*Editorials*

## Eat Dirt — The Hygiene Hypothesis and Allergic Diseases

THERE has been an epidemic of both autoimmune diseases (in which the immune response is dominated by type 1 helper T [Th1] cells, such as type 1 diabetes, Crohn's disease, and multiple sclerosis) and allergic diseases (in which the immune response is dominated by type 2 helper T [Th2] cells, such as asthma, allergic rhinitis, and atopic dermatitis), as documented in the article by Bach in this issue of the *Journal*.[1] The occurrence of these diseases is higher in more affluent, Western, industrialized countries. One theory proposed to explain this increase in the prevalence of autoimmune and allergic diseases is that it results from a decrease in the prevalence of childhood infection. Although this theory dates back to at least the mid-1960s in relation to Th1-mediated diseases, Strachan first proposed in 1989 that this theory might also explain the increase in Th2-mediated diseases,[2] and it has subsequently come to be called the hygiene hypothesis. A gradual change in the frequency of childhood infection has been occurring for a long time, affected by the introductions of indoor plumbing in the 19th century, antibiotics in the middle of the 20th century, and cleaner, more energy-efficient homes at the end of the 20th century.

Bach details a number of potential mechanisms by which the decrease in the frequency of childhood infections might influence the frequency of autoimmune diseases. In the light of the article by Braun-Fahrländer and coworkers,[3] also in this issue of the *Journal,* two mechanisms deserve special attention. The first is that the decrease in antigenic stimulation related to the decrease in the frequency of childhood infections has resulted in a decrease in the levels of regulatory cytokines — specifically, interleukin-10 and possibly transforming growth factor $\beta$ (TGF-$\beta$). CD25-positive T cells and other regulatory T cells produce interleukin-10 and TGF-$\beta$ and act to down-regulate both Th1-mediated responses and Th2-mediated responses. It is unclear how interleukin-10 and TGF-$\beta$ affect T-cell differentiation and regulation to generate a normal, robust, and balanced Th1 and Th2 immune response in the developing child, and this is clearly a fruitful area for immunologic investigation. Unfortunately, the data on cytokines in the article by Braun-Fahrländer and coworkers shed little light on this issue, because they used only one measurement, which was obtained after the peak age for the onset of asthma. The second mechanism addressed by Braun-Fahrländer et al. is that stimulation of the innate immune system by endotoxin may be important in the ontogeny of the normal immune system.

A series of epidemiologic reports suggests that there has been a decrease in the frequency of allergy and asthma among children of farmers in Western, industrialized countries.[4,5] The current study by Braun-Fahrländer et al.[3] is a cross-sectional study involving 812 children between 6 and 13 years of age from farming and nonfarming households in rural areas of central Europe. The investigators measured endotoxin levels in mattress dust and found a relation between higher levels of endotoxin in the dust and a decreased frequency of hay fever, allergic asthma, and allergic sensitization in these children.

Endotoxin is a lipopolysaccharide that forms the outer layer of the cell membrane of all gram-negative bacteria. Endotoxin levels vary widely but tend to be highest in environments where there are farm animals such as cows, horses, and pigs, because the fecal flora of larger mammals is a major source of endotoxin. Endotoxin is also found in the dust in houses and outdoors in dirt and can be measured in dust or air. In its airborne form, endotoxin can be inhaled or swallowed and acts as a potent immunostimulatory molecule through its lipid A moiety, which signals, through CD14 and toll-like receptor 4 (TLR4), other molecules (MyD88 and toll-like receptor 9 [TLR9]) of the innate immunity pathway.

How does endotoxin decrease Th2-mediated diseases such as allergies and allergic asthma? At low levels, lipopolysaccharide is a potent inducer of interleukin-12 and interferon-$\gamma$, which are cytokines that stimulate Th1-mediated immunity, and also decreases the production of Th2 inflammatory cytokines such as interleukin-4, interleukin-5, and interleukin-13. Finally, lipopolysaccharide increases defensins and collectins, such as surfactant protein A in the lungs, which enhance the developing immune response of a neonate. The effects of endotoxin are dose-dependent; at high doses, endotoxin produces hypersensitivity pneumonitis and stimulates the release of inflammatory mediators.[6] Even at low doses, endotoxin is associated with wheezing during the first year of life.[7] Given these potential opposing effects of endotoxin exposure, greater knowledge about what dose of endotoxin is protective and what dose is a risk factor is needed.

Beyond the dose, whether exposure to endotoxin is protective or harmful is likely to depend on a complex mixture of the timing of exposure during the life cycle, environmental cofactors, and genetics. In both animal models and studies in humans, exposure to endotoxin early in life, during the development of the immune system, seems to be most important in providing protection against the development of allergic disease. That exposure to farming during the first year

of life conferred an additional protective effect over and above that of the current endotoxin level, as demonstrated by Braun-Fahrländer et al., is indicative of the importance of the timing of exposure and other, as yet poorly understood, aspects of farm life.

Environmental cofactors may also be important. Endotoxin is a hitchhiker that can attach itself to particulate air pollutants that might potentiate the immune effects of endotoxin. The levels of heat-shock protein and beta 1,3 glucan, the latter an immunostimulatory cell-wall component of fungi, yeast, and plants, correlate with levels of endotoxin in house dust. These factors, which were not measured in the current study, may also play a part in the immune effects that were observed. A final environmental cofactor may be the presence in bacterial DNA of greater numbers of unmethylated cytidine–phosphate–guanosine sequences than are present in mammalian DNA. These sequences are sensed by TLR9, which interacts with TLR4 and may potentiate immune stimuli when activated by lipopolysaccharide.[8]

Finally, genetics is an additional determinant of the response in any given person. Case–control association studies have suggested that a TT polymorphism in the promoter region of CD14, the receptor that binds lipopolysaccharide, is associated with higher levels of soluble CD14 in peripheral blood and, in persons with allergies, with lower serum IgE levels and decreased sensitization to allergens.[9] Although TLR4 polymorphisms and haplotypes do not appear to be associated with the asthma or allergy phenotype (Raby B: personal communication), it is a reasonable hypothesis that the promoter variants in TLR4 interact with endotoxin levels in determining susceptibility. Although the study by Braun-Fahrländer et al. represents an important advance, it was a cross-sectional association study involving patients with diagnosed asthma. We will need longitudinal studies of birth cohorts with appropriate timing of environmental sampling in order to address the issues of dose, timing, cofactors, genetics, and their effects on the development of disease.

Eating dirt or moving to a farm are at best theoretical rather than practical clinical recommendations for the prevention of asthma. However, a number of environmental factors are known to be associated with a lower incidence of allergic disease in early life. Oral supplementation with *Lactobacillus ruminus*[10]; the presence, from before birth onward, of a dog or other pet in the home[11]; and attendance at day care during the first year of life[12] are all environmental factors that protect against the development of allergies and allergic asthma in childhood. The challenge will be to elucidate the immune mechanisms involved and to determine the extent of exposure that will ensure safety and have the desired outcome — the development of a healthy child with a very low risk of autoimmune disease.

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## SYNCOPE — GETTING TO THE HEART OF THE MATTER

SYNCOPE is the sudden and transient loss of consciousness accompanied by a loss of postural tone. The term derives from the Greek word *synkoptein*, meaning "to cut short," and purportedly, Hippocrates himself provided the first description of a patient with the disorder.[1] Syncope accounts for 3 percent of emergency room visits and 1 to 6 percent of all hospital admissions, and it costs $750 million per year to diagnose and treat.[2,3] The causes of syncope range from the benign to the lethal. Rational patient care is facilitated by an understanding of the pathophysi-