

## Editorial

## A new beginning!

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*The beginning of knowledge is the discovery of something we do not understand.*

—Frank Herbert

For more than 20 years, we have understood that asthma is more prevalent and severe among residents of largely impoverished urban or inner-city environments in the United States.<sup>1</sup> Tremendous efforts have been made to better understand which exposures in urban environments drive the high prevalence of asthma.<sup>2</sup> As allergists, it seemed essential that studies of urban environments largely focus on finding dominant allergens in these environments, with less interest toward other exposures.<sup>3</sup>

Coincident with the efforts to understand urban asthma has been the development of the hygiene hypothesis, suggesting that “clean living” was partially responsible for an increasing prevalence of allergic disease. Some have asserted that the high prevalence of asthma in city environments is evidence against the hygiene hypothesis, assuming that housing in impoverished urban areas is substantially less hygienic and therefore that there must be higher levels of bacteria in urban homes. The glaring flaw in this assertion is the assumption that all bacteria found in homes have similar effects on human subjects. It is unlikely that the types of bacteria found in urban homes in the United States resemble those found in traditional family farm houses of Bavaria.

The article in this issue by Lynch et al<sup>4</sup> suggests that we must radically shift our thinking about which environmental exposures most strongly influence the risks of allergic disease and asthma in urban homes. The key insight presented in this article is the role that exposures to specific types of bacteria appear to play on the risks of allergic sensitization and asthma and the fact that these exposures are correlated with exposures to well-known allergens. The authors go so far as to suggest that the sources of major allergens (eg, cockroaches and mice) are also the sources of the bacteria associated with a reduced risk of allergic disease. If it is true that cockroaches and mice are important sources of both major allergens and potentially allergy-suppressive bacteria, we have an interesting yin and yang that might explain some of the inconsistencies and apparent contradictions of previous reports regarding allergen exposures and urban asthma.<sup>5,6</sup> Indeed, this article confirms the findings of many others that cumulative

allergen exposure over the first 3 years of life was significantly associated with allergic sensitization and that detectable allergic sensitization at age 3 years was associated with recurrent wheezing. The paradoxical finding is that high exposure to mouse and cockroach allergens in combination with high exposure to the bacteria correlated with the presence of these allergens, in particular Firmicutes and Bacteroidetes, was associated with less atopy and wheezing.<sup>4</sup> This finding is most clearly illustrated by Fig 3 in the article, showing that children with neither atopy nor wheeze were exposed to both high microbe and allergen levels 41% of the time in contrast to exposure only 28% of the time to high microbe and low allergen levels.

Although the study by Lynch et al<sup>4</sup> suggests the need for an immediate reassessment of our conceptual framework relating exposures to allergic disease, many previous studies have supported a central tenant of the hygiene hypothesis, which is that there is a strong inverse relationship between exposure to sources of high bacterial diversity and allergic disease.<sup>7</sup> The current findings are also similar to those of Lau et al,<sup>8</sup> showing that sensitization to indoor allergens was related to wheezing at age 7 years but that there was no relationship between early indoor allergen exposure and the prevalence of asthma, wheeze, and bronchial hyperresponsiveness.

Despite the striking findings of Lynch et al,<sup>4</sup> there are important limitations to consider. Only 104 children were studied in a nested case-control design of the 560 children originally enrolled in the study. It is impossible to know whether a bias was created when the subsample of 104 was selected. The main clinical outcome of the study was an unverified parental report of wheezing at 3 years of age. A previous study has shown that of 186 parents reporting wheezing in children less than 3 years of age, immediate examinations by physicians were able to confirm wheezing in only 130 (70%).<sup>9</sup> We have also learned that 60% of children who wheeze before 3 years of age will not wheeze at 6 years of age.<sup>10</sup> The children and homes in this study were spread across 4 study cities, and little information is given about differences beyond racial makeup in these cities.

As with many breakthrough articles, this article raises many more questions than it answers. The data presented by Lynch et al<sup>4</sup> suggest that certain types of bacteria were associated with a lower risk of allergic sensitization and wheezing, which is consistent with some other studies.<sup>11</sup> However, other studies have suggested that the overall variety of bacterial types in an environment (bacterial richness) is the parameter related to less disease.<sup>7</sup> The dust samples analyzed for bacterial content in the current study were from living room floors, but others have shown substantial variation in the microbial richness of samples taken from different locations in homes, with door frames and television screens showing the greatest diversity.<sup>12</sup> Similarly, if specific types of bacteria are more strongly associated with a lower risk of allergic disease, do the home locations in which these bacteria are found affect the association with risk? By design, the current study examined children in urban environments, raising the question

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of whether studies of children in suburban or rural settings would yield similar findings. Also, would findings be similar in different regions of the United States or different countries?

Another important challenge from the study by Lynch et al<sup>4</sup> is to learn how children in homes are exposed to potentially beneficial microbes and what happens after exposure. The 2 most obvious routes of exposure are inhalation and the oral route. There is a literature showing that children and adults ingest approximately 50 mg of dirt per day. These estimates of soil ingestion are based on measuring the quantities of trace elements found in soil but not in foods in stool samples. These estimates allow the demonstration of a clear correlation between the frequency of hand-to-mouth activity in children and their exposure to dust-borne pollutants, such as lead.<sup>13</sup> It will be more challenging to estimate the quantities of airborne microbes reaching different levels of the respiratory tract during respiration. Bacteria trapped in the mucus of the nose are predominately swallowed, but some are likely to penetrate at least into the larger conducting airways, contributing to the lung microbiome.<sup>14</sup> Finally, there is direct contact between many surfaces in the home and a person's skin, and there is a well-established skin microbiome. The skin microbiome is clearly important in diseases such as atopic dermatitis, but little is known about whether the skin microbiome influences the function of the immune system beyond the skin.

If we accept that exposure to certain common environmental bacteria can substantially reduce the risk of allergic sensitization and atopic wheeze, the question becomes whether this knowledge can be used therapeutically. Trials of prebiotics and probiotics have shown modest effectiveness, but is this because the wrong bacteria were used or because whole communities of bacteria are required before risk is substantially reduced? Alternatively, probiotics might not be given at optimal times or in a way that will allow meaningful colonization. Will it be necessary to administer live bacteria, or will substances from killed bacteria be effective? Given the challenges of trying to conduct studies administering live bacteria to infants, perhaps it will be easier to attempt to intervene with the home microbiome?

This article provides a brief glimpse of how important bacteria-human interactions are in allergic disease within the confines of an urban environment. The article shows how the emergence of culture-independent techniques for studying

bacteria has opened a new avenue for increasing our understanding of the health effects of exposure to the massive array of bacteria in human living environments. Many more studies will be required to more fully appreciate the extent of these interactions on the broad range of human allergic diseases.

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