Is Asthma Caused by Atopy (Positive Skin Prick Tests)? Epidemiologic Evidence Suggests a Negative Answer

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Abstract: In this paper we shortly discuss epidemiological data on the relationship between asthma and atopy according to recent personal and literature epidemiological publications. The coexistence in several subjects of asthma (and of other "atopic" diseases) and IgE hyperproduction generated the dogma that these two biological conditions are mainly genetic in origin and are linked by a strong casual relationship. In the last decades atopy increased at 5-10% annual rate and at present atopy prevalence, although variable in different countries, reaches somewhere the prevalence of more than 60%. Similarly, asthma prevalence increased in the last decades, especially so in western and English speaking countries, reaching in certain countries prevalence values higher than 40%. For these reasons, although certainly dependent on a genetic predisposition, atopy and asthma can nowadays be considered to be largely determined by environmental factors. Moreover, the analysis of epidemiological data derived from studies conducted worldwide, showed that the prevalence of the two conditions were clearly not correlated so that in certain countries with a 50-60% prevalence of atopy asthma prevalence is lower than 2-6%, while in other countries asthma prevalence is double than atopy prevalence. Further, in countries with high atopy, the prevalence this conditions is high both in asthmatics and in normal subjects and in the places where asthma prevalence reaches high levels this condition is high both in atopic and non atopic people. In conclusion, epidemiological data show that environmental factors affecting asthma prevalence are different from those affecting atopy prevalence and that subjects bearing one of the two conditions don't show any preferential tendency to develop the other one. From aetiological and pathogenetic point of view asthma and atopy appear to be independent conditions. We therefore believe that the association between asthma and atopy demonstrated in almost all the "population studies" (atopy prevalence has always been found 20-30% higher in asthmatics than in non asthmatic subjects) doesn't prove the existence of a "causal" relationship between the two conditions: this could be a kind of association without causative meaning as is the association between blond hair and blue eyes which in no way can be considered a prove that one of the two conditions is the cause of the other.

A relevant number of epidemiologic studies clearly show that atopic diseases (classically asthma, rhinitis, eczema but not only these ones) statistically prevail in subjects with specific IgE hyperproduction (positive "atopy skin prick tests", ASPT). That this association has a genetic component is demonstrated by the high incidence of atopic diseases in patients born in atopic families (3-5 times compared to the rest of the population) [1]. The coexistence in several subjects of atopic diseases and IgE hyperproduction generated the dogma that these two variables are linked by a strong casual relationship: many scientists, medical practitioners and the general population have nowadays the deep belief that IgE hyperproduction is an important cause of asthma, rhinitis and eczema [2, 3]. According to the most accepted pathogenetic model, a genetic trait induces IgE hyperproduction towards common allergens and consequently "normal antigenic stimuli" induce increased release of histamine (and of other mediators) by mastocytes and by many other cells which is thought to be a sufficient condition to induce symptoms of atopic diseases.

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Challenging these well rooted concepts appears hard if not impossible. Recent qualified editorials, however, opened a breach in this wall surrounded beliefs suggesting that we probably overestimated the importance of IgE as a cause of atopic diseases [4, 5].

In this paper we would like to shortly synthesize the discussion according to recent epidemiological data: we will focus on the relationship between atopy and asthma, an item to which we dedicated most of our recent activity.

Atopic state can be defined as the situation of a subject who reacts with a wheal of at least 3 mm to ASPT performed with common environmental allergens (*Dermatophagoides*, pollens, etc.).

The threshold of significance of 3mm wheal is a mere convention with practical aims: a 4-10 mm wheal characterizes highly atopic subjects while a 2-1 mm wheal shows a light tendency to produce IgE in a continuum which is the rule in biological phenomena. Although wheal dimensions mainly depend on the amount of specific IgE in the skin, the final result of the test is also highly influenced by the sensitivity of the skin structures to histamine, the most important mediator released by mastocytes under allergenic

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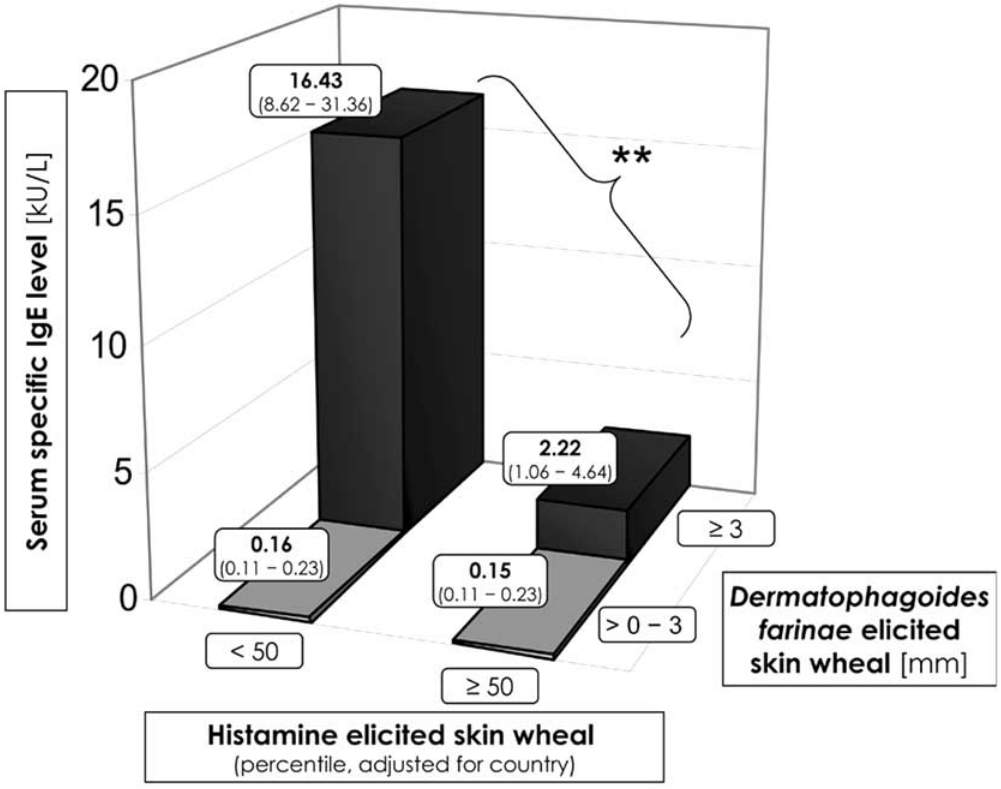

Fig. (1). Serum specific IgE for *Dermatophagiodes farinae* in subjects with measurable skin wheal elicited by this allergen and with higher or lower histamine skin reactivity. Values are reported as geometric means with 95% confidence interval. In children with allergen wheals >-3 mm serum specific IgE were significantly higher in those with low skin reactivity (P= 0.001 by Mann-Whitney U-test).

stimuli in the presence of specific IgE. Skin sensitivity to histamine is highly variable among individuals of the same population or among groups of different populations [6, 7]. This fact has the important consequence that, in order to produce a 3mm allergenic wheal, subjects of whatever population, who have high histamine sensitivity (> of 50° percentile) need 8 times less specific IgE (kU/L) compared to subjects who have low histamine sensitivity (< of 50° percentile) (Fig. **1**) [8].

Skin histamine sensitivity is not unchangeable: in two studies on 9-13 school-children skin histamine sensitivity was shown to increase of 30-50% in the period of 13-16 years (Fig. **2**) [9, 10].

Therefore, even in the absence of any change in the IgE production, environmental factors capable of inducing changes in the mechanism regulating skin histamine sensitivity can transform in ”atopic” subjects (with a 3mm wheal) those individuals who previously had a 1-2mm wheal.

The conclusion is that, in a given population, the number of persons with positive ASPT both depend on the amount of skin IgE and on the sensitivity of skin structures to histamine: for sure the two mechanisms are not alternative.

As a matter of facts, atopy increased in the last decades at 5-10% annual rate and at present atopy prevalence, although variable in different countries, reaches somewhere the prevalence of more than 60% [8]. These observations raise reasonable doubts on the concept of the prevalent genetic origin of atopy: most of the actual “atopic” subjects would not be atopic without the influence of environmental factors. For sure, these factors contribute to the development of the epidemic of atopic status that we are experiencing nowadays.

Very similar considerations can be made concerning asthma, rhinitis and eczema. These illnesses are generated by complex biological situations the severity of which highly varies among individuals and in the same individual in different periods of the life. Asthma is an illness empirically defined in epidemiology often simply by a positive answer to the question “do you have asthma?”. Whatever the definition, asthma prevalence increased in the last decades, especially so in western and English speaking countries and although variable in different places of the world, in certain countries its prevalence reached values higher than 40% [8]. For these reasons, although certainly dependent on a genetic predisposition, asthma can nowadays be considered to be largely determined by environmental factors.

Obviously, discussing on the causal link between asthma and atopy, we would like very much to find out one or more environmental factors causing a parallel increase of both conditions: in the presence of such a finding we could reasonably conclude that asthma and atopy have a common and/or interdependent pathogenetic mechanisms. Unfortunately, at present we are still ignorant about environmental causes of the asthma and atopy increase: vaguely, several data suggest that western style of life is linked to the increase of these two conditions. For example atopy prevalence is significantly higher in those populations with an annual gross domestic product higher than 25,000 dollars (unpublished personal observation).

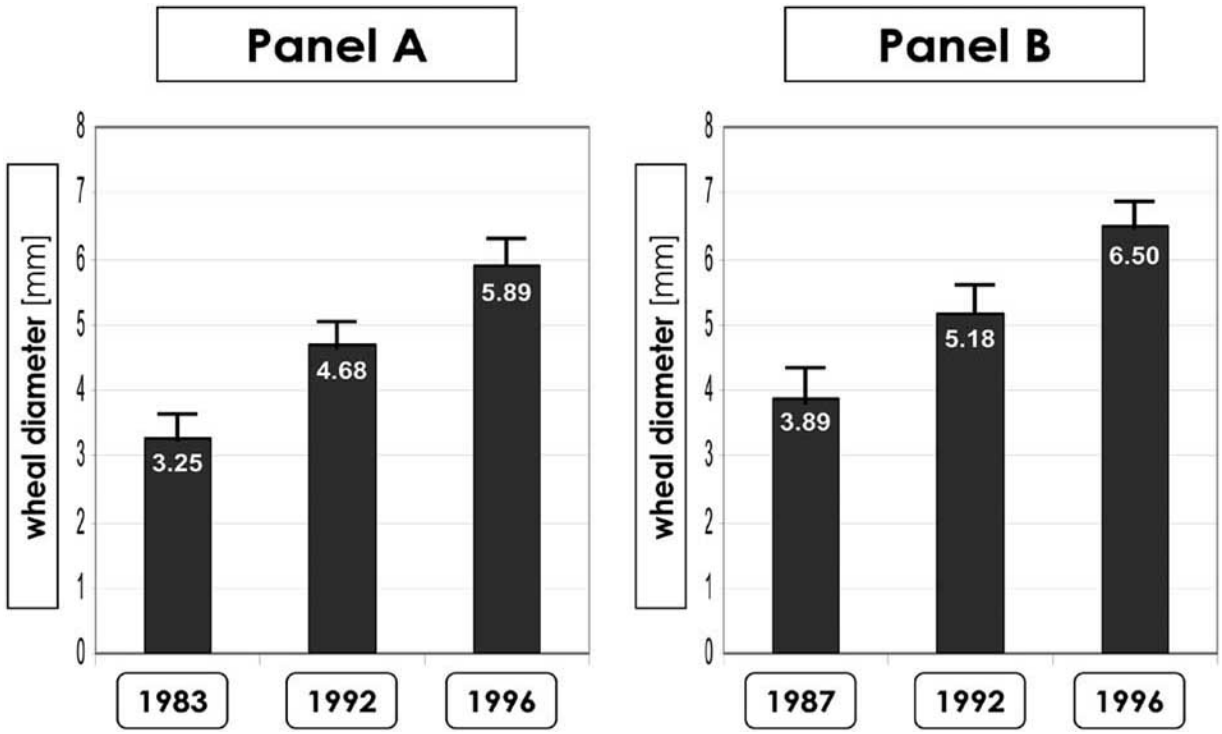

Fig. (2). Mean (± SE) diameters of wheals induced by histamine skin prick tests (10 mg/ml). In three surveys conducted in 9 year old (panel **A**) and 13 year old children (panel **B**). In each panel all comparisons were statistically significant ($P<0.001$ by Student's *t* test).

Global epidemiological data, however, suggest some reasonable conclusions. We consider verisimilar the hypothesis that if the two conditions were casually related, in the countries where atopy reached very high prevalence also asthma, if caused by atopy, should tend to the highest prevalence values. Obviously the contrary should hold true: in countries with low atopy the prevalence of asthma should be present at the lowest rates. The analysis of epidemiological data derived from 37 studies conducted worldwide on unselected children populations [11, 12] showed that this hypothesis is absolutely not true. It was found that the prevalence of the two conditions were clearly not correlated so that in certain countries with a 50-60% prevalence of atopy asthma prevalence is lower than 2-6% (Malaysia and China), while in other countries asthma prevalence is double than atopy prevalence (Eastern European countries) (Fig. **3**) [11, 12].

Another reasonable hypothesis is that if atopy and asthma were causally linked the environmental factors causing an increase of atopy prevalence would be more active in persons predisposed to atopy, asthmatics in first place: at the same time asthmogenic factors should exert more intense effect on atopics if these persons had a predisposition to become asthmatics. On the contrary, the analysis of the epidemiological studies demonstrate that in countries with high atopy prevalence this conditions is high both in asthmatics and in normal subjects and that in the places where asthma prevalence reaches high levels this condition is high both in atopic and non atopic people (Fig. **4**) [11, 12].

In conclusion, epidemiological data show that environmental factors affecting asthma prevalence are different from those affecting atopy prevalence and that subjects bearing one of the two conditions don't show any preferential tendency to develop the other one: from aetiological and pathogenetic point of view asthma and atopy appear to be independent conditions.

It must be noticed however that in almost all the "population studies" quoted above atopy prevalence has always been found 20-30% higher in asthmatics than in non asthmatic subjects [11, 12]. This finding demonstrates an association between asthma and atopy, probably explained by a common genetic trait characterizing the two conditions, but obviously doesn't prove the existence of a "causal" relationship between asthma and atopy.

A "causal" relationship between two biological conditions implies that the existence of one of the two not only predicts the existence of the other but is also a cause of the second. As an example, the presence of proteins HLA-DQ2 and DQ8 in a patient both predicts the existence of celiac disease but verisimilarly demonstrates the existence of pathogenetic gluten intolerance. On the contrary, on the base of the findings quoted above, the epidemiological association between asthma and atopy appears to be a kind of association without causative meaning: this is the case of the association between blond hair and blue eyes which in no way can be considered a prove that one of the two conditions is the cause of the other.

The idea of a causal relationship between IgE hyperproduction and atopic diseases is, however, so deeply rooted in medical science that in many epidemiological papers this association is presented as "causal". As an example in the excellent paper by Illi and co-workers [13],

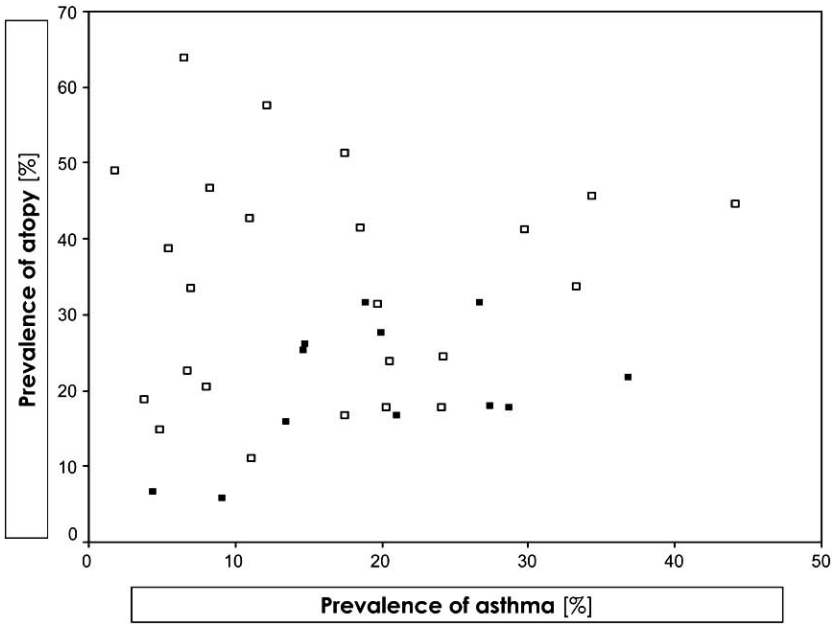

Fig. (3). Absence of correlation between the population prevalence of asthma (affirmative answer to the question: Have you ever had asthma?) and of atopy (at least 1 positive allergen skin prick test response) in 37 studies conducted in unselected children populations ($p = 0.761$, $r = 0.052$). Open squares: populations studied by the author's group, closed squares populations studied by others.

the authors underline that subjects with early atopy, compared to the rest of their population, have 4-6 times higher probability of developing asthma: this "aetiological" contribution of atopy for asthma, however, was only found in those subjects who had a family history of atopic diseases. As it is well known that asthma prevalence is 3-5 times higher in subjects with a positive family history, the aetiological contribution of the sole atopy appears not to be determinant: as a matter of fact in this study, in the many subjects without a family history for atopic diseases, a positive ASPT was not associated with higher prevalence of asthma.

At the times when atopy was considered to be a major cause of asthma scientists logically conceived the existence of two different phenotypes of the diseases: "allergic asthma" as opposed to asthma without allergy ("non allergic" or "intrinsic asthma") [14]. The former was considered to be more prevalent in young male subjects while intrinsic asthma was thought to preferentially affect older women frequently affected by nasal polyposis, aspirin intolerance and obviously with negative ASPT.

In the last decades many studies were carried out with the aim to compare atopic and intrinsic asthma from immunological and pathological point of view. Should laboratory data have documented substantial differences between these two asthma phenotypes, an atopic pathogenesis in at least a part of asthma cases would have received support. On the contrary a rich literature on this item, especially the most recent one, clearly shows that asthmatic subjects with or without atopy do not exhibits differences in immunologic parameters: in both phenotypes studies found the same type of mucosal infiltration with cells expressing the same interleukins (e.g. interleukins 4 and 13) chemokines (e.g. eotaxin, RANTES) and the same type of receptors (e.g. IL-5, CCR-3 for the chemokines, etc.). Obviously, and by definition, asthmatic subjects with atopy showed in addition functional and clinical findings originated by their atopic status (e.g. T_H2 activity of the lymphocytes, mast-cell degranulation, etc.) [15-17].

In summary these findings suggest that the etiopathogenesis of the disease is highly similar in the two phenotypes of asthma: the additional presence of atopy in some asthmatics can obviously trigger asthmatic symptoms in the presence of sufficient antigenic exposition. In this line of reasoning and from a clinical point of view probably the distinction between allergic and non allergic asthma should not be simply made on the base of positive ASPT: the label of "atopic" to a case of asthma should only be applied when most of the symptoms are triggered by antigenic exposition.

We reported epidemiological data confirming that asthma and atopy have highly different prevalence in world countries: the two conditions appear nowadays on the increase in most places and should therefore be considered mainly generated by environmental factors. The ecological conditions facilitating one of the two illnesses are different from those facilitating the other and the prevalence of atopy doesn't affect the prevalence of asthma and vice versa. These findings strongly urge the scientific community to reconsider the theorem of the central role of IgE in the pathogenesis of asthma and probably of the other atopic diseases.

We should not however completely disregard the biological meaning of IgE. Atopic status significantly increased worldwide and its spread at present continues at unchanged rate (apparently asthma follows a different behaviour as its prevalence remained unchanged in the last decade [18]). If the whole world or at least Western countries will follow the example of Australia or Malaysia, being atopic will become the prevalent and therefore "normal" condition with which we have to learn to co-exist elaborating preventive and control strategies: asthma could obviously

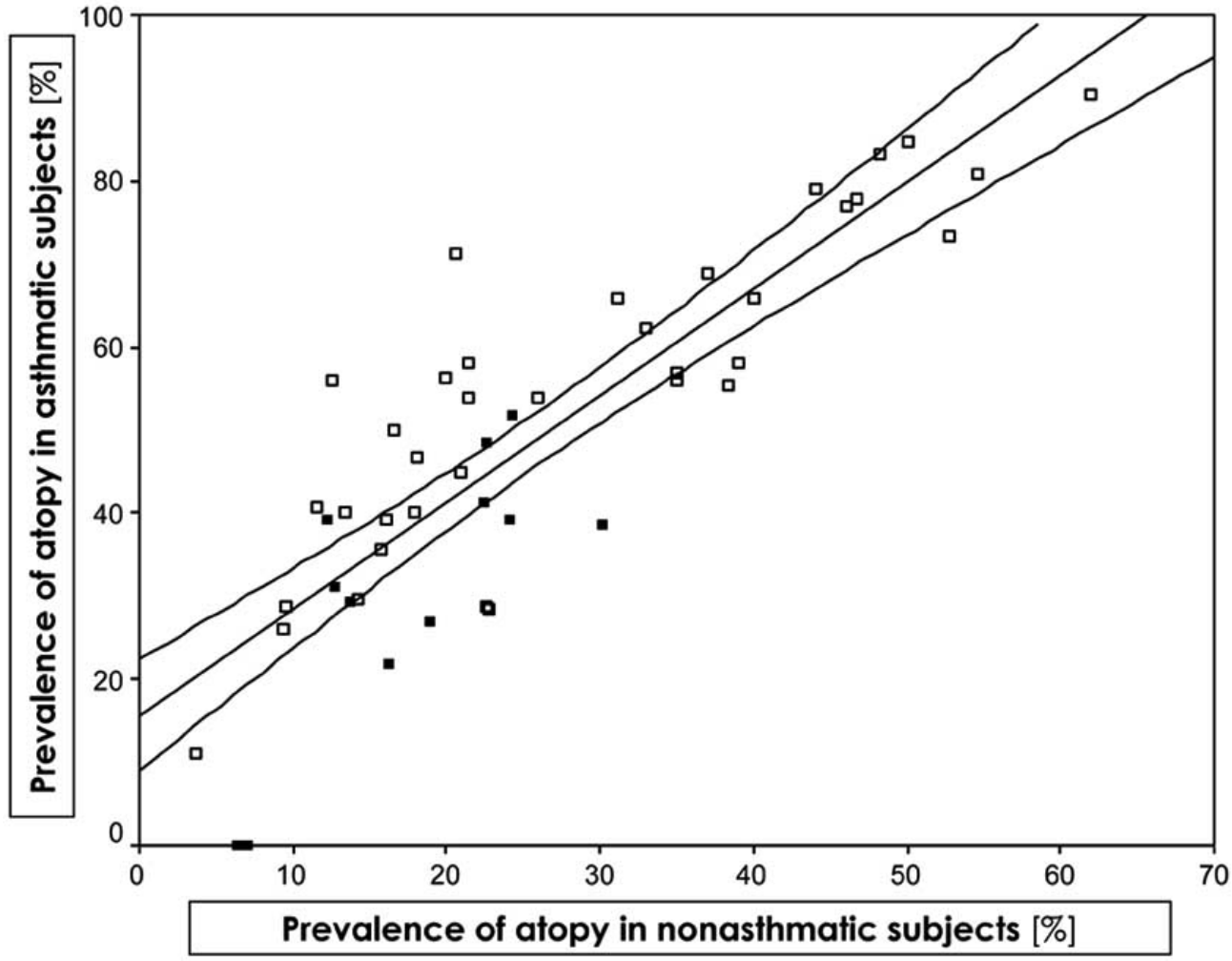

Fig. (4). Linear correlation between the prevalence of "atopic asthma" (asthmatic subjects with positive prick tests) and the prevalence of atopy (at least 1 positive allergen skin prick test response) in the rest of the non asthmatic population in 37 studies conducted in unselected children ($y = 1.364\ x + 12.145$; $p < 0.001$, $r = 0.900$). Open squares: populations studied by the author's group, closed squares populations studied by others.

result more severe due to the spreading of IgE sensibilization.

We must retain, however, that verisimilarly a person does not become asthmatic (and presumably nor eczematous or rhinitic) only or mainly because he or she is an atopic person.

REFERENCES

[1] Bjerg, A.; Hedman, L.; Perzanowski, M.L.; Platts-Mills, M.; Lundba, B.; Ronmark, E. Family history of asthma and atopy: in-depth analyses of the impact on asthma and wheeze in 7- to 8-year-old children. *Pediatrics*, **2007**, *120*, 741-48.

[2] Remes, S.T.; Korppi, M. Asthma and atopy in schoolchildren in a defined population. *Acta Paediatr.*, **1996**, *85*, 965-70.

[3] Custovic, A.; Smith, A.; Woodcock, A.; Chapman, M.D. Indoor allergens are a primary cause of asthma. *Eur. Respir. Rev.*, **1998**, *53*, 155-8.

[4] Pearce, N.; Pekkanen, J.; Beasley, R. How much asthma is really attributable to atopy? *Thorax*, **1999**, *54*, 268-72.

[5] Pearce, N.; Douwes, J.; Beasley, R. Is allergen exposure the major primary cause of asthma? *Thorax*, **2000**, *55*, 424-31.

[6] Ronchetti, R.; Haluszka, J.; Martella, S.; Falasca, C.; Guglielmi, F.; Parmiani, S.; Zakrzewski, J.; Bednarek, A.L.; Barreto, M.; Villa, M.P. Skin reactivity to histamine and to allergens in unselected 9-year-old children living in Poland and Italy. *Pediatr. Allergy Immunol.*, **2003**, *14*, 201-6.

[7] Ronchetti, R.; Bohmerova, Z.; Martella, S.; Falasca, C.; Barreto, M.; Lesiak-Bednarek, A.; Zakrzewski, J.; Bednarek, A.L.; Barreto, M.; Villa, M.P. Skin reactivity to histamine and codeine in unselected 9-year-old children from Italy, Poland and Libya. *Int. Arch. Allergy Immunol.*, **2004**, *135*, 136-42.

[8] Ronchetti, R.; Villa, M.P.; Rennerova, Z.; Haluszka, J.; Dawi, E.B.; Di Felice, G.; Al-Bousafy, A.; Zakrzewski, J.; Barletta, B.; Barreto, M. Allergen skin weal/radioallergosorbent test relationship in childhood populations that differ in histamine skin reactivity: a multi-national survey. *Clin. Exp. Allergy*, **2005**, *35*, 70-4.

[9] Ronchetti, R.; Villa, M.P.; Pagani, J.; Martella, S.; Guglielmi, F.; Paggi, B.; Bohmerova, Z.; Falasca, C.; Barreto, M. Immediate skin reactivity to histamine and to allergens in cohorts of 9-year-old schoolchildren studied 16 years apart. *Clin. Exp. Allergy*, **2003**, *33*, 1232-7.

[10] Ronchetti, R.; Villa, M.P.; Ciofetta, G.; Barreto, M.; Falasca, C.; Martella, S. Changes over 13 years in skin reactivity to histamine in cohorts of children aged 9-13 years. *Allergy*, **2001**, *56*, 436-41.

[11] Ronchetti, R.; Rennerova, Z.; Barreto, M.; Villa, M.P. The prevalence of atopy in asthmatic children correlates strictly with the prevalence of atopy among non-asthmatic children. *Int. Arch. Allergy Immunol.*, **2007**, *142*, 79–85.

[12] Ronchetti, R.; Jesenak, M.; Rennerova, Z.; Barreto, M.; Ronchetti, F.; Villa, M.P. Relationship between atopic asthma and the

population prevalence rates for asthma or atopy in children. *Asthma Allergy Proc*., **2009**, *30*, 55-63.

[13] Illi, S.; von Mutius, E.; Lau, S.; Nickel, R.; Niggemann, B.; Sommerfeld, C.; Wahn, U. and Multicenter Allergy Study Group. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J. Allergy Clin. Immunol*., **2001**, *108*, 709-14.

[14] Rackemann, F.M. Intrinsic asthma. *J. Allergy*, **1940**, *11*, 147-62.

[15] Jayaratman, A.; Corrigan, C.J.; Lee, T.H. The continuing enigma of non-atopic asthma. *Clin. Exp. Allergy*, **2005**, *35*, 835-7.

[16] Romanet-Manent, S. ; Charpin, D.; Magnan, A.; Lanteaume, A.; Vervloet, D.; EGEA Cooperative Group. Allergic *vs* nonallergic asthma: what makes the differences? *Allergy*, **2002**, *57*, 607-13.

[17] Humbert, M.; Menz, G.; Ying, S.; Corrigan, C.J.; Robinson, D.S.; Durham, S.R.; Kay, A.B. The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. *Immunol. Today*, **1999**, *20*, 528-33.

[18] Ronchetti, R.; Villa, M.P.; Barreto, M.; Rota, R.; Pagani, J.; Martella, S.; Falasca, C.; Paggi, B.; Guglielmi, F.; Ciofetta, G. Is the increase in childhood asthma coming to an end? Findings from three surveys of schoolchildren in Rome, Italy. *Eur. Respir. J.*, **2001**, *17*, 881-6.

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