introduction of solids food has been used as a methods for preventing atopy in infants born to atopic parents for decades. However its advantages are still an issue under heated debate. Several reports have demonstrated the advantages of breast feeding over cow's milk feeding in the reduction of prevalence of atopic diseases, mainly for atopic dermatitis and in some instances for the reduction of severity of asthma. [19] Moreover, the levels of IgE were found to be lower at less than 4 months [20] and at 1 year age [21] among infants who were fed with breast milk as compared with those fed with cow's milk. Nevertheless, some well designed studies have failed to demonstrated the efficacy of breast feeding in the prevention of atopy over the control group. [22,23] Recently, a large multicenter study in the United States has demonstrated that (a) severely restricting the maternal diet during the third trimester of pregnancy and during lactation (devoid of milk, eggs, and peanuts) and (b) limiting the feeding of infants only to breast milk with casein hydrolysate formula (nutramigen) supplementation along with a significant delay in the introduction of solid foods (especially those with high allergenic potentials such as eggs and peanuts) could lead to a lower incidence of urticaria, atopic dermatitis and gastrointestinal allergy among the infants allocated in the prophylactic diet group (5.1%) as opposed 16.4 percent observed in those whose diet was not controlled. [24] However, the incidence inhalant allergies such as asthma, and allergic rhinitis among the two groups was similar for the entire 24 months of the study. This is in contrast to the previous observation by Hattevig who demonstrated that the presence of egg-specific IgE is associated with frequent development of asthma and allergic rhinitis in later life. [25] From this evidence, it is apparent that diet control alone would certainly not be sufficient in preventing further development of respiratory atopic diseases, some of which could potentially be life-long and debilitating to the patients. To be ideal, control measures for inhalant allergens would have to be utilized as well. It was recently demonstrated that lower mite-specific IgE levels were correlated with lower mite-allergen exposure. [8] The implementation of a strict mite-allergen avoidance measure by Murray *et al* have led to a decrease in asthmatic symptoms among children who had already been allergic to house dust mites; [26] however, the effects of these measures on mite-specific IgE were not examined. In constrast, avoidance of incriminated foods in a subset of patients with atopic dermatitis has been found to result in a clinical improvement and also a reduction of total IgE. [27]

Allergen immunotherapy or allergen desensitization have been utilized in the treatment of atopic diseases since 1912. [28] Current evidence, from several double-blind placebo-controlled studies, has demonstrated that, indeed, this mode of therapy is effective in the reduction of the allergic rhinitis and asthma symptoms. [29,30] The role of (allergen) immunotherapy in the treatment of

food allergy is currently not as firm as for asthma and allergic rhinitis. The mechanisms of action of immunotherapy have not been completely delineated, but are felt to be related to a blunting in a seasonal rise of specific IgE after exposure to natural allergens such as to ragweed and to grass antigen.[31] There is also a rise in allergen specific IgG, especially IgG4 during immunotherapy, the significance of which remains to be determined.[32] More recently, immunotherapy has been shown to produce antigen-specific suppressor T cells which are capable of suppressing specific IgE production *in vitro*.[33] Despite its proven efficacy, few data exist in regard to its final effect on total IgE production. In contrast to inhalant immunotherapy, venom immunotherapy has been found to be highly effective and is associated with the production of specific IgG and a significant decline in venom-specific IgE.[34]

Finally, the increasing knowledge on cytokines in the regulation of immune response has enable us to recognize that IgE secretion from B cells is under significant T cell control. The T cell signals involved in controlling IgE synthesis can be divided into two stage: the first is the signal which drives B cells from the uncommitted stage into the IgE-committed stage which is perhaps mediated through IL-4 and IL-5 (also known to be an eosinophil differentiation factor). Gamma interferon, on the other hand, provides a negative signal for this (IgE) isotype switching by B cells.[35] The second signal is the interaction between IgE, the IgE binding factors (existing in both potential and inhibiting forms) and the Fc receptor of B cells; this interaction drives the IgE-committed B cells to produce and secrete IgE.[3] Current research is probing the *in vitro* modulation of these aforementioned systems along with a possible way to block the interaction between IgE and IgE receptor in order to terminate the initiating signal for hypersensitivity. With these new *in vitro* technologies as well as with continuing efforts in clinical research such as in mite-induced asthma, in food allergy and in venom immuno-therapy, we may witness the control of allergic diseases becoming a reality in the near future.

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REFERENCES

1. Coca AF, Cooke RA: On the classification of the phenomena of hypersensitiveness. J Immunol 1923; 8 : 163.
2. Coca AF and EF Grove: Studies in hypersensitiveness XIII. A study of atopic reagins. J Immunol 1925; 10 : 445-64.
3. Ishizaka K. Twenty years with IgE: from the identification of IgE to regulatory factors for the IgE response. Presidential Address. J Immunol 1985; 135 : i-x.
4. Siraganian RP. Biochemical events in basophil/mast cell activation and mediator secretion. *In* Kaplan AP, ed. Allergy. New York: Churchill Livingston, 1985 : 31-46.
5. Vercelli D and Geha RS. The IgE system. Ann Allergy 1989; 63 : 4-11.
6. Park HS, Oh SH and Hong CS: The comparison of allergic responses to *Dermatophagoides farinae* between bronchial asthma and allergic rhinitis. Ann Allergy 1989; 63 : 399-404.
7. Burrow B, Martinez FD, Halonen M *et al* : Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med 1989; 320 : 271-7.
8. Lau S, Falkenhorst G, Weber A *et al:* High mite-allergen exposure increases the risk of sensitization in atopic children and young adults. J Allergy Clin Immunol 1989; 84 : 718-25.
9. Pollart SM, Chapman MD, Fiocco GP *et al :* Epidemiology of acute asthma: IgE antibodies to common inhalant allergens as a risk factor for emergency room visits. J Allergy Clin Immunol 1989; 83 : 875-82.
10. Marsh DG, Bias WB and Ishizaka K: Genetic control of basal serum IgE level and its effect on specific reaginic sensitivity. Proc Natl Acad Sci USA 1974; 71 : 3588.
11. March DG. Immunogenetics of allergic diseases. *In:* Middleton, Reed, Ellis, Adkinson, Yunginger eds. Allergy, Principles and practice, 3rd Edition. St Louis: CV Mosby, 1988; Vol. 1 ; 94.
12. Maternowski CJ and Mathews KP: The prevalence of ragweed pollinosis in foreign and native students at a mid-western university and its implications concerning methods for determining the inheritance of atopy. J Allergy 1962; 33 : 130-40.
13. Ziegler RS: Development and prevention of allergic diseases in childhood. *In:* Middleton, Reed, Ellis, Adkinson, Yunginger eds. Allergy, Principles and Practice, 3rd edition. St Louis: CV Mosby, 1988; vol 11 : 934.
14. Sherman WB, Hampton SF and Cooke RA:Placental transmission of antibodies in the skin sensitive type of human allergy. J Exp Med 1940; 72 : 611.
15. Kjellman NIM, Johansson SGO, and Roth A. Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). Clin Allergy 1976; 6 : 51-9.
16. Rowntree S, Cogswell JJ, Platts-Mills TAE *et al.* Development of IgE and IgG antibodies to food and inhalant allergens in children at risk of allergic diseases. Arch Dis Child 1985; 60 : 727-35.
17. Kaufman HS, Frick OL. The development of allergy in infants of allergic parents: a prospective study concerning role of heredity. Ann Allergy 1976; 37 : 410-5.
18. Welliver RC, Wong DT, Sun M, *et al.* The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. N Engl J Med 1981; 305 : 841-6.
19. Blair N. Natural history of childhood asthma: 20 year follow up. Arch Dis Child 1977; 52 : 613-9.
20. Saarinen UM, Backman A, Kajossari M *et al.* Prolonged breast-feeding as prophylaxis for atopic disease. Lancet 1979; 2 : 163-6.
21. Zierring R, O'Connor R, Mellon M *et al.* University of California in San Diego prophylaxis of allergy in infancy study: an interim report (Abstract). J Allergy Clin Immunol 1979; 63 : 199.

22. Hide DW and Guyer BM. Clinical manifestation of allergy related to breast and cow's milk feeding. Arch Dis Child 1981; 56 : 172-5.

23. Van Asperen PP, Kemp AS and Mellis CM. Relationship of diet in the development of atopy in infancy. Clin Allergy 1984; 14 : 525-32.

24. Zieger RS, Heller S, Mellon MH *et al.* Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: A randomized study. J Allergy Clin Immunol 1989; 84 : 72-89.

25. Hattevig G, Kjellman B, Johansson SGO *et al.* Clinical symptoms and IgE responses to common food problems in atopic and healthy children. Clin Allergy 1984; 14 : 551-9.

26. Murray AB and Ferguson AC. Dust-free bedrooms in the treatment of asthmatic children with house dust or house dust mite allergy: a controlled trial. Pediatrics 1983; 71 : 418-22.

27. Sampson HA and McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. J Pediatr 1985; 107 : 669-75.

28. Noon L. Prophylactic inoculation against hay fever. Lancet 1911; 1 : 1572-3.

29. Norman PS. Immunotherapy for nasal allergy (Symposium). J Allergy Clin Immunol 1988; 81 : 992-6.

30. Ohman JL. Allergen immunotherapy in asthma: Evidence for efficacy. J Allergy Clin Immunol 1989; 84 : 133-40.

31. Gleich GJ, Zimmerman EM, Henderson LL and Yunginger JW. Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: a six-year prospective study. J Allergy Clin Immunol 1982; 70 : 261-71.

32. Gurka G and Rocklin R. Immunologic response during allergen-specific immunotherapy for respiratory allergy. Ann Allergy 1988; 61 : 239-43.

33. Tamir R, Castracane JM and Rocklin RE. Generation of suppressor cells in atopic patients during immunotherapy that modulate IgE synthesis. J Allergy Clin Immunol 1987; 79 : 591-8.

34. Reisman RE. Insect Allergy. *In:* Middleton, Reed, Ellis, Adkinson, Yunginger eds. Allergy, Principles and Practice, 3rd edition. St Louis: CV Mosby 1988; Vol II : pp. 1345-60.

35. Geha RS. Regulation of IgE synthesis in atopic diseases. Hosp Pract [off] 1988; 23 : 91-102.