

Atopic and Nonatopic IgE-Mediated Allergy: A New Interpretation of Old Facts?

A.L. de Weck

Gerimmun Foundation, Fribourg, Switzerland

Key Words

Atopy · Non atopic allergy · IgE · Allergic breakthrough · Allergy prevention · High IgE responders · Low IgE responders

Abstract

Coined 80 years ago, the term 'atopy' to designate a group of diseases associated with IgE and a hereditary background has raised many discussions. In particular, it is difficult to consider as part of an atopic syndrome cases of IgE-mediated allergies to isolated allergens without evidence of a familial inheritance. The postulate expressed in this essay is that in humans we are essentially dealing with an atopic IgE-mediated allergy, which is the equivalent of a genetically determined high IgE response, and with a nonatopic IgE-mediated allergy, which is the equivalent of a low IgE response in mammals and rodents.

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Introduction – Definitions of Atopy

Although the term 'atopy' or 'atopic' has been used in the medical literature since Greek antiquity [1], it was reintroduced in the modern medical literature almost 80 years ago by Coca and Cooke [2] to designate a group of allergic diseases linked by a marked hereditary tendency.

In their first definition, atopy was essentially a clinical entity, encompassing hay fever and bronchial asthma, associated with immediate-type (wheal and flare) reactions, occurring in a small group of genetically predisposed individuals and following some natural sensitization.

Atopy was thereby quite different from anaphylaxis and allergy, which could be induced experimentally, mostly by injection, in almost any human or animal.

A few years later, following the report of Prausnitz and Küstner [3] on the passive transfer of immediate skin reactivity by serum, Coca and Grove [4] defined 'atopic reagins' as specifically reacting substances in the serum of atopic individuals, responsible for the passive transfer of skin hypersensitivity. For a long time, reagins, however, were not considered as classical antibodies, since they were lacking a number of antibody features (e.g. precipitation with allergen). Somewhat later, around 1933, atopic eczema, also called 'atopic dermatitis' was added to the list of atopic diseases [5].

The identification of reagins in 1967 [6, 7] as a special class of immunoglobulins denominated IgE brought some twist in the concept and definition of atopy, since Pepys [8] then defined atopy as 'a form of immunological reactivity of the subject in which reaginic antibody, now defined as IgE antibody, is readily produced in response to ordinary exposure to common allergens in the subject's environment. This does not imply the presence of symptoms and is a description of the immunologic reactivity of

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Correspondence to: Prof. Dr. Alain L. de Weck
Beaumont 18
CH–1700 Fribourg (Switzerland)
Tel. +41 26 424 69 10, Fax +41 26 424 69 11
E-Mail aldeweck@bluewin.ch

the subject'. With this, atopy became an immunological condition rather than a group of diseases or a syndrome.

The definition of atopy, however, continued to raise numerous discussions [9–11]. At a WHO conference in 1984 [12], atopy was defined as a 'genetic predisposition to develop an IgE immune response to low concentrations of common environmental allergens as a result of natural exposure'. Recently, an EAACI Task Force on Allergy nomenclature [13] has proposed the following definition: 'A familial tendency to produce IgE antibodies in response to low doses of allergens and to develop typical symptoms, such as asthma, rhinoconjunctivitis or eczema/dermatitis'.

The major problem with the usual definitions of atopy, based on an immunological phenomenon (IgE response) and/or a clinical syndrome (atopic diseases) is that they do not explain the following observations: (a) some cases of apparently atopic disease (e.g. so-called intrinsic atopic dermatitis) may not be due to IgE; (b) some cases of atopic disease with high IgE responses occur in isolated individuals, without evidence of a familial genotype, and (c) many cases of high IgE response and clinical 'atopic-like' disease occur to isolated allergens, without any evidence for genetic predisposition or other signs of atopy.

Accordingly, there is some permanent uneasiness about what should be included under the name of atopy, and some authors postulate a 'heterogeneity of atopy' [14–16], which is another way of suggesting that atopy may cover more than one syndrome and/or one immunological and genetic condition.

My own view, as expressed in this paper, is that humans are not alone to suffer from an atopic syndrome associated with a high IgE response, but that most higher animals, such as rodents and mammals, may also manifest some kind of 'atopy' and that we should therefore learn from such animal models [17]. As discussed in this review, all animal species so far investigated in this respect have shown to be divided genetically into 'high and low IgE responders'. A number of high IgE responders also spontaneously manifest clinical diseases which very much resemble the corresponding diseases in man (e.g. atopic dermatitis in dogs, bronchial asthma in horses). My postulate is that humans can also be divided genetically into high and low IgE responders, a status which influences their clinical reaction to allergens. I distinguish therefore '*atopic IgE-mediated allergy*', which is the equivalent of a high IgE responder status, from '*nonatopic IgE-mediated allergy*', which is the human equivalent of a low IgE responder status.

Genetics of Atopy and IgE Immune Response

The fact that atopic diseases like hay fever (rhinoconjunctivitis) and bronchial asthma occur preferentially in some families in humans has been recognized quite early [18] and has constituted an important aspect of all atopy definitions [11].

The importance of genetic factors in the development of atopy and high IgE responses in humans has also been confirmed by a number of twin studies [19–24]. However, the mode of inheritance of the atopic syndrome or of some of its constituents has still not been elucidated, despite intensive research, particularly in the last 20 years. In a first study on a large number of atopic families, Coca and Cooke [2] concluded that atopy is dependent upon a dominant gene, which, however, has a relatively low degree of expression or penetrance [18]. This first evaluation is seldom seriously considered nowadays, since much of the modern studies rather point to the involvement of multiple genes inherited in a recessive manner [25–28]. As discussed below, however, some evidence in animal models should foster renewed analysis of the available data for human IgE responses under the hypothesis of a dominant gene which may require appropriate environmental and time conditions to become properly expressed and/or which may be easily suppressed.

A large number of recent genetic studies on atopic families have led to the tentative identification of numerous candidate genes located on chromosomes 2, 4, 5, 6, 7, 11, 12, 13, 16, 17, 19, 20 and 22 [25–32]. A number of these candidate genes are also associated more or less closely with immunologically functioning molecules, such as FcεR1, IL-4, IL-4R, IL 13 or RANTES which are of significance in IgE-mediated responses [32]. However, in my opinion – and probably also in that of many readers of this journal – the multiplication of these candidate genes has not contributed to a clarification of the genetic inheritance of the atopic state. First, most of the human studies are based on the analysis of heterogeneous clinical phenotypes [33], the spontaneous occurrence of atopic disease and/or the level of serum IgE. It is well established that these parameters are very dependent upon environmental factors and upon the time in life at which they are evaluated. Accordingly, it is not too astonishing that a study claiming identification of some candidate gene related to atopy is almost always followed by some studies disclaiming this original finding in another study population [27, 28, 32]. Second, as was well shown by animal studies mentioned below, candidate genes for clinical parameters,

such as bronchial asthma, bronchial hyperreactivity, dermatitis lesions, should not be mixed up with candidate genes for immunological and serological parameters such as total or allergen-specific IgE levels. Third, it has become obvious that the route of administration of allergens, the mode and timing of sensitization play an important role as well in the development of the immune response and its compartmentalization. As discussed below, these factors may also be subject to different genetic controls. Finally, how could the complex interplay of the multiple currently listed candidate genes explain the nevertheless rather straightforward clinical distinction between atopic and nonatopic individuals, despite the attempts to relate a multiple heterogeneous genetic background to an apparently single and defined functional phenotype [34].

At this point, it may become useful to turn to experimental animal models, in which phenotypes may be defined and followed in a more precise fashion than in humans and in which selective breeding enables to make faster and more accurate predictions about the mode of genetic inheritance. In animal species such as horses and dogs, which spontaneously manifest 'atopic-like diseases' associated with IgE antibodies, genetic inheritance, confirmed by selective breeding, is well known [35]. In such cases, however, environmental factors are not controlled either.

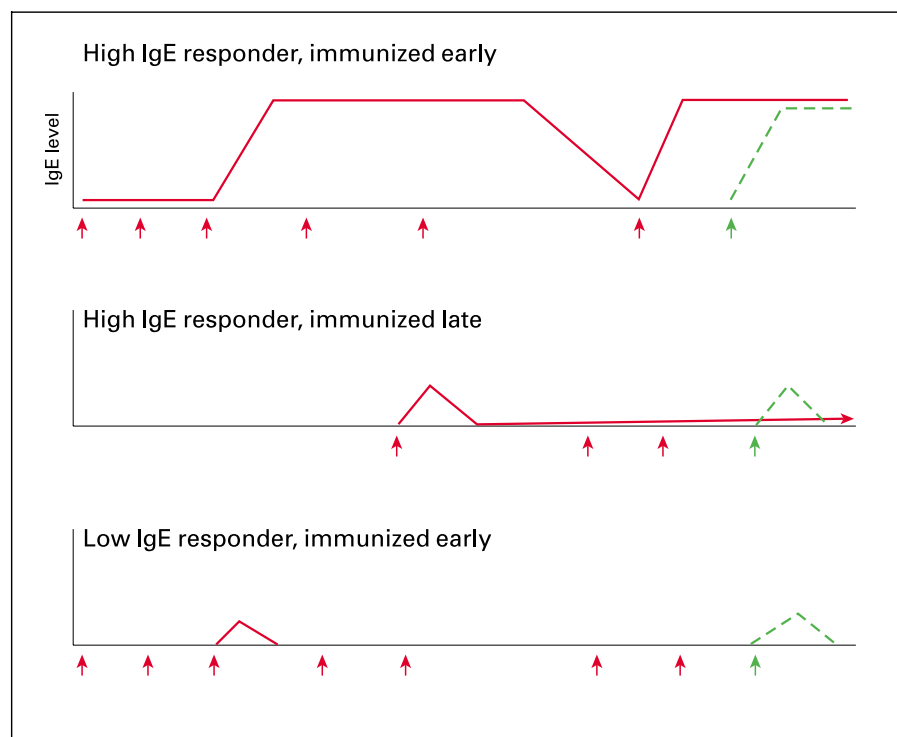
Therefore, in recent years, most relevant information has come from experimental animal studies, with a precise follow-up of the IgE and other antibody responses. Genetic control of the immune responses in rodents has been recognized already 50 years ago, particularly by Biozzi [cited in Puel et al., 36], but the specific genetic control and the rules governing the production of homocytotropic antibodies or reagins, as they were called at the time and later recognized as IgE, were established in the 1960s by Levine et al. [37] and Ovary's team [38]. The main findings at the time were: (a) the phenotypic distinction between low and high IgE responders among inbred strains of mice, based on genotypes. (b) The requirement for immunization with very small doses of antigen (in the microgram range) administered at distant intervals (no more than 2 weeks apart) while higher doses administered at frequent intervals foster the formation of IgG, even in high IgE responders. (c) The existence of a potent IgE-suppressing mechanism associated with normal T cells in low IgE responder animals but also to some extent in high IgE responder mice [38–43]. Similar findings were obtained in rats [18, 44–46] with the corresponding identification of high and low IgE responder strains. Curiously,

with some exceptions [47], the molecular and/or functional characterization of genes controlling the IgE response and responsible for the definition of high or low IgE responder mice strains does not seem to have attracted as much attention yet as the much more difficult task of distinguishing between atopic and nonatopic humans. While some studies suggest that a high IgE immune response is inherited in a recessive manner, others point to the low IgE response as a result of recessive inheritance [27]. In one instance at least, in which the high IgE response is the consequence of a chemically induced mutation, the high IgE trait seems due to an autosomal dominant gene [H. Behrendt, M. Vogel, pers. commun.].

In the 1990s, we have made some interesting observations in experimentally immunized Beagle dogs, selectively bred for high or low IgE response [17, 48–51]. These observations can be summarized as follows: (a) When immunized by injection of allergens, Beagle dogs may be divided into high and low IgE responder animals, like mice. The high IgE response status is inherited in a dominant manner [48, 51]. (b) Several conditions are required for establishing a high IgE response and expression of a high IgE genetic status: immunization with small amounts of allergen (in the microgram range) injected at infrequent intervals, immunization starting at birth or at least within the first month of life [52], immunization by injection. (c) In high IgE responders, late immunization, i.e. at the 3rd to 4th month, leads to a transient IgE response which is soon permanently suppressed (fig. 1). (d) In low IgE responders, even immunization at birth leads only to a transient IgE response which is soon suppressed (fig. 1). (e) Only high IgE responder dogs develop spontaneously specific IgE against ubiquitous allergens (e.g. house dust mites, pollens), similarly to atopic people. (f) Only high IgE responders, in some dog families, develop an eczematous skin condition very much resembling atopic dermatitis [51].

In addition to the dominant gene(s) governing the IgE response, there are obviously some additional genes involved in the IgE- and atopic-like responses of these dogs [49, 51]. For example, only some animals of litters with a high IgE genetic background develop IgE antibodies to allergens administered by aerosol inhalation, even if all animals of the same litter produce high IgE responses to other injected allergens. Furthermore, even the high IgE responders not producing IgE upon inhalation do so when the same allergen is injected later on [49, 51]. Similarly, spontaneous IgE sensitization to ubiquitous inhalation allergens (house dust mites, pollens) only affects some of the high IgE responder dogs of the same litter. From a total of 95 dogs with a high IgE responder genetic back-

Fig. 1. Schematic representation of the IgE response in high or low IgE responder dogs. Early immunization at birth or within the first month of life with one allergen (red arrows) leads to a sustained IgE response as long as exposure to allergen at infrequent intervals (about once every 2nd to 3rd month) occurs. However, renewed exposure to allergen leads to IgE boosting. Exposure to some new allergen later on in life (green arrow) also leads to allergen-specific IgE formation (upper panel). High IgE responder dogs with the same genetic background develop only a transient IgE peak, which is not boostable if they are first immunized later than the 3rd to 4th month of life. They also do not respond with just a transient IgE peak to some other allergen injected later on (green arrow) (middle panel). In low IgE responder dogs, even early immunization does not lead to sustained and boostable IgE responses (lower panel).



ground, only about 30% developed IgE to the Der p 1 house dust mite allergen, while 100% developed IgG, indicating that they had all been exposed to the allergen. Only some of the high IgE responder dogs develop IgE to Der p 1 while none of the low IgE responders do so. In addition to the dominant IgE response gene(s), this strongly suggests the involvement of some additional recessive gene(s) controlling sensitization by inhalation (equivalent to the 'asthma gene(s)' postulated in humans?). Unfortunately, we had no opportunity to engage in selective breeding for this trait of IgE response to inhaled allergen, so that the formal proof of genetic control for that trait is still lacking.

While breeding numerous dog litters for high IgE responses and immunizing them repeatedly with multiple allergens, we observed the appearance of eczematous skin lesions very much resembling the spontaneous atopic dermatitis that is well known in atopic dogs. These lesions were first clearly associated with the administration of allergen (by injection) but could thereafter take an independent course on their own.

They were also more frequently grouped in some litters. In that case, selective breeding [51] confirmed that atopic dermatitis, aside from the high IgE genetic trait required, was controlled by some additional, probably recessive, gene(s).

It may be appropriate at this point to remember that in humans as well, in the realm of the atopic syndrome, there seems to be some kind of genetic inheritance for its diverse clinical manifestations. Atopic children more frequently manifest their atopic state in the same manner, such as asthma or atopic dermatitis, as their parents. There is possibly, as is apparently the case in dogs, the same 'hierarchy of genes' controlling first the high or low IgE response and then the various clinical manifestations ('asthma genes', dermatitis genes'). This could be consistent with the apparent multitude of candidate genes found when investigating complex clinical phenotypes, as is the case in human studies [27].

Regulation of IgE Response in Atopy

As is well known, the classical atopic syndrome in man in its most fully expressed form includes atopic dermatitis starting in early infancy (usually due to cow's milk) followed a few years later by rhinoconjunctivitis and asthma due to inhaled ubiquitous allergens, such as pollens and house dust mites. This constitutes the 'atopic march' and is associated with the progressive development of high levels of specific IgEs against multiple allergens.

In many ways, the observations made in humans spontaneously developing IgE and the atopic syndrome in early infancy resemble the findings in experimental high IgE responder dogs. For example: (a) the high IgE response develops only when the first contact with some IgE-inducing allergen occurs very early in life, in the case of dogs within the first month of life [48, 52, 53]. The same is the case in rabbits [54]. Similarly, in humans, it seems that early sensitization, even in utero, is associated with the development of IgE and the atopic march in infants with the proper atopic genetic background [55–62]; (b) at some later point (in dogs around the 3rd–4th month of life), a strong IgE suppressor mechanism develops in high IgE responder dogs. In animals immunized late, the IgG responses start to predominate and IgE responses cannot be induced later on without additional immunological manipulations. This very much resembles the Th2-skewed response of atopic newborns which, spontaneously or under the effect of external stimuli (hygiene hypothesis), may turn towards a Th1-dominated response [63–69]. Possibly, the spontaneous suppression of IgEs to milk and egg allergens occurring around the 2nd or 3rd year of life in atopic infants first sensitized to these allergens [70] may depend on similar suppressor mechanism(s). It is not yet established to what extent the IgE suppression observed in dogs and to some extent in atopic infants (at least for some allergens such as milk or egg) is the expression of some spontaneous maturation of the immune system, of induction of IgE tolerance by allergen feeding or of some external environmental factor causing Th1 skewing (e.g. hygiene hypothesis); (c) once established, the IgE response declines relatively fast in the absence of allergen exposure, but remains capable of being boosted at any time later on [48, 52], and (d) in animals with established IgE response to some allergen, later immunization with some other allergen also leads to IgE formation. In other words, early development of IgE to some allergen (in atopic infants mostly to cow's milk and egg) paves the way for multiple IgE sensitization; Th2 skewing becomes established [52, 71].

The possible roles of internal and external factors influencing the development of IgE in genetically atopic individuals (table 3) have been much discussed recently and made responsible to a large extent for the abrupt increase in the past 20–30 years in the prevalence of atopic diseases, as well as for the epidemiological differences in the prevalence of IgE-mediated diseases according to regions and degree of urbanization [72]. At present, within the frame of the so-called hygiene hypothesis [19, 73], several factors able to cause Th1 skewing or acting

Table 1. Nonatopic IgE-mediated allergic diseases

Rhinoconjunctivitis, asthma, urticaria, anaphylactic shock due to
– Hymenoptera venoms
– Drugs (e.g. betalactams, myorelaxants, pyrazolones)
– Isolated pollen allergies (cypress, mountain cedar, Japanese cedar, ficus)
– Isolated occupational allergens (e.g. flour, latex, wild silk)
– Isolated food allergens (starting in adulthood)

through other indirect mechanisms have been implicated: gut flora, bacterial infections, environmental endotoxins, air pollution [62, 65, 68, 74–77]. Systematic study of such factors could well facilitate an active prevention of atopic diseases. In humans, however, direct experimentation on pregnant women, newborns and infants has obvious limitations.

Human epidemiological approaches, as mostly used up to now, are imprecise, long lasting and cumbersome. Accordingly, the use of a closely related experimental model, such as high IgE responder dogs could be quite rewarding.

An additional factor does influence IgE formation in high IgE responder rodents and dogs or man, namely early feeding with allergens [78–83]. As we have shown [48, 84, 85], early feeding with allergens, namely between the 1st and the 6th month of life, regularly induces a 'split IgE tolerance', called by some immune deviation [64, 86], in which a normal IgG response but no IgE develops upon a later sensitizing contact with the same allergen. This apparent IgE tolerance in high IgE responder dogs also occurs spontaneously, as documented by the relative resistance of high IgE responder dogs to IgE sensitization with allergens present in their food and by the marked regional differences in the prevalence of food-specific IgEs in atopic dogs [51, 84]. Depending upon the dose administered, anergy or active T-cell-induced suppression may be the mechanism involved [87].

Regulation of IgE Response in Non-Atopics: The 'Allergic Breakthrough'

One of the major problems with the current definitions of atopy is that a number of patients clinically present 'atopic-like' manifestations, such as rhinoconjunctivitis or asthma associated with some high allergen-specific IgE but without the usual familial background. There are also patients who present IgE-mediated symptoms such as

Table 2. Differences between high and low IgE responders

	High IgE responders	Low IgE responders
High IgE response to low dose of allergen		
Upon injection	yes	no
Upon inhalation	some*	no
Time of IgE triggering	early	none
IgE suppressor mechanism	yes	yes
Breakthrough factors	yes	yes
IgE response to allergens	multiple	isolated
Duration of IgE response	sustained	transient
IgE boosting	any time	none
IgE response to new allergen	yes	no

Table 3. Factors affecting the IgE response of High IgE responders ('atopics')

Intrinsic factors affecting the Th1/Th2 balance (e.g. IL-4, IL-10, IL-12 cytokines)
Bacterial and viral infections
Gut flora
Early contact with allergens (newborn immune response skewed for Th2)
Early feeding with allergens (induces split IgE tolerance)

urticaria or anaphylactic shock which are not part of the atopic syndrome and which most of the time occur without a history of familial inheritance.

These patients usually exhibit the following features: (a) IgE sensitization occurs at any time in life, without a history of early IgE development in infancy and with none of the classical other manifestations of atopy. (b) IgE sensitization is frequently directed against a single allergen or a restricted number of allergens. The allergens implicated are mostly drugs (e.g. betalactams), insect venoms, single occupational allergens (e.g. flour, latex) or individual foods [88]. This contrasts with the history of classical atopic patients, who generally demonstrate multiple sensitivities. (c) The onset of such IgE sensitization and manifestation is usually rather abrupt, the allergen-specific IgE may then persist for many years upon repeated exposure, but it may also disappear relatively fast. It is not really established whether the abrupt onset of such IgE sensitization directly follows some event potentially affecting the immune system, such as a viral infection or some trau-

matic event (e.g. operation, drug therapy, changes in the gut flora, bereavement, psychological trauma).

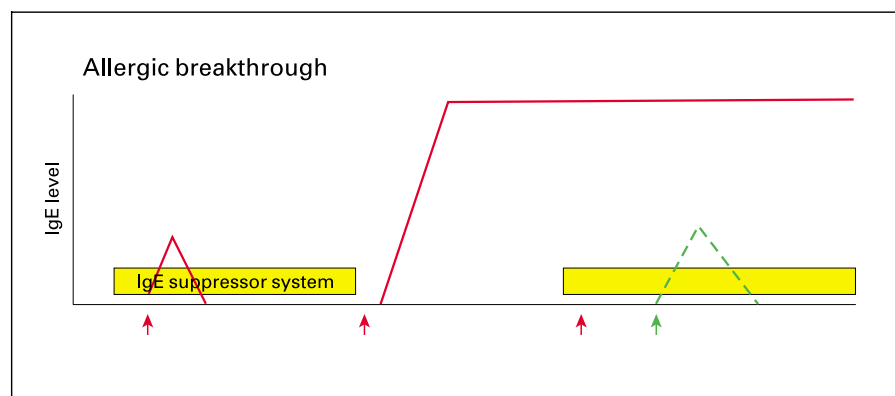
While a large population of allergic patients with isolated allergies due to IgE but without obvious link to classical atopies fills allergy clinics (table 1), it is also clear that similar individual allergies occurring later in life may also affect people with an atopic constitution [14, 89]. The relationship between these two categories of patients continues to be much discussed. Could there be atopic patients with mono- or restricted sensitivities, as suggested by some authors [14, 15]?

A brief review of what is known about animals described as low IgE responders may be useful at this point. At present, some inbred mouse [37, 43] and rat [46, 90] strains as well as selectively bred Beagle dogs [48, 49, 51] have been recognized as such. The common features of such low IgE responder status are: (a) the fact that even with immunization conditions optimal for IgE production, including starting with immunization early in life, the IgE response observed is low, soon aborted and is not boosted upon repeated allergen exposure (fig. 1); (b) under some special circumstances and immunological manipulations, such animals may nevertheless develop IgE responses, usually against isolated allergens. (c) In such animals, IgE production is the only decreased immunological response; the IgG response is unaffected and even often stronger than the IgG response of high IgE responders. Low IgE responders could perhaps be considered Th1 skewed.

Almost 30 years ago, the groups of Katz [39, 41, 91, 92] and Ovary [38] in mice and Tada [44, 46] in rats described a phenomenon which Katz termed 'allergic breakthrough', which means that a number of internal or external factors may temporarily disable the normal suppressor (or 'damping') apparatus which prevents the IgE response. Among such factors, mild irradiation, low dose therapy with immunosuppressive drugs (e.g. cyclophosphamide) and anti-thymocyte serum were the preferred experimental tools in order to induce a strong IgE immune response following concomitant allergen exposure in low IgE responder mouse strains [42, 43, 92]. Target of these immunosuppressive agents were T cells, the transfer of which reconstituted the suppressor mechanism [38].

Beyond experimental immunosuppression, there are probably a number of other factors which are also able to temporarily suppress the IgE suppressor mechanism in nonatopic individuals (table 4). One of them appears to be some viral infections, such as infectious mononucleosis, influenza or measles, which are often accompanied by a transient IgE increase. Some tumoral or paratumoral

Fig. 2. Schematic representation of allergic breakthrough in low IgE responders ('non-atopics'). As long as the IgE suppressor system (yellow area) functions, exposure to allergen (red arrow) leads to no or only a transient low IgE response. If and when the suppressor system is temporarily switched off, renewed exposure to allergen may lead to an IgE response which remains sustained even when the IgE suppressor system resumes its function. At that point, exposure to a new allergen (green arrow) also leads to no or only a low transient IgE response.



affections of the lymphoid system, such as lymphoid leukemias and Hodgkin's disease, are also accompanied by an increase in IgE levels.

Some of the important phenotypic features of the phenomenon of allergic breakthrough are the following: (a) the IgE response induced by some allergen exposure during the event temporarily depressing the IgE suppressor system is relatively long lasting, dependent upon renewed allergen exposure and can be boosted (fig. 2). It may persist even if the IgE suppressor system recovers its efficiency. At that time, however, no further IgE responses may be induced and the existing IgE response remains isolated; (b) such an isolated IgE response may be induced at any age in any low IgE responder strain, meaning in fact that anyone may, under appropriate conditions, develop an IgE-mediated allergy, and (c) the same immunological factors or manipulations which block the IgE suppressor system and allow induction of IgE in low IgE responder strains also increase IgE formation in high IgE responder strains. As was well shown in mice and in dogs (see above), high responder individuals also possess an IgE suppressor mechanism.

The discovery that various immunological manipulations could either block IgE suppression, thereby improving IgE production, directly activate mechanisms enhancing IgE production or on the contrary activate the IgE suppressor mechanism promptly led to intensive search for soluble factors derived from T cells, which appeared to be the key elements responsible for directing IgE homeostasis. The most active groups in this field, those of the Ishizakas [93, 94], Katz [95, 96] and Ovary [97] described a number of 'suppressor factors of allergy' and of 'enhancing factors of allergy', mostly characterized from their functional activity in IgE mouse models; they raised great hopes at the time (late 1970s and early 1980s) that some

Table 4. Factors causing 'Allergic breakthrough' in Low IgE responders ('nonatopics')

Factors affecting the normal IgE suppressor mechanism
Anti-T cell antibodies
Immunosuppressive drugs (e.g. cyclophosphamide)
Some tumors (Hodgkin, leukemias)
Low X ray doses
Tobacco smoke (?)
Changes in gut flora (decrease in IFN)
Viral infections (measles, mononucleosis, influenza)
Air pollution (e.g. diesel exhaust)
IL-4-producing causes

concrete possibilities for therapy and prevention of IgE-mediated diseases would soon be at hand. At this time, the molecular biology of cytokines and lymphokines was in its infancy and it is likely that some of the factors described at the time as influencing the IgE response would ultimately turn out to be cytokines such as IL-4 [98], IL-13, IFNs, IL-10 or TGF- β . In any case, as is often the case in biological research, disappointment caused by the impossibility to translate basic experimental observations into some practical clinical approach led most investigators to abandon the field and to forget about the 'allergic breakthrough' phenomenon.

Attention was rather given to the new subclasses of T lymphocytes such as CD4 and CD8, Th1 and Th2, and most of the speculations on the regulation of the IgE response now rely on the equilibrium between IgE-fostering Th2 and IgG-fostering Th1 lymphocytes [71, 99]. The existence of IgE suppressor T cells is questioned and one may wonder whether the various immunological manipulations experimentally shown to promote IgE responses in

low IgE responder individuals may not in fact merely reflect some actively induced Th1/Th2 switch.

Whatever the immunological mechanism(s) implicated, it remains that a number of factors and external events may promote IgE production in animals who do not have a genetic background associated with high IgE responses and the development of atopic-like clinical diseases. From there it is a short step to postulate that the isolated IgE responses occurring at any time of life in apparently nonatopic humans closely resemble the IgE response of low IgE responder rodents and mammals.

This contention is amenable to experimental verification. Since the dog model of atopy and IgE response is obviously closer to man than rodents, it would be quite tempting to revisit the 'allergic breakthrough' phenomenon in low IgE responder dogs. This, unfortunately, could not yet be done.

An Integrated View of Atopic and Nonatopic IgE-Mediated Allergies

As discussed above and summarized in table 2, many of the clinical features and immunological features that characterize high IgE responder rodents and dogs are found in humans presenting the classical 'atopic march' developing from infancy and associated with high levels of multiple allergen-specific IgEs.

It is not reasonable to believe that atopy means a 'strange/out of place' disease restricted to humans. In fact, veterinary experience with dogs and horses documents that some form of atopy also occurs in other mammals. And the increasing mimicry by some high IgE responder mouse models [75] of atopic symptoms speak for the same unitary concept: *the genetically determined classical atopy syndrome in humans is the equivalent of the genetically determined high IgE responder status in animals*.

If this postulate is accepted, it would be clarifying to restrict the definition of atopy proposed by EAACI [13] to 'a familial tendency to produce IgE antibodies to low doses of *ubiquitous and multiple*¹ allergens, *usually starting in infancy*¹, and to develop typical symptoms such as asthma, rhinoconjunctivitis or eczema/dermatitis'. For such individuals developing the classical atopic syndrome, we could speak of '*atopic IgE-mediated allergy*'.

On the other hand, the numerous cases of IgE-mediated allergy occurring at any age later in life, which sometimes present as asthma or rhinoconjunctivitis but often as urticaria or anaphylactic reaction, which are usually caused by single isolated allergens and show no evidence of familial inheritance could rather be understood as '*nonatopic IgE-mediated allergy*'. If one believes in the unity of biology and considers the numerous similarities between the IgE responses of these nonatopic individuals and that of low IgE responder rodents and mammals (table 2), it should be postulated that *individuals exhibiting nonatopic IgE-mediated allergies are the equivalent of low IgE responder animals*. In order to complete the demonstration, however, it would be required to determine the concomitant immunological factors or events that cause a low IgE responder to develop a temporary IgE response (table 4). Although it is tempting to transpose the mechanism of IgE production found in low IgE responder animals to nonatopic humans, leading to advise jocularly 'not to eat shrimp while suffering from acute influenza', one should be able to investigate the immunological status of such individuals while they develop some allergen-specific IgE for the first time. Some authors have suggested that tobacco smoke [100] or the dose of allergen [14, 15] might be responsible for IgE formation in nonatopic individuals. It is unlikely, in my opinion, that merely a higher allergen exposure could trigger the 'allergic breakthrough'. In all experimental situations, a higher allergen dose leads to the formation of IgG and not of IgE. It is the same in humans, where high dose inhalation of protein antigens (e.g. moulds) leads to IgG formation and to allergic alveolitis (e.g. farmer's lung), not to IgE. It cannot be excluded however that, based on their chemical structure or some immunomodulating secondary properties, some allergens are able to selectively cause an 'allergic breakthrough'.

Although the concept presented here has the advantage of being straightforward and to explain many experimental and clinical observations difficult to reconcile under a single definition of atopy, it must be recognized that it may be an oversimplification and that in both atopic and nonatopic IgE-mediated allergies, genetic heterogeneity and various subcategories of atopy may be present [14, 15, 34].

In any case, molecular genetic research in animal models of high and low IgE response, in parallel to molecular genetics of human atopy, should be encouraged.

¹ Proposed addition to the EAACI definition.

Consequences for Allergy Prevention

If the postulate according to which atopy and the development of the atopic march may be equated with a genetic high IgE responder status following the rules established in experimental animals, some direct consequences arise for allergy prevention. First, it is essential to avoid triggering the IgE-forming apparatus since once started, IgE production and the susceptibility to become sensitized by new allergens persist for life. Theoretically, strict allergen avoidance until the natural IgE suppressor mechanism has matured and Th2 skewing has been replaced by a Th1-dominated response could be effective. Allergen avoidance certainly helps to avoid clinical reactions, once IgE sensitization has become established. But in practice, particularly considering the frequent sensitization in utero, the mere avoidance of allergens – which has been the main recommendation of allergy prevention

programs in recent years – will usually not prevent entering the atopic march. The failure of allergen avoidance, to effectively prevent the atopic march is therefore not astonishing. Effective prevention would in fact only be achieved by some active switching of Th2 towards Th1 responses (e.g. by bacterial products, modifications of gut flora etc.) and/or induction of split IgE tolerance (e.g. by allergen feeding). Interventional strategies in early infancy will most likely become the best way to achieve active prevention in atopic infants.

For the majority of nonatopic individuals, susceptible of developing isolated IgE-mediated allergy to some food, insect venom or drug at any time in life, more research is still required to understand the rules and events leading to an allergic breakthrough. It is likely that measures maintaining the normal Th1/Th2 balance of the immunological system, particularly in times of stress and intercurrent viral disease, would have some preventive effect.

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