ENVIRONMENTAL FACTORS ASSOCIATED WITH ASTHMA

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Asthma, a disease of attacks and remission, continues to account for substantial morbidity and direct economic costs. Numerous studies—epidemiologic, toxicologic and clinical—present evidence for a broad spectrum of environmental risk factors associated with asthma. This review summarizes current thinking on a subset of these factors. Knowledge of potential environmental determinants of asthma is important to both the patient and healthcare professional in the application of multiple modalities of medical and environmental intervention for management of the development, and exacerbation of this chronic inflammatory disorder of the airways. (*J Natl Med Assoc.* 2003;95:152-166.)

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Few environmentally-related diseases, or diseases that may be the outcome of gene-environment interactions, have attracted as much attention as asthma. This chronic inflammatory disorder of airways affects about 15 million individuals in the United States and accounts for substantial morbidity in all age groups. Asthma results in an excess of 2 million emergency room visits, over 500,000 hospitalizations, and more than 5500 deaths each year. Direct and indirect costs attributed to asthma approaches $12 billion a year.[1] As a result of scientific and policy interest, attention allotted to the effects on asthma of environmental contaminants, ambient and indoor, have increased dramatically in the past decade. This interest was recently fanned by the widely publicized environmental aftermath of the September, 11, 2001, attack on the World Trade Center and by the ongoing reclamation activities at the site. These activities added numerous types of pollutants to the New York/New Jersey airshed. For instance, very fine particles collected near Ground Zero in October 2001 contained silica, lead, dioxin and other products of combustion.[2]

The effects of environmental pollution on the development and exacerbation of asthma also have been topics and subtopics in seminars and workshops on environmental justice and on racial and ethnic health disparities, often enmeshed in social and economic parameters.

This article reviews current thinking regarding environmental risk factors for asthma. Much of this thinking evolves from a number of investigational approaches: occupational and environmental epidemiology, inhalation toxicology, and exposed human studies, including residential assessment for environmental hazards. These approaches are not typically used by practicing physicians.

This review is somewhat selective and covers

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only a sampling of agents or conditions that may increase the risk of environmental asthma.

Readers are directed to other sources for more detailed information desired.[3,4,5] It should also be noted that the impetus for the preparation of this review was an informal discussion among members of the National Medical Association (NMA) who were reacting to a recently published report on the racial gap in asthma treatment.[6] That study found that asthma care given to blacks failed to meet national guidelines for treatment more often than that given to whites. The researchers also found that only 38% of blacks said they had been given enough information about how to avoid environmental triggers (examples listed in this paper) that can cause an asthma attack, compared with 54% of whites. The study was based on 5062 adults with asthma symptoms in managed care plans.

Other studies have etched in sharp relief racial disparities in asthma healthcare. A common theme among these reports is that because blacks fail to receive quality care—including attention to environmental risk factors—they may face complications that could have been lessened or prevented altogether.[7,8,9] The authors' own observations of at-risk groups in the District of Columbia and Atlanta indicate that many blacks do not have a good understanding of environmental triggers for asthma, do not know precisely how to avoid stressful exposures, including appropriate home cleaning/maintenance procedures, and are unaware of other basic interventions and their limitations (unpublished data).

Concerns also are being raised in other circles about the inadequate attention given by clinicians to workplace exposure in the management of occupational asthma, the most common type of work-related lung disease in industrialized countries.[10]

In this context, a prominent deficiency in case management was the failure to ask the appropriate questions even with high-risk candidates for work-related asthma. This inadequacy has been especially pronounced in non-specialty clinics, at a time when environmental and occupational health concerns are increasingly being raised in primary care clinics.[11]

Addressing evidence of environmental determinants of asthma in patient education and related interventions is difficult, partly because of multiple barriers to implementation. The most relevant barrier for the present review is the lack of knowledge of the best current evidence of environmental risk factors. This is not surprising given the abundance of studies that have been published, with new information emerging monthly, as is evident from a cursory review of the vast databases in the National Library of Medicine.

It was in this setting that NMA members inquired as to whether these issues could provide a basis for a review article focused on current thinking, principles, and concepts of environmental components of asthma. We concluded that such a presentation was feasible, drawing heavily on the existing literature on inhaled environmental and occupational irritants and allergens. (Note: Clinical dimensions of asthma, including pathophysiology, diagnostic, and treatment models are beyond the scope of this review.)

ASTHMA

Asthma has been described as a disease of the industrial 20th century. First described in the mid-1800s, it may have existed before that time but was rare. In the last two decades, asthma rates have increased substantially—doubling in the United States since 1980. The incidence of the disease is also high in such well-established health service systems as Sweden, Australia, the United Kingdom and New Zealand. The precise reasons for these increases are unknown. In fact, the key issues and questions for the future involve defining the complex interaction between a challenge from the environment and host response, including genetic variations, in the lungs.[12,13]

Ambient Air Quality

Substandard ambient air quality may exacerbate asthma. The Clean Air Act mandates that

National Ambient Air Quality Standards be set to protect the most sensitive members of the population, such as children with asthma. However, sorting out the impact of air pollutants on asthma is made difficult because of the many types of air pollution and the vast array of indicators of adverse effects on the respiratory system.

There is clear evidence of an association between gaseous pollutants, such as sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) and symptoms in children with asthma.[13] Since 1960, outdoor levels of SO_2 have decreased because of the elimination of high-sulfur coal use. NO_2 is a common indoor and outdoor pollutant. Significant increases in adverse respiratory outcomes in children with asthma was observed when traffic density was used as a surrogate for air pollution.[13] In a study of children under a physician's care for mild to moderate asthma, air pollutants emitted from combustion sources were believed to aggravate the condition. Still other studies report increased cough, phlegm production, and sore throat associated with particulate air pollutants in children with asthma.[14,15]

Occupational Asthma

Many agents found in the workplace have been implicated as risk factors for asthma. Although a number of these agents have been less well investigated. Two groups of agents have been identified: high-molecular-weight compounds, including those that are proteins, polysaccharides and peptides (i.e., animal products: dander, excreta secretions), plants, grain, dust, tobacco, tea, hops. Another group of occupational agents includes the low-molecular-weight compounds. Examples are wood dust, metals, organic chemicals, medications such as penicillin, tetracyclines cephalosporin.[16]

A variety of exposure characteristics influence asthma development or aggravate the disease. The chemical characteristics of an allergen influences its antigenicity and its ability to cause asthma. Such relevant characteristic as chemical type and reactivity, chemical source and concentration are also important. Equally important is the intensity of workplace exposure. The scope of irritant exposure includes not only workplace gases, vapors and fumes, but also dust that possess the potential for allergic sensitization.

A large number of wood dusts have been reported to cause asthma (e.g., California redwood, central American walnut, oak and Western redwood). Flour and grains cause allergy and asthma among millers, bakers and farm workers. Outbreaks of asthma have been reported in people exposed to prevailing winds carrying grain dust from neighboring grain-handling operations.[17]

Among workers in the rubber and latex industry, asthma is a frequent manifestation of rubber latex allergy. Chemical irritants that probably accounts for the largest number of reported cases of occupational asthma are isocyanates, highly reactive compounds. They are used to manufacture polyurethanes, foam surface coating, and adhesives. Primary prevention of isocyanate asthma is difficult because industrial exposures are widespread and difficult to characterize, measure and control. Prevention of progression of isocyanate asthma is limited because no simple way has been found to diagnose isocyanate asthma or identify specific at-risk groups.

Another occupational risk factor for asthma is indoor dampness and mold growth. A recent study provides new evidence of the relationship between exposure to indoor molds and the development of asthma in adulthood. The risk of asthma was related to the presence of visible mold and/or mold odor in the workplace but not to water damage or damp stains alone. The relation was strongest in the youngest age group and significant in current smokers. The relative risk was essentially similar in those with and without atopy.[18]

Airline Cabin Environment

The increase in travel by commercial aircraft in recent years has raised concerns about the presence of "asthma triggers" in airline cabins.

A number of studies have attempted to collect data on occupant exposure to air contaminants in

aircraft cabins under routine conditions. The data collected represented only a small number of flights, and the studies have varied considerably. Consequently, cabin air quality under routine conditions has not been well characterized.

In terms of health effects, available exposure information suggest that environmental factors, including air contaminants can be responsible for some of the numerous complaints of acute and chronic health effects in cabin crew and passengers. The complaints tend to be so broad and non-specific and can have so many causes that it is difficult to define or discern a precise illness or syndrome.

In a 2002 study of these issues, the National Academy of Sciences Committee on Air Quality in Passenger Cabins of Commercial Aircraft recommended that the US Federal Aviation Administration establish an air-quality and health surveillance program. The data should be collected in a manner to allow analysis of the suggested relationship between health effects or complaints and cabin air quality. The committee also noted that the environmental control system (ECS) of aircraft is designed to minimize the introduction of harmful contaminants into the cabin and to control cabin pressure, ventilation, temperature and humidity.[19]

Diesel Exhaust

The contribution of diesel exhaust to the incidence of asthma has been the focus of much debate as urban transportation officials consider replacing diesel buses in the public transportation system. Diesel exhaust is a mixture of chemicals such as elemental carbon, polycyclic aromatic hydrocarbons (PHAs), acid aerosol, volatile organic compounds (VOCs), carbon monoxide (CO), nitric oxide (NO), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2).

Data now suggests that diesel exhaust and diesel exhaust particles (DEP) can cause biologic responses that are related to asthma. For example, Pandya's group has conducted a comprehensive review of the molecular mechanism by which exhaust may facilitate and promote asthmatic symptoms.[20] DEPs alone may augment levels of IgE triggers, eosinophil degranulation, and stimulate release of numerous cytokines and chemokines. Furthermore, the immune event leading to an asthmatic response are intertwined, and DEPs likely act at numerous points on the pathway.

Other evidence underscores the biological plausibility that diesel exhaust and associated particles increase the risk of asthma and other allergies in humans. As Pandya's group rightly concludes, there is ample evidence to justify investing resources in the reduction of community exposure to diesel exhaust. Such reduction efforts should pay particular attention to infants and children and be a critical part of a coordinated effort to improve the prevention and management of childhood asthma.

Ozone

Ozone has been the subject of considerable toxicological interest because it induces a variety of adverse human health effects, including morphological, functional, and biochemical alterations in the respiratory system. The poor water solubility of ozone enhances its ability to penetrate deep into the lungs.

The knowledge of the properties of ozone gives biological plausibility to epidemiologic studies that have demonstrated significant associations between daily asthma hospitalizations and/or emergency room visits and daily outdoor ozone concentrations. Higher ozone levels induce coughing and shortness of breath in asthmatics and non-asthmatics and exacerbates symptoms in asthmatics. High outdoor concentrations of ozone result from the interaction of sunlight with airborne VOCs and nitrogen oxides derived primarily from the combustion of fossil fuels. Urban and industrial areas of the western and southern United States are prone to high levels of ambient ozone. A number of communities in southern California and Texas frequently experience ambient concentrations of ozone that pose significant respiratory health risks.[5]

Studies in Mexico City, which has high ambient levels of ozone, found that its residents had substantially more histologic alterations in their nasal mucosa than people living in other parts of Mexico with low concentrations of air pollution. Ozone inhalation also exacerbates bronchoconstriction

and allergic symptoms in asthmatic individuals.[21] Studies by Hilterman's group and by Frischer and colleagues, found increases in airway inflammatory response of asthmatics correlate with fluctuations in ambient ozone concentrations that occur between May and October.[22,23] Epidemiologic investigations have consistently found an association between high levels of ozone and hospital emergency room visits by asthmatics.

A 1995 study of 11 asthmatics who were allergic to dust mites found that ozone exposure had both a primary effect on allergen-induced response and an intrinsic inflammatory action in the nasal airway. Thus, asthmatics are deemed susceptible groups to the respiratory health risk of ozone.[24,25] Some of the epidemiological evidence is weak and contradictory, but studies underway should add significant weight to the existing databases.

Outdoor ozone penetrates dwelling only partially, depending on ventilation rates and reaction with indoor surfaces. A primary indoor residential source of ozone is an appliance called an ionizer or ozone generator, which is sold as an air freshner or air cleaning device. Xerographic copying machines—found in offices, schools and some indoor environments—also produce ozone.

Waste Incineration

Physicians serving underserved communities have frequently been confronted with questions about the effects of local or regional waste incineration emissions on asthmatics. Incineration is widely used to reduce (1) the volume of municipal solid waste, (2) the potential infectious properties and volume of medical waste, and (3) the potential toxicity and volume of hazardous chemical and biological waste. In the US, more than 100 facilities incinerate municipal solid waste and more than 1600 facilities incinerate medical waste. Also, almost 200 incinerators and many industrial boilers combust hazardous and nonhazardous waste.[26]

Poorer communities are more likely than affluent communities to be located close to waste incinerators, and environmental justice debates have been fueled by these waste management systems and the suspicion that they increase the risk of asthma symptoms. Few epidemiologic studies have attempted to assess whether adverse health effects actually occurred in groups living near individual incinerators. While some studies did report adverse health effects, often findings were not supported by convincing evidence. This is not surprising given the population typically available for study and the fact that such effects, if any, might occur infrequently or may take years to develop. In addition, factors such as emissions from other sources of asthma irritants and allergens and variations in human activity patterns often decrease the likelihood of determining a relationship between the relatively small contribution of pollutants from incinerators and observed respiratory effects. Studies of workers—many of whom are from socio-economically disadvantaged communities—at solid-waste incinerators show that workers are at much higher risk for respiratory dysfunction than residents in the surrounding neighborhoods.[26]

Unanticipated Releases

Another potential air pollution exposure problem stems from chemical incidents, especially in regions with facilities that make and use large quantities of toxic and flammable chemicals which may contribute to the overall air pollution burden of a neighborhood. To prevent such potential risks for asthmatics, the 1990 Clean Air Act required risk management plans for some 15,000 facilities. The Clean Air Act requires these operations to develop accident prevention programs and emergency plans, as well as to calculate the impact of a hypothetical accident (i.e. the size of the chemical plume and the number of people put at risk). The plan gives key information to emergency planners, including healthcare providers, and residents living near a plant. This provision of the Clean Air Act is the last in a string of chemical right-to-know laws passed since the 1980s.[27] Such information can be relevant to the clinical approach to environmental assessment because it gives the physician some clue as to the potential and real exposure of patients and thereby enhances diagnostic inferences.

Minority Exposure

Another aspect of air pollution and asthma deals with the exposure burden on racial minorities. Unfortunately, literature in environmental epidemiology or toxicology includes few studies on the potential impact of air pollution on these groups. Some of the most recent thinking on this topic is reflected in a study of New York City, which has over 7 million residents (52% white, 25% black, and 23% Hispanic). Although potential racial differences in pollution exposure could not be explored as a factor, within-race analyses indicate that the most apparent differences in air pollutant effects found across races were explained by socioeconomic and/or healthcare disparities.[28]

Despite the limitations of this study, its results are consistent with the hypothesis that racial minorities can be more affected by air pollution because these groups are more likely to be socioeconomically disadvantaged or underserved. Socioeconomic disparities place the greatest burden of air pollution on non-white asthmatic patients.

Ambient air pollution is not the results of a personal decision and has no direct benefit to an individual. Thus, we believe that a large subset of the US population may be at increased health risk from exposure to environmental irritants and allergens over which they have little control, merely because of their social and economic status. However, these issues raise a broad spectrum of societal questions that are beyond the scope of this review.

Although the use of the regulatory approach to managing air quality has been successful in the US, a number of areas classified as "non attainment areas"—areas that do not meet air quality standards—still exist. For instance, almost 113 million people live in US counties with ozone levels above the National Ambient Air Quality standards of daily exposure limits (0.08 parts per million [ppm] for 8 hours). In fact, ozone alerts on warm days have become commonplace in urban centers. These media alerts warn the public in given neighborhoods to avoid prolonged exposure to ozone in outdoor activity and thus limit their exposure to ozone in outdoor air. These alerts often complement broader public and patient health education programs aimed at health promotion and disease prevention.[29]

Global Air Pollution

As the world economy becomes increasingly interconnected and globalized, concerns about environmental risk factors for asthma must include the influence of global air pollution on the health of local patients and on the world's citizens. Among developing nations, the magnitude of, and control of, air pollution varies considerably. In many of these communities the goal of economic prosperity often blurs the benefits of investing in clean air strategies. In specific terms, the issues of communicable diseases, malnutrition, and vulnerability to natural disaster have been at the top of the health/medical agenda in these regions.

In developing countries, complicated interdependent factors are implicated as primary and secondary risk factors for respiratory disease. But much attention has been focused on the risk of exposure to indoor air pollution from combustion of products such as wood, charcoal, agricultural residue, and dung. The potential magnitude of this risk is indicated by the fact that more than 2-billion people rely on biomass as the primary source of domestic energy. Particulate matter is only one of the pollutants in the complex mixture of biomass smoke. Gaseous products in the mixture include nitrogen dioxide and formaldehyde, which are known allergens and irritants. To reduce these asthma risks in developing countries, a number of international development and public health organizations are pursuing technology transfers and public health initiatives.[30]

At the same time, a continuing concern is the transfer of hazardous industries and related hazardous waste to developing regions.[31] Western European countries produce between 30 to 40 tons of hazardous waste, while the US produces more than 200 million tons annually.[31] The export of electronic waste, including consumer devices, computer monitors, and circuit boards is increasing the potential exposure to environmental allergens and irritants in the developing world.

Some 50 to 80% of electronic waste collected or recycled in the United States is sent to developing countries where it is reused or recycled under largely unregulated conditions. Recycling operations in these countries usually involve children, many of whom are unaware of the health risks of their work. The hazardous operations include open burning of plastics and wires, the melting and burning of soldered circuit boards, and the cracking of cathode ray tubes laden with lead. All of these operations add significant levels of pollution to the air, which may then be carried offsite. In this connection, recent studies provide evidence that air pollution effects on respiratory health are similar worldwide. For instance, Hong Kong and London are worlds apart in many ways, but data on air pollution patterns correlate with similar respiratory health effects in both cities. Hong Kong and London had similar concentrations of pollutants and the hospital admission rate for asthma complaints, for example, was generally associated with changes in the level of pollutants (i.e., nitrogen oxide [NO_2], sulfur oxide [SO_2] and ozone). Another common thread was that respiratory illness occurred most frequently in each city's time of lowest humidity (the cool season in Hong Kong and the warm season in London). These studies bolster the argument that air pollution contributes to respiratory health problems, including asthma, no matter where it occurs.[32]

In Central and Eastern Europe, many industrial operations were shut down after the collapse of Communism, lowering the level of air pollutants emitted simply by default. However, exposure to air pollutants is still a problem in much of the region. In fact, respiratory disease is the area's worst environmental health problem.[33]

China has significantly reduced air pollutant levels, despite a 36% growth in its domestic product. The end of coal subsidies, energy conservation, and initiatives to reduce coal use are among the factors in China's achievement of improved air quality.[34]

Germany's unification has resulted in a sharp decline in emission of major air pollutants.[35] Cleanup in East Germany initially occurred as a by product of unification; low demand for products and energy led to the collapse of almost the entire industrial and agricultural structure in East Germany, sharply decreasing emissions between 1989 and 1991.

Closer to home, the rapid industrial growth along the Texas-Mexico border has caused tremendous increases in air pollution and a rise in resultant diseases such as asthma. In Mexico City, the second most populated city in the world, air pollution has become one of the leading health problems affecting approximately 20 million inhabitants.[36]

Environmental Tobacco Smoke

Numerous studies have identified involuntary tobacco smoke (ETS) or "passive smoke" as a risk factor for asthma. The chemical products of tobacco smoke include significant amounts of some 30 VOCs, including acetaldehyde, formaldehyde, nicotine 3, vinylpyridine, toluene pyridine, benzene, and many others. Many VOCs remain in the air for prolonged periods of time following the smoking of a cigarette (at least four hours) and do not appear to undergo significant chemical reaction within this period.[33]

The activity patterns of both children and adults have been studied in relation to exposure to ETS. For all ages, home is where the average person spends the most time, and primarily in the bedroom. The next greatest amount of time spent by children is in school or child care; in other peoples' homes, and in transit. For children, home is clearly the most likely source of exposure to ETS because smoking has been banned in many schools and day care facilities.[37] This information is important because it helps the clinician define potential and real exposures.

Some of the most interesting progress in the study of cigarette smoke and asthma has occurred in the areas of prenatal and postnatal ETS exposure.[38] Attention has been called to the important distinction between prenatal and postnatal exposure to smoking products, including nicotine and many other chemical components of tobacco, because the routes of exposure and consequences of exposure differ. Smoking products cross the

placenta. The past decade has seen advances in our understanding of in-utero effects of ETS, including deficits in expiratory flow at functional residual capacity. The ETS–associated reduction flow is believed to represent a reduction in airway size. Also, experimental animal studies have demonstrated that in-utero ETS exposure is associated with reduced elasticity in fetal lungs.

In addition, Murray's group studied 415 nonsmoking children between 1 and 17 years of age who were referred to an allergy clinic for asthma or recurrent wheezing.[39] Children of smoking mothers had significantly higher indices of asthma severity than children of nonsmoking mothers. They also had significantly more hyper-responsiveness to histamine. The effects were stronger in older children (12 to 17 years of age) than for children 6 years of age or younger. Seasonal fluctuation in urinary cotinine in children exposed to ETS and the effect of passive smoking on asthma severity suggest that ETS effects on asthma severity may be reversible and that decreasing ETS exposure could prevent asthmatic attacks.[40]

Cotinine, a metabolite of nicotine, is the most reliable biomarker of exposure to ETS, and has an average half-life of approximately 16 to 19 hours. In infants and children, the half-life is appreciably longer, from more than approximately 40 hours in children older than 18 months of age to approximately 65 hours in neonates. Hence the cotinine level provides information about more chronic exposure to tobacco smoke in both active and involuntary smokers. Whether cotinine has the same half-life in plasma, saliva, and urine is presently controversial, as is the choice of optimal body fluid for measuring cotinine.[41]

The National Academy of Sciences Committee on Assessment of Asthma and Indoor Air Exposure provides a comprehensive discussion of environmental tobacco smoke and childhood asthma. Several of the committee's points are worth mentioning. Evidence shows that there is causal relationship between ETS exposure and exacerbation of asthma in preschool-aged children. Evidence also indicates that there is an association between ETS exposure and the development of asthma in younger children. In the limited number of studies that have been able to separate the effects of maternal active smoking during pregnancy from the effects of ETS exposure after birth, evidence suggests that, while both exposures are detrimental, maternal smoking during pregnancy has the stronger adverse effect.

Insects

Moths, crickets, locust, beetles, lake flies, and houseflies are among the numerous insects that are sources of environmental allergens. But the only insect that has been repeatedly recognized as a common source of indoor allergens is the cockroach. This insect and its allergens are more prevalent in southern humid climates of the United States than in dry western areas. In the Northeast, high levels of cockroach allergens have been associated with urban residents living in apartments.[42]

Evidence regarding asthma exacerbation and development induced by exposure to cockroach allergens has been obtained from case reports and epidemiologic studies, as well as experimental animal toxicology. One of the most recent examples is an environmental medicine case report by O'Connor and Gold.[43] A 30-year-old Puerto Rican man with a history of asthma was given an allergy skin test. He had been hospitalized twice for asthma exacerbations, most recently three years earlier, and he had several asthma-related emergency room visits in the past year. The patient reported ongoing symptoms of intermittent wheezing, dyspnea, productive cough, and chest tightness. He reported living in a severely cockroach-infested apartment and he sometimes noticed red bumps on his skin after getting out of bed in the morning. Allergy testing by the epicutaneous technique showed a positive reaction to cockroach extract. An inspection of the patient's apartment found living cockroaches in numerous locations in the kitchen and entryway of the apartment. Dead cockroaches were also seen in all cabinets, and roach stains were noted in numerous locations. Dust samples collected in the apartments were positive for cockroach allergen.

Additional evidence is corroborative. Dust

samples from bedrooms of 476 inner-city asthmatic children were analyzed for dust mite, cat, and cockroach allergens. Multivariate analysis revealed that cockroaches were the most common cause of children's asthma. In the children's bedroom, 50.2% had cockroach allergen levels that exceeded the disease-induction threshold compared with 9.7% for dust mite allergen levels, and 12.6% for cat allergen levels. The rate of hospitalization for asthma was 3.4 times higher among children whose skin tested positive to cockroach allergens and whose bedrooms had high cockroach-allergen levels. The same group also had 78% more visits to healthcare providers, experienced significantly more wheezing, and had a high rate of missed schools days.[44,45]

The characteristics of exposure and spectrum of effects (i.e., sensitivity) come together in a correlative relationship customarily referred to as the dose-response relationship. Such a relationship has been established in asthmatic children. Researchers report that children who also were exposed to cockroach allergens of one unit per gram (u/g) or higher demonstrated skin sensitivity. A dose-response relationship was also demonstrated in the inner city asthma study between cockroach allergen exposure and morbidity. Asthmatic children who were exposed to more than 8 u/g of allergen were more likely to be hospitalized for asthma symptoms than those who were exposed to less.[46]

Because allergens in the environment exacerbate and trigger the development of asthma, it is important to determine which residential settings are the most likely sites of the highest exposure. The bed has been identified as the most important site of cockroach allergen exposure because of the high level of exposure during sleep, the proximity of the subject to the source, the proportion of time spent indoors at the site, and the large amount of dust present in the bed. Carpets also are a reservoir of cockroach and many other indoor allergens and may serve as an additional primary source of irritants. Children with combined sensitivity to cat, dog, dust mite, and cockroach allergens—for which carpet may be a source—are at increased risk of having more severe asthma than children with sensitivity to a single allergen.[47,48]

Although there is an increased understanding of the cockroach as a source of indoor allergen, there is still a need for more fundamental research on cockroach allergens and asthma outcome. The antigenic relationship between cockroach species—there are some 60 species—is not well understood. The precise source of the allergen—whether insect feces, saliva, eggs or shed cuticle—is also not well known. In addition, it is unclear as to the precise impact on asthmatics of the combined exposure to cockroach allergens, other environmental insults, limited access to high quality medical care and medications, low birth weight, prematurity, obesity and dietary factors has on asthmatic people is also unclear.

Dust Mite and other Animals

Dust mites, microscopic creatures that grow in household materials such as bedding and carpeting, feed primarily on dead particles of human skin. Some 20 million Americans are sensitive to proteins in dust mite waste.

Since 1967, when dust mites were first identified as an important source of allergens in house dust, research in this area has been ongoing. For instance, we have learned that high altitudes and dry cold climates are not conducive for mite reproduction. On the other hand, we know that most houses have the requirements necessary for mite growth:[49] (1) multiple sites for nests (i.e., carpet, sofas, mattresses, pillows, bedding); (2) food source in the form of skin scales; and (3) optimal temperature and humidity. There are some 12 dust mite allergens and Der p 1 and Der f 1 are the most commonly assessed dust mite allergens in their association with health outcome. In studies of children with at least one atopic parent, bedroom dust levels of dust mite allergen (Der p 1) in children one year of age predicted sensitization to the dust mite by age five, as measured by skin test positivity IgG or IgE. For children sensitized to dust mites, the risk of having current asthma doubled with every doubling of Der p 1 level, according to results of a cross sectional study of children 8 to 11 years of age from six different regions of New

South Wales, Australia.

In addition to data on dust mites, other animals, including dogs, horses, cows, and swine, have been identified as sources of allergens. Estimates are that 19% of inner-city asthmatics are allergic to rats and 15% to mice. Dogs are in 25 to 30% of US households. Dog allergen, like cat allergen, and unlike cockroach, is easily aerosolized and widely disseminated throughout the community. A relationship between dogs, endotoxins—components of some bacterial cell walls—and asthma has been confirmed. Families with dogs have higher endotoxin levels in their homes than those without these animals, and they also have lower rates of asthma. Although still unclear, the link between dogs and household endotoxins may be related to the dirt that dogs introduce into the home.[50,51]

Attention has also been focused on cats and their allergens as risk factors for asthma. Cat allergen—a glycoprotein—in association with particles such as dander is easily airborne, in contrast to cockroach allergen, which is only airborne during disturbance of household dust. Cat allergen is easily carried from home to home, office, school or day-care center by those who touch cats or visit households with cats. Trace amounts of cat allergen have been found in most "non-cat homes." Such amounts may be significant for sensitization or exacerbation of disease in sensitized individuals. For instance, one study measured both settled and airborne cat allergen in hospitals. The amount of cat allergen in settled dust in upholstered chairs was as high as in homes with cats, but airborne levels were low. Cat allergen is almost everywhere, and thus, absolute avoidance is difficult. But no published studies suggest association between elevated cat allergen levels in the home and the development of asthma.

Endotoxin

Concerns about residential environmental quality and its impact on asthmatics cannot ignore the potential effects of endotoxin, a toxic component of the outer membrane of gram-negative bacteria. Endotoxin has also been found in cigarette smoking. Originally, the focus of attention by clinicians because of their potential to cause fever, endotoxin has more recently been documented as a cause of airway inflammation and airflow obstruction. Endotoxin has been detected in house dust and has been associated with childhood and adult asthma. Occupational exposures to endotoxin have long been recognized. However, research on exposure to endotoxin and asthma is not as robust as for other environmental irritants or allergens.

A study of homes in the Boston area identified several predictors of airborne endotoxin in the home: the presence of dogs, a moisture source, and increased amounts of settled dust. The presence of dogs was the strongest predictor of airborne endotoxin level. An earlier study suggested an interaction between endotoxin and dust mite levels in the exacerbation of asthma in dust mite sensitized asthmatics. At the same time, endotoxin has also been proposed as a source of protection against the development of asthma. Central air conditioning may decrease exposure to indoor endotoxin.

Cleaning Chemicals

There is substantial evidence linking the use of carpet shampoos and other cleaning compounds to respiratory irritation and asthma.[52] The most recent evidence, is a case report of a 42-year-old woman who experienced an acute asthma attack, seizures, and unconsciousness immediately after carpet cleaning was conducted in her home.[53] The carpet cleaning solution used was a sodium tripolyphosphate (TSP) solution, which also contained low levels of dipropylene glycol methyl ethyl ether (DPGME) and various fragrance compounds, mixed with water. Being diagnosed with asthma at the age of 19, the female remained in a bedroom with the door closed, isolated from the living room being cleaned. But when she reentered the house after leaving temporarily, she detected a damp smell and an associated chemical odor. The case report indicates that since the asthma attack induced by the carpet cleaning exposure, she has experienced persistent nocturnal and exertional asthma with reduced responsiveness to bronchodilators.

This case study is interesting and instructive. It describes an approach to estimating the exposure—usually a missing piece of data in the management of environmentally-related disease—to the carpet cleaning chemical. The modeling conducted in this study demonstrated that significant exposure to chemicals may occur during carpet cleaning when hot water mist is released into the room. This type of exposure, and dose reconstruction, forms an essential part of the chain of causation that would allow a clinician to determine the likelihood that a particular chemical exposure is responsible for an observed illness.

Another instructive aspect of this case is that none of the material safety data sheets (MSDS)—documents that contain brief information regarding the chemical, physical hazards, and health effects—on the chemical components of the carpet cleaning chemical listed allergen as a health effect. MSDSs are frequently recommended as a source of information on the toxicity of chemicals.

Genetically Modified Foods

The growth of agricultural biotechnology has spurred concerns about potential allergenicity of genetically modified foods. The United States plants nearly 70% of the world's acreage of biotechnology crops. In June of 2001, U.S. farmers increased their combined planting of genetically engineered crops by 18% to 82 million acres, compared to no overall increase in 2000. As a result, there is now widespread agreement that foods produced through the biotechnology process should be assessed for their potential allergenicity and for other safety concerns. To address this issue, a committee of the National Academy of Sciences recently called on the US Department of Agriculture to strengthen its procedures for approving field tests and commercialization of transgenic plants.[54]

In this regard, several groups in the population have been considered susceptible to crop-related air pollution in general, and to particulate matter specifically. In each subpopulation, there is likely to be a range of susceptibility. Taken together, current research efforts are expected to provide a rigorous evaluation of particulate matter in farming risk to susceptible subpopulations with asthma.

It should be noted that concerns about airborne particulate matter in recent years have been driven largely by epidemiological studies that have reported relatively consistent associations between outdoor particulate-matter levels and adverse health effects. However, assessing the specific health risks resulting from airborne particulate matter involves substantial scientific uncertainty about the influence of a number of variables such as copollutants and weather a robust research effort in this field is now underway.

Interaction of Environmental Factors

Because of the large number of potential irritants and allergens, an individual may come in contact with at any given time, one cannot overlook the interactions among multiple exposures when assessing the environmental risk for asthma. In toxicology, chemical interactions are known to occur by a number of mechanisms. Moreover, environmental agents may also interact with other conditions in the environment, including humidity, temperature, and ventilation levels. In this regard, environmental conditions may alter the composition and fate of aeroallergens. For instance, the bio-availability of grass antigen in pollen can be markedly altered by increased humidity, sulfate exposure, and NO_2 exposure. Pollen may complex with ambient particulate pollution, thus altering the exposure characteristics and possibly the biological response to these agents.[55] Unfortunately, only limited data address interactions among environmental agents in the initiation or exacerbation of asthma.

Environmental Interventions

For physicians pursuing multiple modalities of medical and environmental intervention—including patient education—the optimal approach to allergen avoidance is to move the patient from a cockroach infested home to a non-cockroach infested environment.

EXAMPLES OF SUBSTANCES THAT MAY INCREASE THE RISK OF ENVIRONMENTAL ASTHMA

Natural Sources	Anthropogenic Sources
-Domestic Animals (rats, mice, guinea pigs)	- Ammonium thioglycate (hair dressing, cosmetics)
-Birds (feather, serum, droppings)	-Persulfate salts, extracts of henna (hair dress ing product)
-Fish (Bluefish)	-Persulfate salts, extracts of henna (hair dress ing product)
-Beetles	-Reactive dyes
-Moth, butterflies	-Psyllium (laxative powder)
-Mushroom molds	-Pesticides
-Potatoes	-Hexamethylene diisocyanate (auto-body spray paint)
-Wood dusts of numerous types	

When this is not feasible, the source, such as the cockroach population, can be reduced through pest control programs, including the application of modern chemicals and the removal of sources of food and water through effective cleaning and maintenance of the home. Insecticide spray should be avoided because they are less effective than gel bait (abamectin) and bait stations combined with boric acid. Insect spray may also induce asthma symptoms via irritative mechanisms.

However, controlling cockroach-provoked asthma symptoms is not an easy task. The simple killing of cockroaches by fumigation in homes may fail to reduce allergic symptoms. Cockroach allergens are persistent in the residential environment and are still detectable in vacuumed dust after the insect population has been substantially reduced. This persistence is best explained by the recent work of Richard Brenner, a medical entomologist at the US Department of Agriculture's Agriculture Research Service (ARS).[56] He reasons that because insect pests redistribute themselves to optimize their survival in any environment, all infestations are spatial in nature.

Thus, through spatial analysis, Brenner and colleagues learned that cockroaches redistribute themselves rapidly after their food and water were removed or relocated. This meant that allergens associated with them were broadly distributed. Devising a system to determine the allergen distribution and how long the allergen persisted, the researchers found that an enormous allergen load was measured five years after all cockroaches were removed. This research may explain why asthma may not improve even after the cockroaches are removed. Other studies have revealed little rapid impact of professional pest control and cleaning of cockroach allergens. More research is needed to determine the most effective and practical methods to reduce cockroach allergen levels in the home.

Reducing cockroach allergen exposure in a home or apartment may require an equally aggressive intervention at the neighborhood and community level, including in schools. The rationale for this approach is that exposure to cockroach and other allergens may extend beyond the patient's immediate residential environment.

For the nonresidential environment there are both theoretical and empirical evidence that schools are important points of intervention, which will be of concern to physicians. A reduction of exposure in school buildings may well complement the clinical management of asthma. In this connection, air exchange rates in urban school buildings are often low. Smedje's group tested the hypothesis that the incidence of allergy exposure, asthma, and asthmatic symptoms should be lower in students who attend schools with improved ventilation systems than pupils who attend schools with inadequate ventilation systems.[57] In this study, new ventilation systems were installed in a number of schools. As air exchange rates increased, humidity and concentrations of several airborne pollutants were reduced and compared with classrooms in non-improved buildings. The reporting of asthmatic symptoms was less among children who attended schools with new ventilation systems.

In the area of dust mite control, results from a 2001 study on the effects of physical interventions on house dust mite (HDM) allergen levels in low-income urban homes suggest that intensive vacuuming can significantly reduce HDM allergens in bedroom carpet.[58,59] The results also demonstrate that impermeable covers combined with frequent washing of noncased bedding materials can significantly reduce HDM allergen levels in the bed. It also showed that both intensive vacuuming and steam-cleaning have modest effects on HDM levels in upholstered furniture. This study demonstrated that the professional laundry bedding regimen and carpet steam cleaning, plus vacuuming methods, effectively decrease HDM allergens to levels below those associated with increased asthma morbidity. However, it remains to be shown whether controlling HDM allergen in the absence of cockroach control in the inner city will have an effect on asthma prevalence and/or morbidity.

Comments

There is substantial epidemiological evidence, supported by clinical and toxicologic data, on a broad spectrum of asthma risk factors. Unfortunately, there is not much consensus on the relative importance of each of these factors. But there is general agreement that the development of asthma is multifactorial and includes important environmental influences. By most accounts the recent increases in the prevalence and severity of asthma seems to have occurred too rapidly to be mediated solely by genetic shifts.

The present review is a mere subset of information on environmental risk factors for asthma. While research in the past decade has made major advances in many areas related to the multiple environmental risk factors for asthma, much remains to be learned, for example, about the complex interaction between a challenge from the environment and an asthmatic's responses. There are also unanswered questions about optimal methods for "allergen/irritant eradication" in the residential environment and in the larger community.

Given the importance of environmental risk factors for asthma, proper treatment relies on a thorough environmental history. The history should include information about the patient's home environment, heating source, indoor combustion source, evidence of insects, pet(s) and proximity to industrial operations. Such information can enhance patient education, which involves knowledge about asthma, its environmental risk factors, other precipitating factors, and avoidance of known allergens. Empowerment of the patient through education is critical.

Numerous studies demonstrate the value of patient education. These studies also suggest that to ensure optimal outcome, the physician must understand and articulate to the patient the complexity of environmental allergens for asthma, including exposure characteristics: route, magnitude, duration, and frequency. The physician also can assist the patient in understanding the most promising environmental interventions.

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