

Allergens and allergy prevention: Where to next?

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Nature begins with the cause and ends with the experience; we need to operate in the reverse.

—Leonardo da Vinci¹

Incomplete understanding of the roles of both the intrinsic immune system and the environmental causes of allergic disease has necessitated an approach to allergy prevention that starts with the experience while not fully understanding the causes. It is not therefore surprising that both primary and secondary preventative strategies are only partially successful at best.

The latter part of the 20th century has seen large increases in the prevalence of allergic diseases, implicating changing environment and lifestyles as significant causes. Allergic sensitization, rhinitis, asthma, and eczema have all increased over this time, with asthma prevalence doubling over the period from 1970 through 1990 in the United States, Australia, and New Zealand and in much of Europe. Although asthma prevalence appears to be stabilizing in developed communities,² that of atopic eczema continues to increase,^{3,4} as does asthma prevalence in regions of rapid economic development.⁵ Thus important environmental influences might differ for differing manifestations of atopic disease. This further compounds the difficulties in trying to disentangle the influence of the

environment versus genetic variations of the immune system. Understanding the reasons for the global epidemic challenges the boundaries between the fields of human immunology, physiology, genetics, nutrition and neurology in one dimension and quantifying changes in our environment and lifestyle in the other. If anything has emerged from the years of intensive research, it is the complexity of every facet of these diseases. This special edition on allergen prevention addresses and explores some of these complexities, further understanding of which is fundamental to developing more successful preventative strategies.

An essential tenet of primary preventative strategies is the proposition that there is a “critical window”⁶ in early life during which the developing immune system is set on its eventual course. This issue is discussed in the reviews by Holt et al⁷ and Rautava et al.⁸ Starting with neonatal life, the review by Holt et al⁷ proposes an innovative model for asthma involving the acquisition of “memory” or “imprinting” on both the immune and respiratory systems of early-life exposure to viruses and allergens. Although many aspects, particularly those marking the progression of these changes over time and the interaction of innate and acquired immunity in this period remain to be clarified, the hypothesis provides a satisfying linkage of formerly disparate concepts of allergic and nonallergic asthma, the role of some respiratory viruses, and the maturation of the immune and respiratory systems. It is hypothesized that transit through this critical window, with active minimization of allergen exposure and respiratory syncytial virus infection, will reduce the development of persistent disease. The concept of the critical window itself deserves further examination. The incidence of occupational asthma in adults and acquisition of allergic diseases in immigrants to westernized countries from countries where protective factors would be expected to operate in infancy⁹ indicates that not all causes of allergic disease are restricted to early life. To the extent that allergic responses can develop throughout life, the success of strategies applied in infancy will be limited.

The issue of probiotics has captured not only the curiosity of scientists with an interest in allergy prevention but also the commercial world, with the worldwide probiotic market estimated to be about US\$6 billion.¹⁰ However, the scientific understanding of intestinal microbiota

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is in its infancy. The human gut contains about 1.2 kg of bacteria, and although the identity of many of these is unknown and uncharacterized, it appears that each person cultivates a few hundred of the many thousands of types of microbes that occur within a population. The gut is rapidly colonized in the first days of life, and by 2 years of age, the full complement of microbial species is reached and remains relatively constant throughout life. This provides a window in early life at which it might be possible to permanently influence both the long-term microbial environment and the developing immune system.

Rautava et al⁸ trace this relationship of the adaptive and innate immunity and the changing microbial cross-talk between the intestinal bacteria and the host. They further speculate that the principal microbial provocation resulting in nonatopic immune maturation in infancy might be derived not from foreign pathogens but from the indigenous microbiota, expanding the hygiene hypothesis into new territory. Further support for the concept of a critical window comes from the observation that probiotics appear to be effective in the prevention and treatment of atopic disease, particularly eczema, in infancy and childhood, although not in later life.

Many questions concerning the use of probiotics remain and demand exploration. The preliminary findings from the Allergyflora study¹¹ conducted in 3 European cities and presented at this year's Academy meeting showed little effect on total IgE levels or the incidence of atopic dermatitis or food allergy at 18 months associated with the variations in normal microflora in the first year. The process of colonization and gut flora composition in infants living in countries with a low prevalence of allergic disease is markedly different than that of children in a modern sterile society. A related issue is the influence of breast-feeding on the microbial flora and the possibility that some of the allergy preventative effects of breast-feeding might be due to the promotion of gut colonization by favorable intestinal microbes.¹²

In addition to systemic influences on the immune system, local modulations might be important. The article by Fiset et al¹³ suggests possible isotype switching to IgE in airway mucosa and discusses the concept of local IgE production. The proposal that switching might occur on seasonal exposure implies that detectable allergy might be reversible, temporary, and undiagnosed by conventional testing and further blurs the boundaries between allergic and nonallergic disease. A question concerning prevention is to what extent systemic measures, such as primary preventative immunotherapy or probiotic use, would influence local organ-based influences, such as those postulated by Holt et al,⁷ to affect the respiratory muscle hyperresponsiveness or local IgE production, as discussed by Fiset et al.¹³

Nowhere is the challenge of understanding these diseases more apparent than in the genetics of the regulation of IgE. In her review Vercelli¹⁴ notes the need for functional studies to decipher the molecular mechanisms involving gene expression or function that increase susceptibility to allergic inflammation. Allergic diseases re-

sult from combinations of and interactions among mild defects rather than massive genetic disruptions (ie, the sum of many small things). That genetic variants occur at increasing numbers of positions along the complex pathway regulating IgE provides for an almost infinite variety of individual genotypes. Vercelli contrasts the subtle effects of natural genetic variation with the often-profound immunologic effects of genetic manipulations in animal models. She suggests that real-life atopic diseases result from combinations of and interactions among mild genetic defects and highlights IL-13 as a critical effector of allergic inflammation. However, the more critical any one mediator or pathway is, the less the disease is determined by interactions among multiple subtle genetic defects. Zeno's paradox is based on the summation of an infinite incremental series. This raises the question as to how many pathways of inflammation contribute to the expression of atopic disease. The answer is yet to be determined.

That there is a long way to go to understand these diseases, even with modern technologies, is emphasized by the finding that in a simple mouse model allergen challenge upregulated the expression of 291 different genes. Saito et al¹⁵ demonstrate that the very technologies that provide us with such information also have their limitations. Factors currently confounding interpretation include the lack of reproducibility of cDNA arrays compared with oligonucleotide arrays, the relevance of animal cell lines to a human disease, the difficulty of using mixed cell populations, and the bias induced by amplification systems. These technologies have the capacity to eventually enable an understanding of the functional capacity of the elements driving the expression of the immune system and not view it only as isolated elements. The introduction of systems biology will hopefully provide additional insight into allergic diseases, as it has for cardiac disease.¹⁶

Although proof of principle has been hard to come by and in the case of primary prevention has been sorely challenged, many allergists believe a core approach to reducing the incidence of allergic diseases remains the avoidance of aeroallergens. This is addressed in 3 reviews. Eggleston¹⁷ presents a basic framework to control major allergens built on the cumulated experience in houses and underpinned by the lessons learned from occupational exposure. These methods can significantly reduce allergen sources and reservoirs in houses. The review of O'Connor¹⁸ takes a broader view and questions why trials of such interventions fail clinically if allergen exposure aggravates asthma. The primary reasons are suggested to lie in sensitization to multiple allergens and the ubiquity of opportunities for exposure at different domestic sites coupled with the partial effectiveness of the interventions. This particularly applies when an intervention addresses only one site or one allergen. Although trials can be identified indicating clinical success with an intervention, meta-analysis shows little benefit. What is required is further evidence on how interventions can be optimized. A common conclusion is that interventions need to be tailored to the individual exposure and allergies, address-

ing both allergens and irritants. Many approaches to exposure reduction are suboptimal, and better methods and quantification of those reductions are required.¹⁹ Why clinical responses to reductions in exposure differ widely is not understood; not all apparently ideal subjects respond to large reductions.²⁰ If the human immune response to chronic allergen exposure occurs over 4 orders of magnitude and allergen reduction is only of 1 order, reduction might not be sufficient to be effective. Paradoxically, in the most rigorous primary intervention to date, the children at age 3 years had better lung function but had more, not less, allergy.²¹ A clear message from all authors is that the current measures cannot be recommended as the basis of global public health strategies for the primary prevention. The steps that currently can be confidently undertaken for allergic disease prevention do not necessarily include attempts at allergen reduction. The review of Ashad²² concludes that only exclusive breast-feeding and avoidance of exposure to tobacco smoke can be safely recommended for the whole population.

The relentless increase in the prevalence of allergic diseases in the last century in affluent countries, their low prevalence in some populations living “indigenous” or “rural” lifestyles, the 2- to 3-fold differences in prevalence of different population groups within US cities, and the remission in disease in low-allergen environments, such as Antarctica and mountain sanatoria, all point to the powerful and fundamental role of the environment in driving both expression of disease and its symptom severity. The lower allergic prevalence in children in anthroposophic communities or in the general community 50 years ago also suggests that some smaller shifts in lifestyle within a broader allergy-prone environment might prove to be helpful. There is an urgent need to further understand the complexity of the interactions of lifestyle and environment on factors governing susceptibility and protection as it relates to the induction and expression of allergic diseases.

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