

Endotoxin-stimulated innate immunity: A contributing factor for asthma

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Exposure to airborne endotoxin in infancy may protect against asthma by promoting enhanced T_H1 response and tolerance to allergens. On the other hand, later in life, it adversely affects patients with asthma. Endotoxin binding to receptors on macrophages and other cells generates IL-12, which inhibits IgE responses. It also generates cytokines like IL-1, TNF- α , and IL-8, which cause inflammation. These signal transduction pathways resemble those leading to the generation of cytokines, such as IL-4, IL-13, and IL-5, which are responsible for the inflammation of IgE-mediated allergic disease. The main difference seems to be that endotoxin recruits neutrophils, but IgE recruits eosinophils, and the details of the tissue injury from these granulocytes differ. Sources of airborne endotoxin include many agricultural dusts, aerosols from contaminated water in many industrial plants, contaminated heating and air-conditioning systems, mist-generating humidifiers, and damp or water-damaged homes. Acute inhalation of high concentrations of endotoxin can cause fever, cough, and dyspnea. Chronic inhalation of lesser amounts causes chronic bronchitis and emphysema and is associated with airway hyperresponsiveness. Airborne endotoxin adversely affects patients with asthma in 3 ways: (1) by increasing the severity of the airway inflammation; (2) by increasing the susceptibility to rhinovirus-induced colds; and (3) by causing chronic bronchitis and emphysema with development of irreversible airway obstruction after chronic exposure of adults. The most effective management is mitigating exposure. The potential of drug treatments requires further clinical investigation. (*J Allergy Clin Immunol* 2001;108:157-66.)

Key words: Airway inflammation, asthma, cell biology, chronic obstructive pulmonary disease, endotoxin, eosinophils, environmental exposure neutrophils, tolerance

Endotoxins are soluble LPS fragments of the outer membrane of gram-negative bacteria that aggregate to form micelles with a minimum molecular weight of about 1,000,000 kd. The polysaccharide portion carries an antigenic determinant specific for the organism, but antibody-mediated reactions are not the primary basis for

Abbreviations used

BAL:	Bronchoalveolar lavage
COPD:	Chronic obstructive pulmonary disease
ICAM-1:	Intercellular adhesion molecule 1
NF κ B:	Nuclear factor for κ chains in B cells
OVA:	Ovalbumin
TLR:	Toll-like receptor

LPS toxicity. The lipid portion is necessary for binding to cells and activation of the processes of nonspecific resistance to infection (ie, innate immunity).^{1,2} Thus it is not surprising that endotoxin causes many of the same inflammatory reactions as specific immune responses. Brief heavy exposure is a well-known cause of acute illness with fever, cough, and dyspnea (eg, humidifier fever and grain fever).³⁻⁵ Repeated exposure leads to tolerance of the acute effects but causes chronic obstructive lung disease.^{6,7} More recently, it has become apparent that chronic exposure to lesser concentrations can contribute to the development of obstructive lung diseases, including emphysema, chronic bronchitis, and asthma.⁸⁻¹³

Compelling evidence from cell biology and clinical research link endotoxin to the pathogenesis of asthma. The recent editorial by Schwartz¹⁴ discussing an article on house dust endotoxin and wheeze in the first year of life points out that endotoxin probably both causes and prevents asthma, depending on dose, timing, and host genetics, and also exacerbates asthma if it already exists.¹⁵ Exposure to endotoxin in infancy may protect against developing asthma.¹⁶⁻¹⁸ However, exposure in later life may adversely affect patients with asthma in 3 ways: (1) by increasing the severity of the airway inflammation; (2) by increasing the susceptibility to rhinovirus-induced colds; and (3) by causing chronic bronchitis and emphysema with development of irreversible airway obstruction after chronic exposure of adults.

This problem of multidirectional effects is perhaps best illustrated by 2 recent animal models of the effect of endotoxin aerosol on the development of asthma. Wan et al¹⁹ used a model in which IgE-specific tolerance to the antigen developed in mice repeatedly exposed to aerosolized ovalbumin (OVA). They found that exposure to aerosolized endotoxin from a low-concentration solution of LPS (40 ng/mL) just before and once during the 2-week OVA inhalation protocol reversed the develop-

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Received for publication February 26, 2001; revised March 27, 2001; accepted for publication March 30, 2001.

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0091-6749/2001 \$35.00 + 0 1/10/116862

doi:10.1067/mai.2001.116862

TABLE I. Products of endotoxin stimulation of human or animal cells

Monocyte-macrophage	Respiratory epithelial cell
TNF- α ²²⁻²⁴	TNF- α ²⁵
IL-1 α/β ^{26,27}	IL-1 α/β ²⁵
IL-6 ²⁸⁻³⁰	IL-6 ³¹
IL-8 ²⁹	IL-8 ²⁵
IL-10 ^{23,32}	
IL-12 ³³⁻³⁵	
GM-CSF ³⁶	
G-CSF ³⁷	
MCP-1 ³⁶	
MIP-1 α and MIP-1 β ^{29,36}	Increased expression of mucin genes ³⁸
MIP-2 α ^{22,29,30,36,39}	
ICAM-1 ³⁹⁻⁴²	
P-selectin ^{40,43}	
E-selectin ⁴⁴	
CD11/CD18 ³²	
COX-2 ⁴⁵	
iNOS ^{41,46,47}	

After endotoxin deposition in the lung, most of the proteins listed above appear in lung lavage fluid, and some even pass into the peripheral blood, but it is not certain whether they are produced by macrophages, epithelial cells, or both.⁴⁸⁻⁵⁰ Also, after stimulation by IL-1 or TNF- α , epithelial cells produce the eosinophil chemoattractants RANTES and eotaxin, as well as other cytokines. IL-1 and TNF- α also stimulate epithelial cells to produce ICAM-1, the receptor for leukocytes and many rhinoviruses. *G-CSF*, Granulocyte colony-stimulating factor; *MCP-1*, monocyte chemoattractant protein 1; *MIP-1*, macrophage inflammatory protein 1; *COX-2*, cyclooxygenase 2; *iNOS*, inhaled nitric oxide synthase.

ment of IgE-specific tolerance. The resulting level of antigen-specific IgE was greater, and the eosinophilic airway inflammation was similar to that seen after a single intraperitoneal injection of OVA. They also found that the effect of endotoxin inhalation on lung cells was to increase the IL-10/IL-12 ratio, giving a net shift toward a T_H2 response compared with that seen in saline solution-exposed control animals.

Tulić et al²⁰ addressed the effect of endotoxin inhalation on asthma risk in a rat model of exposure to an endotoxin aerosol either 1 day before or 1 to 10 days after a single intraperitoneal injection of OVA. Exposure before or up to 6 days after OVA injection prevented the IgE response. Exposure 6 to 10 days after the primary injection did not affect the IgE response but did increase the airway inflammation from aerosolized OVA and increased neutrophil influx. They used aerosol exposure methods similar to those of Wan et al,¹⁹ except that the LPS solution of Tulić et al was approximately 1000-fold more concentrated (50 μ g/mL). It may turn out that the key difference between these experiments is the endotoxin exposure level and that a high-level endotoxin exposure will not reverse tolerance to inhaled antigen but will produce a net shift toward a T_H1 milieu in the lung. If we assume that this is true, then this implies that endotoxin exposure will be protective against sensitization and asthma at some sufficiently high level, that endotoxin will increase the risk of sensitization and asthma at a

somewhat lower level, and that endotoxin may have little effect at some yet lower level.

CELL BIOLOGY

Alveolar macrophages and type II epithelial cells are the predominant airway cells stimulated by inhaled endotoxin. Their stimulation produces many cytokines, chemokines, adhesion molecules, and other products that cause inflammation, especially by recruiting and activating neutrophils. Endotoxin released during gram-negative sepsis stimulates many other cells, including dendritic cells, B lymphocytes, neutrophils, basophils, mast cells, endothelial cells, fibroblasts, and myocytes, but endotoxin instilled into the airways does not pass into the vascular compartment to enter the circulation.²¹ At least one product of endotoxin stimulation, TNF- α , is also compartmentalized (Table I).²²⁻⁵⁰

The effects of these cytokines, chemokines, and adhesion molecules are the result of a complex intercellular network of mechanisms that act synergistically through different pathways with both feedback amplification and feedback inhibition.⁵¹ For example, transforming growth factor β inhibits monocyte production of cytokines.⁵² For the production of lung disease, the 2 most important end results are the recruitment and activation of leukocytes, especially neutrophils, and the increased production of mucus. There are effects on histamine release from mast cells and basophils, and RANTES and GM-CSF release from fibroblasts, but these effects seem important primarily in conjunction with IgE-mediated events.⁵³⁻⁵⁵

In addition to increasing the production of the phospholipase 2 receptor, circulating endotoxin is associated with activation of the phospholipase A-2 enzyme and with the production of eicosinoids and platelet-activating factor.⁵⁶⁻⁵⁹ It is probable that these effects also occur in the respiratory tract, although this issue has not been examined.

The cellular receptor or receptors for endotoxin have been studied extensively.⁶⁰ A soluble acute-phase protein, LPS-binding protein, produced by the liver and many other tissues of endodermal origin, including respiratory epithelium, has a high affinity for endotoxin but does not bind to cell membranes.²⁸ It may act as a transporter to deliver endotoxin to cell receptors. CD14 bound to cell walls, as well as in its soluble form (sCD14), has high affinity for endotoxin. However, CD14 lacks a cytoplasmic domain, and alone it cannot act as a receptor to initiate signal transduction. Three different molecules appear to be required. The most important member of this triumvirate is the toll-like receptor 4 (TLR4).⁶¹ TLRs are responsible for innate immunity and are highly conserved across the animal kingdom, having been first recognized in *Drosophila* species.^{1,2} After TLR4 associates with the CD14-LPS complex and with another molecule, MD2, it initiates the signaling cascade. The first step in this cascade is activation of IL-1 receptor-associated kinase through the adaptor protein MyD88. Then a series of kinases, including extracellular signal-related kinase, mitogen-activated protein kinase, and STAT kinase, leads

to the activation of the nuclear factor κ B (NF κ B). Activation of a separate set of tyrosine kinases leads to the production of activator protein 1. Translocation of NF κ B and activator protein 1 to the nucleus promotes nuclear transcription and expression of inflammatory cytokines.^{36,62,63} Information about human TLRs is still limited, but monocytes-macrophages and respiratory epithelium do express TLR4.^{1,62}

Although the cascade leading to activation of NF κ B is the primary signal transduction pathway, it does not account for all of the responses to endotoxin.^{41,45,64} The cellular response to endotoxin also requires activation of a glycine-gated chloride channel that increases intracellular calcium ions.^{32,65,66} Insulin is required for the production of TNF- α .⁶⁷

Generation of cytokines is inhibited by β -adrenergic agonists, vasoactive intestinal peptide, phosphodiesterase inhibitors, and other agents that increase intracellular cyclic adenosine monophosphate.^{33,35,68-74} Macrolide antibiotics and pentamidine also suppress generation of cytokines.⁷⁵⁻⁷⁷ Additional inhibitors include nicotine,⁷⁸ acetylcholine,⁷⁹ inosine (a purine metabolite acting on A-2 adenosine receptors),³⁴ and A-1 adenosine receptor antagonists.⁸⁰ Nonsteroidal anti-inflammatory drugs do not cause such inhibition.²⁶ Surprisingly, there is relatively little information about the effect of glucocorticoids on endotoxin-stimulated production of cytokines, but what information is available indicates that glucocorticoids only weakly suppress the production of proinflammatory molecules.^{72,81-83} Intravenous, but not aerosolized, glucocorticoids inhibit airway obstruction and the appearance of TNF, IL-8, macrophages, and eosinophils in bronchoalveolar lavage (BAL) fluid after inhalation of corn dust containing endotoxin by healthy volunteers.⁸³

Acute exposure to endotoxin induces a degree of tolerance to at least some of its effects on subsequent exposure. For example, workers exposed daily to endotoxin have tolerance to fever and other acute effects (ie, the Monday morning fever of byssinosis). The mechanism of this tolerance is only partly understood but seems to be the result of interference with transcription factor pathways and reduced gene expression.³⁶

These signaling pathways of innate immunity resemble those of IgE-mediated inflammation in many ways. Consideration of the cell biology of the 2 pathways would predict that their effects would be quite different. Endotoxin generates cytokine IL-12, which promotes differentiation of T_H1-type lymphocytes, and allergen generates IL-4 and IL-13, which promote T_H2-type lymphocytes. Endotoxin generates IL-8, which activates neutrophils, and allergen generates IL-5, which activates eosinophils. This dichotomy implies that exposure to endotoxin early in life would protect against a T_H2 response to allergens.^{16,84} On the other hand, after allergic sensitization has occurred, the 2 pathways of inflammation seem to act together synergistically (Fig 1). However, endotoxin also stimulates production of IL-10, often considered a T_H2 cytokine, and endotoxin tolerance may be a T_H2 predominant state.^{85,86} Thus, as

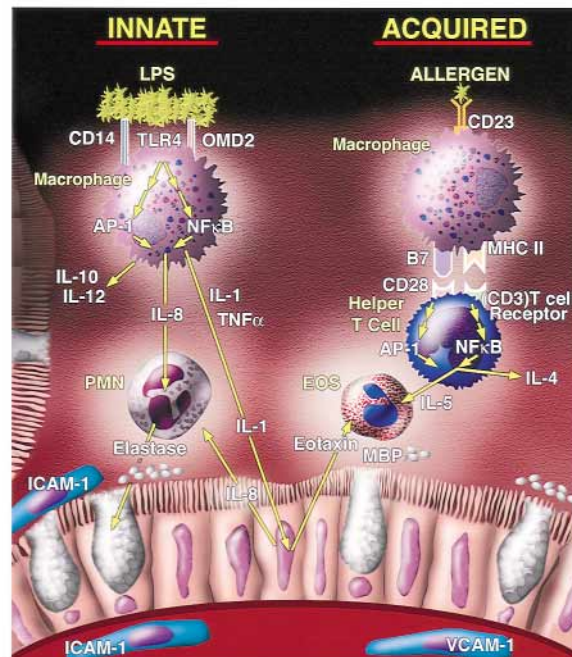


FIG 1. Pathways of immunologic airway inflammation. Endotoxin (LPS) and allergen often occur together in indoor air, and after inhalation into the airways, both cause inflammation. They act through different pathways. LPS stimulates innate immunity, leading to the prompt production of cytokines from macrophages that stimulate the acute-phase response and cause local inflammation. One of these important cytokines is IL-8, which recruits and activates neutrophils. Neutrophil elastase promotes the growth of goblet cells and the production of mucus and damages the elastin in alveolar walls. Allergen, after binding to IgE on cell surface receptors, stimulates the production of a different set of proinflammatory cytokines that include IL-5, an activator of eosinophils. Eosinophil granule proteins, including major basic protein, cause a complex inflammation that includes desquamation of the respiratory epithelium. This drawing has been simplified to emphasize the point that there are parallel pathways. The complete chain of both are much more complex. AP, Activator protein; PMN, polymorphonuclear neutrophils; EOS, eosinophils; MBP, major basic protein; VCAM, vascular cell adhesion molecule.

described above, low but tolerizing exposure to endotoxin early in life may have very different effects than higher level exposures do later.

PATHOPHYSIOLOGY

Neutrophils are attracted to the site of inflammation in the airways by the chemokines IL-8 and macrophage inflammatory protein 1 α and pass into the tissue after binding to P-selectins and intracellular adhesion molecule 1 (ICAM-1), molecules increased by endotoxin.⁴⁰ In addition, direct endotoxin activation of neutrophils generates increased expression of the binding protein CD11b/CD18. Endotoxin stimulation also inhibits apoptosis.⁸⁷ Neutrophil elastase from activated neutrophils is considered to be the primary factor responsible for the loss of elastic fibers in lung parenchyma and the development of emphysema. Many cotton mill workers with

byssinosis have low serum levels of α_1 -antitrypsin, the major antagonist of neutrophil elastase.⁸⁸ Both asthma and chronic obstructive pulmonary disease (COPD) are characterized by hypertrophy of the goblet cells and mucus glands and overproduction of mucus. Endotoxin is one of the candidate causes for this abnormality.⁸⁹⁻⁹¹ TNF- α , along with transforming growth factor α , is a potent inducer and stimulator of the epidermal growth factor receptor in respiratory epithelial cells, leading to their proliferation of goblet cells.⁹² Also, neutrophil elastase is a potent stimulus for mucus secretion.⁹³

The effect of endotoxin on eosinophil recruitment and activation is less certain, although exposure to aerosolized endotoxin elicits an increase of eosinophil cationic protein in the sputum.⁹⁴ Because neutrophil granules also contain eosinophil cationic protein, it cannot be interpreted with certainty that endotoxin recruits eosinophils.⁹⁵ Acute exposure to low-dose aerosolized endotoxin does not evoke eosinophilia in the sputum of asthmatic patients, but IL-5 does.⁹⁶ On the other hand, nasal challenge with endotoxin elicits eosinophilia but only in atopic subjects.⁹⁷ In subjects with ragweed allergy, bronchial instillation of ragweed extract contaminated with endotoxin elicits neutrophil exudation; endotoxin-free allergen elicits eosinophils.⁹⁸ However, swine dust inhalation increases the number of eosinophils in the BAL fluid.⁵⁰ Nasal challenge with endotoxin evokes influx of eosinophils into the nasal cavity but only in atopic individuals, possibly the result of eosinophil activation by GM-CSF.⁹⁷ Neutrophils and macrophages appeared in the lungs of guinea pigs in 4 hours, but recruitment of eosinophils required 24 hours, a late response reminiscent of the late IgE-mediated eosinophil recruitment.⁹⁹ In healthy volunteers, inhaling swine dust containing 1.3 $\mu\text{g}/\text{m}^3$ endotoxin recruits neutrophils, macrophages, lymphocytes, and eosinophils into the BAL fluid after 24 hours.⁵⁰ Increase in neutrophils correlates with increase in IL-8. Aerosol inhalation of endotoxin elicits a greater neutrophil response at 6 hours in asthmatic subjects than in normal subjects, and this increased neutrophilia correlates with a greater baseline CD14 expression in the cells of the asthmatic subjects.¹⁰⁰ Clearly, a time-course study in human subjects with endotoxin alone is needed to resolve the question of whether it can recruit eosinophils.

Like the inflammation from allergen exposure, the inflammation from airborne endotoxin increases airway responsiveness to nonspecific stimuli. In rats and mice aerosolized endotoxin or TNF- α increases airway responsiveness.^{73,101,102} However, it reduces bronchial responsiveness in guinea pigs.^{99,103,104} In human subjects, particularly in subjects with asthma, aerosolized endotoxin elicits a fall in FEV₁ and increases bronchoconstriction from histamine.^{48,49,105-108} But other studies have not confirmed an abnormal acute response in asthmatic subjects, perhaps because of exposure to smaller doses.^{96,109} Chronic occupational exposure of nonasthmatic workers to dust containing high concentrations of endotoxin increases histamine response.¹¹⁰ Swine dust, cotton dust, or grain dust exposure increases IL-1 β , IL-6, IL-8, TNF- α , and circulating neutrophils in the airways and causes airway

obstruction and methacholine responsiveness.^{4,48,111-117} The severity of the drop in FEV₁ correlates with the amount of IL-6 and IL-8 produced by in vitro stimulation of the subjects' monocytes with endotoxin.¹¹⁸

Endotoxin increases the skin test reaction and increases IgE-mediated histamine release from mast cells and basophils.^{53,119,120} Conversely, allergen challenge increases the response to endotoxin.¹²¹⁻¹²³ The airway response to the combination of endotoxin and allergen is greater than either alone.¹²⁴ Concomitant aerosol exposure of mice to endotoxin and allergen increases the production of IgE to OVA.¹⁹

MEASUREMENT OF ENDOTOXIN

Endotoxin is usually assayed with a *Limulus* amoebocyte lysate method. Results are expressed relative to a reference standard in endotoxin units and may vary 100-fold according to the methods of collecting dust or air samples and details of extraction, dilution, and storage and because of inherent variability of the commercially available lysates.¹²⁵⁻¹²⁸ Because of these variabilities, it is difficult to estimate concentrations that are safe either in settled or airborne dust. Chronic occupational exposure to airborne concentrations in the range of 50 to 100 EU/m³ is associated with chronic airway obstruction.¹²⁹⁻¹³¹ However, like allergen challenge, concentrations required to cause acute effects are much higher.¹³² Concentrations 1000 time higher occur in some exposures.^{11,133}

SOURCES OF ENDOTOXIN IN THE ENVIRONMENT

In addition to agricultural dusts in grain, poultry, and swine buildings; dairy barns; cotton mills; and compost and refuse collecting, potato processing, and woodworking plants, endotoxin is an important contaminant in industries in which contaminated water systems generate a mist, such as metal working and paper, nylon, and fiberglass manufacture.^{4,8,42,94,134-143} Significant concentrations of endotoxin may also be present in the dust of office buildings, and airborne endotoxin may contribute to the sick building syndrome.^{144,145} In as much as gram-negative organisms proliferate in stagnant water, it is likely that these increased indoor concentrations are related to pools of water in heating and ventilation systems. As Baer et al reported over 20 years ago, extracts of dust from some houses contain substantial concentrations of endotoxin.^{16,146-148} Very likely the concentration is related to home dampness and cleanliness. Typically, gram-negative organisms grow in humidifiers and in areas of homes that are wet and water damaged. The strongest predictor of endotoxin levels in homes is the presence of a dog.^{15,149} High levels of *Dermatophagoides* species are not strong predictors.^{147,150-152} However, reported mold and the use of cool mist humidifiers is associated with increased endotoxin levels, whereas the use of dehumidifiers is associated with decreased endotoxin levels in family room air. Cigarette smoke contains high levels of endo-

toxin, and smoking a pack a day delivers a respirable dose comparable with that of exposure in cotton mills.¹⁵³

CLINICAL DATA LINKING ENDOTOXIN EXPOSURE TO ASTHMA AND COPD

Frequency and severity of asthma in both children and adults correlates with home dampness and with endotoxin concentrations in house dust.^{150-152,154-156} Endotoxin challenge in asthmatic subjects has produced conflicting results. One study reported bronchoconstriction and increased histamine response.¹⁵⁷ However, another experiment did not elicit a fall in FEV₁, an increase in neutrophils, or a production of IL-8 that was greater in asthmatic than in normal subjects.¹⁰⁹ Endotoxin exposure at work causes a greater fall in FEV₁ in atopic than in nonatopic workers.¹² Allergen challenge potentiates human bronchial response to endotoxin.¹²¹ Observations that suggest a role of innate immunity in asthma are an increase in IL-8 and neutrophils in the sputum or BAL fluid, especially during acute, severe episodes of asthma.¹⁵⁸⁻¹⁶⁰ Some patients who have died suddenly of asthma have only neutrophils and not eosinophils in the bronchial mucosa.¹⁶¹

Decline in FEV₁ correlates with endotoxin exposure in pig farmers, swine confinement workers, and cotton textile workers.^{129,136,141,162-166} Cotton textile workers have more chronic bronchitis and lower FEV₁ than workers exposed to man-made fibers.^{9,12} Endotoxin exposure causes loss of lung function across the work shift.^{135,140,164,167,168} Prevalence of chronic airway obstruction is doubled in a wool carpet weaving factory, where endotoxin levels are high.¹⁶⁹ Finally, animal models confirm that chronic airway exposure to endotoxin can cause emphysema.¹⁷⁰

IRREVERSIBLE AIRWAY OBSTRUCTION IN ASTHMA

Traditionally, asthma, bronchiectasis, and COPD are considered different diseases, but of course these disease designations do not mean that a person with asthma cannot have bronchiectasis or COPD, too. In fact, many do. Many adults with asthma, especially those whose disease began later in life, have irreversible obstruction.¹⁷¹ At least 3 different abnormalities contribute to this irreversibility:

1. airway remodeling,
2. bronchiectasis with postinfectious linear pulmonary fibrosis, and
3. emphysema and chronic bronchitis.

The *Journal* has recently published a review of airway remodeling.¹⁷² It is unlikely, however, that airway remodeling accounts for all of the irreversible obstruction that so many elderly patients exhibit, even at the outset of their symptoms of asthma.

Perhaps the central saccular bronchiectasis and pulmonary fibrosis of allergic bronchopulmonary aspergillosis can serve as a model of the more common development of bronchiectasis and fibrosis in elderly adult

asthmatic subjects. Paganin et al^{173,174} have studied subjects with chronic asthma by using high-resolution computed tomography. They found cylindrical and varicose bronchiectasis and linear shadows in a quarter of their patients. These abnormalities correlated with disease severity.¹⁷⁵ Park et al¹⁷⁶ and Grenier et al¹⁷⁷ have confirmed these findings. Bronchiectasis and patchy segmental fibrosis after necrotizing infections presumably result from the complex inflammation of infections rather than from the direct remodeling effect of the lymphocytic-eosinophilic inflammation of asthma.

These reports cited above also disclosed that centilobular and paraseptal emphysema is frequent in older asthmatic subjects, even in nonsmoking asthmatic subjects. The frequency of emphysema increases with age and is more common in asthmatic subjects who do smoke, occurring in up to 20% of patients. Other reports confirm this association.¹⁷⁸⁻¹⁸⁰ The pathogenic mechanism of the emphysema in the patients who do not smoke is not clear. Patients with intrinsic asthma have been reported to have an increased frequency of abnormally low α_1 -antitrypsin levels associated with MZ and SZ phenotypes, but as yet, these phenotypes have not been linked to the development of emphysema in asthmatic patients.¹⁸¹ Neutrophil elastase is an important link in the chain of pathogenesis of emphysema, and neutrophils are prominent in the sputum during exacerbations of asthma, as they are in patients with emphysema.^{158,160,182} The factors responsible for the neutrophilia are unclear, although the number of neutrophils in the BAL fluid of asthmatic subjects correlates with the amount of IL-8.¹⁵⁸ Furthermore, patients with severe asthma, especially those treated with long-term glucocorticoids, have increased neutrophils in their bronchoalveolar fluid.^{183,184} Whether this increased neutrophilia after glucocorticoid treatment is due to the fact that glucocorticoids do not inhibit neutrophil accumulation in the tissues or to the fact that glucocorticoids increase the number of circulating neutrophils (or both) is not known.

A major conclusion from review of these extensive data is that repeated exposure to airborne endotoxin is one of the factors responsible for the presence of neutrophils and the development of irreversible airway obstruction and emphysema.

LINKAGE BETWEEN ENDOTOXIN EXPOSURE, ICAM-1 EXPRESSION, AND RHINOVIRUS INFECTION

ICAM-1 is the epithelial cell receptor for most rhinoviruses. The increase in soluble ICAM-1 in respiratory secretions suggests that endotoxin stimulates expression of ICAM-1 on respiratory epithelium, but this effect has not been specifically studied in the upper airways or in human subjects. There are some data, however, that demonstrate that endotoxin can stimulate ICAM-1 expression in respiratory epithelium.^{185,186} Perhaps a contributing reason for the seasonal increase of emergency visits for asthma each fall is the seasonal increase in endotoxin.^{15,151} One bit of direct evidence supporting

this hypothesis is that pig farmers, a group regularly exposed to airborne endotoxin, have more colds.¹⁶⁵

RECOMMENDATIONS

On the basis of this current information, 2 recommendations for clinicians stand out:

1. Enquire closely into the details of the patient's environment, both at home and at work. In the home look for areas of water damage, especially in climates where the humidity is high. Consider contaminated heating and air-conditioning systems, especially if there is a humidifier component. Correct these conditions. At work, consider exposure to plant or animal agricultural dusts, mist-generating steps in manufacturing jobs, or contaminated heating and air-conditioning systems or water damage in an office building.
2. If an adult with asthma has a major component of irreversible obstruction, perform high-resolution computed tomography to determine the cause. Many of these patients have coexisting lung diseases that do not respond to glucocorticoids and may have been the result of the inflammation of innate immunity from endotoxin exposure.

Areas in which future clinical research is needed include the following:

1. More quantitative information about exposure in the home to endotoxin during childhood and the development of tolerance or allergy to environmental allergens.
2. More epidemiologic information about the relationship between exposure of adults to airborne endotoxin and the severity of their disease and its progression to irreversibility.
3. Determination of the efficacy of various pharmacologic treatments, including aerosol glucocorticoids, on the chronic airway inflammation from airborne endotoxin.

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