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From Farming to Engineering: The Microbiota and Allergic Diseases

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ABSTRACT

The steady increase of IgE-dependent allergic diseases after the Second World War is a unique phenomenon in the history of humankind. Numerous cross-sectional studies, comprehensive longitudinal cohort studies of children living in various types of environment, and mechanistic experimental studies have pointed to the disappearance of "protective factors" related to major changes in lifestyle and environment. A common unifying concept is that of the immunoregulatory role of the gut microbiota. This review focuses on the protection against allergic disorders that is provided by the farming environment and by exposure to microbial diversity. It also questions whether and how microbial bioengineering will be able in the future to restore an interplay that was beneficial to the proper immunological development of children in the past and that was irreversibly disrupted by changes in lifestyle. The protective "farming environment" includes independent and additional influences: contact with animals, stay in barns/stables, and consumption of unprocessed milk and milk products, by mothers during pregnancy and by children in early life. More than the overall quantity of microbes, the biodiversity of the farm microbial environment appears to be crucial for this protection, as does the biodiversity of the gut microbiota that it may provide. Use of conventional probiotics, especially various species or strains of *Lactobacillus* and *Bifidobacterium*, has not fulfilled the expectations of allergists and pediatricians to prevent allergy. Among the specific organisms present in cowsheds that could be used for prevention, *Acinetobacter* (*A.*) *lwoffii* F78, *Lactococcus* (*L.*) *lactis* G121, and *Staphylococcus* (*S.*) *sciuri* W620 seem to be the most promising, based on experimental studies in mouse models of allergic respiratory diseases. However, the development of a new generation of probiotics based on very productive research on the farming environment faces several obstacles that cannot be overcome without a close collaboration between microbiologists, immunologists, and bioengineers, as well as pediatricians, allergists, specialists of clinical trials, and ethical committees.

1. Introduction: Changes in lifestyle and the emergence of allergic/atopic diseases

In the second half of the 20th century, the impressive increase in IgE-dependent allergic diseases—also called "atopic diseases," and including asthma, allergic rhinitis, atopic dermatitis/eczema, and food allergies—became an embarrassing enigma. Since the 1980s, epidemiologists and immunologists have been addressing the questions raised by this unexpected increase, and all studies point to the responsibility of the major changes in lifestyle and environment that occurred in so-called "developed countries" after the Second World War [1–3]. Not all answers have been obtained yet; however, numerous studies (see Refs. [4–8] for a review) have now provided us with a conceptual and operational framework to better understand this unique phenomenon in the history of humankind. Coincidentally, there has been a renewal of interest in the microbiota: the billions of microorganisms that constitute the microflora, and that exert a symbiotic function in the gut of mammals. These microorganisms must definitely be considered as important actors in human homeostasis; their genome, the microbiome, interacts with

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the host's genome in many different ways [9,10]. The link that has been established between environmental influences and the gut microbiota in promoting immune tolerance, combined with progress in microbiota engineering, causes us to expect an exciting future for the treatment and/or prevention of allergic diseases. This issue is crucial: Even though the allergy epidemic seems to have now reached a plateau in most countries with a "westernized" lifestyle, it has become a global public health problem in countries with an emerging market economy, as well as in the continually growing cities of low-resource countries [11].

After summarizing the essential historical steps that led to our current understanding of the link between allergies and the microbiota, this review will focus on a particularly puzzling issue that emerged in the 1990s: the protection against allergic disorders that is provided by a farming environment. It will also question whether and how microbial engineering will be able to restore an interplay that was beneficial to the proper immunological development of children in the past and that was irreversibly disrupted by changes in lifestyle. Most of the results come from key cross-sectional studies performed in Europe—especially the Allergy and Endotoxin (ALEX) study [12], the Prevention of Allergy-Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) study [13], and the Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL) [14]—and from a European five-country case-control birth cohort that was specially designed to elucidate the relationship between farming and allergy—the Protection against Allergy: Study in Rural Environments (PASTURE), in which we have been involved for the past 13 years [7]. Complementary data is found in other studies performed all over the world [15–17] and in comprehensive reviews on allergy prevention using conventional probiotics [18–21]. Although it has become clear in the last few years that the microbiomes of the upper respiratory tract, skin, and lung, as well as that in breast milk, which was long considered to be sterile, are involved in the genesis and/or manifestation of allergic conditions [22–27], the cause-effect relationships are less well elucidated; thus, these relationships will not be taken into account in this review, which will focus on the gut microbiome.

2. Risk factors for the development of allergic diseases: Genes versus environment

2.1. Genetic factors

The family/hereditary nature of a series of disorders, including asthma, hay fever, and other types of allergic rhinitis, atopic dermatitis, urticaria, and food allergy, was first introduced in 1923 by Coca and Cooke [28], who proposed the common denomination of "atopic diseases." It is now accepted that a multifactorial determination combines genetic and environmental factors. Common genetic determinants operate for all diseases associated with an excessive or inappropriate IgE antibody response toward environmental antigens, and specific genetic determinants operate for the various clinical conditions [29,30]. Of allergic children, 50% have an allergic family history if grandparents are considered [31]; a tendency toward the same type of clinical manifestation in monozygotic twins also provides evidence of the genetic nature of atopy [32]. Recent genome-wide association studies have uncovered several novel genes underlying asthma, including single-nucleotide polymorphisms in *IL18R1*, *IL33*, *SMAD3*, *ORMDL3* (corresponding to variants on chromosome 17q21 and specific to childhood-onset disease), *HLA-DQ,* and *IL2RB* loci [33]. Most asthma/atopy genes are not replicable across populations because of differences in the epidemiology of these genes, as may be observed between Chinese subjects and subjects from other ethnic groups [34]. Studies on the gene polymorphisms of *ORMDL3* at chromosome17q21 somehow gave discordant results in different Chinese populations, although recent studies have shown that these polymorphisms were actually associated with childhood-onset asthma in the Han population of Northeast China, as found in Caucasian children [35].

The genes controlling IgE levels have been found to have little overlap with the genes mediating asthma susceptibility; the former are more directly involved in the "atopic" background [36,37]. The atopic—or IgE-dependent—immune profile is immunologically characterized by a predominance of type 2 T-helper cell (Th2) immune response, including the secretion of interleukin (IL)-4, IL-5, and IL-13, a profile that is also observed in helminth infections and in fetal life. This is in contrast to the type 1 T-helper cell (Th1) profile, which is dominated by the secretion of the pro-inflammatory cytokines tumor necrosis factor (TNF)-α and interferon (IFN)-γ, and which is adapted to fighting against bacteria and intracellular infectious agents [38]. Nevertheless, it may be kept in mind that 23% of children without any family disposition also develop asthma and/or allergy [19], and that this percentage is likely to increase with time in those countries where the incidence of allergy is still on the ascending slope.

2.2. Personal history and environmental factors

It is now well established that environmental factors play a major role both in the development of allergic sensitization and in the clinical expression of disease. As an example of family/personal environmental risk factor, maternal tobacco smoking is well recognized [39], and recently identified genes underlying asthma have been shown to interact with *in-utero* and early-life tobacco smoke exposure [40]. The increase in allergy incidence in western/northern Europe and in the US and the difference observed with "developing countries" were initially attributed to better diagnosis, as well as to new contacts with allergenic substances that were not or little encountered in the past. It soon appeared, however, that the incidence of allergic diseases might also be markedly different between "developed" regions/countries with a similar level of healthcare management, between urban versus rural environments, and/or between wealthier versus less wealthy regions/countries. A similar observation had already been made by a 18th century English family doctor who had stressed that, despite their usual contact with hay, farmers' children suffered extremely rarely from the seasonal hay fever observed in their rich and noble counterparts [41]! Comparisons between allergy prevalence in regions with different levels of development in China (e.g., Hong Kong, Guangzhou, and Beijing; or Hong Kong, Beijing, and Urumqi) and between the incidence of allergic diseases in the first versus the second generation of immigrant populations from developing to developed countries have fully supported the role of lifestyle changes, irrespective of the genetics of the populations [15–17,42–45]. Epidemiology research in the 1980s and 1990s globally ruled out the responsibility of air pollution in the increased incidence of allergy and confirmed its responsibility in the severity of respiratory clinical symptoms [46]. Studies on breast feeding and/or food diversification in the first year of life provided rather non-conclusive results, which are summarized in reviews and meta-analyses [47,48].

Cross-sectional studies performed in the 1980s and 1990s stressed a series of environmental situations that could explain the "post-industrial revolution epidemic" of allergies. For example, the "protective effect" of a high number of siblings was the origin of the popular "hygiene hypothesis" proposed by Strachan in 1989 [49], which was further supported by similar observations in other countries [50,51] and by the protective effect of early-life day-care attendance and of common viral infections of childhood such as hepatitis A, measles, or *Toxoplasma gondii* infection [52–55].