Does Inhalation of Endotoxin Cause Asthma?

Asthma is a chronic inflammatory disorder of the airways that is characterized by reversible airflow obstruction, airway hyperreactivity, and airway remodeling (1). Although the prevalence, incidence, severity, and mortality rate of asthma are increasing in the United States (1), we are only beginning to identify the environmental, genetic, and biological factors that are responsible for this epidemic. The article by Park and coworkers (pp. 322–328) (2) in this issue of the *Journal* raises the intriguing possibility that chronic inhalation of endotoxin contributes to the development of this disorder.

Endotoxin or lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria, is ubiquitous in the environment, and is often present in high concentrations in organic dusts (3), as well as in air pollution (4) and household dusts (5). Given the potent inflammatory effects of endotoxin, it is logical to consider the role of this agent in the development and exacerbation of asthma.

Inhaled endotoxin can exacerbate airflow obstruction and airway inflammation in individuals with allergic asthma. Among those with allergic asthma who are sensitive to house dust mite allergen, the concentration of endotoxin in the home environment, but not the concentration of mite allergen (*Der* p1), was significantly associated with the severity of asthma (5). Experimentally, subjects with allergic asthma are more sensitive to the bronchoconstrictive effects of inhaled endotoxin (6). Moreover, among those with allergic asthma, prior allergen challenge significantly augments the inflammatory response to inhaled endotoxin (7). The enhanced response to inhaled endotoxin among individuals with allergic asthma may simply reflect the additive effect of preexisting airway inflammation but could also be caused by release of lipopolysaccharide-binding protein (LBP) when subjects with allergic asthma are challenged with allergen (8). In mice sensitized to ovalbumin, inhalation of LPS has been shown to exacerbate the inflammatory response to ovalbumin (9). In aggregate, these findings indicate that allergic airways can enhance the response to inhaled endotoxin, and that endotoxin can enhance the airway response to allergens.

However, when considering the interaction between endotoxin and allergens, the timing of the exposure appears to be critical. Emerging evidence suggests that early exposure to endotoxin, a potent inducer of T helper cell type 1 (Th1) cytokines (interferon γ [IFN-γ] and interleukin 12 [IL-12]), may minimize the risk of allergen sensitization (9, 10), which could have profound effects on the development of allergic asthma. Although this provides further support for the importance of a Th2 phenotype in the development of allergic asthma (11), it is necessary to interpret these findings cautiously. Th1 responses alone have been shown to induce reversible airway inflammation and airway hyperreactivity (12), and the findings of Park and colleagues (2) clearly demonstrate an independent relationship between endotoxin exposure and repeated wheezing during infancy.

Independent of its effect in allergic asthma, several studies demonstrate that inhalation of air contaminated with endotoxin is associated with the classic features of asthma (reversible airflow obstruction and airway inflammation, airway hyperreactivity, and airway remodeling). Epidemiological studies have shown that the concentration of inhaled endotoxin in the bioaerosol is strongly and consistently associated with reversible airflow obstruction among cotton workers (13), agricultural workers (14), and fiberglass workers (15). In fact, the concentration of endotoxin in the bioaerosol is the most important occupational exposure associated with the development (16) and progression (14) of airway disease in agricultural workers. Experimentally, inhalation of endotoxin can cause reversible airflow obstruction and airway inflammation in previously unexposed healthy study subjects (17). In fact, healthy study subjects challenged with dust from animal confinement buildings develop airflow obstruction and an increase in the serum concentration of neutrophils and IL-6, all of which are most strongly associated with the concentration of endotoxin (not dust) in the bioaerosol (18). Finally, after subchronic inhalation of grain dust, endotoxin-sensitive (C3H/BFeJ), but not endotoxin-resistant (C3H/HeJ), mice develop persistent airway hyperreactivity and airway remodeling, suggesting that endotoxin is one of the principal components of grain dust that causes the development of chronic airway disease (19).

However, not everyone exposed to endotoxin-containing dust will develop airway disease. In fact, we have found that there is a broad range of stable and reproducible physiologic responses to inhaled endotoxin among healthy, nonasthmatic study subjects; approximately 10–15% of the subjects develop either airflow obstruction after inhaling minimal amounts of LPS or have a negligible airway response to high doses of inhaled LPS (20). Furthermore, we have found that cosegregating missense mutations in the extracellular domain of TLR4 (a transmembrane receptor for LPS) are associated with a significantly blunted response to inhaled LPS in humans (21). Polymorphisms in the promoter region of the gene encoding CD14 appear to regulate the concentration of soluble CD14 (22), which may also prove to influence the airway response to inhaled endotoxin. These findings indicate that gene sequence changes can alter the ability of the host to respond to environmental stress and may ultimately explain why certain people develop disease when challenged with environmental agents and others remain healthy.

Asthma is a complex disorder that has multiple clinical subtypes, a polygenic pattern of inheritance, and is influenced by a large number of environmental exposures (1). Given these features, it is patently clear that asthma is a heterogeneous condition (or syndrome) with multiple biologically unique etiologies involving allergic and nonallergic mechanisms. The findings of Park and coworkers (2) provide further evidence that endotoxin causes a biologically unique form of asthma and that this ubiquitous environmental toxin should be considered one of several environmental risks responsible for the development and exacerbation of asthma. Understanding the

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epidemiology and biology of specific gene–environment–asthma phenotypes will undoubtedly advance our scientific understanding of asthma, and may provide a sound rationale to reverse the disturbing trends in this disorder.

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Examining the Link between Sarcoidosis and Depression

Sarcoidosis is a multisystem disease that commonly involves the pulmonary, cutaneous, and ocular systems, but can also affect many other systems, including the liver, heart, and nervous system (1). While sarcoidosis can be a mild and self-limited disease, it can be chronic, progressive, and even life-threatening in its more severe forms and can have profound effects on functional status and quality of life (2, 3). In this issue of the *American Journal of Respiratory and Critical Care Medicine* (pp. 329–334), Chang and colleagues highlight another way sarcoidosis can affect the lives of patients: it is associated with a high prevalence of depressive symptoms (4). These investigators conducted a cross-sectional study of 154 patients with sarcoidosis at six tertiary care centers in the United States. Of the 144 for whom depression-screening data were considered adequate for analysis, 60% scored above the authors' cutoff for "clinical depression" on an abbreviated form of an established instrument, the Center for Epidemiologic Studies—Depression scale (CES-D). This high prevalence of depressive symptoms is an important finding, but should be put into context.

First, are the depressive symptoms identified by the CES-D indicative of a clinical depressive disorder that requires further evaluation and treatment? As Chang and colleagues point out, patients who screen positive on the abbreviated CES-D do not necessarily have a DSM-IV-defined major depressive illness. This adaptation of the CES-D has not been validated against formal diagnostic criteria for depression and, of the 11 items included, 5 encompass constitutional symptoms common to patients with sarcoidosis. Therefore, the results cannot be assumed to reflect the proportion of patients who require either antidepressant or psychotherapeutic treatment. Nonetheless, the high prevalence of depressive symptoms is an important finding relevant to clinicians caring for patients with sarcoidosis.

Second, how does this prevalence of depression compare with prior studies? In the only prior report on depression in sarcoidosis, Drent and colleagues found a substantially lower prevalence of depression among 64 patients identified from eight hospitals in the Netherlands (2). This study used a different screening instrument, the Beck Depression Inventory, and found the prevalence of depression to be 18%. The difference