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Outdoor Allergens

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Outdoor allergens are an important part of the exposures that lead to allergic disease. Understanding the role of outdoor allergens requires a knowledge of the nature of outdoor allergen-bearing particles, the distributions of their source, and the nature of the aerosols (particle types, sizes, dynamics of concentrations). Primary sources for outdoor allergens include vascular plants (pollen, fern spores, soy dust), and fungi (spores, hyphae). Nonvascular plants, algae, and arthropods contribute small numbers of allergen-bearing particles. Particles are released from sources into the air by wind, rain, mechanical disturbance, or active discharge mechanisms. Once airborne, they follow the physical laws that apply to all airborne particles. Although some outdoor allergens penetrate indoor spaces, exposure occurs mostly outdoors. Even short-term peak outdoor exposures can be important in eliciting acute symptoms. Monitoring of airborne biological particles is usually by particle impaction and microscopic examination. Centrally located monitoring stations give regional-scale measurements for aeroallergen levels. Evidence for the role of outdoor allergens in allergic rhinitis is strong and is rapidly increasing for a role in asthma. Pollen and fungal spore exposures have both been implicated in acute exacerbations of asthma, and sensitivity to some fungal spores predicts the existence of asthma. Synergism and/or antagonism probably occurs with other outdoor air particles and gases. Control involves avoidance of exposure (staying indoors, preventing entry of outdoor aerosols) as well as immunotherapy, which is effective for pollen but of limited effect for spores. Outdoor allergens have been the subject of only limited studies with respect to the epidemiology of asthma. Much remains to be studied with respect to prevalence patterns, exposure and disease relationships, and control. *Key words*: asthma, exposure, fungal spores, outdoor allergens, pollen, predictive models. — *Environ Health Perspect* 108(suppl 4):653–659 (2000).
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People are exposed throughout life to outdoor allergens either directly or after the allergen-bearing particles penetrate interiors. The most widely recognized and abundant sources for these outdoor allergens are pollen grains and fungal spores (*1*). At least some allergen-bearing particles are present in outdoor air throughout the world, although in very low concentrations during periods where snow covers their sources (*2*). They also penetrate interiors, and some outdoor fungi colonize indoor substrates and become essentially indoor allergens. Pollen allergens are commonly considered to play a role in allergic rhinitis (*3*), but the particle size of pollen has been considered too large to penetrate the lower airways, and therefore too large to lead to asthma. However, evidence is increasing for a relationship between exposure to pollen (*4*), fungal (*5,6*), and other airborne allergens such as soy (*7,8*) and exacerbation of asthma.

We present here a brief review of the nature and patterns of outdoor allergens and the evidence for an association between outdoor allergen exposure and allergic disease, particularly asthma.

Characteristics of Outdoor Allergens

Nature of Pollen and Pollen Allergens

Pollen grains are the male gametophyte in the sexual reproduction of flowering plants (angiosperms) and conifers (gymnosperms). Pollination, the transfer of pollen grains from male to female reproductive structures, can be accomplished via three vectors—wind, water, or animals. In wind-pollinated plants, pollen grains are released into the atmosphere to passively find their way onto an appropriate receptive female stigma. Because this is a less efficient transfer than in insect pollination, anemophilous plants produce copious amounts of pollen to ensure successful fertilizations. In addition, the flowers of these plants often have no petals, and the anthers (pollen sacs) are exposed to air movement. Hence, pollen from anemophilous plants is the most abundant in the atmosphere and is also the most important in terms of human exposure. Anemophily is a common strategy for plants in the temperate regions of the world, whereas tropical plants often produce insect-pollinated flowers. Pollen grains are usually more or less spherical, at least when hydrated, with a rigid cell wall formed of a complex polysaccharide-based substance called sporopollenin. Pollen grains are identified using light microscopy by the shape and size of the grain, and its wall structure. Many grains have apertures (pores and/or furrows) that aid in identification. Some have sculptured wall surfaces, and others have distinctive inclusions. Based on morphological features, some grains can be assigned to very specific taxonomic categories (e.g., *Typha latifolia*—broad-leafed cattail). Other less distinctive types are assigned only to relatively large groupings (e.g., grass pollen). The size range within a genus is typically small and can often be used as a diagnostic feature (*9*). Most airborne pollen grains are 15–50 μm in diameter, although the overall range for pollen may be as broad as 10–100 μm.

Isolation of pollen allergens has shown that they are typically low-molecular-weight proteins or glycoproteins (5–60 kDa) that are released quickly upon contact with aqueous solutions (*10*). Speculations on the function of these proteins include cell recognition factors, enzymes involved in pollen germination, or reserve storage proteins for pollen-tube growth (*10*). However, only sparse evidence exists that suggests these proteins can be involved in recognition systems for incompatibility responses within and between plants (*11*), or that they have enzymatic activity (*12–14*). Therefore, the functional role of pollen allergens in the plant has still not been clearly established.

The potency of pollen allergens is not simply a matter of protein abundance as, for example, comparable amounts of two allergens in rye grass pollen produce widely differing allergenicities based on radioallergosorbent test (RAST) inhibition (*15*). Hence, structural and/or compositional differences occur that confer allergenicity (*16*). In addition, a considerable degree of cross-reactivity of allergens occurs between taxa (*17–19*). Immunogold labeling experiments have localized allergens on or as part of the pollen grain wall (exine) and in the cytoplasm (*20*). A moderate amount of allergen is also found associated with apertures.

Pollen allergens have been recovered from small particle fractions of outdoor air (independent of the respective pollen grains). Schäppi et al. (*21*) recovered birch pollen allergen 1.2 ng Bet v $1/m^3$, equivalent to 200 birch pollen grains (typically 25 μm in diameter) from the particle fraction less than

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7.5 μm. Ragweed allergens have also been recovered from small particles (*22–24*). Grass pollen allergen (Lol p 5) has been recovered on particles < 5 μm during rainfall, and ruptured pollen grains are often seen on air sample slides. Grass allergens have been measured in fine-particle aerosols and attached to starch grains and combustion (diesel exhaust) particles (*25,26*). The role of pollen-derived allergens associated with small particle fractions remains speculative. However, the ability of these particles to penetrate the lower airways may play a role in asthma exacerbations. In addition, longer airborne residence times of smaller particles, due to lower settling velocities, potentially increase the risk of exposure to the associated allergens.

Pollen Prevalence Patterns

Pollen source distributions. Distribution of pollen-producing plants is naturally a result of floristic patterns. For example, the northern boreal forests produce large amounts of pine, spruce, hemlock, and birch pollen. Oak–hickory forests cover large areas in the United States, and maples are abundant in the East. Some of the Southwestern mountains support forests of mountain cedar that shed copious amounts of pollen. Grass is an important pollen source throughout the world. Ragweed, long the dominant pollen allergen source in the Midwestern United States, is increasing in importance in many parts of the world, especially in Eastern Europe (*27*).

Landscaping has significantly changed the air biota in many parts of the world. The historical planting of elm trees throughout eastern U.S. cities probably led to early spring pollen peaks in these population centers. Dutch elm disease has done much to remediate this problem. In the Southwestern United States, irrigation of the desert and planting of lawns and street trees has destroyed what was once a refuge for allergy sufferers. In particular, mulberry trees have been widely planted and have become major allergen sources. Their planting has been outlawed in some communities (*28*).

Pollen production and release. The presence of pollen in the air depends on the abundance of source vegetation, and factors controlling release and dispersal. Many different factors affect production of pollen, and the subject cannot be treated in depth here. A few especially important aspects of this interesting field are presented. The reader is referred to Wodehouse (*29*) for further information.

Plants produce pollen in response to internal, genetically controlled cycles impacted by environmental factors such as temperature, available moisture, and light. In temperate regions of the world, most trees produce pollen in the spring following winter dormancy. Some trees (e.g., birch) produce reproductive structures (catkins) in the fall, and the pollen matures in the spring. Others (e.g., maple) form flowers in the spring. Due to the need to coordinate reproductive efforts, particularly in wind-pollinated plants, pollen release is signaled by unambiguous environmental cues. To maximize the likelihood of successful fertilizations, flowering periods of tree types are typically short (1–2 weeks) but intense. In addition, some tree taxa (e.g., birch, pine, beech) exercise mast cycling in reproduction, where a particularly bountiful year in pollen production and seed set is followed by 1 or 2 years of greatly reduced production. This can present particularly bad years for allergy sufferers sensitive to the pollen of these taxa.

All annual plants and perennials that die back each year require several months for vegetative structures to grow before the plants are mature enough to produce pollen. For example, in cold climates grass seeds germinate early, but several months (April–June) are required for growth before flowering in the summer. Flowering and pollen seasons for some grasses and many herbaceous taxa often last 1 month or more.

Nature of Fungal Spores and Their Allergens

Fungi are saprobic or (more rarely) parasitic organisms that occupy a kingdom of their own. They are responsible for most of the aerobic decay of plant materials (e.g., dead grass, leaves, etc.) and are present in air throughout the world, often as the dominant biological component (*2,30*).

The fungal cell is eukaryotic, containing well-developed membrane systems (including mitochondria) and one to several nuclei. The rigid cell wall is composed of acetyl glucosamine polymers (chitin) and β-glucans, or mannans. The wall also often contains waxes (dry spores), and most are coated with extracellular polysaccharides.

Fungi are identified primarily by the method of spore production, including the nature of the spore production process and the morphology of the spores (*31,32*). Fungal spores may be colorless to nearly black, with brown melanin pigments commonly present. Each spore may include one to many cells arranged in lengthwise chains or in two or three-dimensional arrays (*33*). Some fungal spores can be assigned to a genus and species on the basis of their morphology, with no other reproductive information (e.g., *Epicoccum nigrum*). Most, however, can currently be assigned only to larger categories (i.e., *Cladosporium,* the *Penicillium/Aspergillus* group, and basidiospores), although efforts are underway to expand the number of differentiable spore categories (*34*).

Although airborne fungal spores can range in diameter from < 2 to > 50 μm, most fall into the range of 2–10 μm and thus readily penetrate into the lower airways. However, some very common types implicated in asthma are pollen sized (e.g., *E. nigrum*). Few fungal spores are spherical, and some have rather asymmetrical shapes for which aerodynamic diameters are difficult to estimate.

The current state of knowledge of the isolation and characterization of fungal allergens was recently reviewed by Horner et al. (*35*). Advances in the characterization of fungal allergens has been hampered by production and stability variations under differing conditions, the difficulty in standardizing extraction and isolation protocols, and the overall enormous diversity of fungi. More than 80 fungal genera have been associated with allergic respiratory symptoms. However, few fungal allergens have been characterized to date. The allergens from *A. fumigatus, C. herbarum,* and *Alternaria alternata* have been the best characterized. Most isolated allergens have been found to be proteins or glycoproteins with molecular weights of 6–90 kDa. Although in some cases carbohydrate portions of fungal extracts show allergenic activity, most IgE-binding activity is associated with the protein component. Often several allergens (up to 20) are detected in each of the fungal types examined. This emphasizes that exposure involves complex allergen mixtures. In addition, cross-reactivity is common among phlyogenetically related taxa. Shared allergenic and antigenic epitopes have been found among various ascomycetes. The molecular, biochemical, and functional characterizations of fungal allergens are enormous endeavors, and progress has been slow. Application of molecular biological techniques should rapidly expand our knowledge in this field.

Fungal Prevalence Patterns

Spore source distributions. Floristic patterns also play some role in the types of fungal spores that enter the air. Many fungi grow either on or in close association with specific plant hosts. For example, many mushroom species are associated with very specific tree species, and in the absence of the tree, the mushroom is not found. Likewise, the rust fungi can be highly host specific. The cedar/apple rust, for example, only occurs where cedar (juniper) trees occur near members of the apple family.

Agricultural practices have significantly changed floristic patterns throughout the world. Much of the central United States, for example, is covered with field crops throughout most of the growing season. The crops themselves are not considered major allergen sources, but they support massive populations

of fungi that have come to dominate the air spora, especially during the harvest season (*36*). Grain storage and handling are other agricultural practices that may introduce very large concentrations of specific spore types into the air locally (*37,38*).

Disposal of organic waste is an increasing concern in the world. Dumping in water supplies and the ocean is no longer an ecologically sound practice. Incineration requires energy and contributes to air pollution with combustion products. Composting is a process that uses microorganisms to reduce organic waste to (essentially) carbon dioxide and water. Sewage waste is mixed with wood chips and stored in piles that are periodically turned to provide oxygen to the microorganisms using the mixture for food. Cellulose and wood-decaying fungi and bacteria play an especially important role in this type of composting. A succession of organisms occupies the piles. Many of these produce spores that become airborne in enormous numbers when the piles are moved. Among the spore-forming organisms occupying compost are *Aspergillus fumigatus*, several mushroom species, and the thermophilic actinomycetes (bacteria that produce airborne spores). Exposure to any of these can lead to asthma or hypersensitivity pneumonitis, and *A. fumigatus* is a well-recognized human pathogen. Very little research exists that can guide decisions regarding citing of composting facilities and handling of the compost to control exposure of surrounding occupants. Occupational exposures, of course, are also of concern (*39*), but exposure control probably would have to include personal respiratory protection.

Spore production and release. Production of fungal spores is also controlled by internal factors impacted by the environment. Many fungi have seasonal patterns of spore production coinciding with availability of host material to colonize. Thus, many of the plant pathogens (e.g., the leaf spot fungi such as *Venturia*) produce spores in the spring when plants are young and vulnerable. Those that decay dead plant material (e.g., the common species of *Penicillium* and *Aspergillus*) are produced in response to temperature and moisture conditions. Many mushrooms require a season of mycelial growth to accumulate energy for fruiting-body production.

Fungal spores are released from the spore-bearing cells either by active or passive mechanisms. The active mechanisms all depend on changes in moisture conditions. Ascospores and basidiospores are released as the spore-bearing cell absorbs water, either during rainfall or as humidity increases. Some dry-weather spores (e.g., *Cladosporium*) are shaken loose as the spore-bearing cell twists as it dries. In other cases, air movements alone are sufficient to cause release of spores (*2,30*).

Other Allergen-Bearing Particles

Other organisms produce airborne spores that can be locally abundant. Algae and lower plants (mosses, liverworts, club mosses, and ferns) also release reproductive units (spores) into the air. Lichens are formed of algae and fungi in a symbiotic relationship. They release typical fungal spores as well as algal cells that may be entwined with fungal hyphae.

Any living organism can release fragments into the air. Humans, for example, are constantly releasing skin scales that can be found abundantly in indoor air, but also are surely present outdoors. Arthropod fragments are noticeable components of the outdoor bioaerosol. Some occupational activities cause the release of masses of biological particles. The classic example of this aerosol is the soybean allergen clouds identified in Barcelona, Spain, during unloading of container ships (*40,41*). They caused 26 outbreaks of asthma involving 687 subjects and resulting in 1,155 emergency room admissions. Remediation, involving the installation of bag filters in silos, reduced outdoor soy allergen levels significantly, and asthma outbreaks disappeared. However, half of the patients remained sensitized to soy, and no further improvement in asthma episodes was seen after the initial 2 years (*42*). Weak associations between soybean unloading and asthma outbreaks have also been reported for Valencia and Coruna, Spain (*43*). Soybean dust inhalation allergy has also been reported in a child who played with a soybean-filled beanbag (*44*).

Transport and Removal

Airborne allergen-bearing particles follow the same physical rules as any particle of the same aerodynamic diameter. They are dispersed via air movements and settle and impact in relation to their aerodynamic diameter, available impaction surfaces, and factors such as rain that enhance removal.

Spores are usually released by air movement within a laminar boundary layer surrounding their sources. Many remain in the layer and eventually settle near the source. Many dispersion models predict that the majority of particles of the size of pollen and spores will be deposited close to the source (< 100 m) (*2,45*). Others are carried aloft with turbulence and may be transported with wind for long distances. Wind gusts may be especially important in dislodging spores from surfaces, either by direct sweeping of the surfaces or by causing adjacent surfaces to rub together (*46*). Wind and gusts also affect removal by bringing the spores near impaction surfaces and by increasing their inertia so that impaction occurs. Impaction is related to the aerodynamic particle diameter (as for nonbiological particles). Most pollen and spores have a density near unity, so that this diameter is primarily dependent on the shape and size of the spore. Many spores are hygroscopic, and aerodynamic diameter may increase with increasing humidity. Pollen diameters are also probably affected by humidity, traveling as collapsed units when dry and as inflated cells when moist. The extent of this humidity effect has not been reported. Most deposition occurs on narrow surfaces such as leaf edges or thin fibers (*47*).

Rainfall is well known to cause release of spores by splash and by so-called tap and puff mechanisms (*48*). Rain also removes particles from the air by both rainout and washout effects. Rainout involves spores acting as condensation nuclei and falling with the resultant droplet. In washout, raindrops capture spores and pollen as they fall. Frontal rains are more efficient at capturing particles than long drizzle (*49*). Because rainfall both disperses and removes spores, it is difficult to predict airborne spore concentrations during rainfall. During long gentle rains, release mechanisms strongly exceed washout, often leading to much higher spore concentrations during rain than on sunny days without rain. However, the spores released during rain are different from those that were in the air before rainfall began, hence there exists qualitatively distinct wet-air spora and dry-air spora.

Predictive Modeling

Because the presence and abundance of outdoor allergens cannot be controlled, avoidance of outdoor allergen exposure is the major strategy for allergic individuals. However, this requires adequate forewarning of potentially high aeroallergen levels. Several investigators have published models designed to forecast concentrations of specific allergen-bearing particles. Arizmendi et al. (*50*), used neural network technology on historical 2-hr total pollen concentrations, without accounting for the effects of meteorological variables, to forecast near-future concentrations. Stephen et al. (*51*) combined an estimated diurnal rhythm of spore concentrations with a one-parameter time-series model that provided good short-term forecasts up to 24 hr in advance. The one-step (2-hr) prediction error variance was reduced by 88% for *Cladosporium* and by 98% for basidiospores. Moseholm et al. (*52*) forecast grass pollen concentrations using time-series analysis and regression using meteorological parameters. They found high predictive capability using a 2-day lag in temperature. Stark et al. (*53*) used Poisson regression models to forecast ragweed pollen concentrations. Seasonality was modeled by day of the year and the influence of the weather was incorporated through analysis of temperature trends, wind, and rainfall. They accurately forecast 79% of the

days into the appropriate high, moderate, or low categories set by the American Academy of Allergy Asthma and Immunology (AAAAI) Aeroallergen Monitoring Network. Norris-Hill (*54*) used accumulated weather variables to model seasonality of airborne grass pollen and a multiple regression model with maximum temperature, relative humidity, and rainfall to forecast daily values. The model explained 59% of the variation in the data with a forecast accuracy of ±25% that was achieved on 71% of the days.

Although forecasting models continue to improve, published models fail at least 25% of the time and are available for a very few particle types. Also, none predict the magnitude of any pollen or spore season. However, because both biological and environmental factors affect prevalence, once the spatio-temporal scale and magnitude of these relationships are determined, these types of models can be developed and a much higher level of accuracy can be expected.

Exposure

Particle size considerations. The mechanism whereby large particles cause asthma remains speculative. Pollen and large fungal spores are inhalable (i.e., they penetrate into the respiratory tract) but are considered too large to be respirable (i.e., penetrating into the lower respiratory tract). However, Michel et al. (*55*) demonstrated that some pollen grains do penetrate the distal lower airways. In addition, many fungal spores are well within the respirable size range, and pollen allergens (as mentioned above) have been shown to be present in outdoor air on particles smaller than intact pollen (*22,23,25,56*).

Personal exposure. At this point, little if any data exist on personal exposure to outdoor allergens. The methods usually used for outdoor monitoring involve rooftop collections at central sites. Indoor exposures are rarely analyzed with respect to the contributions of the outdoor aerosol, and the effects of the intense exposures that can be found locally at the breathing zone have not been well studied. Gautrin et al. (*57*) have studied personal exposure in lawn cutters. They conclude that these workers are more heavily exposed to fungal spores than the general population and that such exposure results in an increased rate of sensitization to fungi. There are likely to be similar differences in exposure for other occupational and leisure categories, and personal exposure measures are essential for evaluating the relationship between exposure and disease in individuals. In epidemiological studies, personal exposure monitoring would improve the representativeness of exposure measures, but methods currently are unavailable that can reasonably be used in this context (see monitoring methods section below).

Indoor exposure. It is well recognized that people in developed countries spend most of their time indoors (*58*). Outdoor allergens do penetrate indoor environments. In fact, indoor spore concentrations in uncontaminated environments closely parallel those outdoors. In naturally ventilated environments, concentrations are also similar. Where penetration barriers exist, indoor levels are usually much lower than those outdoors (*59*). Pollen allergens also are found indoors (*60*).

Models that estimate overall average exposures use factors to account for both indoor and outdoor exposures, although these have yet to be applied to outdoor spores and pollen (*61*). However, this approach is only appropriate if average, or cumulative, exposure is the important parameter. With allergen exposure, it is likely that short-term peaks in exposure exacerbate symptoms. Thus, during the ragweed season, the 10% of time spent outdoors in the relatively intense aerosol may be sufficient to induce serious symptoms, which may persist during the 90% of time spent indoors with low exposure.

Monitoring for outdoor allergens. Microscopic identification and counting of allergen-bearing particles from either rotating arm impactors (pollen) or from suction spore traps located generally on urban/suburban rooftops has been the standard method for assessing outdoor allergen exposure (*62,63*). Although such methods continue to be useful for assessing exposure to recognizable allergen-bearing particles, spores and pollen are only indicators of the presence of allergens. Recognizable particles of different kinds may contain similar allergens, all particles of a particular type may not contain the same amount of any specific allergen, and as previously mentioned some allergens may not be readily associated with an identifiable particle and may be present as unrecognizable and possibly very small particles. In addition, suction spore traps, while more efficient than rotating arm impactors, collect fewer than 50% of particles smaller than about 5 μm, thereby providing little information about many small, potentially important fungal spores.

The collection of high-volume samples on filters, which have high collection efficiencies well below the smallest fungal spore, is of increasing interest. Immunochemical methods can be used for analysis of these samples, and these methods have been compared to pollen or spore counting by others. Specifically, Johnsen et al. (*64*) found a strong correlation between pollen counts and immunochemical measures of birch, grass, and mugwort allergens. D'Amato et al. (*4*) report similar results for *Parietaria judaica.* Agarwal et al. (*65*), used immunochemical measures on high-volume air samples for Alt a 1, one of the principal allergens of *Alternaria.* However, immunochemical assays are restricted to well-characterized allergens for which specific antibodies are available, and do not reveal exposure to unknown allergens or to allergen mixtures.

Methods for outdoor allergen monitoring are currently restricted to central site monitoring, although interest is increasing in personal monitoring. Poulos et al. (*66*) have developed a nasal sampler that shows promise, and other studies have investigated the utility of portable filtration devices (67).

Outdoor Allergens and Asthma

Existing studies that have sought to relate outdoor allergen exposure and asthma generally fall into two categories: studies of the association between skin test sensitivity and the presence of asthma, and studies comparing symptom data and exposure.

Sensitivity and Asthma

Pollart et al. (*60*), reported that elevated IgE to grass allergens was associated with emergency room visits for asthma [$\chi^2 = 69$; $p < 0.0001$; odds ratio (OR) = 69] in a California population. Pollart et al. (*68*) reported an association between asthma and elevated IgE to grass pollen ($\chi^2 = 8.8$; $p < 0.005$) in a Virginia population. In a study of allergy to laboratory animals, Newill et al. (*69*) incidentally report a positive association between hyperreactive airways disease and skin sensitivity to (ragweed) pollen allergens. In this study, 17 of 36 lab animal workers with one or more positive methacholine challenges were skin-test positive to ragweed extract, whereas only 2 and 7 of these patients had positive reactions to lab animals and household allergens, respectively ($p < 0.004$). Lehrer et al. (*6*), report a significant association (χ^2; $p < 0.005$) between skin reactivity to basidiospore extracts and atopy, asthma, and asthma with rhinitis (but not rhinitis alone). Basidiospores are generally not produced indoors and are often the most abundant outdoor allergen-bearing particle. The incidence of asthma has also been associated with skin reactivity to *Alternaria* (OR 5.1; 95% confidence interval [C.I.] 2.9–8.9). Thirty-nine percent of inner city asthmatic children had positive skin test to *Alternaria* (far more abundant outdoors than in), and an additional 4% were sensitive to *Penicillium* (common both out and in) (*70*). O'Hollaren et al. (*71*) suggest that sensitization to *Alternaria* allergens in young asthmatics is a risk factor for respiratory arrest. It should be noted that a significant relationship between symptoms and skin test reactivity is not proof of a direct relationship between exposure to a specific allergen and symptoms. Many patients have skin reactivity

to allergens that do not induce symptoms on exposure. Specific skin test/symptom relationships may reflect multisensitization.

Outdoor Allergen Exposure and Asthma

Exposure to outdoor allergens has been related to respiratory symptoms in several studies. In the California study discussed above by Pollart et al. (*60*), exposure to grass pollen was measured using a gravity collector, the data from which was strongly correlated with counts from a rotorod. They present emergency room admissions for asthma and pollen counts graphically, and the peak of asthma visits is near the center of the pollen peak. However, they do not present a statistical analysis of these data. D'Amato et al. (*4*) used symptom diaries and spore trapping to relate symptoms and exposure to *P. judaica* pollen. Exposure to grass pollen allergens has been associated indirectly with epidemic asthma (*72,73*). These studies used filter collections and immunoassays for grass allergens for exposure assessment. Johnsen et al. (*64*) report relationships between exposure to birch, grass, and mugwort pollens (Burkard spore-trap measurements) and allergens (measured immunochemically from a high-volume filter sampler) and symptom scores but do not discuss the kinds of symptoms recorded. Neas et al. (*74*) related changes in peak expiratory flow rate (PEFR), a measure of lung function and bronchoconstriction, in 108 children and incremental exposure (using spore trap data) to several outdoor fungal spore types (*Cladosporium*, 10,000 spores/m^3; *Epicoccum*, 60 spores/m^3). Delfino et al. (*75*) revealed positive relationships between outdoor concentrations of total fungal spores (spore trap data), spores for which skin test material was available (primarily *Cladosporium*), spores for which skin test material was not available (primarily basidiospores and ascospores), and daily asthma symptoms and inhaler use in a time-series diary study of 12 children with asthma. Although symptoms were associated with exposure to the comparable fungal spore type in children with positive skin tests, most associations were found for spore types for which skin-test materials were unavailable.

Associations between Asthma, Air Pollution, and Meteorological Factors

Atmospheric pollution has been proposed as a possible factor in the continuing increase in asthma mortality and morbidity. Kesten et al. (*76*) report an association between NO_2, SO_2, ozone, air pollution and air quality indices, and emergency room visits for acute asthma when the data are lagged by 1 and/or 7 days but no relationship for any exposure index for the day of the visit. Marzin et al. (*77*) report an association between emergency service for asthma and both SO_2 and high atmospheric pressure. Forsberg et al. (*78*) report a relationship between relatively low levels of black smoke particulate matter and asthma symptoms as reported by diary. Schwartz et al. (*79*) reported an association between particulate air pollution and emergency room visits for asthma in patients under 65 years of age. Although exposure to outdoor allergens clearly is related to allergic disease, few studies control for allergen exposure when studying effects of air pollutants. Delfino et al. (*75*) related PEFR decrements and personal exposure to ozone while controlling for fungal spore exposure in 12 children, and controlled for ozone exposure with respect to the relationship between spore exposure and asthma.

Interrelationships among air pollution, meteorological factors, and fungal allergens with respect to their effects on asthma remain largely unexplored. Such relationships could involve interactive effects on the nature of exposure as well as synergistic effects on the disease process itself. Clearly, meteorological factors influence concentrations of outdoor allergen-bearing particles [e.g., see Stark et al. (*53*)]. Small (< 3 μm) particles released from grass pollen during thunderstorms are the reported link between thunderstorms and asthma epidemics in the grass pollen season (*72*). Using these small particles, Suphioglu et al. (*73*) elicited IgE-mediated responses in patients with asthma and produced bronchoconstriction with inhalation challenge in four patients. A few studies suggest direct effects of air pollutants on the nature of allergens. Ruffin et al. (*80*), exposed oak, grass, and elm pollen to CO, SO_2, and NO_2 and noted changes in amino acid and molecular-weight profiles and in precipitin banding patterns.

Controlling Outdoor Allergen-Induced Disease

Avoidance. As discussed above, penetration by outdoor allergens into interiors is related to the types of barriers to their entrance. All buildings have inadvertent openings that allow penetration of gases, vapors, and even particles. However, the recognized allergen-bearing particles do not readily penetrate buildings that are mechanically ventilated with filtered air. Thus, in otherwise clean, modern office buildings, exposure to outdoor allergens is minimal (*81*). In residences, a similar effect is seen, with air-conditioned homes having lower outdoor particle levels than naturally ventilated homes (*82*).

The indoor environment is only protective if it remains relatively allergen free. Removing indoor sources (i.e., outdoor allergens in settled dust, fungal growth in reservoirs) is an obvious approach but one that has yet to be tested with respect to improvement in allergy symptoms.

Another potentially effective exposure control approach is to stay indoors during the times when the allergen-bearing particle is abundant outdoors. This approach requires an in-depth knowledge of the patterns of prevalence for each particle of concern, including seasonal, spatial, and diurnal variation patterns (*83*). The development of predictive models may increase the precision of these avoidance approaches.

Outdoor source control is another approach that has been tried for pollen reduction. Laws now exist that forbid the planting of pollen-rich trees (e.g., mulberry in the Southwestern United States). Ragweed control has been attempted, but is difficult because of the aggressiveness of the plant in colonizing disturbed ground (*83*). No attempts have been made to control the airborne fungi that are important allergen sources.

The use of masks to reduce particle exposure is well accepted in the industrial environment. However, few people are willing to wear respirators that adequately prevent exposure to fungal-size particles.

Some symptom relief can be obtained from some allergens by moving to an environment where the allergen is absent. This used to be the case for ragweed, which was isolated to the eastern United States. There are still some pollen types for which this type of prevention could be used. However, in most cases, new allergies will develop to whatever allergens are abundant in the new environment. In addition, fungal exposure outdoors is essentially universal.

Immunotherapy. Historically, immunotherapy has been the treatment of choice for outdoor allergens, and when the allergen is well defined, the approach works well. Unfortunately, although many pollen allergens are well recognized, the specific fungi that cause allergic diseases are unknown for the most part. In cases where fungal allergens have been clearly identified, and purified forms have been used in immunotherapy trials, outcomes have been good (*84*).

Areas for Future Research

Prevalence and Exposure

Global climate change is generally considered to be imminent, but its potential impact on biological systems is not well understood. In the near future, changes in climate and climate variability could potentially alter the timing and abundance of airborne allergens. Preliminary studies on the impact of increased atmospheric CO_2 on ragweed reproduction have shown a 60% increase in pollen production with a doubling of CO_2 (*85*). Over longer time scales, climate change could also induce shifts in species ranges, potentially expanding areas of

favorable growth for allergen-producing taxa. Expansion of agricultural practices to feed the expanding world population will alter land use patterns and increase source areas for fungal spore release. Hence, in some areas increased exposure to pollen or fungal allergens could occur. The continued development of accurate forecasting systems will be necessary to compensate for exposure uncertainty due to increased climate variability.

Large-scale documentation of the magnitude and importance of outdoor allergens as a cause of acute asthma exacerbations in the general population of asthmatics is required. In particular, knowledge of the subpopulations of asthmatics for which outdoor allergen levels are important is needed. Currently no published studies document the connection between asthma and outdoor allergen exposure and clinical sensitivity to specific allergens. No existing studies evaluate the role of indoor allergen sensitivity on outdoor allergen–induced asthma or control for other potentially confounding variables. The synergistic effect of outdoor allergens and air pollutants on asthma must be measured. Priming effects and subsequent exposures to allergens or pollutants are also critical areas of future study.

Monitoring

Monitoring of outdoor allergen levels will remain a key aspect of assessing the impact of global climate change on airborne allergen concentrations and on potential exposure. Cost-efficient and less labor-intensive technological advancements in detection and identification of allergen-bearing particles for use in broad temporal and spatial scale monitoring programs are desperately needed. There remains a suite of unknown fungal spores that have defied classification and detection. Although microscopic identification of fungal spores has advanced greatly in recent decades, there are practical limitations to identification through microscopy. Continued development of specific allergen determination and detection methods (particularly for small particle fractions) is required for accurate assessment of outdoor allergen exposure.

Personal exposure monitoring remains an intractable problem of balancing cost versus sensitivity. Current technology prevents the use of personal monitoring on a wide scale, which would allow a broader interpretation for exposure. Continued development of new low-cost personal monitors would be beneficial for determining more exact indoor versus outdoor allergen exposures.

Disease Relationships

Certainly, much remains to be accomplished in clarifying the role of outdoor allergen exposure in human disease. To date, a clear relationship between exposure, sensitization, and symptoms has not been made for any of the outdoor allergens. The role of pollen exposure in asthma and the mechanism of the effect are important research areas. Fungal allergy remains one of the most frustrating and poorly studied areas in allergic disease. The kinds of fungi and the nature of their allergens that lead to asthma development and exacerbation need intensive study. In addition the need for relevant and potent fungal allergens for skin testing and immunotherapy trials is crucial.

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