

## Editorial

# Infections preventing atopy: facts and new questions

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In 1989, Strachan proposed that common infections acquired early in infancy may prevent the development of hay fever (1). Later, he proposed (“hygiene hypothesis”) that declining cross-infections within young families are the most significant cause of the increase in atopy and atopic diseases in countries with a Western lifestyle (2). These hypotheses are now gaining more and more support: first, biologic plausibility has been extended to the hygiene theory by expanding knowledge of the TH1/TH2 paradigm (3); second, a large body of evidence has shown how important the very first period of life is in the development of atopy (4); and, finally, inverse relationships of atopy to measles (5) and hepatitis A virus (6) infections or to skin reactivity to tuberculin (7) have been reported.

In this issue of *Allergy*, Serafini reviews the whole subject from three distinct points of view (clinical/epidemiologic/pathogenetic), summarizing all data available in support of the theory. He includes a series of anecdotal but intriguing cases of remission of atopic diseases after acute fever or common infections such as measles or viral hepatitis (8). According to Serafini, the hygiene hypothesis now seems to be by far the best explanation of why atopy and atopic diseases are increasing in Western countries. Therefore, even if much more work is needed to establish a causal link between infections and atopy prevention, new questions

have already been raised by this idea, and we need further hypotheses to pursue our studies.

### Which and how many infections would protect from atopy?

The great diversity of infections reported to be inversely related to atopy (measles and hepatitis A and reactivity to *Mycobacterium tuberculosis* components) means that one must be very cautious before attributing a direct cause-effect link to all these associations. According to the hygiene theory, the infection(s) preventing atopy must satisfy precise epidemiologic criteria, as they must be characterized by a lower recirculation in Western than in Eastern Europe, in affluent and small families than in others, and in the last two decades than in earlier years. In addition, the frequency of these infection(s), even if characterized by great variability throughout socioeconomic strata, must be, on average, very high in the general population. Finally, their means of transmission must be very much hindered by higher hygienic standards.

Given this premise, epidemiologic data are still insufficient to identify the kind of infections involved in prevention of atopic diseases. Nevertheless, they suggest that protection from atopy is due to a more complex series of diversified infectious events, consisting also of repeated contact

with the same microbial agents, rather than the acquisition of a single infection. The following questions may be useful to investigate this point.

### **What tissue, organ, or system must be affected by the infections involved?**

Lower respiratory tract infections in early life are likely to prevent allergic diseases due to sensitization to common airborne allergens (9). Nevertheless, infections involved in prevention of respiratory allergic diseases might act mainly where immune events leading to allergen sensitization start rather than on the target organ of atopic sensitization. Four considerations are relevant here:

- 1) the “inhalant” allergens are not only inhaled, but also, and in significant amounts, ingested (10)
- 2) it is presently unknown where *in vivo* priming of T cells for airborne allergens occurs, but there is evidence, in animal models, that IgE-bearing B cells arise in GALT (11)
- 3) lymphocytes of bronchial and enteric mucosae (BALT and GALT) belong to the same recirculating pool
- 4) duodenal inflammation processes, mimicking those observed in the bronchial mucosa, have been recently observed in asthmatic and in asymptomatic atopic subjects sensitized to airborne allergens (12).

Therefore, it is an interesting possibility that digestive tract infections participate, together with infections of other mucosae, in the development of a TH1-like or TH2-like immune response to common airborne allergens. Thus, not only fecal contamination of the environment, but also the total microbial food contamination and the composition of digestive flora might affect atopy development. These concepts are in keeping with studies performed in animal models that show how microbial stimulation via gastrointestinal tract commensals and pathogens plays a major role in the postnatal maturation of the overall immune competence in mammals, lowering the risk of developing atopy (13).

### **Protection from overall atopic tendency or protection from sensitization to limited sets of allergens?**

It is still not clear whether infections occurring early in life affect the overall propensity of the immune system to produce IgE against every kind of environmental antigen (an “all or nothing” phenomenon), or whether this effect is antigen specific. It is still not possible to answer this

question, because the relations observed so far affected only the immune response to common airborne allergens in children or young adults (5–7).

*In vitro* data indicate that antigen-specific T helper cell precursors differentiate into TH1 or TH2 cells mainly according to the pattern of cytokines in the microenvironment at the time of antigen presentation (14). This suggests that infections influence only the immune responses to antigens encountered simultaneously in the same microenvironment. Infections occurring early in life and inducing a predominance of TH1-like cytokine profile in relevant microenvironments might thus affect only the differentiation of allergen-specific T cells whose priming and clonal expansion occur soon after birth (such as T cells specific for common inhalants).

It is well known that workers classified “non-atopic”, because they are not sensitized to common environmental allergens (the priming of which occurred in early infancy or *in utero*), can develop IgE sensitization to high-molecular-weight allergens, encountered for the first time at work. New IgE sensitization in such “nonatopic” adults would be explicable if these subjects were exposed during infancy, but not during adulthood, to the atopy-protective influence of relevant infections.

### **Is the length of exposure to infections a factor in the maintenance of protection against atopy?**

Several lines of evidence indicate the importance of the very first period of life in determining the future development of atopy through genetic-environmental interactions (4, 15). Even intrauterine life is important in the maturation of the immune interaction with environmental antigens (16). Therefore, it could be hypothesized that the influence of infections on atopy is a “once ever” phenomenon occurring only very early in life.

Nevertheless, persons acquiring a Western lifestyle by migration may become sensitized to common environmental allergens during adulthood (17). Thus, “removal” of protection during adulthood (by reduction of exposure to infections) might release atopic responses in genetically predisposed subjects. On the other hand, the examples reported by Serafini (8) show that the opposite is also possible (allergic disease remission induced by infections during adulthood).

In subjects and families more prone to atopy, the “window” period of life during which environmental stimuli such as infections are required to suppress sensitization to airborne allergens may be prolonged to adulthood. As a corollary, the number

of years necessary for a genetically predisposed subject to develop IgE sensitization and, later, allergic symptoms may be directly proportional to the length of exposure to the protective influence of relevant infections. This is suggested also by the observation that the number of younger siblings, not only that of older siblings, is strongly associated with a lower prevalence of hay fever (2, 18).

### Is exposure to infections more important than genetic predisposition in modulating atopy?

Hygienic standards and vaccination policies continue to reduce recirculation of many infections in developed countries; therefore, we should consider the possibility that the epidemic of atopy will expand in the following decades. In a new equilibrium in the "absence" of infection (19), atopy may be a "normal" state. It may be asked whether any person, given the right environmental conditions and lifestyle, can become atopic, or whether the lack of genetic propensity in a consistent part of the population would limit the epidemic to a plateau, preventing a large percentage of subjects from becoming atopic.

Among 867 Japanese children (97% of whom received BCG vaccination at 3 months of age), subjects with positive skin responses to intradermal tuberculin injection at 12 years of age had lower serum levels of total IgE and serum TH2 cytokines (interleukin [IL]-4, IL-10, and IL-13), higher serum levels of interferon-gamma, and lower prevalences of atopy and atopic diseases (7). The authors considered that many of the tuberculin responses observed and their putative repression of TH2-mediated atopic diseases were probably the result of natural exposure to tuberculosis rather than immunization (20). The examined sociodemographic characteristics, lifestyle indicators, and chest radiograph reports of tuberculosis in the families of positive tuberculin responders did not differ from those of negative tuberculin responders; therefore, the exposure to environmental airborne allergens was considered similar (7), and a differential exposure to *M. tuberculosis* might be disputed. Exposure to helminths was minimal in the whole population examined (7). An alternative interpretation is that, in the virtual absence of helminthic infestations and in the presence of very low recirculation of *M. tuberculosis* infection, high skin reactivity to tuberculin after BCG immunization and high total IgE serum concentration represent mutually exclusive phenotypes of the same set of genes regulating predisposition to a TH1 or TH2 predominance in the immune responses. Indeed, the

possibility of a genetic explanation of the reported associations has not been completely refuted (7).

Thus, the intriguing inverse relation between tuberculin reactivity and atopy might rather imply that even in the most favorable environmental conditions ("absence" of infections), subjects genetically predisposed to mount strong TH1 responses will hardly develop a specific IgE/TH2 response to environmental allergens.

### Will we learn from infections how to prevent atopy?

It has been proposed that prevention of IgE sensitization to a given allergen might be easier than to counter the effects of IgE sensitization once it has already been established (21). According to Holt, such prevention might be achieved by the parenteral vaccination at the appropriate time during childhood with the relevant inhalant allergens, especially in combination with an appropriate TH1-selective adjuvant. (21). Data from the infections-atopy inverse relationship suggest that if we could determine when and how infections prevent sensitization, we might be able to mimic their action and prevent sensitization as well.

### Is the atopy increase the only immune "adverse" effect of declining infections?

The rising prevalence of atopy might be just the first, more easily verifiable, indicator of a different homeostatic equilibrium of the immune system in populations with a Western lifestyle. At present, we do not know whether other immune-mediated conditions (e.g., chronic urticaria, autoimmunity) are also facilitated, in predisposed subjects, by improvement of hygienic standards and reduction of the overall microbial exposure.

### A time for caution but also for optimism

In conclusion, while future studies will tell us whether common infections really do prevent atopy, the new questions raised by the "hygiene hypothesis" have already challenged immunologists, epidemiologists, and microbiologists (22). The answers may prove that the research opportunities offered by the epidemiology of allergic diseases are no longer being neglected (23).

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