

EDITORIAL

What is needed for allergic children?

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I confess: I am not a pediatrician. But I am a father of three (two allergic) and grandfather of four children (one allergic). My medical thesis was titled: 'Allergy in young people'. I lived through the era of total avoidance, more or less foods, pets, mites, plants, forests, grasslands, boulevards decorated with deciduous trees, food additives, chemicals, etc. All that meant dangerous life for an allergic child or a child at hereditary risk. And yes, avoidance of potentially severe symptom-causing agents is still, and should stay, in the armamentarium of a competent allergist. But something has fundamentally changed. Let us face it.

An ever-growing proportion of populations suffers not only from allergies and asthma but also from other chronic inflammatory diseases, also referred as non-communicable diseases (1, 2). To quote UN General Secretary Ban-Ki Moon: 'Non-communicable diseases are a public health emergency in slow motion'. More and more people around the world are living in cities and experiencing little contact with nature. Environmental microorganisms, especially commensals, previously ubiquitous and abundantly present, for example, in drinking water and milk, are key players for the induction and maintenance of immunoregulatory circuits and tolerance. Adaptation to modern urban life is a challenge to immune development and mismatched immunologic mechanisms lead to symptoms and disease. Contact with natural environments rich in species seems to be strongly related to immunotolerance via the presence of beneficial protective microbes of the skin, gut, and airways. These microbes create a living interface between human body and the environment and extend deeper in the tissue than known before (3).

Karelia allergy study

In the Karelia area, northeastern Finland, we found that environmental biodiversity, human skin microbiome, and atopic allergy are interrelated (4). Teenagers were tested for sensitization to a range of common allergens. Skin swabs were taken from the forearm to identify the composition of the skin microbiota (bacteria living on their skin). The environment

surrounding the homes of the participants was recorded, including the identification of plant species and type of land use.

The results suggested that contact with biodiverse natural environment with abundant bacteria, and probably with other microbes, can protect people from becoming sensitized to allergens, by building up the immune system. In particular, the sensitivity of teenagers to allergens appeared to be linked to diversity of plants around the home. Healthy teenagers had a greater diversity, especially of one group of indicator bacteria, gammaproteobacteria, on their skin compared with sensitized (atopic) teenagers. The abundance of certain bacteria on the skin of healthy teenagers was also positively associated with the expression of the anti-inflammatory signaling molecule, interleukin-10, in the peripheral blood mononuclear cells.

The study implies that a high genetic diversity of bacteria on the skin is linked to increased tolerance against allergens. For example, gammaproteobacteria are found in the soil, on plant surfaces, on grass pollen, and in dust and are more diverse in the natural than in the urban environment. In women, they are especially found on the skin, but also in axilla (breast-feeding) and vagina (birth) (5). Babies born by cesarean section (bypassing vaginal microflora) are at increased risk of asthma (6), and supplementation with probiotics may be especially useful for them (7).

The allergy protective 'farm effect' is well known and includes exposure to diverse composition of bacteria and fungi (8, 9).

Concepts of biodiversity

According to Convention of Biological Diversity, biodiversity is the variability among living organisms from all sources, including diversity within species, between species and of ecosystems (10). In practice, the key elements of biodiversity include genetic diversity of populations and species.

Biodiversity does not only concern plants and animals but also includes microorganisms, which are less visible but comprise the bulk of living matter on our Earth (11). Thus,

biodiversity concerns both environmental and commensal microbiota.

We have proposed that biodiversity at the level of macrobiota and microbiota is interrelated in that biodiversity loss of the former is likely to be associated with loss of diversity of the latter (12). Moreover, biodiversity loss leads to reduced interaction between environmental and human microbiotas. This in turn may lead to immune dysfunction and impaired tolerance mechanisms in humans.

The rate of biodiversity loss is escalating as the indicators reflecting the various pressures on natural environments continue to increase. For example, one-third of the sufficiently well-known species of animals and plants are currently classified as threatened (56,000 species). Human activity has accelerated the natural rate of extinction of species 100–1000 times. The ecologists are speaking of the sixth mass extinction, which is caused by one species only, man (13).

What these observations mean?

Health implications

Biodiversity loss has a variety of possible adverse consequences for humanity. Indeed, the two global megatrends, one in the state of biodiversity, that is, altered biosphere, and the other in the prevalence of mucosal inflammatory diseases, may be closely linked. Recently, even emergence and transmission of infectious diseases have been associated with the impacts of biodiversity (14).

Humans have evolved with microorganisms, which may not only comprise bacteria and fungi, but also viruses and microscopic protozoans, although hardly any data on the latter are available.

Human commensals are no longer considered as passive bystanders or transient passengers, but increasingly as active and essential participants in the development and maintenance of barrier function and immunologic tolerance (15). The indigenous flora does not elicit defensive immune responses, but rather induce immunoregulatory circuits. A suddenly reduced abundance or diversity of these microorganisms, previously ubiquitous, may have led to failures to regulate and restore appropriate immune and inflammatory responses.

Inflammation

Inflammation is a cardinal feature of asthma and allergic diseases, autoimmune diseases, and many forms of cancer, but more recently, less tangible associations have been linked to these trends such as an increased incidence of obesity and depression with inflammatory markers (16, 17). Also autism and Alzheimer disease have been associated with microbial deprivation (18, 19). Thus far, the increase in the prevalence of inflammatory disorders is a phenomenon largely restricted to the developed world, while such disorders are still uncommon among populations in non-affluent regions, that is, those regions, which still have more traditional non-urban lifestyles (20).

Table 1 Practical advice to buildup and improve tolerance for primary prevention, symptom prevention (secondary prevention), and prevent exacerbations/attacks (tertiary prevention) (26, 29)

Primary prevention
Support breastfeeding, solid foods from 4 to 6 months
Do not avoid environmental exposure unnecessarily (e.g., foods, pets)
Strengthen immunity by increasing connection to natural environments
Strengthen immunity by regular physical exercise
Strengthen immunity by healthy diet (e.g., traditional Mediterranean or Baltic type)
Use antibiotics only for true need, majority of microbes build up healthy immune function
Probiotic bacteria in fermented food or other preparations may strengthen immune function
Do not smoke (e.g., smoking parents increase asthma risk in children)
Secondary and tertiary prevention
Regular physical exercise is anti-inflammatory
Healthy diet is anti-inflammatory, (e.g., traditional Mediterranean or Baltic diet improves asthma control)
Probiotic bacteria in fermented food or other preparations may be anti-inflammatory
Allergen-specific immunotherapy:
Allergens as is (foods)
Sublingual tablets or drops (pollens, mites)
Subcutaneous injections (e.g., insect stings)
Hit early and hit hard respiratory/skin inflammation with anti-inflammatory medication
Find treatment for long-term control
Do not smoke (e.g., asthma and allergy drugs do not have full effects in smokers)

*Much like a rainforest,
your body is an ecosystem of microbes
that constitute a newly discovered 'organ'
– your microbiome weighing around 1 ½ kg.*

Dysbiosis

The reduced diversity and disturbed composition of the human microbiotas may have caused an imbalance of 'proinflammatory' and 'anti-inflammatory' microbes, that is, dysbiosis and increased susceptibility of the host to inflammatory conditions (21). Collectively, sedentary lifestyle in affluent urban environments does not provide adequate microbial exposure to develop 'healthy' microbiota on the skin and mucosa. An indirect illustration of this concept is that fecal microbiota transplant has been successfully used to restore the microbiota balance in severe *Clostridium difficile* infections resistant to all other treatments (22).

Immune tolerance

The concept of inducing tolerance and homeostasis may become a prime target for prevention and treatment strategies for many diseases of the modern time in which dysregulation of

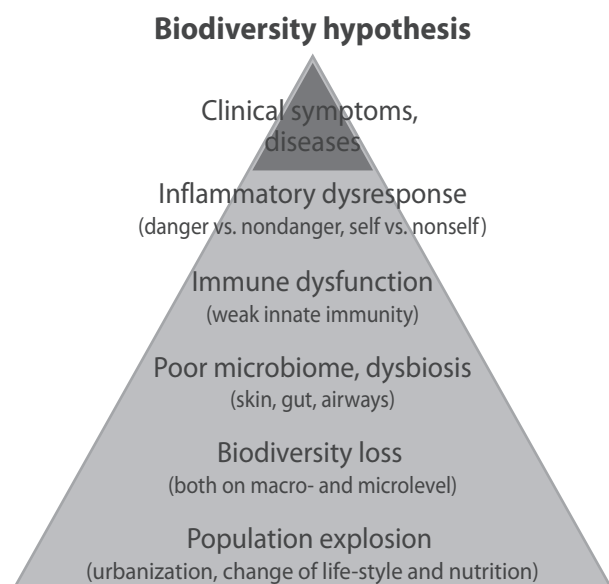


Figure 1 The biodiversity hypothesis linking environmental and lifestyle changes to immune dysfunction and human disease (31).

the immune system plays an essential role. We know, that in allergy treatment, inducing immune tolerance to allergens is characterized by establishment of a long-term clinical recovery (23, 24). However, both the adaptive and innate immunity should be targeted to obtain long-term results. An interesting natural remedy is birch pollen honey, where also commensal bacteria like several strains of lactobacilli live (25).

From theory to practice

The aim of the ongoing Finnish Allergy Programme 2008–2018 was to take the step from treatment to prevention and endorse health instead of allergy (26, 27). A clear distinction is made between those who have mild disease and those who are at risk of suffering severe consequences from these diseases. In the praxis of allergy, prevention and treatment medicalization is not uncommon.

Strategies and recommendations for prevention of allergies have typically been quite restrictive based on relatively poor scientific evidence. New data imply that most children do not benefit in longer term from avoidance diets or by taking extra precautions to avoid environmental allergen exposure (28). Therefore, the health of children is best served by giving

similar recommendations to every child, that is, a balanced diet, physical activity, and a close connection with the natural environment, whether he/she is allergic or not (29). This does not mean that the environment should not be improved in many ways. Anti-smoking advice and legislation stopping smoking should be implemented as exposure of children to environmental tobacco smoke is still a major problem. Indoor and ambient air pollution should be tackled accordingly.

Food allergies and asthma have been on the increase from a global perspective until recently although in countries such as Finland, the incidence of many allergic diseases seems to have reached a plateau. The numbers are so big that not all children with allergies can receive specialist medical care. It is neither in society's nor in the patients' interests to provide specialist treatment to large numbers of people with mild symptoms that can hardly be diagnosed as a disease. Both GPs and nurses at well-baby clinics, healthcare centers, and schools need to be provided with straightforward instructions to take care of children with mild symptoms. An important aspect is also relaying the correct public health messages (30). Overall, the population should be encouraged to adopt sensible behaviors, getting rid of unnecessary diets, but consume diets that promote general health and immune balance. The Finnish recommendations are listed in Table 1. Everything the child eats, drinks, touches, or breaths modulates the microbiome and keeps immune processes alert. Tolerance is an active process, trained and tested by the environment on line. It is not by mistake that babies, when starting to get familiar with their environment, put everything in their mouth.

Action needed

Recently, the World Allergy Organisation Special Committee on Climate Change and Biodiversity launched a position statement of the new biodiversity hypothesis (31). It can be regarded as an extension of hygiene or 'old friends' hypothesis and microbial deprivation (microbiota) hypothesis. Population growth (urbanization) leads to loss of biodiversity (poor macrobiota/microbiota), poor human microbiota (dysbiosis), immune dysfunction (poor tolerance), inappropriate inflammatory responses, and finally symptoms and clinical disease (Fig. 1). The interplay of environmental genome (macrobiome), human microbial genome (microbiome), and human genome determines health and diseases. It is time to revisit the allergy paradigm and consider new kind of actions to combat the burden.

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