

Appearance of IgE antibodies to ingested and inhaled allergens during the first 12 years of life in atopic and non-atopic children

Hattevig G, Kjellman B, Björkstén B. Appearance of IgE antibodies to ingested and inhaled allergens during the first 12 years of life in atopic and non-atopic children.

Pediatr Allergy Immunol 1993; 4: 182–186. © Munksgaard 1993.

The appearance and course of serum immunoglobulin E-antibodies (IgE-ab) to egg-white (EW), cow's milk (CM) and inhalants (pollen, danders and mite) were followed from birth to 12 years of age in 84 children unselected for family history of atopy. During the follow-up 36 children developed atopic symptoms and 48 children did not. IgE-ab to EW and CM reached a peak prevalence at 8 months of age – with high concentrations almost exclusively in atopics and disappeared successively during childhood. IgE-ab to inhalants appeared from 2 years of age and then in increasing frequency during childhood. Similar to the pattern of IgE-ab to EW and CM, transient low levels of IgE-ab to inhalants were commonly encountered in non-atopic children while high concentrations without tendency to decline were almost exclusively seen in atopics. High responders to EW-antigen during infancy were usually also high responders to inhalants during childhood. Clinical allergy to EW and CM and subsequent tolerance appeared early in childhood, whereas allergy to inhalants appeared later and did not disappear. The temporary low-grade IgE antibody response in non-atopic individuals to eaten and inhaled allergens is similar to the results of animal studies demonstrating a transient IgE production followed by tolerance.

**G. Hattevig¹, B. Kjellman¹,
B. Björkstén²**

Departments of Pediatrics, ¹Central Hospital, Skövde, ²University Hospital, Linköping, Sweden

Gunnar Hattevig, Department of Pediatrics, Central Hospital, S-541 85 Skövde, Sweden

Key words: allergens; IgE antibodies; children, atopic, non-atopic

Received April 27, 1993

Accepted May 28, 1993

We have previously reported the development of atopic symptoms and serum IgE antibodies (IgE-ab) to common allergens in 86 girls unselected with regard to family history of allergy followed from birth to 7 years of age (1, 2). We concluded that IgE-ab to egg-white (EW) and cow's milk (CM) appeared frequently during infancy both in atopics and non-atopics, but in high levels almost exclusively in infants with present or future atopy. The highest concentrations of IgE-ab to foods were seen at 8 months and then decreased, while IgE-ab to inhalants appeared later.

We report here the results of a follow-up performed when the children were 12 years of age and discuss the appearance and course of IgE-ab during the first 12 years of age in atopic and non-atopic individuals.

Subjects and methods

The study group, which originally comprised 86 girls, has been presented in detail previously (1, 2). Since the follow-up at 7 years of age two non-atopic children had died. All the remaining 84 children reported for the follow-up at 12 years of age. Briefly, they were all Rh-negative and results of uncomplicated pregnancies and deliveries. Clinical examinations were made and blood samples were taken at birth and at 3 and 8 months, and at 2, 4 and 7 years of age. A clinical history emphasizing possible atopic symptoms was obtained and a physical examination was made by one and the same physician as previously. The clinical criteria of atopy were the same as those used previously (1). Briefly, bronchial wheezing three times or

Table 1. Cumulative number of children with clinical symptoms of atopy ($n = 36$) out of 84 children followed from birth to 12 years. EW = egg-white, CM = cow's milk, m = months, y = years.

Symptoms	Age					
	3 m	8 m	2 y	4 y	7 y	12 y
Atop. dermat.	2	8	12	18	18	26
Allerg. rhinit	0	0	0	4	8	11
Urticaria	0	1	4	5	6	7
Asthma	0	1	1	2	2	2
Gastro-intest allergy	0	0	0	0	0	2
Allergy to EW/CM	0	3	7	7	7	7
Allergy to pollen/danders	0	0	0	1	6	10

more was regarded as asthma. Allergic rhinitis (AR) was defined as rhinitis and conjunctivitis appearing at least twice after exposure to a particular allergen and not associated with infection. Atopic dermatitis (AD) was defined as pruritic, chronic or chronically relapsing dermatitis with typical morphology and distribution as described by Hanifin and Rajka (3). Allergic urticaria was defined as generalized urticaria appearing at least twice within approximately 1 h after exposure to a particular allergen and not associated with infection. Gastrointestinal allergy was defined as an obvious reaction after an exposure to an allergen within 1 h after exposure on at least two occasions.

Venous blood samples were obtained through a cubital venepuncture and all were frozen and stored at -20°C until analyzed. Total serum IgE (S-IgE) levels were determined with Phadebas PRIST^R (Pharmacia Diagnostics AB, Uppsala, Sweden) as recommended by the manufacturer and described in detail elsewhere (1). The levels of IgE-ab to EW and CM, house dust mite (*Dermaphagoides pteronyssinus*), birch, thimothy and mixed animal danders were estimated with Phadebas RAST^R (Pharmacia Diagnostics AB, Uppsala, Sweden). Sera that were RAST^R negative, i.e., <0.35 PRU/mL (Phadebas RAST Units/mL), were tested a second time with an extra sensitive assay allowing identification of antibodies in levels of ≥ 0.10 PRU/mL as described in detail elsewhere (1). Sera that were positive to the mixed animal dander discs were subsequently tested for IgE-ab to cat-, dog- and horse epithelium.

The Mann-Whitney U-test was used for estimation of differences between S-IgE concentrations in different subgroups of children. Fisher's exact two-tailed test was used to estimate differences between subgroups. Odds ratio (OR) and the 95% confidence interval (CI) are given.

All parents of the children gave their informed consent. The study was approved by the Human

Research Committee of the Medical Faculty of the University Gothenburg.

Results

The cumulative number of children with atopic symptoms during the first 12 years of life was 36 (43%). Twelve of the 24 children reporting such symptoms at the present follow-up had previously not shown any atopic symptoms (Table 1). Allergy

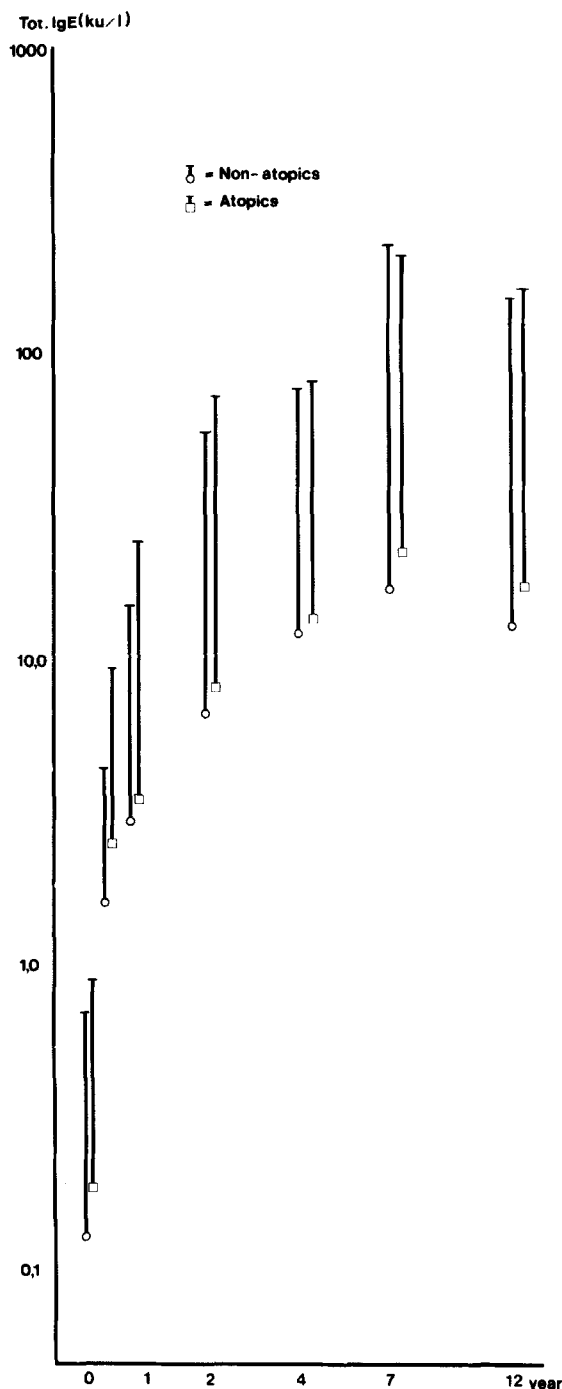


Fig. 1. Serum IgE levels (kU/L). Medians and 90th percentiles (T) in children developing atopic symptoms during the 12 years of follow-up ($\square$) and they who did not ($\circ$).

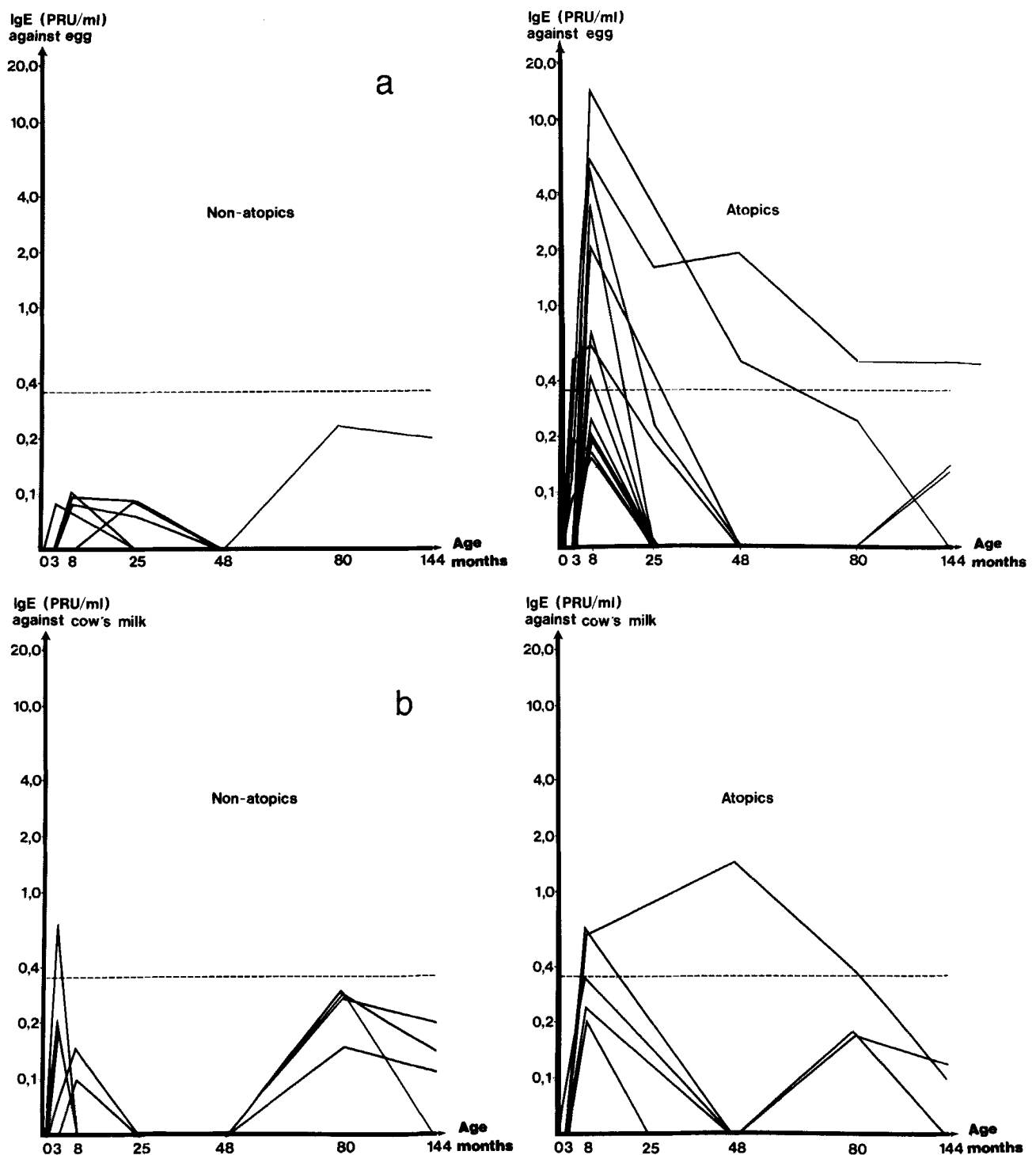


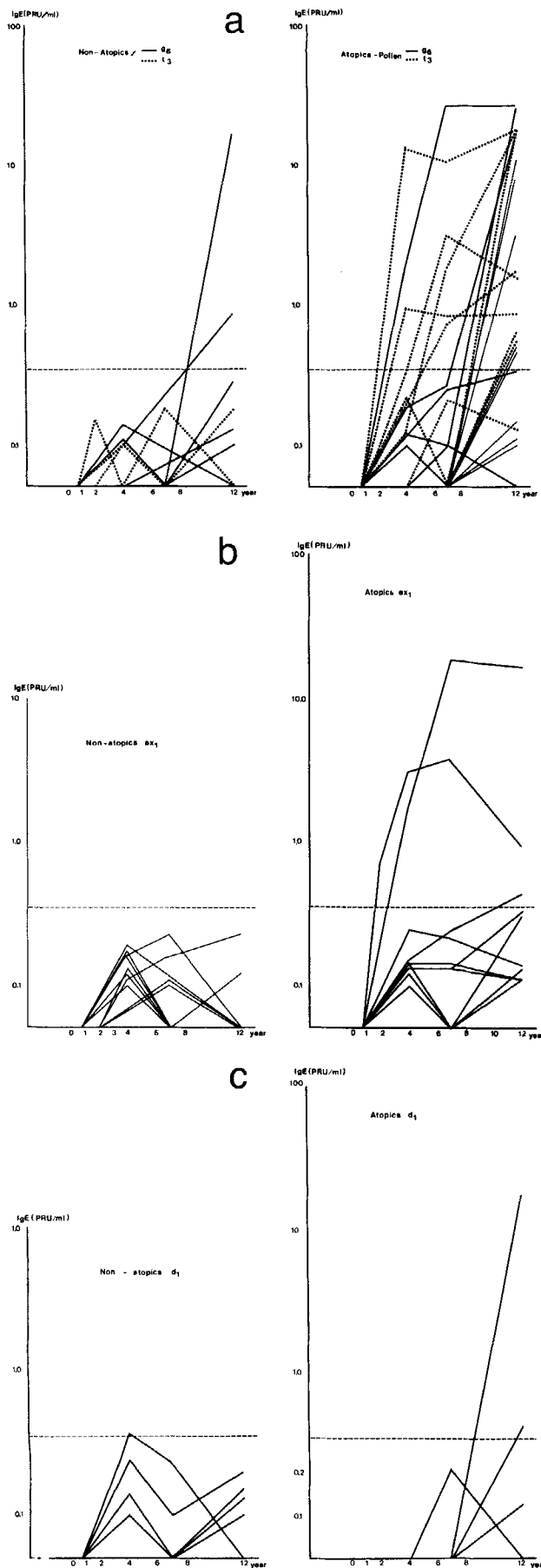
Fig. 2. Levels of IgE-antibodies to egg-white (a) and cow's milk (b) (PRU/mL) at various ages in children who did or did not develop atopic symptoms during the first 12 years of life. The unbroken horizontal lines indicate 0.35 PRU/mL, which is the lower limit of Phadebas RAST[®] class 1.

to EW or CM did not develop after two years of age and was still present at 4, 7 and 12 years in 6, 2 and 0 children respectively.

Clinical allergy to pollen and/or danders appeared between 2 and 4 years in one child, between 4 and 7 years in 5 children and in other 4

children up to 12 years age. At that age all of them had clinical symptoms.

Serum IgE levels did not differ significantly between the atopic and non-atopic children at any time over the 12-year period (Fig 1). This was true both for cumulative incidence and prevalence at all ages.



The concentrations of IgE-ab against EW and CM are shown in Fig 2. An essentially biphasic response of IgE-ab to food allergens was seen both in atopics and non-atopics with a peak at 8 months of age prior to a decline. The differences between atopics and non atopics are the higher peak concentrations in the atopics and the slower decline in some of them. No child developed concentrations above 0.35 PRU/mL after the first year of life and high levels of IgE-antibodies, i.e. ≥ 0.35 PRU/mL were almost exclusively seen in children who developed atopic disease at some time during the observation period.

Table 2 shows the number of children with sera available for titration and the number of children with detectable IgE-ab to inhalants during the follow-up. The 40 children with sera available for titration up to 2 years of age included five of the six children with IgE-ab ≥ 0.35 PRU/mL at 4 years and four of the five children developing such antibodies between 4 and 7 years. Their sera had no detectable IgE-ab to inhalants before 2 years.

The concentrations of IgE-ab to inhalants are shown in Fig 3. Such antibodies were detectable in 22 of the 36 children with atopic manifestation (60%) and in 17 of the 48 (35%) non-atopic ones (OR: 2.9, 95% CI: 1.1–7.8). The number of atopic children with low levels of antibodies (8/36) was similar to the number of non-atopics with low levels (15/48) whereas high titres were seen in 14 atopic individuals and in only 2 non-atopic children (OR: 14.6, 95% CI: 2.8–102.7). The two non-atopic children had IgE-ab to pollen and only at the last follow-up.

An essentially biphasic response of IgE-ab to inhalants was seen in the non-atopics with low peak concentrations between 2 and 7 years of age. Declining concentrations were not seen in the atopics.

Discussion

A pattern similar to the IgE-ab development to EW and CM, was commonly found in the IgE-ab development to inhalants both in atopics and non-atopics, but high levels were almost exclusively seen in atopics. The IgE-ab to inhalants appeared, however, later both in atopics and non-atopics. Furthermore, a biphasic pattern of IgE-ab to inhalants was only seen in the non-atopics, consistent with the picture seen in experimental animal

Fig. 3. Levels of IgE antibodies to pollen (birch and timothy) (a), mixed animal danders (b), and to house dust mite (c) at various ages in children who did or did not develop atopic symptoms during the first 12 years of life. The unbroken horizontal lines indicate 0.35 PRU/mL, which is the lower limit of Phadebas RAST[®] class 1.

Table 2. IgE-ab (PRU/mL) to inhalants obtained in 84 children followed from birth to 12 years of age

Age (years)	Number of children with		
	IgE-ab ≥ 0.35	IgE-ab < 0.35	available sera
0-2	1	1	40
4	5	22	84
7	10	15	76
12	16	14	84

models which demonstrate transient IgE-ab production to inhaled allergens prior to the onset of tolerance (6).

The pattern of clinical allergy followed the pattern of IgE-ab; i.e. allergy to EW and CM appeared early and tolerance developed during childhood whereas allergy to inhalants appeared later with increasing prevalence.

Two groups of children could be identified with regard to appearance of IgE-ab to foods and inhalants. One group had no or only low concentrations of IgE-ab (low responders) and another group developed high concentrations of these antibodies (high responders). In the high-responders the high levels of IgE-ab to both foods and inhalants were reached rapidly after their first appearance. This pattern agrees with experimental data suggesting that subjects with propensity to hyperproduction of IgE-ab have a genetically determined deficiency in regulation of IgE-ab production (4-7).

The reasons why the high-responders developed high levels of IgE-ab to food allergens earlier than to inhalants can only be speculated upon. We know from previous studies of this cohort and of children with heredity for atopy (high allergy risk children) that high-responders develop high concentrations of IgE-ab to EW soon after stimulation with very small doses of the antigen e.g. by the small doses supplied through the breast-milk (1, 2, 8-10). As a matter of fact, almost all children in this and another study with high levels of IgE-ab to EW developed them during the first 8 months of life and before eggs had been introduced into the diet (1, 2, 8). It is not known why the small doses of inhaled allergens such as pollen, danders and mite elicited a similar response only later in life. Differences in the immunological responsiveness of the gut and lung, differences in allergenicity between food and inhaled antigens or age-related differences in IgE-response to the various allergenic proteins may explain the differences between sensitization to nutrients and inhalants.

The factors behind the development of clinical and immunological tolerance are not fully known. It has been proposed that high-responders develop tolerance by switching T-cells from TH₂, producing IL-2 and IL-4 to TH₁, producing IFN-gamma (7, 11). Such switching concerning an individual allergen seems not to facilitate a future switch for another allergen, as 6 of 8 children developing high levels of IgE-ab to EW also developed and preserved high levels of antibodies to inhalants during the study period.

In conclusion, temporary, low-grade IgE-ab response to both foods and inhalants was common both in atopic and non-atopic children, whereas high levels were almost exclusively seen in atopics. IgE-ab to foods appeared during infancy and disappeared during childhood, whereas IgE-ab to inhalants appeared later and in increasing frequency from 2 years of age. IgE-ab to foods during infancy were strongly associated with future development of IgE-ab to inhalants.

References

- HATTEVIG G, KJELLMAN B, JOHANSSON SGO, BJÖRKSTÉN B. Clinical symptoms and IgE responses to common food proteins in atopic and healthy children. *Clin Allergy* 1984; 14: 551-9.
- HATTEVIG G, KJELLMAN B, BJÖRKSTÉN B. Clinical symptoms and IgE responses to common proteins and inhalants in the first 7 years of life. *Clin Allergy* 1987; 17: 571-8.
- HANIFIN JM, RAJKA G. Diagnostic features of atopic dermatitis. *Acta Derm Venerol (Suppl)* 1980; 92: 44-7.
- STRANNEGÅRD I-L, STRANNEGÅRD Ö. The T-cell deficiency in atopic disease and its relation to hyperproduction of IgE. *Acta Dermatovenerol (Stockholm) Suppl.* 1981; 36: 263-8.
- HOLT PG, VINES J, BRITTON D. Suppression of IgE responses by antigen inhalation: failure of tolerance mechanism(s) in newborn rats. *Immunology* 1988; 63: 591-3.
- HOLT PG, McMENAMIN C, NELSON D. Primary sensitisation to inhalant allergens during infancy. *Pediatr Allergy Immunol* 1990; 1: 3-13.
- PARRONCHI P, MACCHIA D, PICCINNI AP, et al. Allergen- and bacterial antigen - specific T-cell clones established from atopic donors show a different profile of cytokine production. *Proc Natl Acad Sci, USA* 1991; 88: 4538-42.
- HATTEVIG G, KJELLMAN B, SIGURS N, GRODZINSKY E, HED J, BJÖRKSTÉN B. The effect of maternal avoidance of eggs, cow's milk, and fish during lactation on the development of IgE, IgG, and IgA antibodies in infants. *J Allergy Clin Immunol* 1990; 85: 108-115.
- CANT AJ, BAILES JA, MARSDEN RA, HEWITT D. Effect of maternal dietary exclusion on breastfed infants with eczema: two controlled studies. *Br Med J* 1985; 293: 231-3.
- KILSHAW PJ, CANT AJ. The passage of maternal dietary proteins into human breast milk. *Int Archs Allergy Appl Immunol* 1984; 75: 8-15.
- WIERENGA EA, SNOEK M, DE GROOT C, et al. Evidence of compartmentalization of functional subsets of CD4+ T-lymphocytes in atopic patients. *Immunol* 1990; 144: 46-51.