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Hygiene hypothesis: wanted—dead or alive

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The hygiene hypothesis is an intriguing attempt to explain the rise in allergy and asthma (and other immunological diseases) in populations undergoing changes in the environment towards increasing cleanliness, use of vaccinations and antibiotics, lower rates of infections, etc. In many ways this idea is appealing and seems to offer a unifying explanation of many epidemiological observations. However, in a recent issue of the *IJE*, Douwes and Pearce¹ summarize different controversies relating to the hygiene hypothesis in their commentary on the observed recent decrease in asthma in Australia.² As pointed out by Douwes and Pearce, recent downward trends of asthma/allergy prevalence reported in some countries seem unlikely to be explained by a decrease in hygiene and they conclude that new aetiological theories may be required.

The hygiene hypothesis assumes that exposure to micro-organisms—by their binding of their antigens to innate immune receptors—skews the immune system towards a Th1 response favouring a ‘non-allergic’ immune response. In other words, increased exposure to antigens from microbes ‘protects’ against allergy/asthma. Although experimental data has often supported this idea, the hygiene hypothesis does not seem to explain all-time trends and differences in prevalence between and within different populations. This author has recently proposed³ that one of the reasons why the hygiene hypothesis fails to explain many epidemiological trends is due to the possibility that it—in its current version—does not take into account reduced exposure to the quantitatively most important environmental airborne antigens, i.e. antigens of common allergens such as allergens from pollen, house dust mites, animals and moulds. Reduced

allergen exposure may be one of the factors underlying the higher risk of IgE-mediated allergic disease in populations with urbanized, Westernized and affluent lifestyle.³ This lower allergen exposure results in failure to induce and maintain immune tolerance to common environmental allergens and increased risk of allergic disease in genetically susceptible individuals. Several lines of evidence support this idea. First, numerous experimental animal studies have shown that exposure to high allergen doses (introduced by the oral or respiratory route or by injection) induces tolerance, whereas exposure to low allergen doses confers an increased risk of IgE sensitization. Second, many, but not all, observational epidemiological studies suggest that exposure to pets decreases the risk of pet allergy. Third, randomized intervention studies of house dust mite allergen avoidance (both primary/secondary and tertiary prevention) do not support that avoidance has beneficial effects on sensitisation or clinical outcomes.^{4–7} Finally, there is a large body of evidence to support that the induction of immune tolerance in allergic patients can be obtained by allergen-specific immunotherapy (large doses of allergens introduced via the oral, mucosal, intravenous or subcutaneous routes) underlining the pivotal role of the concept of immune tolerance induction by high-dose allergen exposure.^{8,9}

The complexity of this issue should be acknowledged to the greatest extent possible. Many apparently contradictory data might be explained by the possibility that the dose–response relationship between allergen exposure and sensitization is bell-shaped, i.e. increasing exposure in the lower range increases risk of sensitization, while increasing exposure in the higher range decreases risk of

sensitization.^{10–13} Lower allergen exposure as a contributing factor to the allergy epidemic may be viewed as an extension of the hygiene hypothesis. But the question is whether the recent decrease in atopic diseases in some countries can be explained by an increase in allergen exposure, which remains to be addressed. It is likely that recommendations/guidelines for allergen avoidance in families with atopic predisposition (that may also have been taken up by non-atopic families) may have been endorsed with decreasing enthusiasm by physicians as the negative trials of allergen avoidance were published. Thus, although the environment has not become cleaner, it is possible that allergen exposure has increased.

When it comes down to all, the best evidence to prove or dispute the hygiene hypothesis will probably come from ongoing and future randomized trials of interventions, e.g. treatment with probiotics and microbial products, that have been developed in the light of the hygiene hypothesis. In the mean time, we must prepare ourselves to face the results of these trials as well as of other types of evidence. It is a possibility that it may turn out that the hygiene hypothesis is more dead than alive, or at the least needs another revision. This author proposes that it should take into account exposure to antigens not only from microbes, but also from allergens abundantly present in environment and foods.

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Author's Response

Hygiene hypothesis: wanted—dead or alive

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Linneberg in his letter¹ offers a complementary explanation for the previous large increase and the recent small decline in asthma prevalence in several high

income countries. Linneberg argues that the increase in allergic disease observed earlier may have been due to a *lack* of high allergen exposures in many westernized