

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

populations,² and that a more recent *increase* in common environmental allergen exposure may have contributed to the recent decrease in prevalence by inducing immune tolerance.¹ For this to be true, a relatively large change in exposure would be required, with a strong decrease in exposure levels several decades ago, the maintenance of relatively low levels in the past few decades and a return to relatively high levels in the past 5–10 years, i.e. the trends for allergen exposure in the population would have to be the inverse of the trends in asthma prevalence.

In the past the opposite hypothesis has been advanced, i.e. that allergen exposure levels had increased and were the cause of the increasing asthma prevalence between the 1960s and 1990s.³ In fact, there is relatively little evidence to support either hypothesis. Few studies have assessed allergen levels at different time points. The only study of English homes at two time points (1979 and 1989) did not demonstrate any change in house dust mite allergen levels⁴ whereas asthma levels appeared to have increased from the early seventies to the early nineties in England and Wales.^{5–7} This argues against a prominent role for allergens, but results are based on only one exposure study and the increase in asthma prevalence for the relevant time period reported by Anderson *et al.*⁶ was only very modest (a 15% increase); the increases measured in asthma prevalence in the other two studies^{5,7} was more substantial (a 50–100% increase). Thus, there is little evidence for the hypothesized change in allergen exposures and we do not consider the explanation provided for a potential increase in allergen levels (i.e. that the largely negative results of allergen avoidance trials have lead to fewer people taken up allergen avoidance measures resulting in higher allergen exposure levels¹) very plausible.

Similar arguments have also been advanced in the past to explain geographical differences in asthma prevalence,³ i.e. that countries or regions with high levels of allergen exposure may be more (or less) likely to have high levels of asthma prevalence. Once again, there is little consistent evidence to support either version of this hypothesis. Some of the highest house dust mite allergens have been measured in New Zealand and Australia which are both countries with a relatively high prevalence of allergies and asthma.⁸ Similarly, inner city dwellings in the United States are known to have very high levels of indoor allergens including cockroach, dust mite and rat and mice allergens and the occupants have high prevalences of allergies and asthma.⁹ However, comparisons between centres in Australia, New Zealand and the United States show very similar levels of asthma and atopy prevalence across these countries, and across centres within these countries which have widely differing allergen exposure levels.¹⁰ Other available evidence on the association between allergen exposure and the subsequent risk of asthma at the

population level is also less than persuasive. For example, Leung *et al.*¹¹ reported that asthma prevalence was high in Hong Kong (6.6% for asthma ever), and low in San Bu, China (1.6%), but exposures to house dust mite allergen were similar in both places. Similarly, Von Mutius *et al.*,¹² found that asthma was significantly higher in Munich, West Germany (5.9%) than in Leipzig, East Germany (3.9%), and this paralleled the pattern of skin prick test positivity (19.2% and 7.3%). However, house dust mite allergen levels were similar in the East and the West.¹³ This therefore does not suggest that indoor allergen levels play a major role (either positively or negatively) in the prevalence of asthma, and that they are therefore also not very likely to play a role in the observed time trends.

Linneberg further argues that the dose–response curve may be bell-shaped with intermediate allergen exposures showing the greatest risk and high and low exposures showing a low risk. Under this scenario, most Western populations would have exposure levels that moved up and down the ‘right-hand’ side of the bell curve, with high allergen levels and low prevalence of atopic disease before the sixties, decreased levels after the sixties with increased prevalences of allergies and asthma, and increasing levels with a subsequent decline in atopic conditions in the past 5–10 years. There is some published evidence for a bell-shaped dose–response relationship for house dust mite allergen exposure and mite sensitization and asthma including a recent birth cohort study in Australia,¹⁴ as well as several cross-sectional studies in the general population (cited by Linneberg). Bell-shaped dose–response curves have also been shown for occupational allergens, such as rat and wheat allergens.^{15,16} However, these were shown predominantly in cross-sectional studies where the non-linear relationship may be explained by the ‘healthy worker effect’ whereby symptomatic and/or atopic workers avoid high exposure jobs and/or migrate from high to low exposure jobs.¹⁶ Prospective studies in occupational populations, which are less prone to these selection effects, have shown mixed results with some suggesting bell-shaped associations¹⁷ and others showing linear dose–response relationships with the greatest risk of sensitization or symptoms in the most highly exposed groups.^{18–20} The evidence for a modified Th2 response (or tolerance) at high exposures is therefore not consistent.

In fact, the bell-shaped dose–response curve observed in some of the studies cited above may not be a direct function of high allergen exposure itself, but could be due to other immunomodulating agents associated with high allergen exposures that could protect against allergies and asthma. For example, pets in the home have previously been shown to be associated with elevated endotoxin levels,²¹ which may protect against allergies and asthma. Similarly, in occupational environments high allergen exposures

are likely to be associated with high exposures to other (protective) agents present in organic dust, which may be responsible for the attenuation of the dose-response association observed in some studies. Also, a non-linear dose-response curve observed in the general population may be caused by allergen avoidance measures taken by parents of high risk and/or symptomatic children (comparable to the healthy worker effect described above), although this would be less of a concern in the study by Tovey *et al.*¹⁴ who followed children from birth and included only high risk children.

In summary, although there is some (inconsistent) evidence for non-linear dose-response relationships between allergen exposure and atopy and asthma both in the general population and occupational populations, the evidence that tolerance could explain the observed time trends in allergy and asthma prevalence is currently weak. This conclusion is reinforced by the observation that at most about one-half of asthma cases involve allergic mechanisms,²² and it is only these cases that would be affected by the mechanisms hypothesized by Linneberg, so the changes in allergen levels, and the resulting health effects, would have to be very strong. In fact, there is no indication that allergen levels are on the rise (and have declined previously), and evidence at the population levels does not suggest that highly exposed populations have lower (or higher) asthma prevalence. Also, what is perceived as tolerance may in fact be caused by protective effects of immune-modulating co-exposures. Nonetheless, we cannot exclude the possibility that allergen tolerance plays a minor role in explaining recent and previous time trends. We therefore agree that future studies should not only focus on the potentially protective effects of microbial agents, but should also take into account exposures to common allergens. Using occupational models of asthma¹⁵ employing detailed exposure assessment strategies for both allergens and other potentially protective co-exposures is likely to shed new light on the roles of these exposures in the development of asthma and the validity of the hygiene and allergen tolerance hypotheses more generally.

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