



# Is there a causative role for tetanus toxoid vaccination in the development of allergy-like symptoms and in the increasing prevalence of atopic diseases? ☆

Adriano Mari\*

*Allergy Unit, National Health Service, Rome, Italy*

Received 20 April 2004; accepted 20 April 2004

**Summary** Allergic diseases are a worldwide health problem. They mainly affect people living in developed countries where an increasing prevalence of allergy symptoms has been recorded in the last 20–30 years. The cause of this increase is still disputed, and, among others, the “hygiene hypothesis” supported the concept that relevant changes in lifestyle could have a relationship with the phenomenon. More recently the recorded parallel increase in autoimmune diseases has suggested to consider the “hygiene hypothesis” as a cause of a more general dysregulation of the immune system leading to both allergy and to autoimmunity.

Here are reported a series of observations, evidence, and data from the literature leading to a different hypothesis. The key points are: (1) the presence of two subsets of patients having allergy symptoms based on an IgE-mediated mechanism or not; (2) the positive results obtained with the autologous serum skin test in either cutaneous or respiratory affected subjects, mainly in children and adult females; (3) the presence of IgG autoantibodies against the  $\alpha$ -chain of the high affinity IgE receptor (Fc $\epsilon$ RI $\alpha$ ) in non-IgE-mediated urticaria and even in respiratory subjects; (4) the cross-reactivity between epitopes of the tetanus toxoid molecule and the Fc $\epsilon$ RI $\alpha$  detected by means of an  $\alpha$ -chain affinity purified IgG fraction; (5) the positive skin reactivity obtained using IgG anti-tetanus toxoid preparations in allergic and non-allergic volunteers. The presence of IgG autoantibodies actively generated by the population-based vaccination with tetanus toxoid could induce both mediator release from activated mast cell and Th2 cytokine production early in life. There are epidemiological evidences that tetanus toxoid vaccination could be linked with an increased tendency to have allergy symptoms. The different epidemiological distribution of non-IgE-mediated symptoms, mainly affecting young infants would be in agreement with the present hypothesis. The prevalent mother-to-child relationship in terms of risk for allergy symptoms could be explained with the *trans*-placenta transfer of IgG. A similar transfer could also take place through the mother milk during breast feeding.

It may thus be hypothesized that the increased prevalence of allergic diseases could be caused by the generalized tetanus toxoid immunization procedure, progressively extended to most of the countries worldwide in the last 30–40 years. Both the induction of non-IgE-mediated symptoms caused by the mast cell activation via the anti-Fc $\epsilon$ RI $\alpha$  IgG

☆ Note: The hypothesis formulated in the present study reflect author's personal opinions and it is not related to any official position of Regional and National Health Authorities within the Italian National Health Service.

\* Tel.: +39-330860005; fax: +39-0773620787.

E-mail address: [a.mari@panservice.it](mailto:a.mari@panservice.it).

and the long lasting Th2 inflammation of affected tissues would be the inducing mechanisms. This hypothesis would re-configure part of the allergic diseases as a Th2 phenotypic expression of an autoimmune disease.  
© 2004 Elsevier Ltd. All rights reserved.

## Background

Asthma, rhinitis, urticaria and atopic dermatitis are among the most common diseases worldwide [1–10]. Lowest prevalence values range between 3% and 10%, but in some countries allergy-related diseases may affect up to 40–50% of the general population [11,12]. In developed countries an increasing prevalence of allergic symptoms has been recorded in the last 30–40 years [13–16], involving both children [17–19] and adults [13,20,21]. When atopic manifestations occur in very young infants [22,23] in most of the cases there are no demonstrable risk factors at birth [24].

Several hypotheses have been done to explain such increasing prevalence. Outdoor and indoor pollution, changes in lifestyle including diet, hygiene, and housekeeping, decrease of parasitic infestations and also potential transmissibility are the most claimed causes, but several others have been studied [25–34]. The “hygiene hypothesis” [35–39], supporting the increasing prevalence of allergic diseases on the basis of the reduced exposure to infective agents, is supposed to be the mechanism leading to a reduced Th1 versus an increased Th2 tendency to respond to environmental stimuli including allergens [40]. This would lead subjects to more easily mount an IgE response to otherwise innocuous antigens. The recent finding that the increasing prevalence of some autoimmune diseases, mainly driven by a Th1 mechanism, similarly parallels the decrease of the microbial burden [41–43] is leading to a different interpretation of the “hygiene hypothesis”. Other immunological mechanisms working behind both allergic and autoimmune diseases have thus been suggested [44–50]. Furthermore, the parallel increase of autoimmune and allergic disease prevalence seems to exclude an inverse relationship between autoimmune diseases and allergy symptoms, as also suggested by studies reporting co-morbidity for both diseases [41,42,51,52].

## IgE-mediated versus non-IgE-mediated allergic diseases

Allergic diseases are mainly caused by the presence of IgE antibodies recognizing allergens. The IgE-

based pathogenic mechanism beside the allergy symptoms is not always demonstrable and the presence of an allergic disease does not always match any IgE sensitization to any allergenic source [53]. This has been reported for both cutaneous and respiratory symptoms, and such clinical conditions have usually been defined as “non-allergic”, “intrinsic”, “idiopathic”, “vasomotor”. More recently the “non-IgE mediated” definition has been adopted for all these forms as a part of a revised allergic disease nomenclature [54]. Several papers which addressed and reviewed clinical [55–58] and immunopathological features [59–64] of IgE and non-IgE-mediated forms at different organ levels have underlined that much more similarities rather than differences can be found between these two conditions [65,66]. Nevertheless, the distribution of the IgE- and the non-IgE-mediated diseases changes according to age and gender of the cohorts examined [20,67–71].

## Role, of IgG autoantibodies against the $\alpha$ -chain of the high affinity IgE receptor

A recent study showed that urticaria, rhinitis and asthma, due to non-IgE-mediated mast cell activation, could depend on the presence of one or more histamine releasing factors that are present in patients’ sera [53]. The autologous serum skin test (ASST) applied to these patients showed a positive reactivity in either the chronic cutaneous disease or in the respiratory ones, or in a combination of the two [53]. Several independent groups reported that in subjects with chronic urticaria the disease is caused, and the positive ASST is determined, by the presence of IgG autoantibodies directed toward the  $\alpha$ -chain of the high affinity IgE receptor (Fc $\epsilon$ RI $\alpha$ ) [72–78]. These autoantibodies lead chronic urticaria to be classified among the autoimmune disorders [79–81]. A possible role of anti-Fc $\epsilon$ RI $\alpha$  autoantibodies in non-IgE-mediated respiratory symptoms has been suggested [82] and preliminary data on their presence have been reported for non-allergic asthma patients [83]. These findings would suggest a unifying pathogenic role for anti-Fc $\epsilon$ RI $\alpha$  in both cutaneous and respiratory allergy-like non-IgE-mediated diseases [53]. Furthermore, anti-Fc $\epsilon$ RI $\alpha$  have been detected in sera from patients associating an atopic respiratory disorder to chronic urticaria, in healthy control, and in

very young infants [84]. In all cases a histamine-release activity has been demonstrated [85–88]. These in vitro findings match the recorded positive ASST results in several subsets of patients affected by cutaneous and respiratory allergy symptoms, either non-IgE-mediated or overlapped to an IgE-mediated mechanism [53]. In the same study healthy adult subjects and affected children were recorded positive to the ASST [53]. Finally, recombinant immunoglobulins anti-Fc $\epsilon$ RI $\alpha$  have been cloned from the mRNA obtained from tonsil lymphoid tissue from 3 to 6 years old infants [85,86,88]. Authors showed how these antibodies are fully functional in determining mast cell activation.

### Molecular mimicry between tetanus toxoid and the $\alpha$ -chain of the high affinity IgE receptor

Horn et al. [84] have detected IgG anti-Fc $\epsilon$ RI $\alpha$  in commercial intravenous immunoglobulin preparation. Recombinant  $\alpha$ -chain affinity chromatography

produced an anti-Fc $\epsilon$ RI $\alpha$ -enriched IgG preparation. Surprisingly, unless purified using the  $\alpha$ -chain, such specific IgG were capable to bind the tetanus toxoid (TT) used for affinity chromatography control purposes, but not the diphtheria toxoid. The affinity of the anti-Fc $\epsilon$ RI $\alpha$  IgG-enriched fraction was higher for TT than for the recombinant  $\alpha$ -chain used for the purification procedure, suggesting a potential priming role of TT. An ELISA inhibition experiment clearly showed the cross reactivity between TT and the  $\alpha$ -chain, suggesting a molecular mimicry of epitopes present in the TT molecule and epitopes of the  $\alpha$ -chain. Anti-Fc $\epsilon$ RI $\alpha$  were then detected in newborns, in vaccinated infants, and in normal healthy subject [84,86,88].

An in vivo test has been carried out using commercial intramuscular TT-IgG preparations (Tetabulin 500 UI, Immune AG, Vienna, Austria). Eleven volunteers, either affected by allergy symptoms (eight) or healthy (three), gave their informed consent to the test. All reacted strongly to the intradermal injection of the undiluted preparations, whereas all the control tests were negative in all. Fig. 1(a) shows an example of the reactivity to the

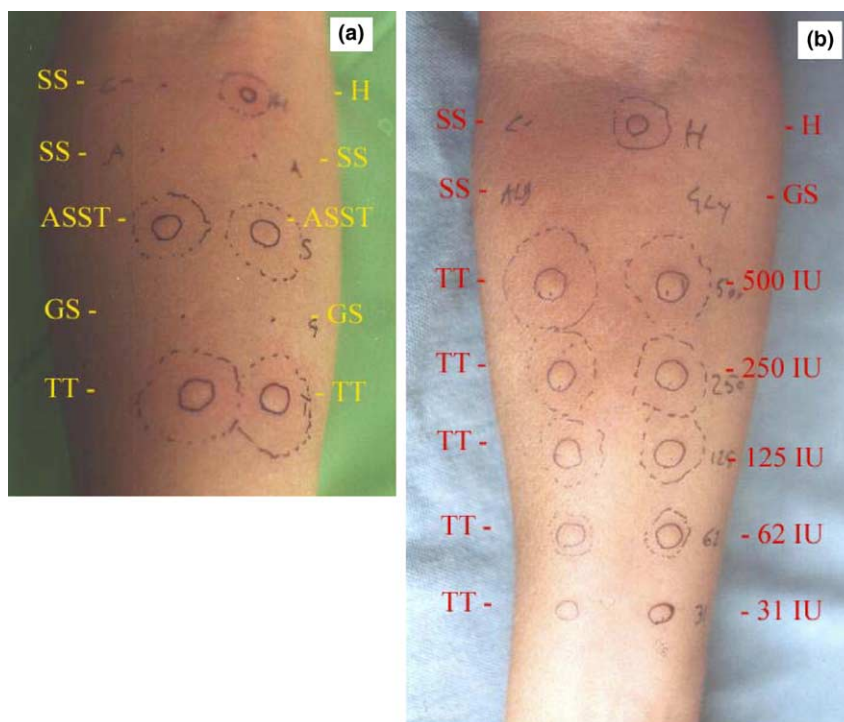


**Figure 1** (a) Autologous serum skin test (ASST) and intradermal test with tetanus toxoid (TT) human IgG enriched preparation for intra-muscular administration in a patient with non-IgE-mediated allergy-like respiratory disease. ASST and TT intradermal test have been performed as reported in reference [53]. Histamine (H), saline solution (SS), and glycine solution (GS) have been used for positive and negative control purposes. TT has been tested at the highest concentration of 500 international units. (b) Twofold dilution of TT human IgG enriched preparation for intramuscular administration used for intradermal test in a healthy control subject. TT intradermal test has been performed as reported in [53]. Dilution has been made with saline solution. TT concentrations are expressed in international units (IU). Histamine, saline solution, and glycine solution have been used for positive and negative control purposes.

TT-IgG preparation of a patient with non-IgE-mediated allergy symptoms having a positive ASST. Fig. 1(b) shows a twofold dilution duplicate testing of the same preparation in a healthy volunteer. Similar dose-response curve was obtained in an allergic subject. These results seem to confirm the above reported *in vitro* findings in favor of the potential histamine releasing activity of TT-IgG preparations.

## Hypothesis

All the data and observations reported above would lead to hypothesize a causative relationship between the TT vaccination and the presence of anti-Fc $\epsilon$ RI $\alpha$  IgG in sera of a large number of subjects. This is also suggested by the healthy subject *in vitro* reactivity [85–88] and by the high number of ASST responders, particularly among children and young infants [53]. This hypothesis would link the worldwide population-based compulsory TT vaccination with allergy symptoms caused by the direct activation of mast cells by means of IgG anti-Fc $\epsilon$ RI $\alpha$  and with the increased prevalence of allergic disorders.

## Epidemiology of tetanus toxoid vaccination and allergic diseases

The relationship between vaccinations and allergic diseases is a recurrent matter of debate [89,90]. Due to co-vaccination schedules, this issue is often explored as the overall impact of vaccines on the prevalence of allergic diseases [91,92]. Some retrospective or cross-sectional epidemiological studies seem to exclude a relationship between TT vaccination and allergic diseases [89,92,93], whereas the following reports seem to suggest a causative role. A study based on the third NHANES survey concluded that TT vaccination increase the risk of allergies and allergy-related respiratory symptoms [94]. Kemp *et al.* [95] reported the absence of asthma in 23 non-vaccinated subjects, whereas Odent and Culpin [96] found only four subjects having asthma among 214 non-vaccinated children belonging to families following an antroposophic life-style [97]. An interesting study has been reported by Yoneyama *et al.* [98]. They comparatively evaluated the presence of allergy symptoms in a small but highly homogeneous

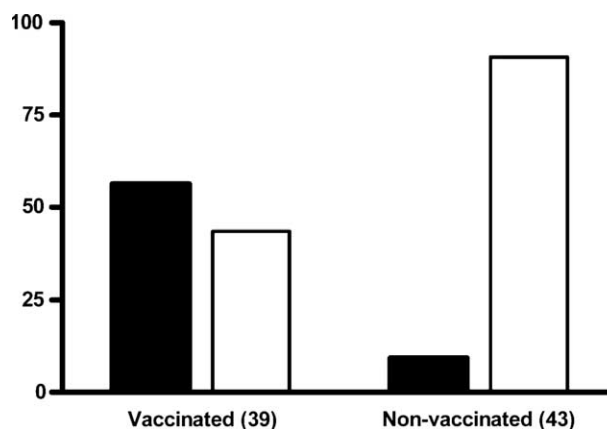


**Figure 2** Overall prevalence of at least one symptom related to bronchial asthma, rhinitis and atopic dermatitis in a cohort of 82 subjects aged 0–3 years old [98]. Black bar = presence of symptoms, white bar = absence of symptoms.

cohort of 82 subjects aged 0–3 years old, 43 of them (52.4%) lacking TT and diphtheria/pertussis vaccinations. Fig. 2 reports the overall comparative results between the two groups. A remarkably low prevalence of allergy symptoms was recorded in the non-vaccinated infant subset.

## Tetanus toxoid vaccination coverage

Mandatory TT vaccination has been introduced at variable time points from country to country [99–101]. The present vaccination coverage vary greatly in different geographical regions [91] and in the number of recommended initial doses and boosters [102–104]. Unless mandatory, coverage varies within the same country for either low coverage levels [100,102,105,106] or hyperimmunization [107]. To be noticed that reported distribution gradients of TT vaccination coverage are very similar either to those reported for markers of infections [108] or to still unknown factors having a protective effect for allergies [109,110]. A trend to a more complete coverage of the whole population has been reached during the time [103,111–113], although some disparities still remain [105,106]. More recently a slight reduction in TT vaccination coverage has been caused by refusing compulsory vaccinations of newborns not on medical bases [114]. The opposite trend to hyperimmunize has been recorded in the past and the need to avoid unnecessary boosting doses causing hypersensitivity reactions has been stressed [112].

## The biological link between tetanus toxoid vaccination and both allergy symptoms and allergic disease prevalence

Assuming the hypothesis that TT vaccination actively induces the production of anti-Fc $\epsilon$ RI $\alpha$  IgG, in a certain proportion of subjects the immunization could be followed by the activation of mast cell with two distinct effects: mediator release and Th2 cytokine production. Mediator release from activated mast cells may cause an immediate induction of allergy-like symptoms in absence of an IgE-mediated mechanism. This is a highly relevant effect as the first course of TT injections is generally scheduled within the first six months of life and there is a general agreement that almost all the children affected by allergy symptoms in the first 3–4 years of life have a non-IgE-mediated mechanism behind [23,53,71], and the large majority starts with symptoms very early in life [53,70]. Moreover, the presence of anti-Fc $\epsilon$ RI $\alpha$  IgG as a systemic phenomenon activating mast cells in different organs would help to explain the comorbidity for different forms of allergic symptoms in the same subject [53,115–117].

Several factors could interact in determining the presence/absence of symptoms at different organ levels and at different time point [86,88,118], causing a variable degree of inflammation in affected tissues. For instance, minimal persistent inflammation could be a sub-clinical or pre-clinical condition in apparently healthy subjects bearing anti-Fc $\epsilon$ RI $\alpha$  IgG [117,119–121]. This condition has already been described for IgE-mediated diseases [122,123]. A variability of the clinical picture could be also due to mast cell physiopathologic heterogeneity at different organ level [124–126], including non-releaser basophils and mast cells [127]. Other physiopathologic conditions could enhance the persistence of symptoms triggered by the anti-Fc $\epsilon$ RI $\alpha$  IgG [128].

Concurrent infections, drug intake, environmental and physical stimuli may cause an exacerbation of symptoms via well-defined or still unknown mechanisms [129–134]. The Th2 cytokine production, the second effect generated by having IgG anti-Fc $\epsilon$ RI $\alpha$  related to TT vaccination, would result in a very early induction of an allergic inflammation of tissues generally involved in allergic diseases. The presence of this condition has been fully documented [135,136] and has been linked to the increased risk of developing an IgE sensitization and the subsequent IgE-mediated diseases [137]. The low genetic propensity to develop IgE-

mediated diseases among the general population would lead this process to take several years to be effective in causing an IgE-mediated sensitization. This time course of IgE sensitization has been reported in several epidemiological studies showing an increase of IgE-mediated diseases mainly after age four or five [23,71]. The two mechanisms may or may not co-exist in older children and adults and may lead to an overlapping IgE- and non-IgE-mediated disease [23,53,57,71,84].

A model to understand the effect of this long lasting mast cell stimulation is provided by HIV-1 infection. Marone et al. [138,139] showed how the gp120 HIV-1-derived molecule may activate mast cells by bridging IgE molecules on the mast cell surface. The following histamine release and the Th2 cytokine production should lead to the well known high prevalence of allergy symptoms in HIV affected patients and to an elevation of the total IgE in otherwise immunodeficient subjects [140]. An IgE elevation can be recorded even in subjects with non-IgE-mediated allergy-like symptoms [141–143]. Fig. 3 reports the comparative distribution of total IgE (Radim, Pomezia, Italy) measured in the IgE- and non-IgE-mediated respiratory subsets as defined in a previous study [53]. Though the higher mean total IgE value in subjects with an IgE-mediated disease was expected and statistically differs from the counterpart,  $\approx 18\%$  of the subjects with non-IgE-mediated mechanism have total IgE values above the average value of the IgE-mediated subset, and 26.7% above 100 IU/ml.

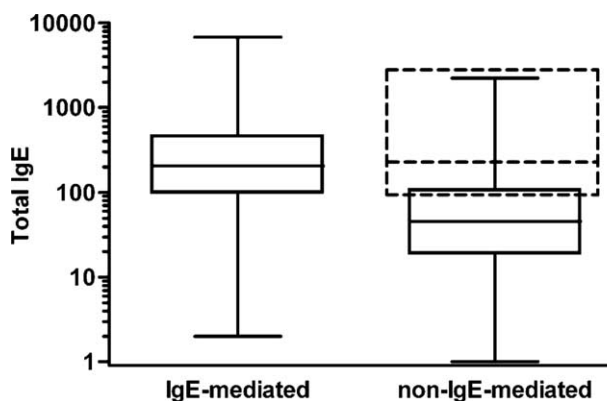


**Figure 3** Distribution of total IgE values in subjects affected by IgE- and non-IgE-mediated respiratory diseases. The smaller dashed box indicates 18% of subjects having total IgE values above the average value of subjects with an IgE-mediated disease. The larger dashed box indicates 26.7% of subjects having total IgE values above 100 IU/ml. Subsets were defined as reported in [53]. Statistics: Mann–Whitney test, IgE-mediated vs. non-IgE-mediated =  $p < 0.0001$ .

## Mother to child transfer

Several studies report the possible role of the physiologically Th2-oriented uterine environment as a risk factor for developing an allergic disease [144,145]. The *trans*-placental transfer of factors inducing allergy could include immunoglobulins that are physiologically transferred from the mother to the child [146–148]. This transfer could occur also for anti-Fc $\epsilon$ RI $\alpha$  IgG and lead to a very early start of the Th2-related events described above [45,136]. Furthermore, IgG could be transferred to the lactating infant through the mother's milk, consistently with the recently reported contradictory evidence of a facilitating effect of breast feeding on asthma symptoms [149–152]. This mother-to-child transfer of the disease should be considered a phenomenon appeared in the last 10–20 years when a new generation is born from TT vaccinated mothers. The impact of this transfer could be more relevant if the higher prevalence of allergy symptoms in female adults is considered [53,70].

Epidemiologically, the vertical transmission of anti-Fc $\epsilon$ RI $\alpha$  IgG could explain why the presence of maternal allergic diseases appears to be a greater risk factor when compared to paternal one [151–158]. Early symptoms in children without familiar risk factors may be explained on the same basis [24] and familiar clustering of the allergic diseases could be interpreted in the same way [159].

## Persistence of symptoms during late infancy and adulthood

Persistence of symptoms by the passive transfer of antibodies via the mother milk or even through a priming effect on the child could also be speculated [160–162], but the active priming role of TT vaccination in the same time period of early infancy must be taken into account. Maintenance of the symptoms by an established immune mechanism [163] could thus explain both perinatal symptoms and their persistence to a later age [18,19,164,165].

In the last 30 years there could also be established a long lasting effect of what happens during childhood and the appearance (or re-appearance) of symptoms in adulthood [20,21,166–169]. This would occur to a different extent between males and females [53,69–71]. The cohort effect reported to be active since early sixties and mainly

related to environmental factors rather than genetic ones could be explained as well [13, 170–172].

## Allergy symptoms as a Th2 phenotype of an underlying autoimmune mechanism

The conflicting evidence between the co-existence of Th1- and Th2-driven diseases in the same subject has been reported above. A study on a population of 1211 subjects belonging to a respiratory cohort has been performed testing for the presence of anti-thyroid IgG autoantibodies. Fig. 4 reports the comparative prevalence in different subsets of adult patients selected on the basis of previously reported criteria [53]. There is evidence that anti-thyroid autoantibodies may be present in subjects with IgE-mediated disorders, and that their prevalence increases in females within the cohort of non-IgE-mediated diseases.

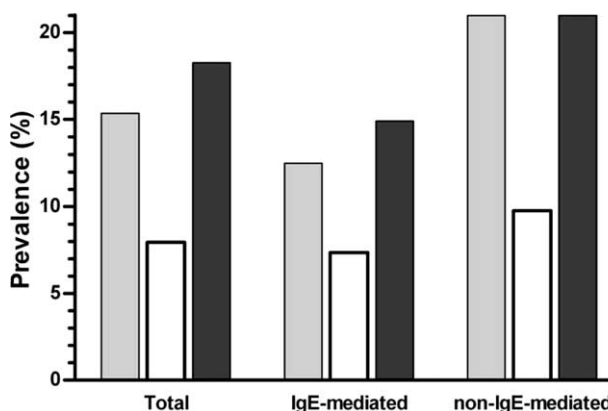


**Figure 4** Prevalence of anti-thyroid autoantibodies in 1211 adult subjects with IgE- and non-IgE-mediated respiratory diseases. Antibodies anti-thyroid peroxidase and anti-thyroglobulin were determined using a commercial kit. A positive result was considered when at least one of the two tests was recorded positive. Subsets were defined as reported in [53]. Grey bar = all subjects, white bar = male, black bar = female, total correspond to the entire respiratory cohort ( $n = 1211$ ; male = 340; female = 871); IgE-mediated respiratory disease subset ( $n = 816$ ; male = 258; female = 558); non-IgE-mediated respiratory disease subset ( $n = 395$ ; male = 82; female = 313). Statistics: Fisher's Exact test, total male vs. total female =  $p < 0.0001$ , total IgE-mediated vs. total non-IgE-mediated =  $p < 0.0001$ , male IgE-mediated vs. male non-IgE-mediated = n.s.s., female IgE-mediated vs. female non-IgE-mediated =  $p < 0.0007$ , male IgE-mediated vs. female IgE-mediated =  $p < 0.002$ , male non-IgE-mediated vs. female non-IgE-mediated =  $p < 0.004$ .

Thus, the reported increasing prevalence of atopic diseases simply parallel the increase of autoimmune disorders as part of the same group of diseases [41–43,173]. This would also lead to reassess the relationship between vaccination and autoimmune disorders, that has been reported in some cases [90,174].

## Conclusions

In the view of the present hypothesis the overall scenario of the epidemiology of allergic diseases could be differently considered. The reported finding of a molecular mimicry between TT and the Fc $\epsilon$ RI $\alpha$  would suggest that epidemiological studies addressing the relationship between vaccination and allergy prevalence should be based on a more appropriate study design, focusing on single immunization procedure, and possibly having some molecular background studies. It should be considered that the development of an IgG response to a defined epitope could be limited to a part of the vaccine recipients.

It can be speculated that the inability of tetanus toxin to exert a natural immunity during tetanus infection [175] did not allow the discovering of the immunological relationship between the  $\alpha$ -chain and epitopes on the toxin itself. Failure to detect the immunochemical/structural relationship could be also due to hidden epitopes of the tetanus toxin molecule that could be exposed during the denaturing process to obtain the TT or to new epitopes that could be generated by the same procedure. From a prevention point of view, birth could be not too late for starting primary prevention but more in depth studies should be carried out on breast feeding role [176]. A control of the phenomenon could be achieved by delaying the TT scheduled vaccination after age six [164] or by using modified TT molecules [177,178] or different routes of administration [179]. Time and type of other immunizing procedures could also counterbalance the effect of TT vaccination. This could be the case of BCG vaccination if administered early in life [180,181]. Moreover, novel therapeutic approaches could be considered in established anti-Fc $\epsilon$ RI $\alpha$ -dependent diseases by blocking the IgE receptor [182].

In the case of the present hypothesis would be proven true, autoimmune diseases should be considered the relevant problem in the epidemiological increasing trend. A relevant part of the currently classified "allergic diseases" would only be the clinical phenotype of an underlying autoimmune disorder [183–185].

Studies should be addressed to understand the impact of no TT vaccination. Due to the severity of tetanus infection [114,186] carefully designed intervention studies should be carried out. Nevertheless, the non-airborne nature of tetanus transmission should also be taken into account. Monitoring of the adverse vaccination events should also consider the long lasting immunological effect of compulsory procedures [187,188]. Finally, the availability of a test [88] for pre-clinical screening as for diabetes and thyroiditis [189] could allow us to predict or to put an early diagnosis of anti-Fc $\epsilon$ -RI $\alpha$ -mediated disease in at-risk subjects.

## Acknowledgements

I thank Dr. Hiroshi Yoneyama for kindly providing me the English translation of his paper.

Testing for total IgE and anti-thyroid autoantibodies has been supported by an internal funding of the Regional Branch of the Italian National Health Service.

## References

- [1] Dotterud LK, Odland JO, Falk ES. Atopic diseases among schoolchildren in Nikel, Russia, an Arctic area with heavy air pollution. *Acta Derm Venereol* 2001;81:198–201.
- [2] Esamai F, Ayaya S, Nyandiko W. Prevalence of asthma, allergic rhinitis and dermatitis in primary school children in Uasin Gishu district, Kenya. *East Afr Med J* 2002;79:514–8.
- [3] Hailu S, Tessema T, Silverman M. Prevalence of symptoms of asthma and allergies in schoolchildren in Gondar town and its vicinity, northwest Ethiopia. *Pediatr Pulmonol* 2003;35:427–32.
- [4] Olivieri M, Verlato G, Corsico A, Lo CV, Bugiani M, Marinoni A, et al. Prevalence and features of allergic rhinitis in Italy. *Allergy* 2002;57:600–6.
- [5] Soriano JB, Kiri VA, Maier WC, Strachan D. Increasing prevalence of asthma in UK primary care during the 1990s. *Int J Tuberc Lung Dis* 2003;7:415–21.
- [6] Weiland SK, von Mutius E, Hirsch T, Duhme H, Fritzsche C, Werner B, et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification. *Eur Respir J* 1999;14:862–70.
- [7] Wickman M, Meln E, Berlind N, Nordvall SL, Almquist C, Kull I, et al. Strategies for preventing wheezing and asthma in small children. *Allergy* 2003;58:742–7.
- [8] Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999;103:125–38.
- [9] Wilson H, Adams RJ, Appleton SL, Hugo G, Wilkinson D, Hiller J, et al. Prevalence of asthma and asthma action plans in South Australia: population surveys from 1990 to 2001. *Med J Aust* 2003;178:483–5.
- [10] Wong GW, Hui DS, Chan HH, Fok TF, Leung R, Zhong NS, et al. Prevalence of respiratory and atopic disorders in Chinese schoolchildren. *Clin Exp Allergy* 2001;31:1225–31.

- [11] Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson HR, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997;8:161–76.
- [12] Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998;351:1225–32.
- [13] Krause T, Koch A, Friborg J, Poulsen L, Kristensen B, Melbye M. Frequency of atopy in the Arctic in 1987 and 1998. *Lancet* 2002;360:691.
- [14] Mannino DM, Homa DM, Akinbanm LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma-United States, 1980–1999. *MMWR Surveill Summ* 2002;51:1–13.
- [15] Maziak W, Behrens T, Brasky TM, Duhme H, Rzehak P, Weiland SK, et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Munster, Germany. *Allergy* 2003;58:572–9.
- [16] Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Increasing prevalence of specific IgE to aeroallergens in an adult population: two cross-sectional surveys 8 years apart: the copenhagen allergy study. *J Allergy Clin Immunol* 2000;106:247–52.
- [17] Lau S, Nickel R, Niggemann B, Gruber C, Sommerfeld C, Illi S, et al. The development of childhood asthma: lessons from the German Multicentre Allergy Study (MAS). *Paediatr Respir Rev* 2002;3:265.
- [18] Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The group health medical associates. *New Engl J Med* 1995;332:133–8.
- [19] von Mutius E, Weiland SK, Fritzsch C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998;351:862–6.
- [20] De Marco R, Locatelli F, Cerveri I, Bugiani M, Marinoni A, Giammanco G. Incidence and remission of asthma: a retrospective study on the natural history of asthma in Italy. *J Allergy Clin Immunol* 2002;110:228–35.
- [21] Upton MN, McConnachie A, McSharry C, Hart CL, Smith GD, Gillis CR, et al. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ* 2000;321:88–92.
- [22] Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? *Lancet* 2001;357:1821–5.
- [23] Wahn U, von Mutius E. Childhood risk factors for atopy and the importance of early intervention. *J Allergy Clin Immunol* 2001;107:567–74.
- [24] Bergmann RL, Edenharter G, Bergmann KE, Guggenmoos-Holzmann I, Forster J, Bauer CP, et al. Predictability of early atopy by cord blood-IgE and parental history. *Clin Exp Allergy* 1997;27:752–60.
- [25] Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *New Engl J Med* 2000;343:538–43.
- [26] Bremner SA, Carey IM, De Wilde S, Richards N, Maier WC, Hilton SR, et al. Early-life exposure to antibacterials and the subsequent development of hayfever in childhood in the UK: case-control studies using the General Practice Research Database and the Doctors' Independent Network. *Clin Exp Allergy* 2003;33:1518–25.
- [27] Celedon JC, Wright RJ, Litonjua AA, Sredl D, Ryan L, Weiss ST, et al. Day care attendance in early life, maternal history of asthma, and asthma at the age of 6 years. *Am J Respir Crit Care Med* 2003;167:1239–43.
- [28] De Marco R, Poli A, Ferrari M, Accordini S, Giammanco G, Bugiani M, et al. The impact of climate and traffic-related NO<sub>2</sub> on the prevalence of asthma and allergic rhinitis in Italy. *Clin Exp Allergy* 2002;32:1405–12.
- [29] Dioun AF, Harris SK, Hibberd PL. Is maternal age at delivery related to childhood food allergy? *Pediatr Allergy Immunol* 2003;14:307–11.
- [30] Kramer U, Heinrich J, Wjst M, Wichmann HE. Age of entry to day nursery and allergy in later childhood. *Lancet* 1999;353:450–4.
- [31] Peterson B, Saxon A. Global increases in allergic respiratory disease: the possible role of diesel exhaust particles. *Ann Allergy Asthma Immunol* 1996;77:263–8.
- [32] Smith JM. Asthma and atopy as diseases of unknown cause. A viral hypothesis possibly explaining the epidemiologic association of the atopic diseases and various forms of asthma. *Ann Allergy* 1994;72:156–62.
- [33] von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;149:358–64.
- [34] Xu B, Jarvelin MR, Pekkanen J. Prenatal factors and occurrence of rhinitis and eczema among offspring. *Allergy* 1999;54:829–36.
- [35] Hopkin JM. Mechanisms of enhanced prevalence of asthma and atopy in developed countries. *Curr Opin Immunol* 1997;9:788–92.
- [36] Kemp A, Bjorksten B. Immune deviation and the hygiene hypothesis: a review of the epidemiological evidence. *Pediatr Allergy Immunol* 2003;14:74–80.
- [37] Matricardi PM. Infections preventing atopy: facts and new questions. *Allergy* 1997;52:879–82.
- [38] Matricardi PM, Ronchetti R. Are infections protecting from atopy? *Curr Opin Allergy Clin Immunol* 2001;1:413–9.
- [39] Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax* 2000;55(Suppl 1):S2–S10.
- [40] Tournoy KG, Kips JC, Pauwels RA. Is Th1 the solution for Th2 in asthma? *Clin Exp Allergy* 2002;32:17–29.
- [41] Kero J, Gissler M, Hemminki E, Isolauri E. Could TH1 and TH2 diseases coexist? Evaluation of asthma incidence in children with coeliac disease, type 1 diabetes, or rheumatoid arthritis: a register study. *J Allergy Clin Immunol* 2001;108:781–3.
- [42] Stene LC, Nafstad P. Relation between occurrence of type 1 diabetes and asthma. *Lancet* 2001;357:607–8.
- [43] Sheikh A, Smeeth L, Hubbard R. There is no evidence of an inverse relationship between TH2-mediated atopy and TH1-mediated autoimmune disorders: lack of support for the hygiene hypothesis. *J Allergy Clin Immunol* 2003;111:131–5.
- [44] Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *New Engl J Med* 2002;347:911–20.
- [45] Zinkernagel RM. On natural and artificial vaccinations. *Ann Rev Immunol* 2003;21:515–46.
- [46] Horner AA, Raz E. Do microbes influence the pathogenesis of allergic diseases? Building the case for toll-like receptor ligands. *Curr Opin Immunol* 2003;15:614–9.
- [47] Matricardi PM, Yazdanbakhsh M. Mycobacteria and atopy, 6 years later: a fascinating, still unfinished, business. *Clin Exp Allergy* 2003;33:717–20.
- [48] Rottem M, Gershwin ME, Shoenfeld Y. Allergic disease and autoimmune effectors pathways. *Dev Immunol* 2003;9:161–7.

- [49] Umetsu DT, McIntire JJ, Akbari O, Macaubas C, Dekruyff RH. Asthma: an epidemic of dysregulated immunity. *Nat Immunol* 2002;3:715–20.
- [50] Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat Rev Immunol* 2001;1:69–75.
- [51] Kikuchi Y, Fann T, Kaplan AP. Antithyroid antibodies in chronic urticaria and angioedema. *J Allergy Clin Immunol* 2003;112:218.
- [52] Simpson CR, Anderson WJA, Helms PJ, Taylor MW, Watson L, Prescott GJ, et al. Coincidence of immune-mediated diseases driven by Th1 and Th2 subsets suggests a common aetiology. A population-based study using computerized general practice data. *Clin Exp Allergy* 2002;32:37–42.
- [53] Mari A. Allergy-like asthma and rhinitis. A cross-sectional survey of a respiratory cohort and a diagnostic approach using the autologous serum skin test. *Int Arch Allergy Immunol* 2004;133:29–39.
- [54] Johansson SG, Hourihane JO, Bousquet J, Bmijnzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813–24.
- [55] Fokkens WJ. Thoughts on the pathophysiology of nonallergic rhinitis. *Curr Allergy Asthma Rep* 2002;2:203–9.
- [56] Romanet-Manent S, Charpin D, Magnan A, Lanteaume A, Vervloet D. Allergic vs nonallergic asthma: what makes the difference? *Allergy* 2002;57:607–13.
- [57] Settipane RA, Lieberman P. Update on nonallergic rhinitis. *Ann Allergy Asthma Immunol* 2001;86:494–508.
- [58] Settipane RA. Demographics and epidemiology of allergic and nonallergic rhinitis. *Allergy Asthma Proc* 2001;22:185–9.
- [59] Ferrer M, Luquin E, Sanchez-Ibarrola A, Moreno C, Sanz ML, Kaplan AP. Secretion of cytokines, histamine and leukotrienes in chronic urticaria. *Int Arch Allergy Immunol* 2002;129:254–60.
- [60] Ghaffar O, Durham SR, Al Ghamdi K, Wright E, Small P, Frenkiel S, et al. Expression of IgE heavy chain transcripts in the sinus mucosa of atopic and nonatopic patients with chronic sinusitis. *Am J Respir Cell Mol Biol* 1998;18:706–11.
- [61] Humbert M, Durham SR, Ying S, Kimmitt P, Barkans J, Assoufi B, et al. IL-4 and IL-5 mRNA and protein in bronchial biopsies from patients with atopic and nonatopic asthma: evidence against “intrinsic” asthma being a distinct immunopathologic entity. *Am J Respir Crit Care Med* 1996;154:1497–504.
- [62] Powe DG, Hiskisson RS, Carney AS, Tenkins D, Jones NS. Idiopathic and allergic rhinitis show a similar inflammatory response. *Clin Otolaryngol* 2000;25:570–6.
- [63] Riccio AM, Tosca MA, Cosentino C, Pallestrini E, Ameli F, Canonica GW, et al. Cytokine pattern in allergic and non-allergic chronic rhinosinusitis in asthmatic children. *Clin Exp Allergy* 2002;32:422–6.
- [64] Ying S, Kikuchi Y, Meng Q, Kay AB, Kaplan AP. TH1/TH2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic urticaria: comparison with the allergen-induced late-phase cutaneous reaction. *J Allergy Clin Immunol* 2002;109:694–700.
- [65] Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol* 2003;112:252–62.
- [66] Humbert M, Menz G, Ying S, Corrigan CJ, Robinson DS, Durham SR, et al. The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. *Immunol Today* 1999;20:528–33.
- [67] Court CS, Cook DG, Strachan DP. Comparative epidemiology of atopic and non-atopic wheeze and diagnosed asthma in a national sample of English adults. *Thorax* 2002;57:951–7.
- [68] Henriksen AH, Holmen TL, Bjermer L. Gender differences in asthma prevalence may depend on how asthma is defined. *Respir Med* 2003;97:491–7.
- [69] Nicolai T, Pereszlenyiova-Bliznakova L, Illi S, Reinhardt D, von Mutius E. Longitudinal follow-up of the changing gender ratio in asthma from childhood to adulthood: role of delayed manifestation in girls. *Pediatr Allergy Immunol* 2003;14:280–3.
- [70] Schatz M, Camargo Jr CA. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Ann Allergy Asthma Immunol* 2003;91:553–8.
- [71] Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson children’s respiratory study: 1980 to present. *J Allergy Clin Immunol* 2003;111:661–75.
- [72] Ferrer M, Kinet JP, Kaplan AP. Comparative studies of functional and binding assays for IgG anti-Fc( $\epsilon$ )RI $\alpha$  ( $\alpha$ -subunit) in chronic urticaria. *J Allergy Clin Immunol* 1998;101:672–6.
- [73] Fiebiger E, Stingl G, Maurer D. Anti-IgE and anti-Fc $\epsilon$ RI autoantibodies in clinical allergy. *Curr Opin Immunol* 1996;8:784–9.
- [74] Greaves MW. Chronic idiopathic urticaria. *Curr Opin Allergy Clin Immunol* 2003;3:363–8.
- [75] Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *New Engl J Med* 1993;328:1599–604.
- [76] Kaplan AP. Chronic urticaria and angioedema. *New Engl J Med* 2002;346:175–9.
- [77] Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol* 2001;107:1056–62.
- [78] Sabroe RA, Francis DM, Barr RM, Black AK, Greaves MW. Anti-Fc( $\epsilon$ )RI auto antibodies and basophil histamine releasability in chronic idiopathic urticaria. *J Allergy Clin Immunol* 1998;102:651–8.
- [79] Confino-Cohen R, Aharoni D, Goldberg A, Gurevitch I, Buchs A, Weiss M, et al. Evidence for aberrant regulation of the p21Ras pathway in PBMCs of patients with chronic idiopathic urticaria. *J Allergy Clin Immunol* 2002;109:349–56.
- [80] Greaves M. Autoimmune urticaria. *Clin Rev Allergy Immunol* 2002;23:171–83.
- [81] Tong LJ, Balakrishnan G, Kochan JP, Kinet JP, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997;99:461–5.
- [82] Marone G, Spadaro G, Palumbo C, Condorelli G. The anti-IgE/anti-Fc $\epsilon$ RI $\alpha$  autoantibody network in allergic and autoimmune diseases. *Clin Exp Allergy* 1999;29:17–27.
- [83] Jouvin MH, Kinet JP. Expression and function of the high-affinity receptor for IgE in asthma. In: Marone G, Austen KF, Holgate ST, Kay AB, Lichtenstein LM, editors. *Asthma and allergic diseases*. London: Academic Press; 1998. p. 59–74.
- [84] Horn MP, Gerster T, Ochsenberger B, Derer T, Kricek F, Jouvin MH, et al. Human anti-Fc $\epsilon$ RI $\alpha$  autoantibodies isolated from healthy donors cross-react with tetanus toxoid. *Eur J Immunol* 1999;29:1139–48.
- [85] Stadler BM, Miescher S, Horn M, Pachlopnik J, Stadler M, Kricek F, et al. Allergic manifestations as the results of a conditional autoimmune response. *Int Arch Allergy Immunol* 2001;124:411–3.
- [86] Horn MP, Pachlopnik JM, Vogel M, Dahinden M, Wurm F, Stadler BM, et al. Conditional autoimmunity mediated by human natural anti-Fc( $\epsilon$ )RI $\alpha$  autoantibodies? *FASEB J* 2001;15:2268–74.
- [87] Miescher SM, Horn MP, Pachlopnik JM, Baldi L, Vogel M, Stadler BM. Natural anti-Fc( $\epsilon$ )RI $\alpha$  autoantibodies isolated

- from healthy donors and chronic idiopathic urticaria patients reveal a restricted repertoire and autoreactivity on human basophils. *Hum Antibodies* 2001;10:119–26.
- [88] Pachlopnik JM, Horn MP, Fux M, Dahinden M, Mandallaz M, Schneeberger D, et al. Natural anti-Fc $\epsilon$ R1 $\alpha$  autoantibodies may interfere with diagnostic tests for autoimmune urticaria. *J Autoimmun* 2004;22:43–51.
- [89] Gruber C, Nilsson L, Bjorksten B. Do early childhood immunizations influence the development of atopy and do they cause allergic reactions? *Pediatr Allergy Immunol* 2001;12:296–311.
- [90] Offit PA, Hackett CJ. Addressing parents' concerns: do vaccines cause allergic or autoimmune diseases? *Pediatrics* 2003;111:653–9.
- [91] Anderson HR, Poloniecki JD, Strachan DP, Beasley R, Bjorksten B, Asher MI. Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. *Am J Public Health* 2001;91:1126–9.
- [92] Gruber C, Illi S, Lau S, Nickel R, Forster J, Kamin W, et al. Transient suppression of atopy in early childhood is associated with high vaccination coverage. *Pediatrics* 2003;111: e282–8.
- [93] DeStefano F, Gu D, Kramarz P, Truman BI, Iademaro MF, Mullooly JP, et al. Childhood vaccinations and risk of asthma. *Pediatr Infect Dis J* 2002;21:498–504.
- [94] Hurwitz EL, Morgenstern H. Effects of diphtheria-tetanus-pertussis or tetanus vaccination on allergies and allergy-related respiratory symptoms among children and adolescents in the United States. *J Manipulative Physiol Ther* 2000;23:81–90.
- [95] Kemp T, Pearce N, Fitzharris P, Crane J, Fergusson D, St GI, et al. Is infant immunization a risk factor for childhood asthma or allergy? *Epidemiology* 1997;8:678–80.
- [96] Odent M, Culpin E. Effect of immunisation status on asthma prevalence. *Lancet* 2003;361:434.
- [97] Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. *Lancet* 1999;353:1485–8.
- [98] Yoneyama H, Suzuki M, Fujii K, Odajima Y. The effect of DPT and BCG vaccinations on atopic disorders. *Arerugi* 2000;49:585–92.
- [99] Baker JP, Katz SL. Childhood vaccine development: an overview. *Pediatr Res* 2003.
- [100] Rosmini F, Gentili G, Wirz M, Collotti C, Pana A, Terzi I, et al. Immunity to tetanus among Italians born between 1956 and 1963. *Eur J Epidemiol* 1987;3:302–7.
- [101] Rushdy AA, White JM, Ramsay ME, Crowcroft NS. Tetanus in England and Wales, 1984–2000. *Epidemiol Infect* 2003;130:71–7.
- [102] Ringler M, Gobel G, Most J, Weithaler K. Fully vaccinated children are rare: immunization coverage and seroprevalence in Austrian school children. *Eur J Epidemiol* 2003;18: 161–70.
- [103] Maple PA, Jones CS, Wall EC, Vyse A, Edmunds WJ, Andrews NJ, et al. Immunity to diphtheria and tetanus in England and Wales. *Vaccine* 2000;19:167–73.
- [104] Schauer U, Stemberg F, Rieger CH, Buttner W, Borte M, Schubert S, et al. Levels of antibodies specific to tetanus toxoid, Haemophilus influenzae type b, and pneumococcal capsular polysaccharide in healthy children and adults. *Clin Diagn Lab Immunol* 2003;10:202–7.
- [105] Anon. Increasing immunization coverage. *Pediatrics* 2003; 112:993–6.
- [106] McQuillan GM, Kruszon-Moran D, Deforest A, Chu SY, Wharton M. Serologic immunity to diphtheria and tetanus in the United States. *Ann Int Med* 2002;136:660–6.
- [107] Wirz M, Gentili G, Rosmini F, Collotti C, Pana A, Terzi I, et al. Prevalence of hyperimmunization against tetanus in a national sample of 18–26 year old immune subjects in Italy. *Vaccine* 1987;5:211–4.
- [108] Matricardi PM, Rosmini F, Ferrigno L, Nisini R, Rapicetta M, Chionine P, et al. Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *BMJ* 1997;314: 999–1003.
- [109] Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy* 2000;30: 194–200.
- [110] Riedler J, Braun-Fahrlander C, Eder W, Schreuer M, Waser M, Maisch S, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001;358:1129–33.
- [111] D'Amelio R, Stroffolini T, Wirz M, Biselli R, Matricardi PM, Gentili G, et al. Tetanus immunity among Italians born after the introduction of mandatory vaccination of children. *Vaccine* 1993;11:935–6.
- [112] Gentili G, D'Amelio R, Wirz M, Matricardi PM, Nisini R, Collotti C, et al. Prevalence of hyperimmunization against tetanus in Italians born after the introduction of mandatory vaccination of children with tetanus toxoid in 1968. *Infection* 1993;21:80–2.
- [113] Aue A, Hennig H, Kruger S, Closius B, Kirchner H, Seyfarth M. Immunity against diphtheria and tetanus in German blood donors. *Med Microbiol Immunol (Berl)* 2003;192: 93–7.
- [114] Fair E, Murphy TV, Golaz A, Wharton M. Philosophic objection to vaccination as a risk for tetanus among children younger than 15 years. *Pediatrics* 2002;109:E2.
- [115] Ledford D. Inadequate diagnosis of nonallergic rhinitis: assessing the damage. *Allergy Asthma Proc* 2003;24: 155–62.
- [116] Wraith DC, Goldman M, Lambert PH. Vaccination and autoimmune disease: what is the evidence? *Lancet* 2003; 361:1–8.
- [117] Semper AE, Heron K, Woollard AC, Kochan JP, Friedmann PS, Church MK, et al. Surface expression of Fc $\epsilon$ R1 on Langerhans' cells of clinically uninvolved skin is associated with disease activity in atopic dermatitis, allergic asthma, and rhinitis. *J Allergy Clin Immunol* 2003;112:411–9.
- [118] Stadler BM, Pachlopnik J, Vogel M, Horn M, Dahinden M, Miescher S. Conditional autoantibodies in urticaria patients: a unifying hypothesis. *J Invest Dermatol Symp Proc* 2001;6:150–2.
- [119] Ciprandi G, Buscaglia S, Pesce G, Pronzato C, Ricca V, Parmiani S, et al. Minimal persistent inflammation is present at mucosal level in patients with asymptomatic rhinitis and mite allergy. *J Allergy Clin Immunol* 1995;96: 971–9.
- [120] Ricca V, Landi M, Ferrero P, Bairo A, Tazzer C, Canonica GW, et al. Minimal persistent inflammation is also present in patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;105:54–7.
- [121] Storms WW. Minimal persistent inflammation, an emerging concept in the nature and treatment of allergic rhinitis: the possible role of leukotrienes. *Ann Allergy Asthma Immunol* 2003;91:131–40.
- [122] Bodtger U, Poulsen LK, Mailing HJ. Asymptomatic skin sensitization to birch predicts later development of birch pollen allergy in adults: a 3-year follow-up study. *J Allergy Clin Immunol* 2003;111:149–54.
- [123] Witteman AM, Mulder M, Aalberse RC, Jansen HM, Van Der Zee JS. Bronchial allergen challenge in subjects with low

- levels of allergic sensitization to indoor allergens. *Allergy* 1999;54:366–74.
- [124] Forsythe P, Ennis M. Clinical consequences of mast cell heterogeneity. *Inflamm Res* 2000;49:147–54.
- [125] Gonzales-Espinosa C, Odom S, Olivera A, Hobson JP, Martinez ME, Oliveira-Dos-Santos A, et al. Preferential signaling and induction of allergy-promoting lymphokines upon weak stimulation of the high affinity IgE receptor on mast cells. *J Exp Med* 2003;197: 1453–65.
- [126] Okuda M. Functional heterogeneity of airway mast cells. *Allergy* 1999;54:50–62.
- [127] Kepley CL, Cohen N. Evidence for human mast cell nonreleaser phenotype. *J Allergy Clin Immunol* 2003;112:457–9.
- [128] Brussee JE, Smit HA, Koopman LP, Wijga AH, Kerkhof M, Corver K, et al. Interrupter resistance and wheezing phenotypes at 4 years of age. *Am J Respir Crit Care Med* 2003.
- [129] Asero R, Tedeschi A, Lorini M, Caldironi G, Barocci F. Sera from patients with multiple drug allergy syndrome contain circulating histamine-releasing factors. *Int Arch Allergy Immunol* 2003;131:195–200.
- [130] Barends M, Boelen A, de Rond L, Kwakkel J, Bestebroer T, Dormans J, et al. Influence of respiratory syncytial virus infection on cytokine and inflammatory responses in allergic mice. *Clin Exp Allergy* 2002;32:463–71.
- [131] Braat JP, Mulder PG, Duivenvoorden HJ, Gerth van Wijk R, Rijntjes E, Fokkens WJ. Pollutational and meteorological factors are closely related to complaints of non-allergic, non-infectious perennial rhinitis patients: a time series model. *Clin Exp Allergy* 2002;32:690–7.
- [132] Genovese A, Bouvet JP, Florio G, Lamparter-Schummert B, Björck L, Marone G. Bacterial immunoglobulin super-antigen proteins A and L activate human heart mast cells by interacting with immunoglobulin E. *Infect Immun* 2000;68:5517–24.
- [133] Holt PG, Sly PD. Interactions between RSV infection, asthma, and atopy: unraveling the complexities. *J Exp Med* 2002;196:1271–5.
- [134] Kotamemi-Syrjänen A, Vainionpää R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancy-the first sign of childhood asthma? *J Allergy Clin Immunol* 2003;111:66–71.
- [135] Yabuhara A, Macaubas C, Prescott SL, Venaille TJ, Holt BJ, Habre W, et al. TH2-polarized immunological memory to inhalant allergens in atopics is established during infancy and early childhood. *Clin Exp Allergy* 1997;27: 1261–9.
- [136] Prescott SL, Macaubas C, Holt BJ, Smallacombe TB, Loh R, Sly PD, et al. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. *J Immunol* 1998;160:4730–7.
- [137] Macaubas C, De Klerk NH, Holt BJ, Wee C, Kendall G, Firth M, et al. Association between antenatal cytokine production and the development of atopy and asthma at age 6 years. *Lancet* 2003;362:1192–7.
- [138] Marone G, Florio G, Petraroli A, De Paulis A. Dysregulation of the IgE/FcεRI network in HIV-1 infection. *J Allergy Clin Immunol* 2001;107:22–30.
- [139] Marone G, Florio G, Petraroli A, Triggiani M, De Paulis A. Role of human FcεRI<sup>+</sup> cells in HIV-1 infection. *Immunol Rev* 2001;179:128–38.
- [140] Marone G, Florio G, Triggiani M, Petraroli A, De Paulis A. Mechanisms of IgE elevation in HIV-1 infection. *Crit Rev Immunol* 2000;20:477–96.
- [141] Beeh KM, Ksoll M, Buhl R. Elevation of total serum immunoglobulin E is associated with asthma in nonallergic individuals. *Eur Respir J* 2000;16:609–14.
- [142] Burney P, Malmberg E, Chinn S, Jarvis D, Luczynska C, Lai E. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1997;99:314–22.
- [143] Sherrill DL, Stein R, Halonen M, Holberg CJ, Wright A, Martinez FD. Total serum IgE and its association with asthma symptoms and allergic sensitization among children. *J Allergy Clin Immunol* 1999;104:28–36.
- [144] Björkstén B. The intrauterine and postnatal environments. *J Allergy Clin Immunol* 1999;104:1119–27.
- [145] Herz U, Ahrens B, Scheffold A, Joachim R, Radbruch A, Renz H. Impact of in utero Th2 immunity on T cell deviation and subsequent immediate-type hypersensitivity in the neonate. *Eur J Immunol* 2000;30:714–8.
- [146] Landor M. Maternal-fetal transfer of immunoglobulins. *Ann Allergy Asthma Immunol* 1995;74:279–83.
- [147] Simister ME. Placental transport of immunoglobulin G. *Vaccine* 2003;21:3365–9.
- [148] Samsami DA, Doroudchi M, Ghaderi A. Placental transfer of tetanus-specific immunoglobulin G in Iranian mothers. *J Matern Fetal Neonatal Med* 2003;14:147–50.
- [149] Bergmann RL, Diepgen TL, Kuss O, Bergmann KE, Kujat J, Dudenhausen JW, et al. Breastfeeding duration is a risk factor for atopic eczema. *Clin Exp Allergy* 2002;32: 205–9.
- [150] van de Perre P. Transfer of antibody via mother's milk. *Vaccine* 2003;21:3374–6.
- [151] Wright AL, Sherrill D, Holberg CJ, Halonen M, Martinez FD. Breast-feeding, maternal IgE, and total serum IgE in childhood. *J Allergy Clin Immunol* 1999;104:589–94.
- [152] Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001;56:192–7.
- [153] Abdulrazzaq YM, Bener A, DeBuse P. Association of allergic symptoms in children with those in their parents. *Allergy* 1994;49:737–43.
- [154] Child F, Lenney W, Clayton S, Davies S, Jones PW, Alldersea JE, et al. The association of maternal but not paternal genetic variation in GSTP1 with asthma phenotypes in children. *Respir Med* 2003;97:1247–56.
- [155] Johnson CC, Ownby DR, Peterson EL. Parental history of atopic disease and concentration of cord blood IgE. *Clin Exp Allergy* 1996;26:624–9.
- [156] Kuehr J, Karmaus W, Forster J, Frischer T, Hendel-Kramer A, Moseler M, et al. Sensitization to four common inhalant allergens within 302 nuclear families. *Clin Exp Allergy* 1993;23:600–5.
- [157] Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med* 1998;158:176–81.
- [158] Sarafino EP. Connections among parent and child atopic illnesses. *Pediatr Allergy Immunol* 2000;11:80–6.
- [159] Asero R. Chronic idiopathic urticaria: a family study. *Ann Allergy Asthma Immunol* 2002;89:195–6.
- [160] Gern JE, Lemanske Jr RF, Busse WW. Early life origins of asthma. *J Clin Invest* 1999;104:837–43.
- [161] Hanson LA, Korotkova M, Lundin S, Haversen L, Silfverdal SA, Mattsby-Baltzer I, et al. The transfer of immunity from mother to child. *Ann NY Acad Sci* 2003;987:199–206.
- [162] Setiady YY, Samy ET, Tung KS. Maternal autoantibody triggers de novo T cell-mediated neonatal autoimmune disease. *J Immunol* 2003;170:4656–64.

- [163] Prescott SL, Macaubas C, Smallacombe T, Holt BJ, Sly PD, Holt PG. Development of allergen-specific T-cell memory in atopic and normal children. *Lancet* 1999;353:196–200.
- [164] Martinez FD. Toward asthma prevention — does all that really matters happen before we learn to read? *New Engl J Med* 2003;349:1473–5.
- [165] Kurukulaarachy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH. Characterization of wheezing phenotypes in the first 10 years of life. *Clin Exp Allergy* 2003;33:573–8.
- [166] Jenkins HA, Cherniack R, Szeffler SJ, Covar R, Gelfand EW, Spahn JD. A comparison of the clinical characteristics of children and adults with severe asthma. *Chest* 2003;124:1318–24.
- [167] Horak E, Lanigan A, Roberts M, Welsh L, Wilson J, Carlin JB, et al. Longitudinal study of childhood wheezy bronchitis and asthma: outcome at age 42. *BMJ* 2003;326:422–3.
- [168] Edwards CA, Osman LM, Godden DJ, Douglas JG. Wheezy bronchitis in childhood: a distinct clinical entity with lifelong significance? *Chest* 2003;124:18–24.
- [169] Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *New Engl J Med* 2003;349:1414–22.
- [170] Broadfield E, McKeever TM, Scrivener S, Venn A, Lewis SA, Britton J. Increase in the prevalence of allergen skin sensitization in successive birth cohorts. *J Allergy Clin Immunol* 2002;109:969–74.
- [171] Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Is the increase in allergic respiratory disease caused by a cohort effect? *Clin Exp Allergy* 2002;32:1702–5.
- [172] Silvestri M, Oddera S, Crimi P, Rossi GA. Frequency and specific sensitization to inhalant allergens within nuclear families of children with asthma and/or rhinitis. *Ann Allergy Asthma Immunol* 1997;79:512–6.
- [173] Liu AH, Murphy JR. Hygiene hypothesis: fact or fiction. *J Allergy Clin Immunol* 2003;111:471–8.
- [174] Wraith DC, Goldman M, Lambert PH. Vaccination and autoimmune disease: what is the evidence? *Lancet* 2003;362:1659–66.
- [175] Casadevall A, Pirofski LA. Exploiting the redundancy in the immune system: vaccines can mediate protection by eliciting 'Unnatural' immunity. *J Exp Med* 2003;197:1401–4.
- [176] Brown MA, Halonen MJ, Martinez FD. Cutting the cord: is birth already too late for primary prevention of allergy? *Clin Exp Allergy* 1997;27:4–6.
- [177] Reveneau N, Geoffroy MC, Lochet C, Chagnaud P, Mercenier A. Comparison of the immune responses induced by local immunizations with recombinant *Lactobacillus plantarum* producing tetanus toxin fragment C in different cellular locations. *Vaccine* 2002;20:1769–77.
- [178] Tregoning JS, Nixon P, Kuroda H, Svab Z, Clare S, Bowe F, et al. Expression of tetanus toxin Fragment C in tobacco chloroplasts. *Nuc Acids Res* 2003;31:1174–9.
- [179] Scheppeler L, Vogel M, Zuercher AW, Zuercher M, Germond IE, Miescher SM, et al. Recombinant *Lactobacillus johnsonii* as a mucosal vaccine delivery vehicle. *Vaccine* 2002;20:2913–20.
- [180] Odent M, Culpin E. Future of BCG. *Lancet* 1999;354:2170.
- [181] Aaby P, Shaheen SO, Heyes CB, Goudiaby A, Hall AJ, Shiell AW, et al. Early BCG vaccination and reduction in atopy in Guinea-Bissau. *Clin Exp Allergy* 2000;30:644–50.
- [182] Nakamura GR, Reynolds ME, Chen YM, Starovasnik MA, Lovvman HB. Stable "zeta" peptides that act as potent antagonists of the high-affinity IgE receptor. *Proc Natl Acad Sci USA* 2002;99:1303–8.
- [183] Julge K, Meriste S, Kemp A, Bjorksten B. Atopic allergy and delayed type hypersensitivity in Estonian children. *Clin Exp Allergy* 2002;32:1420–3.
- [184] Rottem M. Chronic urticaria and autoimmune thyroid disease: is there a link? *Autoimmun Rev* 2003;2:69–72.
- [185] Rottem M, Shoenfeld Y. Asthma as a paradigm for autoimmune disease. *Int Arch Allergy Immunol* 2003;132:210–4.
- [186] Pascual FB, McGinley EL, Zanardi LR, Cortese MM, Murphy TV. Tetanus surveillance — United States, 1998–2000. *MMWR Surveill Summ* 2003;52:1–8.
- [187] Martin B, Nelson M, Hershey J, Engler R. Adverse reactions to vaccines. *Clin Rev Allergy Immunol* 2003;24:263–76.
- [188] Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS) — United States, 1991–2001. *MMWR Surveill Summ* 2003;52:1–24.
- [189] Devendra D, Eisenbarth GS. Immunologic endocrine disorders. *J Allergy Clin Immunol* 2003;111:624–36.

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

