# Etiology and Pathogenesis of Airway Disease in Children and Adults from Rural Communities

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Asthma is the most common chronic disease of childhood and affects nearly 5 million children. The prevalence and severity of childhood asthma have continued to increase over the past decade despite major advances in the recognition and treatment of this condition. A comparison of urban and rural children suggests that the etiology of airway disease is multifactorial and that unique exposures and genetic factors contribute to the development of asthma in both settings. The most important environmental exposure that distinguishes the rural environment and is known to cause asthma is the organic dusts. However, animal-derived proteins, common allergens, and low concentrations of irritants also contribute to the development of airway disease in children and adults living in rural communities. A fundamental unanswered question regarding asthma is why only a minority of children who wheeze at an early age develop persistent airway disease that continues throughout their life. Although genetic factors are important in the development of asthma, recurrent airway inflammation, presumably mediated by environmental exposures, may result in persistent airway hyperresponsiveness and the development of chronic airway disease. Increasing evidence indicates that control of the acute inflammatory response substantially improves airflow and reduces chronic airway remodeling. Reducing exposure to agricultural dusts and treatment with anti-inflammatory medication is indicated in most cases of childhood asthma. In addition, children with asthma from rural (in comparison to urban) America face multiple barriers that adversely affect their health e.g., more poverty, geographic barriers to health care, less health insurance, and poorer access to health care providers. These unique problems must be considered in developing interventions that effectively reduce the morbidity and mortality of asthma in children from rural communities. *Key words*: agricultural, asthma, children, endotoxin, noxious gases, organic dusts, rural. — *Environ Health Perspect* 107(suppl 3):393–401 (1999).
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## Scope of the Problem

Asthma is the most common chronic disease of childhood and affects nearly 5 million children (*1*). The prevalence (*2*) and severity (*1–3*) of childhood asthma have continued to increase over the past decade despite major advances in the recognition and treatment of this condition. Since 1980, the hospitalization rate has increased by 28% for children less than 25 years of age and the mortality has doubled for children between 5 and 24 years of age (*1*). Although demographic factors such as age, race, and socioeconomic status appear to be risk factors for the development and progression of asthma (*2,4–6*), the increasing prevalence and severity of asthma suggest that agents in the workplace (*7*) and general environment (*8–12*) play a particularly important role in the etiology and pathogenesis of this condition. In rural communities, children commonly are exposed to organic dusts, agricultural chemicals, animal allergens, and grain dust mites that are brought into the home on work clothing (*13*). Moreover, for children in rural settings, the farm is their home, playground, and workplace, with children as young as 5 years of age participating in farm chores (*13*).

Comparison of urban and rural children suggests that the etiology of airway disease is multifactorial and that unique exposures may contribute to the development of disease in both settings. Among children, at least five studies have compared the prevalence of airway disease in urban and rural populations. As depicted in Table 1, two studies (*14,15*) found that urban children had a higher prevalence of asthma, two studies reported no difference in the prevalence of asthma (*16*) or airway hyperreactivity (*17*), and one study (*18*) reported a higher prevalence of asthma among children living in rural communities. Because the setting and the definition of asthma vary from one study to the next, it is difficult to draw any clear conclusion regarding urban/rural differences in the prevalence of airway disease.

However, among adults, agricultural workers and those living in rural environments appear to be at high risk of developing chronic airway disease, particularly asthma or bronchitis (*19–25*). The risk associated with the development of chronic airway disease appears to be more than 3-fold greater among those who are more heavily exposed to dusts generated in the agricultural environment (*21*). Among farmers, 15% had symptoms consistent with either asthma or allergic rhinitis (*26*). Cigarette smoking does not appear to account for this excess risk, as farmers have relatively low rates of cigarette smoking (*27,28*). These epidemiologic observations are supported by an increasing number of exposure-specific studies in agricultural workers. In fact, airway disease is relatively common among those exposed to cotton, flax, hemp, grain dust, and other organic dusts (*13,29–31*). Although data are lacking regarding the prevalence of asthma in the rural population, absolutely no data are available concerning the incidence of asthma among agricultural workers and their family members, who are often exposed to similar bioaerosols. Agricultural workers and those other adults living in a rural environment encounter a variety of inhaled organic dusts suspended in the atmosphere, including molds and pollens in the air, dusts generated in silos and barns, aeroallergens, silica from the soil, and general exposure to animal danders, grain dust, feed additives, and mite dust (*32*).

## Potential Causes of Airway Disease

As seen in Table 2, the most important environmental exposure that distinguishes the rural environment and is known to

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cause asthma is the organic dusts. Grain dust, cotton dust, and dusts generated in dairy barns represent a complex mixture of vegetable particles and fragments, microorganisms and their products, insects and insect fragments, feed additives including fish meal and antibiotics, avian and rodent proteins, and pesticides. Several lines of evidence indicate that endotoxin is one of the primary agents in organic dust that causes airway inflammation and airflow obstruction. First, the concentration of inhaled endotoxin in the bioaerosol is strongly associated with the development of acute decrements in airflow among cotton workers (*33–35*), swine confinement workers (*36*), and poultry workers (*37*). The concentration of endotoxin in the bioaerosol is the most important occupational exposure associated with the development (*38,39*) and progression (*40*) of airway disease in agricultural workers. Second, physiologically, inhaled endotoxin (*38,41–44*), grain dust (*45–47*), or cotton dust (*34,48–50*) can cause airflow obstruction in naïve or previously unexposed subjects. Naïve, healthy study subjects challenged with dust from animal confinement buildings develop airflow obstruction and an increase in the serum concentration of neutrophils and interleukin (IL)-6, all of which are most strongly associated with the concentration of endotoxin (not dust) in the bioaerosol (*51*). Finally, our previous exposure–response studies have shown that inhaled grain dust and endotoxin produce similar physiologic and biologic effects in humans (*47,52,53*) and mice (*53–56*); the concentration of endotoxin in grain dust plays an important role in the acute biologic response to grain dust in humans (*52*) and mice (*54,55*); a competitive antagonist for lipopolysaccharide (LPS) (*Rhodobacter spheroides* diphosporyl lipid A) reduces the inflammatory response to inhaled grain dust in mice (*56*); and genetic (Figure 1) or acquired hyporesponsiveness to endotoxin substantially reduces the biologic response to grain dust in mice (*54*). Together, these studies indicate that endotoxin is an important cause of organic dust-induced airway disease.

However, other components of organic dust may play a role in the development of acute as well as chronic airway disease. Organic dusts are composed of a complex mixture of vegetable particles and fragments, microorganisms and their products, insects and insect fragments, feed additives including fish meal and antibiotics, avian and rodent proteins, and pesticides (*57*). Among farmers, longitudinal declines in forced expiratory volume in 1 sec ($FEV_1$) are significantly associated with the use of quarternary ammonium compounds and automated dry feeding systems (*58*). Specific plant components such as bract from grain sorghum have enhanced chemotactic activity for neutrophils (*59*). Moreover, depletion of endotoxin from the grain sorghum dust extract had no effect on *in vitro* neutrophil chemotactic activity or the ability of the extract to activate complement (*60*). Tannins found in grain dust (*61,62*) activate phospholipase C and $A_2$, leading to the release of diacyglycerol, mobilization of intracellular free calcium,

**Table 1.** Prevalence difference in airway reactivity and asthma between children from urban and rural communities.

| | | | Airway hyperreactivity (%) | | Asthma (%) | | |
|---|---|---|---|---|---|---|---|
| Location | *n* | Age (years) | Urban | Rural | Urban | Rural | Source |
| South Africa | 1,375 | 6–9 | | | 3.17 | 0.14 | (*14*) |
| Australia | 170 | 8–12 | 22.0 | 21.3 | | | (*17*) |
| Australia | 915 | 5–18 | | | 20.6 | 22.4 | (*16*) |
| Kenya | 1,172 | 8–17 | | | 9.3 | 2.5 | (*15*) |
| Iran | 400 | 5–11 | | | 0.5 | 4.5 | (*18*) |

**Table 2.** Categories of exposure and selected agents known to cause asthma in the rural environment.

| Category | Occupations | Causative agents |
|---|---|---|
| Organic dusts | Grain and cotton industries, farmers, lumber industry | Endotoxin, tannins, plant proteins and pollens, mycotoxins, insect parts |
| Animal-derived materials | Farmers, animal handlers | Antigenic proteins |
| Irritants | Farmers, pesticide manufacturers | Pesticides, herbicides, fertilizers |
| Fumes | Farmers | Ammonia, oxides of nitrogen, welding fumes |

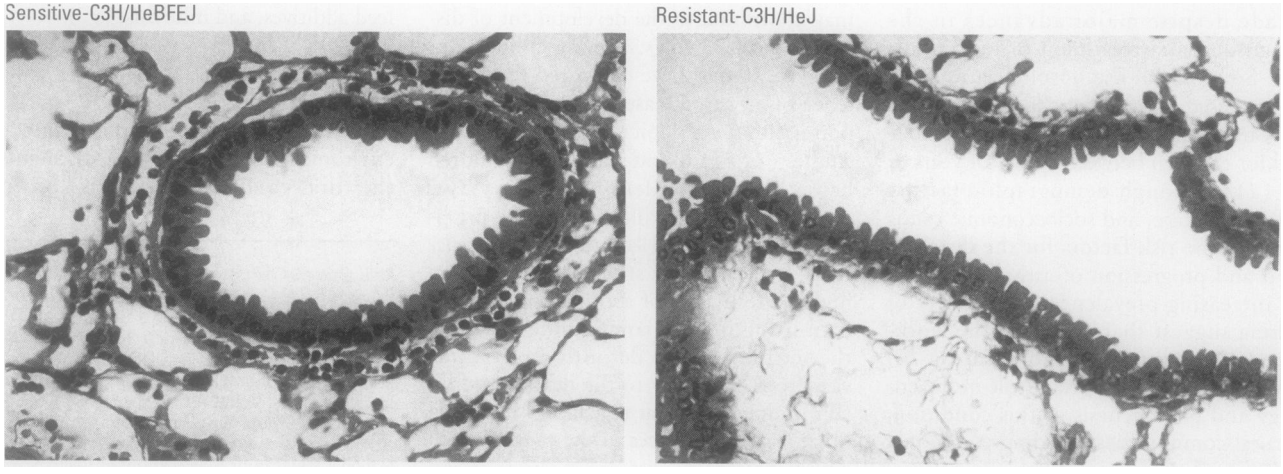


**Figure 1.** Histologic sections of mouse lungs following inhalation of corn dust extract. The endotoxin-sensitive mice (C3H/HeBFEJ) demonstrate a profound neutrophilic inflammatory response primarily localized to the conducting airway, whereas no inflammatory response is observed in the endotoxin-resistant (C3H/HeJ) mice (hematoxylin–eosin, original magnification 1,000×).

and contraction of smooth muscle (*62*). However, the concentration of endotoxin in the bioaerosol is not always predictive of respiratory symptoms among agricultural workers (*63,64*). These studies suggest that other components may be important in the development of organic dust-induced airway disease.

Animal-derived proteins can cause asthma in agricultural workers. This form of asthma is much more common in atopic individuals capable of developing an IgE response to specific aerosolized animal proteins. Animal handlers, especially in sale barns and confinement units, may be intermittently exposed to high concentrations of animal-derived proteins and are at particularly high risk of developing asthma. Cow epithelium is one of the most important inducers of occupational asthma among farmers in Finland (*65*). Antigens such as cockroach dust, common to the urban environment, are also associated with airway disease in the rural environment (*66*). Onset of wheezing is usually immediate and often accompanied by rhinitis and other allergic symptoms.

Low concentrations of irritants may result in airflow obstruction in workers with underlying asthma but do not usually cause asthma. Thus, chemicals common to the agricultural environment, including pesticides, herbicides, and fertilizers, as well as wood smoke and alternative sources of fuel (*67*), may contribute to the exacerbation of airflow obstruction in children with asthma. Organophosphate insecticides (*68*) may induce bronchospasm in exposed individuals. These pesticides inhibit acetylcholinesterase and may result in a cholinergic response, inducing bronchospasm and bradycardia. Although research is lacking in this area, the exposure–response relationship is commonly reported in agricultural workers and may represent an important point of intervention for childhood asthma. Moreover, air pollutants such as ozone may promote the development of airway disease among rural residents (*69,70*).

Reactive airways dysfunction syndrome is an extreme form of irritant-induced asthma that may occur following inhalation of high concentrations of fumes in the agricultural setting (*71*). In particular, noxious gases such as ammonia and oxides of nitrogen may cause acute extensive airway injury and result in recurrent episodes of airflow obstruction. Characteristically, reactive airways dysfunction syndrome occurs only after an overwhelming exposure to irritating gases. The individual should be able to report a specific event where they were exposed to a high concentration of fumes that resulted in an acute respiratory illness. These exposures can cause acute alveolar injury and result in pneumonia or adult respiratory distress syndrome. Subsequent to the acute illness, the individual may develop recurrent episodes of airflow obstruction that are caused by a variety of irritants.

## Clinical Features

Asthma is a chronic inflammatory condition of the airways that results in variable and/or intermittent airflow obstruction (*72*). The objective signs of airflow obstruction are often associated with symptoms of chest tightness, wheezing, coughing, dyspnea, and enhanced sputum production. For the purposes of this article, rural exposures are considered to be relevant to the development and progression of childhood asthma if the asthma is first diagnosed following exposure to agricultural dusts, agricultural allergens, or agricultural fumes, or if previously established asthma is aggravated by exposure to agricultural dusts, agricultural allergens, or agricultural fumes. Diagnosing environmental asthma depends on the demonstration of variable degrees of airflow obstruction that occurs in direct response to specific agents that are aerosolized in the environment. Because immediate and delayed (up to 12 hr) airway responses may occur after these exposures, the specific agent causing the onset of airflow obstruction may not always be obvious. Importantly, acute airway injury caused by exposure to fumes (ammonia and nitrogen dioxide) may result in chronic intermittent episodes of airflow obstruction.

The diagnosis of asthma is based on the demonstration of reversible airflow obstruction (*72*). Standard spirometry, reversible airflow obstruction after bronchodilators, and inducible airflow obstruction with nonspecific airway challenges are considered acceptable physiologic assessments of reversible airflow obstruction. Demonstration of an $FEV_1$ to forced vital capacity (FVC) ratio of less than 65% is considered diagnostic of airflow obstruction. A decrease in the $FEV_1$/FVC ratio is usually associated with a low $FEV_1$ (less than 80% predicted or in the bottom tail of the 90% confidence interval) or a low forced expiratory flow $(FEF)_{25-75}$ (less than 60% predicted). Variability in airflow obstruction is usually demonstrated by sequential spirometry but may be documented by improvement in airflow with bronchodilators (at least a 12% improvement in $FEV_1$ is considered significant) or significant worsening of airflow (≥ 20% decline in $FEV_1$) following inhalation of either histamine or methacholine.

Asthma caused by rural exposures requires the demonstration of a clear temporal relationship to specific exposures in the rural setting that are known to cause asthma. Features in history that are helpful in identifying an environmental etiology include:

- Presence of asthma-causing agents in the home or farm environment
- New onset asthma or worsening of previous asthma
- Exposure to an overwhelming concentration of ammonia or oxides of nitrogen
- Worsening of symptoms during times of more intense exposure
- Improvement of symptoms when away from home or with seasonal changes

However, unlike occupational causes of asthma, the child living on the farm is exposed every day of the week. Thus, the temporal relationship between exposures and symptoms may be difficult to determine. Physiologic testing, either by spirometry, peak flow measurements, or periodic nonspecific bronchoprovocative challenges, can and should be used to critically evaluate the temporal relationship between exposures and the development of airflow obstruction. For instance, demonstration of consistent decreases in either $FEV_1$ of 10% or peak flows of at least 20% when exposed to a specific agent in the rural setting not only helps establish the diagnosis of asthma but may assist in identifying the offending agent. Although peak flow measures are dependent on patient cooperation and are less reliable than traditional spirometric measures of airflow, peak flow measurements are often the only feasible approach to investigating environmental causes of asthma. Specific airway challenges are the most definitive method used to make the diagnosis; however, these inhalation challenges are not entirely accurate, and very few centers are equipped to perform these potentially hazardous exposure–response studies.

## Pathogenesis

A fundamental unanswered question in asthma is why do only a minority of children who wheeze at an early age develop persistent airway disease that continues throughout their lives (*73*). Although wheezing in association with a lower respiratory infection occurs in up to 30% of children less than 3 years of age, only 40% of these children develop persistent

wheezing at 6 years of age (*74*). In a prospective, population-based longitudinal study, persistent wheezing at 6 years of age was associated with recurrent episodes of wheezing, maternal history of asthma, maternal history of cigarette smoking, elevated serum IgE levels in the first year of life, and diminished $V_{max}$ functional reserve capacity at 6 years of age (*74*). However, lung function in the first year of life was not a predictor of persistent wheezing at 6 years of age (*74*). The development of asthma after 6 years of age was significantly associated with mild wheezing and airway hyperresponsiveness at 6 years of age (*75*). Moreover, the diagnosis of asthma at 7 years of age is associated with a progressive deficit in lung function during the next 10 years while the lung should be actively developing (*76*). Airway hyperresponsiveness was also found to be associated with reduced levels and lower rates of increase in $FEV_1$ and $FEF_{25-75}$ in a population of children and young adults followed for up to 12 years (*77*). These findings suggest that in genetically susceptible individuals (*78*), recurrent airway inflammation (not abnormal lung function in the first year of life), presumably mediated by environmental exposures (e.g., viral infections, allergens, cigarette smoke), results in persistent airway hyperresponsiveness and the development of abnormal airway function. Although all forms of asthma can result in persistent disease, environmental models of asthma provide an ideal opportunity to investigate the biologic origin of persistent airway hyperreactivity and airway remodeling (*73*).

The pathogenesis of asthma induced or exacerbated by exposures in the rural setting is highly variable and entirely dependent on the specific nature and intensity of the exposure. Airway narrowing caused by inflammation, edema, or hyperreactivity results in acute and reversible decreases in airflow. Allergic and nonallergic mechanisms of inflammation directly injure the airway epithelia. Recurrent episodes of inflammation may result in chronic remodeling of the conducting airways and could be responsible for the development of progressive airflow obstruction.

Classic allergic mechanisms of airway inflammation involving mast cells, IgE, histamine, and eosinophils may be responsible for the development of asthma after exposure to animal-derived proteins. In patients with an IgE-mediated response, the symptoms and signs of asthma occur in temporal proximity to the exposure. Patients can usually identify the specific agent, and these individuals have an atopic history. IgE–antigen interactions will result in mast cell degranulation with the release of histamine. Histamine can stimulate bronchial obstruction by enhancing vascular permeability, increasing smooth muscle contraction and mucus secretion, and upregulating the production of prostaglandins (*79*).

Several lines of evidence indicate that the physiologic response to organic dust is primarily mediated by an acute nonallergic (or innate) inflammatory response in the lower respiratory tract. First, although atopy may play a role in selected cases of organic dust-induced airway disease (*19,80–82*), the atopic status and the presence of specific antibodies have not been consistently associated with either acute (*45,83–86*) or chronic (*87–90*) airway responses to inhaled organic dust. Second, *in vitro* studies have demonstrated that grain dust can induce macrophages to release neutrophil chemotactic factors (*60*) and IL-1 (*91*), and animal studies have shown that inhaled grain dust causes a neutrophilic response in the lower respiratory tract (*60,92*). Finally, human inhalation studies have demonstrated that organic dust can induce airflow obstruction in previously unexposed individuals (*45–47*); grain-dust induced airflow obstruction occurs within 30 min of exposure (*45–47,53,83–85*); this airway response is dependent on the inhaled dose of grain dust (*45–47,83–85*); and neutrophils, macrophages, and cytokines/chemokines rapidly accumulate in the upper and lower respiratory tract (*46,47,93*).

Macrophages and neutrophils appear to play pivotal roles in the initial inflammatory response to inhaled organic dust. *In vitro,* organic dust is directly chemotactic for neutrophils (*60*) and can induce alveolar macrophages to release IL-1 (*91*) and other mediators that have potent chemotactic activity for neutrophils (*60*). Inhalation studies in humans (*46,47,52, 53,93*) and mice (*53–55*) have shown that following a single exposure to grain dust, neutrophils are rapidly recruited to the lung, and proinflammatory cytokines (IL-1β, tumor necrosis factor (TNF)-α, and IL-6), chemokines [IL-8 and macrophage inflammatory protein-2 (MIP-2)], and growth factors are produced and released for up to 48 hr (Figure 2) (*53*). Immunohistochemical staining (*94*) and *in situ*

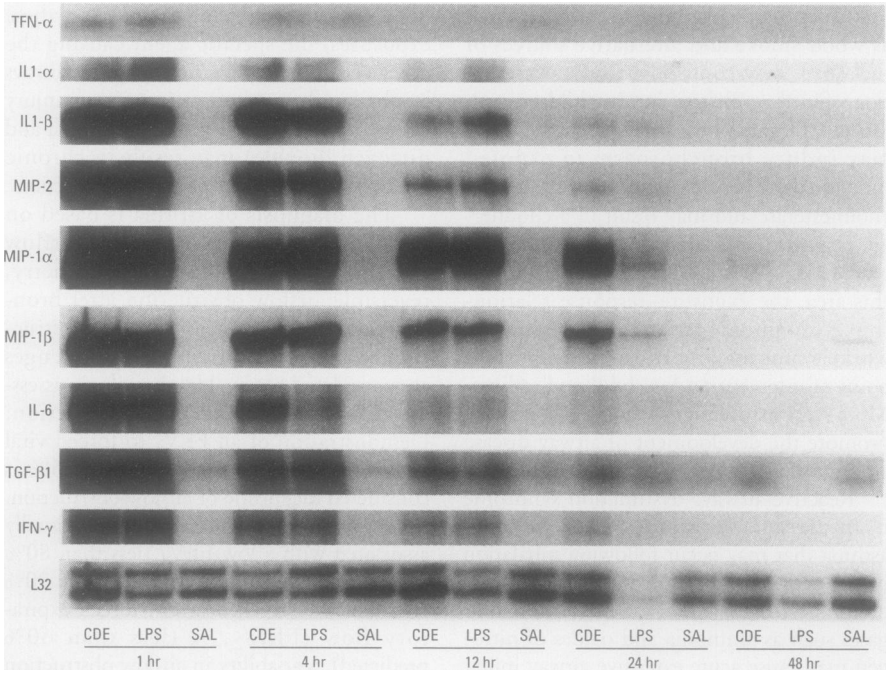


**Figure 2.** RNase protection assay of total RNA obtained from mouse lungs after inhalation of CDE, LPS, or SAL. Abbreviations: CDE, corn dust extract; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; MIP, macrophage inflammatory protein; SAL, saline; TGF, transforming growth factor; TNF, tumor necrosis factor. Equivalent amounts of RNA were examined in each sample, as evaluated by the amount of L32, which encodes a ubiquitously expressed ribosome subunit protein.

hybridization (*95*) indicate that the macrophage and the neutrophil are actively involved in the de novo synthesis of these proinflammatory agents. The influx of neutrophils can be partially inhibited by prior treatment with TNF-α-specific antibodies (*96*).

Epithelial cells may also be involved in recruitment and modulation of the inflammatory response to inhaled organic dust. Epithelial cells (A549 and bronchial epithelia) require a specific host-derived signal (TNF-α or IL-1) for induction of IL-8 (*97–101*). In a baboon model of sepsis, pretreatment with anti–TNF-α antibody significantly reduced the circulating concentration of IL-8 (*102*), suggesting that TNF-α and/or IL-1 are needed to stimulate other cells to release IL-8 and promote neutrophil chemotaxis. MIP-2 is thought to be the murine homologue of IL-8 (*98,103*), has potent chemotactic activity for neutrophils (*104*), is a member of the IL-8 supergene family (*98*), has significant peptide sequence homology with IL-8 (*98*), and is upregulated in rat lungs following intraperitoneal endotoxin challenge (*103*). We have found that human IL-8 (Figure 3) (*94*) and MIP-2 (*95*) are produced and released by airway epithelia following an inhalation challenge with grain dust, suggesting that airway epithelia are activated either directly by grain dust or by cells or cell products that come in contact with the apical or basolateral portion of these cells. In aggregate, these findings suggest that inhaled grain dust initiates a complex interaction between inflammatory (primarily macrophages and neutrophils) and structural (airway epithelial) cells, and that this interaction is mediated by specific proinflammatory cytokines and chemokines that are produced and released in the airway lumen and possibly the interstitium of the lung.

Noxious gases and irritants may directly injure the airway epithelia, resulting in edema, inflammation, and cell death. In fact, the airway epithelia may prove to be an important mediator of the inflammatory response by producing and releasing chemotactic factors such as IL-8 (*98*). Sloughing of the airway epithelia and thickening of the subepithelial region is common in asthma and has been reported in asthma associated with agricultural exposures (*105*). Thus, the airway epithelia may actually contribute to the edema and inflammation following inhalation of particularly irritating stimuli.

There is mounting evidence that asthma involves a fibrotic response that alters the structure and function of the airway. Although thickening and fibrosis of the subepithelial region beneath the basement membrane is a consistent (*106–110*) histologic feature of asthma directly related to the clinical severity of this disease (*111,112*), the biologic factors that cause this localized fibrotic response have not been well defined. Immunohistochemical staining indicates that the subepithelial fibrosis consists predominantly of types I, III, and IV collagen, which probably originate from fibroblasts and myofibroblasts (*108,113*), rather than epithelial cells (which produce branched collagens, types V and VII) (*114*). However, recent studies have shown that transforming growth factor-β (TGF-β) secreted by airway epithelia and inflammatory cells may play a role in the development of subepithelial fibrosis. TGF-β is a family of several similar molecules (β1, β2, β3) whose genes are highly conserved across species and are thought to modulate the development of fibrosis and other biologic processes (*115*). TGF-β is abundant in the lung, can be demonstrated in bronchoalveolar lavage fluid, and appears to play an important role in modulating inflammation in fibrotic forms of lung disease. *In vitro* studies using rat lung fibroblasts stimulated with bleomycin indicate that increases in TGF-β mRNA precede increases in mRNA for procollagen I and procollagen III (*116*). Among individuals with severe asthma, TGF-β1 appears to localize in the submucosa and is produced by macrophages, eosinophils, and fibroblasts; the expression of TGF-β1 was significantly associated with subepithelial fibrosis and disease severity (*111*). In aggregate, these findings indicate that TGF-β1 is released beneath the basement membrane and that TGF-β1 may contribute to airway remodeling in chronic asthma.

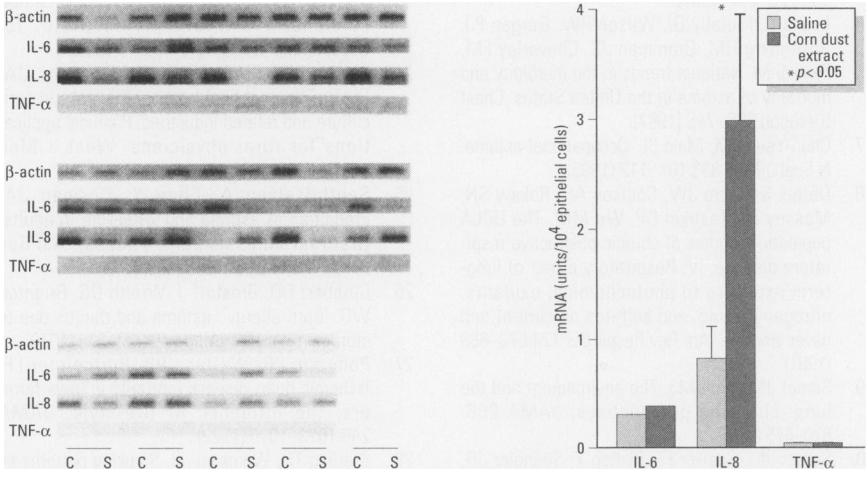


**Figure 3.** Reverse transcriptase–polymerase chain reaction gel and densitometry of airway epithelia mRNA for IL-6, IL-8, and TNF-α 4 hr after inhalation challenge in humans with corn dust extract or saline. Abbreviations: C, corn dust extract; IL, interleukin; S, saline; TNF, tumor necrosis factor.

## Natural History

The acute airway response to grain dust and other organic dusts is predictive of the chronic airway response to these agents. This finding suggests that recurrent episodes of acute airway inflammation result in structural changes in the airway that lead to the development and progression of chronic airway disease. Several epidemiologic studies have shown that the acute workshift-related declines in airflow are independently associated with accelerated longitudinal declines in lung function among grain handlers (*87,88,117*), cotton workers (*118–120*), and agricultural workers (*40*). Although the workshift response to organic dust may simply identify a cohort of individuals with a high intrinsic risk of airway disease, it is equally possible that the acute physiologic and biologic responses to inhaled organic dusts are involved in the pathogenesis of progressive airway disease. This latter possibility is supported by findings from studies in mice (*121*), rats (*122*), guinea pigs (*123–125*), and hamsters (*126*) that demonstrate that long-term inhalation of grain or cotton dust can cause inflammatory lesions in the airway lumen and subepithelial region and hyperplasia of the bronchiolar epithelia. In aggregate, findings from human and animal studies indicate that recurrent exposure to grain dust

can lead to the development of chronic airway disease.

Among patients with environmental asthma, many continue to have asthma despite removal from the exposure (*127*). Remissions appear to be related to the duration and intensity of the disease, with earlier and less severe forms of asthma more likely to improve. Spontaneous recovery has not been reported among workers who remain exposed to the agent causing asthma (*128,129*). Thus, among children in the rural setting, those with asthma caused by specific exposures should be encouraged to modify their exposures by reducing the concentration of inhaled dust and fumes.

## Management

There is increasing evidence in patients with asthma that control of the acute inflammatory response substantially improves airflow and chronic airway inflammation (*130–134*). Because airway inflammation is a major cause of airway hyperresponsiveness in asthma (*4,130,131, 135–139*), control of the acute inflammatory response should decrease the degree of airway hyperresponsiveness. Inhaled steroids (*140–143*) or prednisolone (*144*) substantially improves airflow and airway inflammation in asthma patients. Patients with severe intrinsic asthma treated for 10 years with inhaled steroids demonstrated reduced airway inflammatory cells and restoration of ciliated epithelia (*145*). These findings suggest that the persistent inflammatory response in the airway lumen is essential to the persistence of chronic airway disease and that prolonged treatment with anti-inflammatory medication is indicated in most cases of asthma.

Unique aspects of rural America contribute to the morbidity associated with any chronic disease and may necessitate novel intervention strategies. Rural Americans have inadequate access to health care. Eight million rural Americans lack health insurance, 26.5% of the rural uninsured are children, and 18% of all farm families are uninsured (*146*). Among asthma patients, the distance from an acute care hospital is directly related to mortality (*147*). Shortages of physicians and other health care professionals, combined with a shrinking number of rural hospitals (*148*), have substantially impaired health care delivery in rural communities. As a result, children with asthma from rural (in comparison to urban) America face multiple barriers that adversely affect their health: more poverty, geographic barriers to health care, less health insurance, and poorer access to health care providers (*13*). Access to and availability of high quality health care must be considered when designing intervention programs to reduce morbidity and mortality associated with childhood asthma in children from rural communities. For instance, because emergency transport times may take up to 1 hr, it has been suggested that in rural settings the emergency medical services should be allowed to administer more aggressive therapy while enroute to the hospital (*149*). Similarly, nurse-led home management teams for asthma significantly reduce exacerbations and hospital admissions (*150*). These systematic innovations, in combination with treatment with anti-inflammatory medications and reduction of exposure to agricultural dusts, may substantially reduce the morbidity of asthma in children from rural communities.

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