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Asthma and the Environment

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The Disorder

Asthma is a chronic inflammatory disorder of the lungs characterized by episodic and reversible symptoms of acute airflow obstruction (narrowing of the airways that makes it difficult to breath) (National Institutes of Health). People with asthma can suffer from symptoms ranging from wheezing, cough and a sensation of tightness in the chest, to a severe inability to expel air from the lungs, suffocation and death. Although asthma can begin at any age, it most commonly occurs in childhood. In some cases, as children grow older, their asthma becomes less severe or resolves altogether. People who had asthma as children sometimes experience a recurrence of the disease later in life. Asthma is treated with bronchodilators to help in the event of an acute attack.

Occurrence and Trends

Asthma is a common disease that has been increasing in frequency for many years. The disease affects between 17-26 million people in the United States, and the occurrence is unevenly distributed geographically (Rappaport and Broodram 1998; American Lung Association). Asthma is more common in African Americans, among whom the disease has worse outcomes, with hospitalization rates about four-times higher than among Caucasians and death from asthma about twice as common (Von Behren *et al.*1999 ; Schleicher *et al.* 2000). The disease is also more common among low-income people living in urban areas. Nearly one-third of people with asthma are children. Asthma is the number one cause of hospitalization among children, the number one chronic health condition among children, and the leading cause of school absenteeism attributed to chronic conditions (American Lung Association).

Numerous studies have reported that asthma is increasing in the United States and around the world, with a particularly dramatic increase in young children (Millar and Hill 1998). Increases have been reported in the number of individuals with asthma and in the severity of the disease, including hospitalizations and deaths, despite more awareness of asthma and improvements in asthma treatment. The number of individuals with asthma increased by 42% in the U.S. during the last decade and has roughly doubled since 1980 (Friebele 1996). Among children, the prevalence of asthma increased by 58% between 1982 and 1992 and deaths directly attributable to asthma increased by 78% from 1980 to 1993 (Clark *et al.* 1999). The odds of an adverse outcome (such as intubation, cardiopulmonary arrest, or death) among children hospitalized for asthma in California doubled from 1986 to 1993 (Calmes *et al*. 1998). There is a widespread

consensus among experts that the increases in asthma are real, and are not just due to increased awareness of the disease.

Causes of Asthma

Asthma is known to have both genetic and environmental components. Asthma and allergies often run in families, and some people inherit a genetic predisposition to developing allergic reactions and asthma. This predisposition is called atopy. Atopic individuals are more likely to develop allergies, eczema, and asthma. In fact, 28% of children whose mothers have asthma have themselves been diagnosed with asthma, compared to only 10% of children of non-asthmatic mothers (Millar and Hill 1998). It is clear that the rapidly increasing rates of asthma in the population cannot be due to genetic changes, since genetic changes occur over many generations (Patiño and Martinez 2001). In addition, asthma is occurring increasingly in individuals without atopy or without family histories of allergic disease (Christie *et al.* 1998).

Environmental factors are known to trigger asthma attacks in individuals with the disease. More recent research indicates that environmental exposures may actually cause asthma in some individuals. Environmental factors associated with asthma include viral infections, contaminants in indoor air such as pet dander, dust mites, cockroach feces, fungal contamination, volatile organic compounds (VOCs) and secondhand smoke. In outdoor air, pollen is associated with asthma, as are common pollutants such as ozone, nitrogen oxides (NOx), particulate matter, and diesel exhaust. People can also encounter chemical sensitizers that can cause asthma at work. Chemicals such as the isocyanates, methacrylates, epoxy resins, some pesticides, some types of wood dust, and bacterial toxins can all cause or contribute to asthma in the workplace.

Recent research has begun to uncover important changes in immune function that can set the stage for asthma very early in life (Holt and Jones 2000). Some researchers have discovered that fetuses can become sensitive to environmental contaminants before birth, thus emerging with a strong predisposition to allergies and asthma. Breastfed infants are less likely to develop asthma and allergies compared to those fed infant formula (Chandra 1989). Scientists believe that immune-modulators in breast milk can help the infant's immune system develop in a way that decreases susceptibility to infectious disease and to allergy (Goldman 1986). Other researchers have discovered that a critical type of immune cell, called the T-helper cell (Th cell), can have two different sub-categories. When the Th1-type of cell is most prevalent, individuals do not appear to develop asthma symptoms. The Th2-type, however, causes secretion of interleukins and other chemical signals that can initiate an allergic or asthmatic reaction (Huss and Huss 2000). A shift in the predominant T cell population from the Th1-type to the Th2-type has been associated with asthma (Peden 2000). There is currently much attention to environmental factors that can alter the proportion of Th1 to Th2 cells during infancy and childhood.

Infections and Asthma

Several common diseases of childhood have been associated with airway inflammation, bronchitis, and wheezing (Gern 2000). Both children and adults with asthma commonly wheeze when they are infected with the common cold (rhinovirus). Infants who did not previously have asthma and become infected with respiratory syncytial virus (RSV) or parainfluenza virus may

develop wheezing that can persist as an asthma-like syndrome. These findings have caused some scientists to propose that individuals with a genetic susceptibility to asthma (atopic individuals) may develop asthma following viral infection. Mild, or latent asthma, may then be worsened by subsequent viral illnesses. Viruses may also have synergistic effects with environmental allergies, resulting in more severe asthma symptoms.

In contrast, some studies suggest that early childhood infections may reduce the likelihood of asthma. For example, children who had measles as children had only one-third the likelihood of developing allergies compared to children who were vaccinated against measles (Shaheen *et al.* 1996). Similarly, schoolchildren who had strongly positive tuberculosis skin tests, indicating possible direct exposure to tuberculosis, had lower levels of Th2 cytokines and were less likely to have asthma or other allergic illnesses compared to children vaccinated against tuberculosis with less of an immune reaction against the disease (Shirakawa *et al*. 1997). In possibly related findings, children exposed to farm animals and to endotoxin (a toxin produced by certain kinds of common bacteria) have a lower risk of asthma, as do children with older siblings and those who attended day-care during the first six months of life (Patiño and Martinez 2001; Ball *et al*. 2000). These findings have resulted in the so-called "hygiene hypothesis", in which exposure to childhood diseases, domestic animals, and bacteria is thought to have a protective effect against developing asthma and allergies by encouraging the predominance of the Th1 cells. In contrast, children living in modern urban environments where they have been vaccinated against common diseases may be more at risk for developing the Th2-type immune responses of asthma. This hypothesis, while intriguing, is not consistently supported by the scientific evidence, and fails to explain the higher risk faced by African-American children, and by urban children compared to suburban children (Busse and Lemanske 2001).

Indoor Environmental Exposures

Individuals with asthma are more likely than those without asthma to have allergic responses to common household allergens. Asthmatics commonly have positive skin-prick tests to protein extracts from cockroaches, house-dust mites, cat and dog dander, pollen, and common molds (Ball *et al.* 2000). It is clear that exposure to these allergens can trigger an asthma attack in someone who has asthma and is already sensitized to these proteins. In sensitized asthmatics, efforts to reduce levels of dust mites or other allergens in the home have been shown to reduce the severity of respiratory symptoms (Clark *et al.* 1999). However, the theory that these common allergens actually cause asthma is seriously weakened by three factors: first, there has not been any significant increase in indoor allergen concentrations during the last few decades to account for the doubling of asthma rates during that time (Platts-Mills *et al*. 2000). Second, there are no differences between asthma rates in geographic areas where house-dust mite and fungal concentrations are low (such as dry, cool regions) and warm, humid areas where the concentrations are high (Peat *et al.* 1993). Third, numerous studies have found that children raised in environments with low exposure to allergens are less likely to be sensitized to these particular allergens, but these studies have not found that these children are any less likely to develop asthma (Patiño and Martinez 2001).

Numerous volatile organic compounds (VOCs) are found in modern buildings, particularly those in urban areas (Kinney *et al.* 2002). These chemicals include many respiratory irritants such as

formaldehyde, toluene, and chloroform. VOCs may enter from outside but remain trapped in the indoor environment, or they may be released from building materials, carpets, and furniture. These compounds are also found in some household products including glues, paints, and detergents. Detergents also contain enzymes and surfactants that can be irritating and cause immunological resposes (Poulson *et al.* 2000). Homes with attached garages also contain VOCs from evaporated gasoline emitted from parked cars. Some researchers theorize that these chemicals may have a role in asthma (Larsen *et al.* 2002) . However, at this time there is very little evidence to help determine whether or not VOCs or detergents are important in asthma causation or exacerbation.

Exposure to secondhand cigarette smoke has consistently been associated with increased frequency and severity of asthma attacks in both children and adults, and has also been associated with the development of asthma in children (Forastiere *et al.* 1994). Infants whose mothers smoke during pregnancy have reduced pulmonary function and are more likely to have persistent wheezing until at least age six (Martinez *et al.* 1995). Maternal smoking results in at least a doubling of a child's risk of asthma (Martinez *et al*. 1992). Risk of asthma is associated with both prenatal and postnatal exposure to secondhand smoke, and is clearly dose-related, increasing with more smoking family members and in the homes of heavy smokers. Cigarette smoke resembles diesel exhaust and industrial emissions, containing a similar mix of tiny particles, thousands of toxic chemicals, and numerous respiratory irritants. Exposure to cigarette smoke and to outdoor air pollution may therefore cause similar asthmatic responses.

Outdoor Air Pollution

Asthma is more common in the urbanized areas of industrialized countries, and is particularly common in children living along busy roads and trucking routes (Brunekreef *et al.* 1997). A population-based survey of more than 39,000 children living in Italy found that children living on streets with heavy truck traffic were 60 to 90 percent more likely to have acute and chronic respiratory symptoms such as wheeze or phlegm, and diagnoses such as bronchitis and pneumonia (Ciccone *et al.* 1998). A German study of over 3,700 adolescent students found that those living on streets with 'constant' truck traffic were 71 percent more likely to report hayfever-like symptoms and more than twice as likely to report wheezing (Duhme *et al.* 1996). Studies have also shown that the proximity of a child's school to major roads is linked to asthma, and the severity of children's asthmatic symptoms increases with proximity to truck traffic (Pekkanen *et al.* 1997). Both nitrogen oxides and particulate matter were linked to a significant decrease in lung function growth among children living in the Southern California (Gauderman *et al.* 2000). Although some components of outdoor air pollution are beginning to decline in the United States, ozone and fine particle pollution (PM2.5) from diesel engine exhaust are an ongoing or increasing problem (U.S. EPA 1997).

Numerous studies have demonstrated that specific components of air pollution are associated with asthma attacks (Mortimer *et al.* 2002). For example, particulate air pollution has been linked to increases in emergency room visits for asthma (Norris *et al.* 1999). Nitrogen dioxide (NO2) and sulfur dioxide are directly damaging to the respiratory system. Exposure to sulfur dioxide in laboratory volunteers results in airway constriction, chest tightness, and asthmatic symptoms (Balmes *et al.* 1987). Elevated levels of NO2 in outdoor air are associated with

exacerbations of asthma (Studnicka *et al*. 1997). Because these compounds are airway irritants, it is not surprising that they can trigger asthma attacks.

Air pollutants may act in conjunction with common allergens to dramatically increase sensitivity to pollen or other common proteins. In laboratory volunteers, combined exposures to levels of ozone or NO2 commonly found in urban air and low levels of common allergens such as pollen results in dramatically enhanced asthmatic or allergic reactions (Jorres *et al.* 1996; Strand *et al*. 1998). Air pollutants such as diesel exhaust and ozone may do more than trigger attacks in people with asthma. New data suggests that these substances may actually cause asthma in previously healthy children (McConnell *et al.* 2002). Diesel exhaust is a major source of ambient PM2.5 and NO2 (Ciccone *et al.* 1998). An estimated 26 percent of all particulate matter from fuel combustion sources arises from the combustion of diesel engines. Diesel exhaust also comprises a quarter of the nitrogen oxide smog precursors released nationally. Diesel exhaust has been causally associated with asthma by several lines of evidence (Pandya *et al*. 2002). Several researchers have shown that exposure to diesel exhaust causes direct immunological changes in the airways that are consistent with the inflammatory changes in asthma, and that diesel exposure shifts T helper cells toward the allergic Th2 cell-type (Diaz-Sanchez 1997; Diaz-Sanchez *et al.* 1997). As previously described, the Th2 type is associated with an increased likelihood of developing allergies and asthma. One important study has shown that exposure to common urban levels of diesel exhaust can cause people to develop allergic reactions to proteins to which they did not previously react (Diaz-Sanchez *et al.* 1999). In this study, some volunteers were exposed to a concentration of diesel exhaust roughly equivalent to 1-3 days of breathing Los Angeles air prior to exposure to a new allergen. Subjects exposed to the new allergen alone did not develop antibodies to this compound, whereas subjects exposed to diesel exhaust followed by the allergen developed a full-blown allergy. The similarities between the composition of secondhand cigarette smoke and diesel exhaust also increases the likelihood that the substances may have similar effects in predisposing exposed individuals to asthma development. Recent studies showing that chemicals known as polycyclic aromatic hydrocarbons (PAHs), components of diesel exhaust and cigarette smoke, can cross the placenta and cause effects in the fetus and newborn increase the concern about prenatal exposures (Whyatt *et al*. 2001).

Occupational Asthma

Exposures in the workplace can aggravate pre-existing asthma or can cause new-onset asthma. Some workplace chemicals can even cause asthma in people who are not atopic and therefore have no evidence of a genetic predisposition toward asthma. Some chemicals cause asthma due to a powerful irritant effect of a high-level exposure. For example, exposures to corrosive, acid, or alkaline smoke, vapor or gas can cause an acute onset of asthma-like disease (Alberts and do Pico 1996). Onset of asthmatic symptoms in an adult should be considered a sign of possible work-related asthma.

Several studies have indicated that the proportion of all asthma in the general population that is attributable to workplace exposures is in the range of 8-21 percent (Blanc and Toren 1997). Chemicals that are known to cause asthma include the isocyanates, acid anhydrides, methacrylates, complex amines, metal-working fluids, and several metals (Lombardo and Balmes 2000). Isocyanates are used in polyurethane foams, plastics, paints, and varnishes, while

acid anhydrides are used in epoxy resins and plastics, and complex amines are found in photographic fluids, shellacs and paints. Methacrylates are used in orthopedic surgery and dentistry as a bonding cement. Metals that are associated with asthma when they are in the form of a dust or an aerosol include platinum salts, aluminum, cobalt, chromium, and nickel. People working in various occupational settings can also become sensitized to a wide range of organic proteins, including latex, grain dusts, animal proteins, and wood dusts.

Several pesticides are also known to cause allergic reactions or airway constriction. These may be associated with asthma in workers, and may also be a concern to people exposed to these chemicals when they are used as household insecticides. Case reports and specific bronchial challenge testing have linked several pesticides with occupational asthma. These pesticides include captifol (Royce *et al.* 1993), sulfur (Freedman 1980), pyrethrins and pyrethroids (Box and Lee 1996), tetrachloroisophthalonitrile (Honda *et al*. 1992), and several organophosphate and n-methyl carbamate insecticides (Underner *et al.* 1987; Weiner 1961). For example, the organophosphate insecticides are known to cause increased mucus production and bronchoconstriction (Reigart and Roberts 1999). The pyrethrin and pyrethroid insecticides are related chemically to chrysanthemum flowers and have been reported to cause allergic sensitization (Box and Lee 1996).

Conclusion

Asthma is an illness that has been increasing in frequency and severity in all age groups and in most developed countries. The disease is most common in African American children living urban areas. While it is clear that some people inherit a genetic predisposition to asthma, the increases in asthma rates are due to environmental, rather than genetic factors. Many common allergens can trigger asthma attacks in individuals who already have the disease. The most critical question is what environmental factors can cause new-onset asthma in individuals who did not previously have the disease. In this area, the interactive effects between air pollutants and allergens create an important clue, indicating the possibility that environmental exposures may work together to create asthma. In addition, exposures early in life, including prenatally and during infancy, have been shown to be important in setting the stage for later development of asthma. Many chemicals in common use in workplaces and in homes have also been implicated in initiating or exacerbating asthma.

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