Environmental and occupational allergies

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Airborne allergens are the major cause of allergic rhinitis and asthma. Daily exposure comes from indoor sources, chiefly at home but occasionally at schools or offices. Seasonal exposure to outdoor allergens, pollens, and molds is another important source. Exposure to unusual substances at work causes occupational asthma, accounting for about 5% of asthma in adults. Indoor and outdoor air pollutants trigger airway inflammation and increase the severity of asthma. Diesel exhaust particles increase the production of IgE antibodies. Identification and reduction of exposure to allergens is a very important part of the management of respiratory allergic diseases. The first section of this chapter discusses domestic allergens, arthropods (mites and cockroaches), molds, and mammals (pets and mice). Indoor humidity and water damage are important factors in the production of mite and mold allergens, and discarded human food items are important sources of proliferation of cockroaches and mice. Means of identifying and reducing exposure are presented. The second section discusses outdoor allergens: pollens and molds. The particular plants or molds and the amount of exposure to these allergens is determined by the local climate, and local pollen and mold counts are available to determine the time and amount of exposure. Climate change is already having an important effect on the distribution and amount of outdoor allergens. The third section discusses indoor and outdoor air pollution and methods that individuals can take to reduce indoor pollution in addition to eliminating cigarette smoking. The fourth section discusses the diagnosis and management of occupational asthma. (J Allergy Clin Immunol 2010;125: S150-60.)

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Two key factors influence the development and severity of allergic disease: host factors and environmental factors. Environmental factors include the specific allergens that are the targets of the IgE-mediated immune response, those elements of the environment that influence the presence of those allergens, and indoor and outdoor air pollutants. Also, environmental stimulants of innate immunity influence the development of allergic responses. Although pharmacologic treatments focus on host factors, interventions directed at environmental factors are critical for optimal management of allergic disease, as well as its prevention. Environments can be defined as domestic, outdoors, and occupational, and this chapter will focus on the identification of environmental exposures and methods of intervention for their control.

Abbreviations used
DEP: Diesel exhaust particle
ETS: Environmental tobacco smoke
HEPA: High-efficiency particulate air
NO_2: Nitrogen dioxide
SO_2: Sulfur dioxide

INDOOR DOMESTIC ALLERGY

Background

The primary indoor allergens that contribute to allergic disease include arthropod allergens, mammalian allergens (from either pets or pests), and fungal allergens.[1-5] Additionally, indoor pollutants can also influence host response to allergens and should be considered when developing environmental interventions.[6] Seasonal outdoor allergens can also play a role in the indoor environment when they penetrate into the indoor setting.[6]

Pathogenesis: Allergens

There is overwhelming evidence that indoor domestic allergens play a key role in allergic disease. The primary arthropod allergens associated with allergic disease are house dust mites and cockroaches.

House dust mite allergen. The 2 primary species of house dust mite associated with asthma are *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. The prevalence of IgE sensitization to mites varies with the local environment; arid environments are associated with low-level sensitization (5%), whereas up to 60% of the population can be sensitized in humid locales. Exposure to mite allergens has been associated not only with the severity of allergic disease but also with disease pathogenesis.[3,4,6-8]

These microscopic arachnids do not bite humans or other animals but feed on human and animal dander and are found in bedding, upholstery, and carpeting. House dust mites require humid environments because they directly absorb water from the air, with critical relative humidity ranging from 55% to 75% depending on the ambient temperature. There are 2 major groups of mite allergens, with group 1 being derived from proteins found in the mite gut and group 2 being primarily male reproductive glycoproteins. A major source of mite allergens is mite fecal pellets. These allergens are found on particles that range from 10 to 20 μm in size, which means they tend to settle on surfaces and are not suspended in ambient air.[9,10]

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Cockroach allergen. Cockroaches represent another significant source of allergens, with the German cockroach *(Blatella germanica)* and the American cockroach *(Periplaneta americana)* being the most frequently encountered species in American homes. Cockroach allergy plays a critical role in asthma pathogenesis in the inner city, with the degree of sensitization being linked to the likelihood of requiring urgent or emergency treatment for asthma in urban populations. It has been reported that up 40% of urban children and 20% of suburban children are sensitized to cockroach allergens.[9,10]

Cockroaches tend to feed on discarded human food items. Thus they are attracted to locations in which such materials are readily available. Although they are found in single-family homes, they are more successful in townhomes and multifamily dwellings, which have a higher concentration of persons and, consequently, more discarded food. Cockroaches live in confined spaces, often in walls and between floors in large buildings, and are more active at night.[11]

Cockroach allergens derive from the bodies and feces of these insects. Like mite allergens, cockroach allergens tend to be found on larger particles (10-40 μm in diameter) and thus are more likely to be found in settled house dust rather than on suspended particles in ambient air. Cockroach allergen can be found in high concentrations on floors, carpets, counters, and other flat surfaces, especially in rooms that contain discarded or stored food. Cockroach allergens have also been reported in bedding, although this might be from passive transport of allergens from floor dust to the bed by persons living in cockroach-infested locations.[9,11]

Mouse allergy. Rodent allergens are also important allergens in the inner city, with mice being more common in domestic settings than rats because rats tend to stay outdoors. Mouse allergen exposure has been associated with decreased asthma control in inner-city residents. Mouse allergen has also been found in suburban settings and single-family homes but at levels that are typically 100- to 1,000-fold less than those reported in inner-city dwellings.

Mouse allergens are present in urine and are associated with pheromones and the mating behavior of these animals. Rodent urine is easily aerosolized, and thus rodent allergens can be found in smaller particles (<10 μm in diameter), which can be suspended in ambient air. Like cockroaches, feral mice tend to nest in small hidden spaces and are active primarily at night. Thus it is relatively rare to encounter these animals during the day. These animals are also attracted to discarded human food materials, and thus mouse allergen might be found in greater concentrations in areas where garbage is stored before disposal. In the event that mice are kept as pets, exposure to mouse allergen is similar to that of animal handlers and is principally in the bedding of the cages in which the animals are kept.[7,12-17]

Pet allergy. Mammalian pets are also a source of allergens, with dogs and cats being by far the most common pets in the United States. Common allergens derived from dogs and cats include Can f 1 and Fel d 1 and can be derived from saliva, dander, or other secretions. Like rodents, dog and cat allergens are found in small aerosolized particles (<10 μm in diameter) and can be found suspended in ambient air.[4,18-21] These allergens, especially those from cats, can be carried to other locations on the clothing of persons who own cats. It has also been reported that dog and cat allergens are found in house dust of homes with and without animals. Thus community exposure to these and probably many other domestic allergens likely contributes to exposure to these allergens outside of the home.[7,9]

There is a paradox that has developed with regard to the role that pets have in asthma and atopic disease pathogenesis. It has been argued that many persons with pet allergy do not have cats in their homes, and conversely, many persons who live with mammalian pets do not have clinical disease.[22,23] It has been reported that owning mammalian pets might actually be protective against the development of atopy.[24] Whether this is due to associated increases in domestic endotoxin levels (which, according to the hygiene hypothesis, would protect against atopy) or development of immunologic tolerance is unclear.[24] However, there is strong consensus that in persons with IgE sensitization to mammalian pets and clinical disease, increased exposure to pet allergen is deleterious.

Mold allergy. Mold is a term that encompasses hundreds of species of saprophytic fungi that can be found in the indoor environment. Molds require high humidity and moisture, adequate temperature, and nutrients. It is clear that IgE sensitization can occur to molds, and there is great interest in the role these allergens play in asthma exacerbation and pathogenesis. Quantifying mold exposure can be very complex and is not standardized for clinical practice. Methods for this include culture of spores from recovered environmental samples, spore counts, and assessment of fungal allergens in recovered house dust or other fungal products (eg, 1-3 β-glucans, which themselves exert health effects). Of note, mold spores are between 2 and 10 μm in size and thus can remain in ambient air for extended periods of time.

The variety of measures used in mold quantification has complicated the study of the role of indoor fungi in asthma. However, it is known that *Alternaria* species in outdoor settings is linked to increased asthma severity and airway reactivity. In the Inner City Asthma Consortium Studies indoor mold levels correlated well with outdoor levels, emphasizing that the outdoor environment plays an important role in establishing indoor mold levels. The National Academy of Science reviewed the relationship of mold and fungal exposures to asthma exacerbation and pathogenesis and stated that there was sufficient evidence that fungal allergen exposure caused disease exacerbation in sensitized subjects but that the existing data were inconclusive regarding the role of fungal exposures on disease pathogenesis.

Pathogenesis: Nonallergens

Indoor combustion. Combustion of biological matter results in notable indoor air pollution and often is due to burning of tobacco, wood, and other plant fuels.[25-28] Byproducts of plant-fuel combustion include particulates, which are rich in polyaromatic hydrocarbons, and other constituents that are converted intracellularly to a number of oxidant species.[29] Burning of wood in indoor stoves and fireplaces generates a number of particulates and oxidant gases and is strongly associated with increased respiratory tract illness. However, environmental tobacco smoke (ETS; side-stream smoke from the burning end of a cigarette and exhaled mainstream smoke from a smoker) is the most significant and remediable indoor air pollutant in the United States. An example of the effect of ETS on indoor particulate levels is shown in a study of 11 hospitality locations (primarily restaurants) in which smoking and nonsmoking sections were maintained. The

average concentration of particulate matter with a diameter in the range of 2.5 μm in smoking areas was 177 $\mu g/m^3$ versus 87 $\mu g/m^3$ in the nonsmoking section, which is still 29 times higher than that in truly smoke-free air and 6 times higher than that of local outdoor air.[30]

Exposure to ETS is unequivocally associated with exacerbation of asthma and is a notable contributing factor to disease severity and pathogenesis, with numerous reviews outlining the effect of ETS on asthma exacerbation and sensitization to allergens.[1,25,29,31-38] Experimental exposure to ETS augments nasal responses to allergen in atopic human subjects, with investigators reporting increased allergen-induced specific IgE and IgG4 levels; increased IL-4, IL-5, and IL-13 levels; decreased IFN-γ levels; and increased amounts of postallergen histamine in nasal lavage fluid.[39] Taken together, these studies provide initial mechanistic support to the epidemiologic reports suggesting that ETS exposure enhances the development of atopy and asthma.[29,40,41]

Another significant indoor pollutant is nitrogen dioxide (NO_2), which derives from use of natural gas appliances, especially if they are poorly maintained or poorly vented. Increased levels of NO_2 in domestic settings are associated with increased respiratory symptoms, such as cough, wheeze, production of phlegm, and bronchitis in exposed children, as well as an enhancement of the effect of viral infection in patients with asthma.[42-46]

Biological agents. Biological contaminants certainly contribute to poor air quality, including indoor endotoxin and products from gram-positive bacteria, and 1,3–β-glucans from molds might also affect airway inflammation in both atopic and nonatopic subjects. There are clearly 2 sides to the role that indoor biological agents might play in asthma because a great many articles have described the apparent protective effect that endotoxin and other agents have in the development of asthma. However, others have shown that increased indoor endotoxin levels are associated with increased respiratory tract illness in both allergic and nonallergic persons in both domestic[47] and occupational[48-50] settings. Endotoxin exposure seems to protect infants from asthma but increases it in adults. In domestic settings the number of animals (dogs, cats, and evidence of rodents) and persons living in the home correlate with the amount of endotoxin present.

Humidity. Indoor relative humidity is increasingly recognized as an important factor in determining asthma severity. Decreased levels of humidity are associated with decreased severity of asthma.[51-53] In a large cross-sectional study of fourth-grade schoolchildren in Munich, Germany, Nicolai et al[54] identified 234 children with active asthma, with 155 of these children undergoing lung function and nonspecific airway reactivity tests within a 3-year span. Dampness was associated with increased nighttime wheeze and shortness of breath but not with persisting asthma. Risk factors for bronchial hyperreactivity in adolescence included allergen exposure and damp housing conditions. Mite antigen levels were examined from homes of 70% of the asthma cohort and found to significantly correlate with dampness and bronchial hyperreactivity. However, the effect of dampness was not due to mite allergen alone because bronchial hyperreactivity remained significantly correlated with humidity, even when adjusting for mite allergen levels.

Diagnosis

General considerations. The items outlined in this diagnosis section have been reviewed extensively elsewhere.[7,9,55-57] Evaluation of environmental allergy involves a number of important elements: a clinical history consistent with allergic airway disease, the presence of IgE sensitization to suspect allergens, and determination of exposure to increased levels of environmental allergens, as well as nonallergenic factors that contribute to disease. Frequently, the clinical history includes a number of general points found in most patients with allergic airway disease. These include a history of recurrent respiratory disease, nighttime cough, exercise intolerance caused by cough or wheeze that occurs after aerobic exercise, and exacerbations associated with viral illness. However, other elements of the history might suggest strong environmental factors. This can include improvement of symptoms on vacation or other periods when the patient is away from his or her primary home or, conversely, worsening of symptoms when visiting a new environment. Although much of this discussion has focused on asthma, symptoms of allergic rhinitis and conjunctivitis can also increase at these times.

An environmental health history can be complicated by a number of factors. Many persons, especially children in dual custodial families, might live in more than 1 location on a regular or intermittent basis. Additionally, many patients might not be forthcoming regarding environmental factors in the home that could be relevant. Such factors can include increased symptoms with the addition of a new pet, smoking behavior of a parent (or the patient), or the presence of cockroaches or mice in the home. Patients can also be exposed to allergens in other settings in which they have less control, such as school buildings or work sites. For instance, it has been shown that allergen levels in day care settings might frequently exceed those levels shown to induce symptoms in domestic settings.

It is also important to establish that IgE-mediated processes are viable candidate mechanisms for a given subject's allergic disorders. Skin or serologic testing of allergen-specific IgE to appropriate allergens should be carried out for all patients presenting with a history consistent with allergic disease. Mite allergen testing should be conducted for most patients living in all but the most arid locations, many of which are above 5,000 feet in elevation. Testing for cockroach allergen should be considered for all patients but especially for those patients who live in multifamily dwellings or other institutional housing settings (eg, military barracks, colleges, and detention centers).

Testing for pet allergens should be considered for persons who own a pet or are going to move to a location in which a dog or cat has been owned by the previous occupants. Rodent allergy testing should be considered for those with indications for cockroach allergy. However, mouse allergens might be more widespread than previously thought. Mold allergens should be considered, especially for those living in damp environments. Although there are hosts of molds one might assess, *Alternaria*, *Aspergillus*, and *Penicillium* species are perhaps the most common indoor fungi. This list should also be expanded based on local mold populations. If there is doubt that respiratory symptoms are due to allergic asthma, other evaluations, including chest and sinus imaging, methacholine testing, and perhaps exercise testing should be considered.

Environmental history for mites. There are specific questions that are especially helpful to establish that specific allergen exposures might be contributing to disease. As noted above, house dust mites require humid environments and reasonably warm ambient temperatures. Additionally, if the amount of animal and human dander available to the mites is increased (many persons in a given bed, persons with eczema, and not

TABLE I. Domestic environmental interventions by allergen or pollutant source

	HEPA filter	Dehumidification and air conditioning	Washing bedding in hot water	Professional extermination	Removal of allergen source or contaminant	Cleaning of walls and floors	Securing food waste	Inspect crawlspace	Repair wall and floor cracks
House dust mites		xx	xx			xx		xx	
Cockroach				xx		xx	xx		xx
Pets	xx				xx	xx			
Mice	xx			xx		xx	xx		xx
Molds	xx	xx				XX		xx	
Tobacco smoke	xx				xx				

changing or washing sheets frequently), then the chance of mite allergen exposure is increased. Non–air-conditioned homes also have increased humidity, and this is an increased risk for mite allergen exposure. Indeed, it is not uncommon for persons to actively humidify the bedroom of an asthmatic subject, thinking that this intervention will be helpful. In fact, it often is exactly the wrong thing to do. Recently, home kits have been developed for use by homeowners to determine whether they have increased exposure to mite allergens.

Environmental history for cockroaches. Factors that might increase cockroach exposure include living in multifamily dwellings, the presence of available (open-pail or undisposed) waste food, and infestation with cockroaches in neighboring units of an apartment or condominium. Surveying the living space for cockroaches at night (they are less active during the day), especially in kitchen areas and places where food is consumed, is useful to confirm that cockroach infestation (and thus exposure) has occurred. Additionally, adhesive bait traps can be set, with recovered cockroaches serving as an indicator of total cockroach burden in the dwelling. If it remains unclear whether cockroach infestation has occurred, then a professional exterminator or entomologist can be consulted.

Environmental history for mice. Discovery of rodent droppings is the most common sign of an infestation. However, one might need to inspect crawlspaces, attics, and other hidden areas of the home to find mouse nests. Occasionally, mice can be found moving at night, and therefore nocturnal inspections might be helpful. Scratching sounds can also be heard with mouse infestation.

Environmental history for mold. Determining whether mold exposure is playing a role in a patient's disease is not standardized and can be frustrating. Demonstration of fungal colonies on drywall, caulking, and floor spaces suggests that molds might be playing an important role. Additionally, moisture plays a significant role in supporting mold populations. Homes that have been flooded or have been water damaged are more likely to harbor mold. Examination of plumbing for leaks might reveal an area that has been colonized by mold. Many environmental contractors offer testing for mold spore counts, often by sampling the ambient atmosphere and then determining how many fungal cultures are present. Unfortunately, such tests are not standardized, and it is difficult, if not impossible, to know what level of mold spores in ambient air represent a health risk. However, if one is interested in establishing whether a specific humidity intervention is useful, one might get a baseline assessment and undertake it again when the work is done.

Humidity and pollution. As noted above, there are a number of nonallergenic factors that can affect disease. Humidity and moisture control is one of these factors, and it has been briefly discussed with regard to mold exposures. The best way to determine whether the relative humidity is too high or too low is to measure it with a hygrometer or relative humidity gauge. Mechanical or electronic hygrometers can be purchased at a hardware store or building-supply store and will provide a good assessment of indoor relative humidity levels. Use of air conditioning and dehumidification are essential elements of humidity control in most temperate climates. Ideally, relative humidity should be no higher than 50% to 55% in the summer and 30% in the winter. Fireplaces can also be sources of water vapor, as well as other gases and particulates.

If persons who live in the house are smokers, this will be an important source of indoor pollutants. Although it is preferable that one does not smoke, there is reduced particulate pollution if smokers truly smoke outside. Many indoor air cleaners that are touted to decrease ambient air tobacco smoke are not very effective. Other indoor sources of pollution include gas stoves, furnaces, and artificial logs. Questions should focus on how well these devices are maintained and whether the exhaust is adequately ventilated.

Treatment

Interventions for environmental allergy can be focused on decreasing host reactivity to allergens (medically with inhaled or nasal corticosteroids, leukotriene inhibitors, antihistamines, short- and long-acting β-agonists, or allergen immunotherapy) and decreasing exposure to environmental allergens and adjuvants (Table I). Recent studies suggest that environmental interventions are most effective when an integrated approach is used in which the patient's specific allergen sensitivities and all of the appropriate environmental factors are simultaneously and appropriately addressed.

As noted in preceding sections, control of indoor humidity and moisture is essential for control of many allergens, including house dust mites and fungi, which are very sensitive to humidity. Air conditioning and dehumidification can be useful in decreasing humidity. Appropriate venting of kitchen and bathroom spaces is also an important intervention, as is checking for leaking plumbing fixtures and appropriate vapor shields in crawlspaces.

Indoor sources of combustion should also be assessed for their effect on indoor air quality. Fireplaces are sources of water vapor, particulates, and various gases, including carbon monoxide and nitrogen oxides, in homes. Gas stoves and furnaces can be sources of NO_2 and carbon monoxide. It is important that these sources of pollutants be well ventilated. There is also some evidence that smoking cigarettes only outside the home might decrease indoor particulate levels, although promotion of truly smoke-free homes is the optimal solution.

Some indoor activities have been associated with increased indoor pollutant and allergen levels, including use of humidifiers, gas cooking, sweeping, and smoking. Additionally, as noted

earlier, using air conditioning, keeping windows closed, and staying indoors decreases the likelihood that outdoor environmental agents (humidity, pollens, molds, ozone, and particulate matter) will infiltrate the indoor setting.

High-efficiency particulate air (HEPA) filters might be useful in decreasing exposure to certain allergens or pollutants. They are most helpful for agents found on particles small enough to be suspended in ambient air (generally <10 μm in diameter) and include allergens from mammalian pets or vermin, fungal spores, and particulates derived from wood or tobacco burning (although HEPA filtration should not be the preferred method of decreasing ETS exposure).

Measures used to control house dust mites depend on decreasing humidity, washing bedding in hot water (>130°F), and using mite-impermeable sheets, pillow covers, and mattress covers. However, some studies question the effectiveness of this latter approach. Cockroach control should involve professional extermination, removal of food sources, and checking walls, floors, and plumbing fixtures for holes or gaps and filling these to prevent these insects from entering the building again.[58-62] Ironically, control of mouse allergens includes many of the same concepts as control of cockroach allergen but should also include inspection of crawlspaces and other hidden areas for nests. Because of the large size of the particles that contain most mite and cockroach allergens, HEPA filters are not useful interventions for these exposures, although they can be useful for rodent allergen control.

Optimal control of pet allergen exposure involves removal of the pet and thorough cleaning of the home. However, even with these measures, pet allergens can persist for up to 6 months. Some have reported that washing pets on a regular basis (especially cats) might decrease allergen exposures. In the event that removal of an animal is not feasible, keeping the pet in an area of the home isolated from the patient's bedroom is often recommended.

Although some meta-analyses suggest that there is insufficient evidence to support the use of allergen control measures as a treatment for asthma, many recent studies demonstrate that maneuvers to decrease allergen levels in a domestic setting are effective in decreasing allergens and decreasing asthma severity.[61,62] These studies also suggest that integrated, multifaceted approaches are more effective than one approach alone.[63] An integrated approach includes establishing the IgE sensitization of the patient and designing an allergen control program to account for decreasing the relevant allergen and adjuvant agents that can affect disease.

OUTDOOR ALLERGENS AND CLIMATE CHANGE

Background

Airborne pollens and molds are important causes of allergic rhinitis and asthma and therefore have been a major focus of research since the 19th century. In as much as the details of each local climate determine which plants and molds will grow there, recently, there has been considerable interest in the effect of climate change on outdoor allergens.[64] The dates and amount of exposure to specific allergens at specific locations can be measured by using several methods. The most common is microscopic identification of the individual pollen grains and mold spores using Rotorod samplers or Burkard spore traps. Exposure to particular species of molds can also be determined by culturing of airborne particles. Particle size and allergen concentration can be determined by using filtration samplers with immunochemical assay of the filter.[64-66] Information about outdoor allergen concentrations at many locations is available from the National Allergy Bureau (www.aaaai.org/nab/).

Pollens

Tree pollens are shed in the spring, grass pollens in early summer, and weed pollens (especially ragweed) in late summer and fall. Pollen grains deposit on the nasal mucosa and release allergenic proteins to cause hay fever. Pollen grains are too large to be respirable, and therefore they do not reach the bronchi to cause asthma. Furthermore, the timing of pollen-induced asthma differs from that of hay fever in 2 ways: it starts later in the season and persists after the season ends. Also, it is worse during thunderstorms. Many of the important allergens of pollens lie on the outside of the cell membrane, the exine. They are not produced by the pollen cell itself but are stuccoed onto the exine by other cells of the male flower. A considerable amount of these allergens remain behind for weeks after the pollen is shed. Respirable bits of this part of the plant become airborne, especially from gusts of wind during thunderstorms. It is also possible that allergens extracted from pollen grains by raindrops can become airborne dust particles after drying.[67] This is one reason that asthma symptoms begin after hay fever symptoms and persist longer.

Molds

Allergy to outdoor molds, especially *Alternaria alternata*, is a more important cause of asthma than pollen.[68,69] Other important species include *Cladosporium*, *Penicillium*, *Aspergillus*, and *Helminthosporium*. Because air-sampling methods rely chiefly on mold spores, it is often assumed that the spores are the main source of the allergens. However, a spore is no more the whole organism than an acorn is an oak tree, and *Alternaria* species spores, like pollen grains, are too large to penetrate into the bronchi. More important sources of allergen-containing particles are the hyphae (which are fibrous and therefore stay suspended in the airstream) and dust from the area where the mold was growing and excreting digestive enzymes. This is important because mold proteases are not only allergens but also cause mast cell/eosinophil inflammation and promote IgE to other proteins through stimulation of protease-activated receptors.[64,66,70,71] Unfortunately, unlike the important pollen extracts, commercial mold extracts are not standardized and might not contain all the important allergenic molecules.[72] As a result, *in vitro* tests for IgE antibody to some molds (especially *Aspergillus* and *Penicillium* species but fortunately not *Alternaria* species) are more reliable than skin tests.

Climate change

Global warming is accelerating; an average warming of 1°C to 2°C is certain to occur in this century. If current emissions and land-use trends continue unchecked, increases in the prevalence and severity of asthma and related allergic diseases mediated through worsening ambient air pollution and increased pollen production are anticipated.[64] The sea will rise, and storms and drought cycles will increase. The pattern of change will vary regionally depending on latitude, altitude, rainfall and storms, land-use patterns, urbanization, transportation, and energy production.

TABLE II. What do we know about climate change and asthma?

What do we know?
Ambient air pollution increases the frequency and severity of asthma attacks and the number of symptomatic days.
Pollen, air pollution, and weather interact and affect the clinical expression of allergic disease.
Climate change is unequivocal, accelerating, and largely anthropogenic and will continue through at least the 21st century.
Climate change is measurably affecting the timing, distribution, quantity, and quality of aeroallergens and changing the distribution and severity of allergic disease.
Climate change alters local weather patterns, including minimum and maximum temperatures, precipitation, and storms, all of which affect the burden of allergic disease.
Warming temperatures promote production of ground-level ozone, which worsens asthma.
There are clinical interventions that can be used to minimize climate change–related increases in asthma and allergic disease (secondary prevention).
Greenhouse gas mitigation is the current global recommendation for stabilizing the climate (primary prevention).
What is still unknown?
Future air quality will be determined by energy and transportation choices, economic development, and population growth.
The degree to which human intervention and planning can minimize changes in vegetation and aeroallergen exposure remains unexplored.
The rate and magnitude of climate change in the future will depend on how rapidly and successfully global mitigation and adaptation strategies are deployed.
The outcome of crossing climate tipping points is unknown but potentially very grave for large portions of the global population.
New technologies addressing climate change and air pollution, as well as new medical treatments for asthma, allergic disease, or both could alter current predictions and trends.

Used with permission from Shea et al.[64]

Climate changes have profound effects on vegetation and floristic zones. Between 1990 and 2006, hardiness zones moved substantially northward in the United States because of the warming climate. In urban areas, where CO_2 levels were 30% higher and temperatures were 2°C higher than in matched rural areas, ragweed grew faster and larger and produced more pollen.[64] In general, increased temperatures produce earlier flowering and longer pollen production. Increased CO_2 levels produce pollen production and might cause some plant proteins to become more allergenic. Table II summarizes the effect of climate change on allergic respiratory disease.

Management

In addition to the usual pharmacologic treatment for allergic rhinitis and asthma, avoidance of exposure to outdoor allergens is an important part of management. The patient should be advised to stay indoors in an air-conditioned building as much as possible. Many patients find it practical to take their summer vacation in a location where there is little or no exposure. In exceptional cases in which asthma is unusually severe, such as *Alternaria* species–induced asthma in the Midwest, it might be advisable for the patient to move to a climate where *Alternaria* species is minimal, like the shores of the Pacific Ocean.

AIR POLLUTION AND ASTHMA

Increased exposure to respirable particulate matter (<10 μm in size) is associated with exacerbation of asthma across the world.[74-83] Studies performed in Utah clearly demonstrated the relationship between airborne particulates and occurrence of respiratory disease associated with the activity of a steel mill that was inactive for a year because of a labor dispute.[84,85] Occurrence of asthma and the level of particulates were less during the strike year compared with those during nonstrike years. The relationship of proximity to a roadway, and presumably vehicular traffic, is correlated with increased asthma. In a study of approximately 6,200 German children, traffic counts correlated with active asthma, cough, and wheeze.[51] In a study in the United Kingdom,[86] children less than 5 years old were more likely to be admitted to the hospital for asthma if they lived within 500 m from a heavily traveled road. The effects of specific pollutants are outlined below, and sources for many of these pollutants are listed in Table III.

Diesel exhaust and allergy

Diesel exhaust particles (DEPs) have been shown in numerous animal, *in vitro*, and human challenge studies to skew immune responses toward a T_H2 response.[72,73,87-90] It is thought that this effect of diesel results from oxidative stress generated by the conversion of polyaromatic hydrocarbons to quinones. In human subjects nasal challenge studies have shown that DEPs increased nasal IgE production. In subsequent studies, which are extensively reviewed elsewhere,[29,41,87-89] this group has reported that DEP challenge of the nasal mucosa causes increased T_H2 cytokine production by cells in recovered nasal lavage fluid. DEPs also enhance ragweed-specific IgE and IgG responses to ragweed allergen, which were characterized by increased expression of T_H2 cytokines and decreased expression of IFN-γ and IL-2. DEP challenge can also shift the primary immune responses of the nasal mucosa in human subjects toward a T_H2 phenotype, yielding allergen-specific IgE.[91]

Sulfur dioxide

The effects of sulfur dioxide (SO_2) have been extensively reviewed.[92-95] Total emergency department visits for respiratory problems and increased hospital admission rates have been linked with increased ambient exposure to SO_2. In children decreased lung function has been linked to increases in ambient SO_2 levels, and the likelihood of chronic asthma or obstructive lung disease likewise is associated with lifetime exposure to SO_2. However, in many of these studies, it is difficult to separate the effects of SO_2 from those of particulate air pollutants. Additionally, ambient SO_2 might contribute to acid aerosol (H_2SO_4) formation and might exert effects either as a gas or by contributing to H_2SO_4 particle formation.

TABLE III. Sources for air pollutants that cause asthma (source: http://www.epa.gov/air/emissions/index)

SO_2: Burning of coal, oil, and fossil fuels with a high sulfur content, usually power generation and industrial sites
NO_2: On- and off-road vehicle use, electricity generation, industrial processes, fossil fuel burning
Ozone: Derived from interaction of NO_2 and related nitrogen oxides with sunlight (UV light); thus this depends on vehicle use.
Particulate matter: Uncontrolled fire and planned wood combustion, road dust, electricity generation, and vehicle use

NO_2

There is a strong relationship between ambient air NO_2 levels and changes in lung function. NO_2 challenge enhances airway inflammation, primarily with an influx of airway PMNs. These effects are most notable at higher levels of NO_2 (4.0 ppm) and might affect the airway function of asthmatic subjects.[92-95] SO_2 also has an effect on the response to airway allergen in allergic asthmatic subjects.[96-99] Exposure to 0.4 ppm NO_2 and a combination of 0.2 ppm SO_2 and 0.4 ppm NO_2 have both been shown to enhance immediate bronchial responses of subjects with mild asthma to inhaled allergen. Exposure to NO_2 has also enhanced late-phase responses of asthmatic subjects to inhaled allergen. Likewise, exposure to 0.4 ppm NO_2 for 6 hours increases allergen-induced eosinophil cationic protein levels in the nasal airways of allergic asthmatic subjects. Taken together, these studies demonstrate that NO_2 can augment the acute response to allergen in atopic subjects.

Ozone

There is little debate that increased ambient air ozone levels induce exacerbations of asthma, as measured by hospitalizations, rescue medication use, and symptoms.[92,96-108] These events typically occur 24 to 48 hours after exposure to increased ozone levels. Even very low levels of ozone (less than the current National Ambient Air Quality Standard for ozone) have been linked to increased exacerbations of asthma.[109]

In controlled exposure studies human volunteers experience 2 primary effects of ozone: (1) a temporary restrictive defect characterized by decreased forced vital capacity and FEV_1, which are accompanied by a sensation of chest discomfort with deep breathing and enhanced nonspecific bronchial responsiveness, and (2) development of neutrophilic inflammation, which can be seen as early as 1 hour after exposure but persists for as long as 24 hours after exposure.[109,110] Despite the temporal relationship between these ozone responses, inflammatory and lung function changes do not correlate with each other, suggesting that they are mediated by different mechanisms.

In addition to changes in neutrophilic inflammation, ozone can induce selective increases in macrophages and monocytes,[103] and some investigators have found that ozone induces influx of monocytes and macrophages with increased expression of CD11b and CD14.[104] Overall, it seems likely that monocytes and macrophages might play an important and incompletely understood role in mediating the immunomodulatory effects of ozone. As with NO_2, ozone enhances the response to allergen challenge, with one report suggesting that an ozone exposure as low as 0.12 ppm for 1 hour increased the response to inhaled allergen.[106] Levels of 0.16 and 0.25 ppm ozone have also been shown to increase the response to inhaled allergen,[107,109] as does repeated challenge with ozone at levels o f 0.125 ppm.[109] Air pollution increases airway reactivity and bronchial inflammation.[110-117]

Pharmacologic interventions for the effects of pollutants on airway physiology

Rigorous studies of treatment interventions for environmental lung diseases have not been carried out on a large scale. Thus it is premature to suggest treatment guidelines for prophylaxis of pollutant-induced asthma exacerbation. However, there are reports that examine the effect of pharmacotherapy on responses to pollutants that might provide clues as to important mechanisms by which such agents affect airway disease.

Analgesics. Many investigators have shown in both animal and human studies that COX inhibitors, such as ibuprofen and indomethacin, inhibit ozone-induced decreases in spirometric results, with little effect on the neutrophilic response to ozone or airway hyperreactivity.[118-123] Volunteers treated with sufentanyl (a short-acting narcotic) shortly after ozone exposure were found to have a significant reversal in the ozone-induced decrease in lung function.[115] Taken together, these studies suggest that the immediate decrease in lung function caused by ozone exposure is a pain response, and for those susceptible to this action of ozone, analgesics might be helpful.

Anti-inflammatory agents and ozone. It is not surprising that agents with anti-inflammatory actions have been examined for their effect on the inflammatory response to pollutants, and these studies have been reviewed elsewhere.[116-126] Briefly, cromolyn sodium or nedocromil blunt immediate spirometric responses to SO_2, ETS, and endotoxin[127] in asthmatic volunteers. Inhaled glucocorticoids inhibit the effect of pollutants on airway inflammation. Corticosteroids have been shown to decrease ozone-induced inflammation in allergic asthmatic subjects and healthy volunteers.[124,128]

Antioxidants and ozone. It has been hypothesized that because pollutants exert oxidant stress, antioxidants might be useful interventions in pollutant-induced disease. Studies by Samet et al[129] examining the effect of an ascorbate-rich diet versus an ascorbate-depleting diet in human subjects suggest that antioxidants might be an important defense against the effect of ozone on lung function in healthy volunteers. Trenga et al[130] also examined the effect of vitamin E and C pretreatment on ozone-induced airway responsiveness by using an SO_2 challenge to induce bronchospasm after ozone exposure. Vitamin E and C therapy was also found to have a protective effect on airway function in asthmatic children after ozone exposure in Mexico City, especially in those children with the glutathione-S-transferase Mu null antioxidant genotype.[131,132] These studies suggest that antioxidants might play a role in protection against the effect of pollutants with oxidant activity.

Environmental interventions

One approach that subjects can take to decrease exposure to pollutants is to avoid or minimize outdoor activities during times when ambient air pollutant levels will be increased. The Air Quality Index for "criteria" pollutants can be found on a number of publicly available media sources, including the Web site for the US Environmental Protection Agency, as well as Web sites maintained by many state governmental agencies, and is generally updated on a daily basis. For ozone, the Air Quality Index has generally been

included as a routine part of television and print weather forecasts during the summer months, when ozone levels are increased.

In addition to personal avoidance strategies, public health approaches to decrease air pollutants have been shown to have a measurable effect on health outcomes. One example of this occurred in concert with the 1996 Olympic Games held in Atlanta. Coincident with attempts by the local government to decrease ozone generation by vehicle exhaust, there was not only a decrease in summer ozone levels but also a significant decrease in asthma morbidity noted during this time.[133] Likewise, in Dublin, Ireland, a ban on bituminous coal sales was implemented on September 1, 1990, to improve air quality.[134] In the 72 months after the ban, there was a 70% decrease in black smoke concentrations, a 5.7% decrease in nontrauma death rates, a 15.5% decrease in respiratory death rates, and a 10.3% decrease in cardiovascular death rates when compared with the 72 months preceding the ban.

OCCUPATIONAL ALLERGY

Background

The 2 main occupational allergies are contact dermatitis (see chapter 12 of this Primer)[135] and asthma. Hypersensitivity pneumonitis is uncommon. Farmers' lung has virtually disappeared because silos are no longer used to store food on dairy farms. Occupational asthma is the most common occupational respiratory disorder in industrialized countries, estimated to account for 5% to 15% of asthma cases in adults of working age, especially those with newly developed asthma. More than 250 agents have been reported to cause occupational asthma. The most frequent are isocyanates, flour and grain dust, airborne particles from other foods (especially fish), colophony and fluxes, latex, animals (especially laboratory animals), aldehydes, and wood dust (Table IV).[136-138] Development of asthma is often preceded by allergic rhinitis. Dust or low-molecular-weight compounds released into the outdoor air from the workplace can also cause asthma in the nearby community. Occupational asthma is distinguished from work-enhanced asthma and reactive airway disease syndrome, which are disorders caused by occupational exposure to airborne irritants.

Pathogenesis

High-molecular-weight agents elicit specific IgE antibody responses, and the cellular pathway of pathogenesis is the same as for all other IgE-mediated asthma. The pathogenesis of low-molecular-weight agents, such as isocyanates, is less clear. These patients often exhibit only the late-phase reaction and have more neutrophilia. However, $CD4^+$ lymphocytes do play a role, and some patients might have specific IgE and IgG4 antibodies.[139,140] Concomitant exposure to airborne agents that activate innate immunity enhances the likelihood of occupational asthma.[141,142] Cigarette smoking is another important risk factor, possibly also acting through innate immunity from its contamination with endotoxin.[143] The role of genetic susceptibility is complex and not a useful factor in diagnosis or management at this time.[144] The severity of asthma depends both on the concentration of the allergen in the air and the duration of exposure. Subjects with long-standing heavy exposure often continue to have asthma long after their exposure ceases.

TABLE IV. Some common occupational allergens

High molecular weight	Low molecular weight
Grain dust (including mites)	Diisocyanates (many sources)
Bakery dust	Acid anhydrides
Fish proteins	Western red cedar (plicatic acid)
Laboratory animals	Colophony
Bird proteins	Penicillins
Natural rubber latex	Nickel
Enzymes, especially detergents	Platinum
Mold proteins	Vanadium
Vegetable gums	
Soy bean dust	
Cotton, coffee, and other seed dusts	
Psyllium	

Diagnosis

By far the most important thing is to consider the possibility! Be sure to include details of the patient's occupation in the history of all adult patients with asthma. A history of symptoms improving when the patient is away from work is often more informative than symptoms occurring during work. Occupational asthma is distinct from work-enhanced asthma from exposure to air pollutants at the workplace. Once the diagnosis of occupational asthma is suspected from the history, additional diagnostic procedures include the following[136,145-147]:

- *Skin tests or in vitro tests for IgE antibody to high-molecular-weight allergens*. Unfortunately, standardized reagents are available for only a few occupational allergens, and therefore the material for the test might have to be improvised.
- *Peak flow measurements to correlate obstruction with exposure*. Many cases have a delayed-onset late-phase response and prolonged persistence after exposure, and therefore the peak flow needs to be measured at least 4 times a day for a long period that includes time off work.
- *Correlation of exhaled nitrous oxide concentration, sputum eosinophil counts, or both with exposure*. Again, the inflammation can persist after exposure ceases.

Specific bronchial challenge tests are often considered the gold standard, but for the practicing physician, they have several problems. The reagents are not readily available. Asthma medications inhibit a positive response, and therefore the test is reliable only in patients with mild disease who do not require daily medication. In patients who have not been recently exposed and are asymptomatic, the concentration required to elicit a positive response is 10 to 100 times higher than the concentration that elicits symptoms at work. Provocation tests are more useful for research centers to identify the cause of asthma in the workplace than for the practicing physician to diagnose individual patients' conditions.

Management

The key is avoidance, avoidance, avoidance,[137,145-147] but this is easier said than done.

First, consider the patient. The simplest thing is to change jobs. In fact, many subjects do this themselves, and therefore the prevalence of occupational asthma is often underestimated (ie, the "healthy worker effect").[148] Often, it is possible to continue working for the same employer at a different location, where exposure is less. If changing jobs is not feasible, protective air-fed helmets might be indicated. Simple masks are poorly effective.

The employer is key to avoidance. After the occurrence of occupational asthma at a workplace has been established, management has the responsibility of controlling the exposure, not only for the benefit of the particular subject but also for prevention of asthma in other employees. In many industries this control has been both feasible and effective, and occupational asthma there has been greatly reduced. Of course, the specific changes required depend on the details of the generation of the airborne causative agent. Monitoring of the effectiveness of the control measures involves measurement of the airborne allergen concentration. In those instances in which measurements have been practical (eg, latex and detergent enzymes), the concentration that elicits symptoms is in the range of 100 ng/m^3. Safe concentrations are 1 or at most 10 ng/m^3.

Pharmacologic treatment is the same as for all subjects with asthma. Unfortunately, many subjects with occupational asthma, especially those with more severe disease, continue to be symptomatic long after exposure has ceased. These subjects require the usual pharmacologic management of chronic asthma.

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