

AEROALLERGENS AND HYMENOPTERA

Geographic Distribution and Cross-Reactivity

Richard W. Weber, MD

The potential benefit of allergen immunotherapy is largely predetermined by the appropriate selection of constituent allergens. The summary statements of the Practice Parameters of Allergen Immunotherapy stated: "In choosing the components for a clinically relevant extract, the physician should know the local and regional aerobiology of pollens, fungi, and dust mites and should be aware of potential allergens in the patient's environment."³² One must assess not only the patient's reactivity to a variety of aeroallergens, but also know the relevance of those sensitivities in light of the patient's exposure. The formulation of the allergen vaccine should reflect those exposures likely to be responsible for the patient's symptoms, and contain allergens in optimal concentrations to facilitate treatment response. An attempt to include all vaccines with skin test positivity will usually lead to diminishing the amounts of individual allergens, which may result in a particular component being subtherapeutic. Therefore, one should eliminate items that are either irrelevant owing to lack of exposure or are suitably covered through cross-reactivity with other constituents. For this reason, it behooves the physician to have a firm grasp of geographic distribution of allergenic plants, to know which types are relevant to the area of his or her practice, and have a practical knowledge of allergen cross-reactivity.

From the Austin Allergy Associates, Austin, Texas

IMMUNOLOGY AND ALLERGY CLINICS OF NORTH AMERICA

OUTDOOR AEROALLERGENS

Floristic Zones

The presence of a particular plant in any given locale is dependent on several factors. Foremost is the climate, comprised of such factors as average high and low temperature, precipitation, and humidity. Soil constitution, including elements such as mineral content, pH, and density, also will play a role. Certain plants are fairly cosmopolitan, adapting to and found in a variety of environments, while other plants have adapted to extremes of temperature and moisture and are limited in distribution. Additionally, the range of a plant will be affected by whether it is a native, indigenous species, or introduced. If the latter, aggressiveness of the species and length of time from the point of introduction will determine the extent of its range. For example, the two major tumbleweeds found in the Great Plains, Russian thistle (*Salsola kali*) and burning bush (*Kochia scoparia*), were imported with grain from Russia in the late 1800s. *Kochia*, also called summer cypress, has been used as an ornamental and escaped cultivation through this route.⁷⁰ Over the intervening century these plants have expanded throughout the central states, from the Gulf coast to the California coast, and *Kochia* is now found even in the northeastern states. Introduced plants may become the dominant species in many locations, driving out native plants. Occasionally, however, if a habitat is left undisturbed, native plants may re-establish themselves.

Clues as to what plants may be found in different locations are available from several sources. The United States Department of Agriculture (USDA) defined 10 North American climatic zones that may be found in a number of gardening texts.²⁰ These are "hardiness zones," based on the average annual minimum temperature, beginning with zone 1 at -50°F and progressing by about 10° increments to zone 10 at 30° to 40°F . The USDA map does not take into consideration other factors, such as rainfall or maximum temperature and therefore is only a rough guide. A more exact classification system has been developed for the western 40% of the United States with 24 climate zones described.⁷¹ These were determined by the interplay of six factors: latitude, elevation, Pacific Ocean influence, continental air mass influence, mountains and hills, and local terrain. This system allows those in the western states to clearly define the likely vegetation in any given region. Twenty-four zones, however, are cumbersome to consider. Solomon has popularized a useful compromise of 10 floristic zones that are a cross between the USDA hardiness zones and the factors considered in the western system.^{60, 61} Although the borders of the zones are purposely ill-defined, they are more descriptive of the territory encompassed. The zones are: Northern Forest, Eastern Agricultural, Southeastern Coastal Plain, Florida Subtropical, Central Plains, Rocky Mountain, Arid Southwest, Great Basin, Northwest Coastal, and California Lowland. A useful additional reference source with distribution maps of many native allergenic plants

is *Airborne and Allergenic Pollen of North America* (Johns Hopkins University Press).⁴¹ Distribution maps for a number of introduced major allergenic weeds, however, are not provided. Figure 1 is a compilation of these sources.

Plant and Fungal Aeroallergens

Pollen sources have traditionally been segregated into grass, weed, and tree groups. Whereas such a classification is easy to conceptualize, it tends to obscure botanical relationships. Although grasses are fairly isolated in order and family, other plant families contain members that may be annual weeds, perennial shrubs, or trees. The apparent disparity between form and taxonomic relationships may have a negative impact on understanding cross-reactivity, which is an important consideration for allergen immunotherapy. Additionally, one assumes a set annual sequence of pollination that may not be correct: trees pollinate first, followed by grasses, then weeds. This is generally true, but numerous trees pollinate in the autumn, as is the case with Chinese elm, cedar elm, and September elm (*Ulmus parvifolia*, *Ulmus crassifolia*, and *Ulmus serotina*, respectively).⁴² Certain weeds such as English plantain (*Plantago lanceolata*) and the docks and sorrels (*Rumex* spp) will begin pollinating in May. Pollination periods are modulated by the floristic zone, being generally longer as one moves southward, although pollen peaks may not be as intense. For example, in southern California, Florida, Texas, and Hawaii, grasses may pollinate all year round. Despite such concerns, however, it remains easiest to group allergenic plants into these broad



Figure 1. Vegetative climatic zones. (Data from references 3, 4, 5, and 7.)

categories of grasses, weeds, and trees. Typical plants of the different floristic zones are delineated in Tables 1 and 2.

Grasses

There are thousands of grasses, belonging to the family *Poaceae*, with several subfamilies and a number of tribes, most of which have members incriminated in pollinosis. The most prominent in causing pollinosis is *Festucoideae*, the fescue subfamily, which includes most of the cereal grains and the temperate climate pasture grasses. Examples of *Festucoideae* allergenic pollens include wheat, oat, perennial rye, orchard, meadow fescue, and timothy. These grasses have wide range throughout the United States with examples listed in Tables 1 and 2. Bermuda (*Cynodon dactylon*) is the most important southern grass, generally found south of the 38° parallel, with extension further north along the coasts. Johnson (*Sorghum halepense*) is primarily a southern grass but is found throughout the Eastern agricultural zone and across the arid southwest. Bahia grass (*Paspalum notatum*) is an important aeroallergen in the Gulf states but has a range extending across the south and eastern states.²² Dallisgrass (*Paspalum dilatatum*) is an introduced grass found primarily in the southwest.

Conifers

The most important member of the order *Coniferales* (conifer evergreens) is the cedar family (*Cupressaceae*), containing cedars, pfitzers, junipers (*Juniperus* spp, *Thuja* spp), and cypresses (*Cupressus* spp). Exposure is not only from forest stands but also from the ubiquitous use of junipers in home landscaping. In Texas, mountain cedar (*Juniperus ashei*) pollen counts may be greater than 5000 grains/m³. A related family, *Taxodiaceae*, includes bald cypress, redwoods, sequoias, and the foremost producer of pollinosis in Japan, Japanese red cedar (*Cryptomeria japonica*). The pine family, *Pinaceae*, consists of pines (*Pinus* spp), spruces (*Picea* spp), hemlocks (*Tsuga* spp), and firs (*Abies* spp, *Pseudotsuga*). The pollens of *Pinaceae* are produced in copious amounts, but they are weak allergens and induce little hayfever. Even in midst of the largest standing forest of Ponderosa pine in Arizona, the skin reactivity rate to pine pollen is less than 2%.²⁰

Other Trees

American elm (*Ulmus americana*), with a wide range from the entire east through the Central Plains, has been decimated by disease. Siberian elm (*Ulmus pumila*) is now more common, with a similar range. Cedar elm and September elm (*Ulmus crassifolia* and *Ulmus serotina*, respectively) are found in the southern states and are fall pollinators. Various maples (*Acer* spp) are found across the United States and, with the related species box elder (*Acer negundo*), have a wide range in the Eastern

Table 1. FLORISTIC ZONES AND ALLERGENIC VEGETATION*

Grasses	Trees/Shrubs	Weeds
Northern Forest (extending through Alaska)		
Pasture grasses (lesser pollen burden compared with trees)	Primarily coniferous: juniper (<i>Juniperus</i> , <i>Thuja</i>), cedar (<i>Cedrus</i>), pine (<i>Pinus</i>)†, fir (<i>Abies</i>)† Hardwoods: birch (<i>Betula</i>), alder (<i>Alnus</i>), aspen (<i>Populus</i>), willow (<i>Salix</i>), maple (<i>Acer</i>)	Mugwort (<i>Artemisia</i>), nettle (<i>Urtica</i>), chenopods (<i>Chenopodium</i> , <i>Kochia</i>), pigweeds (<i>Amaranthus</i>) (lesser pollen burden compared with trees)
Northwest Coastal		
Brome (<i>Bromus</i>), orchard (<i>Dactylis</i>), ryegrass (<i>Lolium</i>), fescue (<i>Festuca</i>), velvet grass (<i>Holcus</i>), timothy (<i>Phleum</i>), sweet vernal (<i>Anthoxanthum</i>)	Cedar, fir (<i>Abies</i>)†, ader, birth (<i>Betula</i>), hazel (<i>Corylus</i>)	Plantain (<i>Plantago</i>), short ragweed (<i>Ambrosia</i>), orach (<i>Atriplex</i>), amaranths, chenopods, dock, sorrel (<i>Rumex</i>)
Rocky Mountain		
Pasture grasses: ryegrass, orchard, fescue, brome and chess (<i>Bromus</i>), timothy	Mountain cedar (<i>Juniperus</i>), ponderosa, lodgepole pine (<i>Pinus</i>)†, aspen (<i>Populus</i>), willow, box elder, cottonwood, gambel oak (<i>Quercus</i>), maple (<i>Acer</i>), ash (<i>Fraxinus</i>)	Tumbleweeds (<i>Kochia</i> , <i>Salsola</i>), other chenopods and amaranths, dock (<i>Rumex</i>) giant, western ragweed, sagebrush, prairie sage (<i>Artemisia</i>)
Central Plains		
Ryegrass, orchard, fescue, brome and chess (<i>Bromus</i>), timothy, sweet vernal	As in Eastern Agricultural; cottonwood (<i>Populus</i>), willow (<i>Salix</i>), box elder (<i>Acer</i>), locust (<i>Robinia</i>)	As in Eastern Agricultural; chenopods, amaranths, waterhemp (<i>Kochia</i> , <i>Salsola</i> , <i>Atriplex</i> , <i>Amaranthus</i> , <i>Ancida</i>)
Eastern Agricultural		
Pasture grasses in northeast: ryegrass, orchard, fescue, brome & chess, timothy, sweet vernal	Red cedar (<i>Juniperus</i>), pines white and red oaks (<i>Quercus</i>), beech (<i>Fagus</i>), elms (<i>Ulmus</i>), green ash (<i>Fraxinus</i>), sycamore (<i>Plantanus</i>), maples (<i>Acer</i>), box elder (<i>Acer</i>), alder, red birch, hickory (<i>Carya</i>), black walnut (<i>Juglans</i>), locust (<i>Robinia</i>), hawthorn (<i>Crataegus</i>)	Short, giant, southern, and western ragweed, mugwort, pigweeds, lambs quarter (<i>Chenopodium</i>) nettle, dock and sorrel (<i>Rumex</i>), plantain

*See text for additional detail. Genus listed with first entry in table.

†Low allergenicity.

Table 2. FLORISTIC ZONES AND ALLERGENIC VEGETATION*

Grasses	Trees/Shrubs	Weeds
California Lowland Pasture grasses: Bermuda (<i>Cynodon</i>), Johnson (<i>Sorghum</i>), velvet (<i>Holcus</i>)	Alder (<i>Alnus</i>), walnut (<i>Juglans</i>), sycamore (<i>Platanus</i>), willow (<i>Salix</i>), elm (<i>Ulmus</i>), eucalyptus (<i>Eucalyptus</i>)†, olive (<i>Olea</i>)	As in Great Basin and Arid Southwest; Baccharis (<i>Baccharis</i>), nettle (<i>Urtica</i>)
Arid Southwest Pasture grasses: Bermuda, witchgrasses (<i>Panicum</i>)	Mountain cedar (<i>Juniperus</i>), ash (<i>Fraxinus</i>), mulberry (<i>Morus</i>), acacia (<i>Acacia</i>), mesquite (<i>Prosopis</i>)	Scales (<i>Atriplex</i>), Palmer's amaranth, k tumbleweeds (<i>Kochia</i> , <i>Salsola</i>)
Great Basin Pasture grasses: Bermuda, johnson, witchgrass	As in Rocky Mountain and Arid Southwest	Scales, chenopod/amaranth, k marshelders Iva)
Southeastern Coastal As in Eastern Agricultural; bahia and dallis (<i>Paspalum</i>)	As in Eastern Agricultural; bald cypress (<i>Taxodium</i>), live oak (<i>Quercus</i>), box elder (<i>Acer</i>), elm, hackberry (<i>Celtis</i>), ash, hornbeams (<i>Carpinus</i> , <i>Ostryia</i>), hickory, pecans (<i>Carya</i>), sweet gum (<i>Liquidambar</i>), bayberry (<i>Myrica</i>)	As in Eastern Agricultural; baccharis
Subtropical Florida Bermuda, johnson, bahia, dallis	Pine (<i>Pinus</i>)†, bald cypress, live oak, mulberry, eucalyptus (<i>Eucalyptus</i>)†, palm (<i>Phoenix</i> , <i>Cocos</i>)†, palmetto (<i>Sabal</i>)†	Short ragweed, sea-myrtle (<i>Baccharis</i>), spiny and redroot pigweeds, goosefoots (<i>Chenopodium</i>)

*See text for additional detail. Genus listed with first entry in table.

†Low allergenicity.

zones, Central Plains, Rocky Mountain, Southwest, and California Lowlands.

The order *Fagales* contains two closely related families. *Fagaceae* contains beeches, oaks, and chestnuts. *Betulaceae* includes birches, alders, hophornbeams, hornbeams and hazels. Several birch species (*Betula*) and alders (*Alnus* spp) are found throughout Northern Forest, Northwest Coastal, California Lowlands, and Great Basin. Red and white oaks (*Quercus* spp) have a wide range similar to that of elm. Elms and oaks are the most prolific pollen producers among the hardwoods.

Hickories (*Carya* spp) are found primarily in the eastern and central states, with pecans (*C. illinoensis* and *C. texana*) found in the southern states. In the Southwest, both native and introduced ashes (*Fraxinus* spp), and introduced mulberries (*Morus* and *Broussonetia*), have become troublesome. Olive (*Olea europaea*) is a potent pollinator in the southern tier, from southern California to the Gulf, where it has been introduced as a crop tree. Ash and olive are members of the *Oleaceae* family, and shrubs such as forsythia and privet.

Weeds

The Aster family, *Asteraceae*, is the largest among flowering plants, containing a dozen tribes, most of which have only insect-pollinated plants of little interest to allergists. The sunflower tribe (*Heliantheae*), mayweed tribe (*Anthemideae*), and ragweed tribe (*Ambrosieae*) are closely related, with newer taxonomies classifying *Ambrosieae* as a subtribe of *Heliantheae* (*Ambrosieae*). Ragweeds belong to the genus *Ambrosia*. Also within the same subtribe are cocklebur and the marshelders. The major four ragweeds are short, giant, western, and false. The mayweed tribe contained the mugworts and sages of the genus *Artemisia*.

Short (*Ambrosia artemisiifolia*) and giant (*A. trifida*) ragweeds predominate in the eastern states through the Central Plains, with false (*A. acanthicarpa*) and western (*A. psilotachya*) ragweeds common in Rocky Mountain, Great Basin, Arid Southwest, and California Lowlands. Mugwort (*Artemisia vulgaris*) in the east and sages (*Artemisia* spp) are important pollen producers, with cocklebur (*Xanthium commune*) and the marshelders (*Iva* spp) of lesser significance. *Baccharis* species are found across the southern tier.

Two closely related families are found within the *Chenopodiales* order, *Chenopodiaceae* and *Amaranthaceae*, and the knotweed family, *Polygonaceae*. The chenopod and amaranth weeds are ubiquitous, especially lamb's quarter (*Chenopodium album*), which is a modest pollen producer. Pigweeds such as *Amaranthus retroflexus* show a range similar to lamb's quarter, while western waterhemp (*Acnida tamariscina*) is common in the midwest and south. The two major tumbleweeds found in the Central Plains, Russian thistle (*Salsola kali*) and burning bush (*Kochia scoparia*), are introduced and have expanded throughout the central states to the Gulf and California coasts. *Kochia* now is even found in the northeastern states.

In the knotweed family (*Polygonaceae*), sheep sorrel (*Rumex acetosella*) is considered a moderate hayfever inducer, but is probably significant in the Pacific Northwest. Curly, or yellow, dock (*R. crispus*) is common but a low pollen producer. Nettle (*Urtica* spp) is common across the floristic zones with the exception of Florida and Southeast Coastal. Pellitory (*Parietaria* spp) is found throughout the zones. Plantains (*Plantago* spp) have a wide distribution, with various native species found throughout the United States. Introduced species include English plantain and common plantain (*P. lanceolata* and *P. vulgaris*, respectively). Although these are modest pollen producers, the season extends from May to November, and the plants may be locally important.

Mold Spores

Outdoor fungal sources may be characterized by those that are more common in dry, windy conditions and those that require moisture to flourish. The former include *Alternaria*, *Cladosporium*, *Epicoccum*, *Helminthosporium*, rusts (*Puccinia* spp), and smuts (*Ustilago* spp). These are prevalent, especially in the Great Plains states, in dry, windy conditions due to their growth on grains and prairie grasses. To a lesser degree, *Rhizopus* and some *Aspergillus* and *Penicillium* form species may also be dispersed in dry conditions. *Alternaria* species are the most allergenic, although usually found in much lower concentrations than the more ubiquitous *Cladosporium* (the newer, preferred nomenclature for *Hormodendrum*). Allergenic significance of rusts and smuts (*Basidiomycetes*) is uncertain.⁵ *Ganoderma*, a bracket fungi, is characteristic of numerous other *Basidiomycetes* which are more prevalent in wet conditions. *Fusarium*, *Phoma*, *Cephalosporium*, and *Tricoderma* are examples of spores that peak with rainfall.⁶¹ In the Great Lakes region of the Midwest, ascospores such as *Leptosphaeria* peak during the moister spring months, diminishing in the summer. *Curvularia*, *Dreschlera*, and *Helminthosporium* are other frequent outdoor molds, with the former being more prevalent in warmer regions.

Aspergillus spp, *Penicillium* spp, and *Aureobasidium pullulans* are common outdoor molds that also are frequently found indoors, especially in more humid conditions. *Aspergillus* often may be recovered in greater quantities indoors than outdoors.⁶¹ Common food contaminants include *Rhizopus*, *Fusarium* spp, and *Mucor*.²³

INDOOR AEROALLERGENS

The major aeroallergen burden in house dust is from mites, animal dander, and cockroaches. Molds, pollens, and other allergens are less significant in the average home, although occasionally important in unique settings. The diagnosis and treatment of house dust allergy is more effective when the individual components are used rather than poorly characterized house dust vaccines.

House Dust Mites

Dermatophagoides pteronyssinus and *Dermatophagoides farinae*, the European and American domestic mites, are found worldwide. Both mites thrive at a temperature of 25° to 30°C and relative humidity of 75% to 80%, doing poorly when the relative humidity is less than 50%.^{11, 24} Both may be found in the same homes, although *D. farinae* seems to better tolerate low humidity and will be found in drier areas.³⁷ Dust mites are not common in the Rocky Mountain, Great Basin, and Arid Southwest zones, where the average relative humidity is below 50%. Homes with evaporative coolers or other sources of humidity, however, may harbor mites in these arid or semi-arid environments.¹⁹

Other dust mites, such as *D. microceras* and *Euroglyphus maynei*, may be found in more humid situations but are less important than *D. pteronyssinus* and *D. farinae*.¹ Homes may contain mixed populations of mites, with between 5% and 8% being storage mites such as *Acarus*, *Glycyphagus*, *Lepidoglyphus*, *Tyrophagus*, and *Tarsonemus*. The latter genus includes predator mites that feed on *Dermatophagoides*. Storage mites are found primarily in grain and hay and may be of greater occupational than domestic significance.³¹ A storage mite, *Blomia tropicalis*, has been found in significant numbers in homes in tropical and subtropical climates and contributes to the allergenicity of house in these regions.

Cockroaches

The most cosmopolitan of species is the German cockroach, *Blattella germanica*, found in all 50 states. It is, however, strictly domestic, not surviving outside. Other roaches, such as the American, *Periplaneta americana*, and the oriental, *Blatta orientalis*, are found in and around homes. These three species produce the greatest indoor burden of cockroach allergen, although several other species are clinically important in certain locales, such as the brown-banded and smoky brown roaches in the southeast.¹⁷ Cockroaches have been incriminated as important in inner city asthma, with exposures being greater risks than house dust mite or animal danders.⁵⁸

Danders

Major dander allergens are usually products of sebaceous glands, with lesser contributions of saliva, serum, or urine. Cat dander allergen can be airborne on particles smaller than a micron, and in homes with cats, about 25% of the allergen load is accounted for by particles under 5 microns in size.^{13, 43} Recent studies have demonstrated that Fel d 1 is truly ubiquitous in public places, presumably distributed from the clothes of cat owners.¹⁸ Levels are especially high in seats in public

places, and cat and dog dander allergen can be demonstrated on seats in schools, nurseries, and hospitals.¹²

STINGING AND BITING INSECTS

Hymenoptera

Although bites from a variety of insects and Arachnids may occasionally cause allergic reactions, the major difficulty arises from stinging insects of the order Hymenoptera. Three important families are: *Apidae*, containing honeybees and bumblebees; *Vespidae*, with hornets and yellow jackets; and *Formicidae*, fire ants. Taxonomy is further delineated in Figure 2.

Yellow jackets (*Vespula* spp) are ground-nesters, using bases of trees, fence posts, crevices around foundations, or other such cavities. On the other hand, vespids such as yellow hornets and white-faced hornets (*Dolichovespula* spp) are aerial nesters, making football-shaped covered nests in trees, bushes, or under roof eaves. Paper wasps (*Polistes* spp) make smaller nests on walls or roof eaves, which are uncovered and show the honeycombing of the individual cells. Wild honeybees (*Apis*

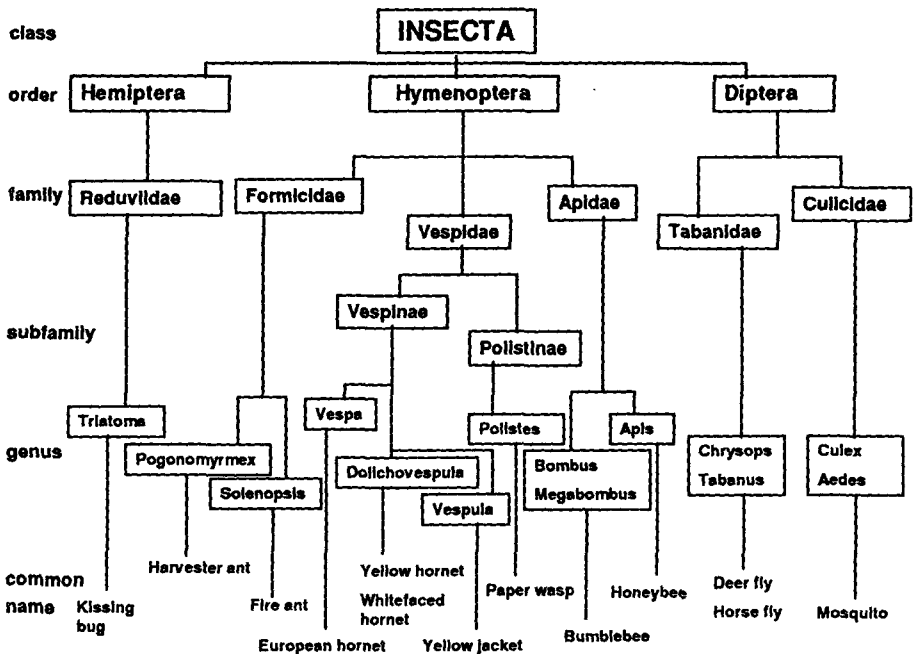


Figure 2. Taxonomy of allergenic stinging and biting insects.

mellifera) will nest in hollow trees, but the majority of bees are domesticated in man-made hives. Bumblebees (*Bombus* spp) are usually ground-nesters.

Yellow jackets are cosmopolitan, found around the globe, and represented by several species. They are distributed throughout the United States, with greater numbers found in areas of milder winters. The yellow hornet (aerial yellow jacket) is more prevalent in the northern states. The white-faced hornet ranges throughout the United States. The European, or giant hornet, *Vespa crabro*, is found primary in the eastern states, with a range from Massachusetts to Georgia and west to Indiana.⁴⁸

The domesticated honeybee is found worldwide, and was introduced into North America in the 1700s. Bumblebees are distributed throughout the United States.⁴⁷ Since the late 1950s, africanized honeybees (killer bees), a hybrid of *Apis mellifera mellifera* and *Apis mellifera scutellata*, have expanded their range from origin in Brazil. They entered the United States in 1993, and by 1995 were in the southern parts of Texas, New Mexico, Arizona, and California.⁵⁹ The expectation is that these bees will expand their territory across the Gulf states. Similar to the imported fire ant, their range will be limited in northward spread by low temperatures in winter.

Although there are native fire ants (*Solenopsis* spp), anaphylactic reactions have been primarily reported with stings by the imported fire ant species *S. invicta* and *S. richteri*.¹⁵ These have a more restricted range, south of the 10°F isotherm; this extends up the coastlines, however, further north than these species have been reported. Hybridization between the imported fire ant species has apparently produced a strain that is more cold hardy. Additionally, fire ants have migrated north under and along roads, which provide greater ambient heat from solar warming. The expectation, then, is that the fire ant range will continue to expand beyond present boundaries.

Diptera

The bites of several insects may provoke reactions, notably mosquitoes, deer and horse flies, or kissing bugs (*Triatoma* spp). The former two are of the order Diptera, the latter Hemiptera. Despite the unlikely nature of systemic reactions to mosquito bites, local reactions to bites do seem to be mediated by IgE antibodies directed against salivary proteins.^{52, 57} There are several species of *Aedes* and *Culex* which have wide distribution throughout the North American continent. Deerflies (*Chrysops* spp) likewise have an extensive range.

CROSS-REACTIVITY

Cross-reactivity is the ability of an antigen to bind with an antibody that was raised to a different antigen. It may arise by one of two

mechanisms: shared epitopes on multivalent antigens, in which case antibodies should bind with the same affinity; or conformational similarity of epitopes, in which case antibodies would bind with lesser affinity. Why should cross-reactivity be of concern to the practicing allergist? It is because such relationships will impact on diagnosis and therapy of inhalant allergy. For example, skin test positivity to a nonendemic plant may be explained either by prior exposure in a mobile population or cross-reactivity with endemic plants. The decision whether to include such a nonendemic vaccine in an allergen immunotherapy formulation depends on several factors, one of which is whether related plants provide adequate coverage.

Information on pollen cross-reactivity is fairly limited. Studies have not been performed for most pollen vaccines used in practice. The most extensive research has been with northern pasture grass pollens, the major ragweeds, cedars and junipers, and with members of the closely related birch and beech botanical families. Preliminary work has been done with chenopod/amaranth weeds and sages.

Because of this limited data, taxonomy has been used to infer the likelihood of cross-reactivity. The validity of this process depends on two premises. The first is that more closely related plants will have greater similarities and more shared antigens. The second premise is that the presently accepted botanical classification truly reflects phylogeny (i.e., two plants in the same genus evolved from a common ancestor, two in the same family from a more distant ancestor, and so on). Research to date generally supports the use of this approach with some exceptions.⁶⁸

Pollens

The pertinent data on pollen interrelationships are summarized in the following section. It is arranged parallel to botanical classification because attention to the taxonomic relationships will strengthen and clarify the concept of cross-reactivity. Major relationships are depicted in Figures 3 to 5. As with other allergens, present usage names the allergenic pollen protein by the first three letters of the genus and the first letter of the species followed by a number which usually designates order of identification of the allergen group (e.g., Jun a 1 for the major allergen of mountain cedar and Lol p 1 for perennial ryegrass or Phl p 5 for timothy grass).

Order Coniferales

Among the evergreens, members of the family *Cupressaceae* are strongly allergenically cross-reactive (see Fig. 3). Most studies have demonstrated consistent cross-inhibition.^{4, 32, 53, 74} A smaller family of *Coniferales*, *Taxodiaceae*, includes bald cypress, redwoods, sequoias, and a important producer of pollinosis in Japan, Japanese red cedar. Limited

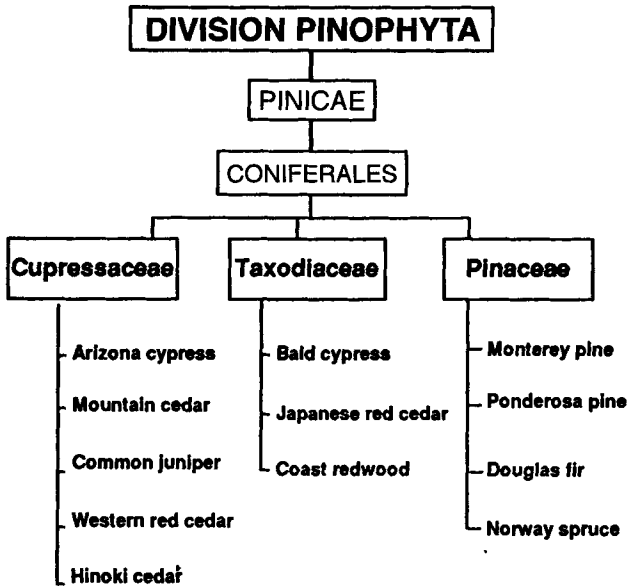


Figure 3. Taxonomy of allergenic members of the order Coniferales, with representative species by common name.

data on *Taxodiaceae* suggests little cross-reactivity between members. Initial conflicting reports concerning Japanese red cedar cross-reactivity with *Cupressaceae* members have been replaced by increasing evidence for similarity between major allergens.^{73, 74}

Poaceae

Members of the fescue subfamily of grasses strongly cross-react with only minor exceptions. This has been demonstrated not only with crude vaccines but also with purified allergens.⁴⁴ Several groups of antigens have been characterized based on molecular weight and isoelectric motility. There are now over 10 allergenic groups described for all grasses. Major grass allergens are designated as groups 1, 3, and 5, with minor allergens in other groups. Epitope homology of varying degree has been demonstrated not only between same group allergens of different grass species, but also between group 1 and 3 as well.^{36, 65, 66} Epitopes found on the timothy allergen Phl p 5 are shared with ryegrass group 1 allergens. Sweet vernal and timothy may each contain some unique allergens. Southern grasses show greater allergenic diversity, with Bermuda appearing to contain unique allergens not shared with the fescue northern grasses. Bermuda demonstrates cross-inhibition with some prairie grasses such as grama and salt grass.⁴⁴ Bahia grass differs by skin

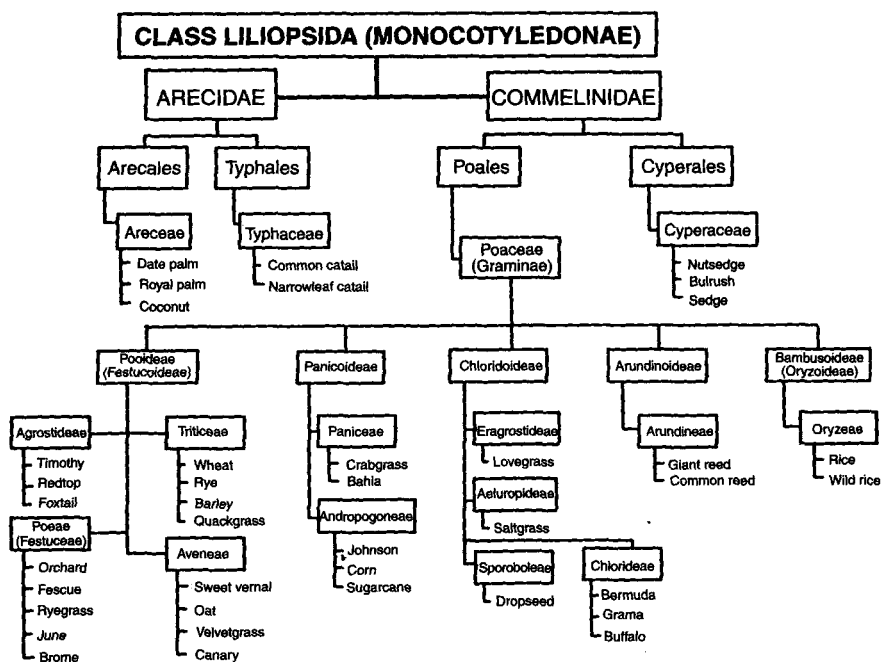


Figure 4. Taxonomy of allergenic members of the class Liliopsida (Monocotyledonae), with representative species by common name.

test comparisons and challenges from timothy, a northern pasture grass.⁵⁴ See Figure 4 for clarification of botanical relationships.

Order Fagales

Although there is some disagreement whether the birch (*Betulaceae*) and beech (*Fagaceae*) families should be in the same or different orders, cross-reactivity data supports considering them together (see Fig. 5). There is strong cross-allergenicity within the birch family and this extends across to the beech family as well. Amino acid sequencing of the major alder allergen, *Aln g 1*, shows partial identity with the corresponding allergens of birch (*Bet v 1*), hornbeam (*Car b 1*), and oak (*Que a 1*) pollens.³⁰ Recombinant DNA studies showed strong homology between *Bet v 1* and these other major allergens.⁶⁴ Although the major allergen of birch pollen is *Bet v 1*, an important second major allergen is *Bet v 2*, a profilin. Both of these allergens have been cloned. A recent study reported cross-inhibition of IgE immunoblots by the mix of recombinant *Bet v 1* and *Bet v 2*.⁵⁰ Homologous inhibition was an average of 92%, while inhibition by alder, hornbeam, hazel, and oak were 88%, 77%, 80%, and 72%, respectively. The mix accounted for an average of 82% of the specific IgE, most being directed against *rBet v 1*. It seems reasonable

that immunotherapy with these two recombinant allergens would effectively cover Fagales tree pollen sensitivity. Additionally, cross-reactivity between birch, mugwort, and celery has been demonstrated with Bet v 1, Bet v 2, and higher-molecular-weight allergens (46–60 kD).⁶

Oleaceae

The Olive family (*Oleaceae*) includes shrubs and trees, including olive and ash. Cross-reactivity has been demonstrated between these two, and several shrubs in the family.⁵⁵ Ash does not share any significant cross-reactivity with the major birch allergen.⁶⁷ One study has shown strong cross-inhibition between olive and Russian olive, trees in different families and orders.³⁴

Order *Chenopodiales*

Cross-reactivity data supports the close relationship between the goosefoot (*Chenopodiaceae*) and amaranth (*Amaranthaceae*) families (see Fig. 5). In the latter family, allergenic identity is almost complete

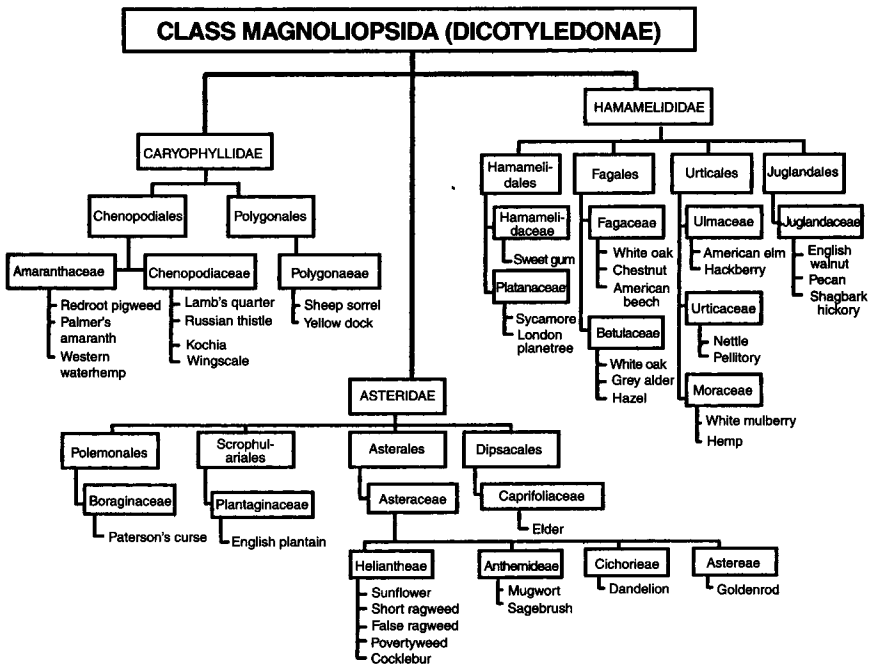


Figure 5. Taxonomy of selected allergenic members of the class Magnoliopsida (Dicotyledonae), with representative species by common name. Not all subclasses with allergenic members are included. See text for further information.

amongst the *Amaranthus* species such as redroot pigweed (*A. retroflexus*) and Palmer's amaranth (*A. palmeri*), and slightly less so with another member, western waterhemp (*Achida tamariscina*).⁶⁹ In the former family there are almost as striking similarities among the saltbushes and scales (*Atriplex* spp). There are varying degrees of cross-inhibition between other chenopods and across to the amaranths. For example, the chenopods smotherweed (*Bassia hyssopifolia*) and burning bush (*Kochia scoparia*) show some similarities. Russian thistle (*Salsola kali*) shows cross-reactivity with other members of these two families, but seems to contain some unique allergens as well.⁶⁹

Asteraceae (Compositae)

Asteraceae members (see Fig. 5) show variable cross-reactivity. The four major ragweeds strongly cross-react. Radioallergosorbent test (RAST) inhibition studies showed overlapping inhibition curves for short, giant, western and false ragweeds; slender and southern ragweeds were less potent, and other members of the family showed no inhibition.³⁸ At least 9 allergens have been isolated from short ragweed, the most important being Amb a 1 (Antigen E [AgE]). Almost all clinically sensitive ragweed sufferers will react to Amb a 1 and Amb a 2 (AgK), which show cross-reactivity. Decreasing percentages will respond to Amb a 3, Amb a 4, and Amb a 5. Certain patients may be able to distinguish between the homologous allergens from short and giant ragweed, such as Amb a 5 and Amb t 5.²¹ Although there is some controversy, Amb a 1 is found in short, giant, southern, and false ragweed, with minimal amounts in slender ragweed. No Amb a 1 was found in cocklebur and marshelder (members of the same subtribe as ragweed), sages and mugwort (members of the same family but different tribe as ragweed), or plantain (same subclass but different orders).

ELISA inhibition and immunoblot studies of *Artemisia* species reveals very strong cross-reactivity.³³ It is therefore not necessary to skin test or treat with multiple *Artemisia*; a single choice will do. In the Midwest and West common sagebrush (*A. tridentata*) seems a reasonable choice, while in the eastern states and Europe, mugwort (*A. vulgaris*) seems most appropriate. A European study has demonstrated, using mugwort sensitized patient sera, that the major allergen Art v 1 was shared by short ragweed. Cross-reactivity with birch profilin Bet v 2 also was found.²⁶ This does not, however, mean that mugwort has significant Amb a 1.

Other Families

There are old data showing inhibition of plantain by grass and ragweed, but not the converse, suggesting that grass and ragweed possess the relevant allergens of plantain but not vice versa. Plantain (family Plantaginaceae) does not contain Amb a 1. Work from Australia has suggested similarities between a common Australian weed, Paterson's

curse in the family Boraginaceae, and plantain.⁴⁶ In the Walnut family (Juglandaceae), skin test correlations are high between hickories and pecans. There are lesser similarities between pecans and walnuts. Cross-reactivity data in the Maple family is limited. There seems to be skin test and RAST inhibition disparity between box elder and other maples. Older studies suggested some cross-reactivity between maples and oaks.

Mold Spores

Cross-reactivity data for molds is rudimentary, owing in large part to the classification system using artificial "form genera." The class Fungi Imperfecti (Deuteromycetes) consists of members with distinct morphology, but many of these just represent the asexual life stages of organisms from the other classes of fungi (Ascomycetes, Basidiomycetes, and Zygomycetes). Thus, the taxonomy is confusing. Antigenic differences have been demonstrated between *Aspergillus* species and again between *Alternaria* species. However, varying degrees of cross-reactivity have been shown among *Alternaria*, *Stemphylium*, *Curvularia*, and *Stachybotrys*.⁹ The major *Alternaria* antigen, Alt a 1, appears to be as abundant in *Stemphylium* as in *Alternaria*. Cross-reactivity has been demonstrated between the yeasts *Candida albicans* and *Pityrosporum orbiculare*.²⁹ Members of the Basidiomycete order Agaricales show strong cross-reactivity, with little to no inhibition demonstrated with members of other orders.¹⁶

Dust Mites

Seven groups of house dust mite allergens have been well described, and four of these have enzymatic activity. The major allergens of Group 1 are cysteine proteases, group 3 are serine proteases, group 4 amylases, and group 6 chymotrypsins.¹ These are gut-associated, appear to be digestive enzymes, and are found in larger amounts in mite fecal pellet extracts. Group 1 allergen (Der p 1, Der f 1) has been localized to the fecal pellet peritropic membrane. Group 2 allergens do not appear to be gut related, and are not found in increased amount in fecal material. A 22 kD group 7 allergen has not been localized.

Several epitopes have been described for Der p 1 and Der f 1, one of which shows cross-reactivity with monoclonal antibodies. Antibodies to crude vaccines have shown at least 21 cross-reacting antigens, half of which are allergens for human antisera. Between 80% and 95% of human mite specific IgE cross-reacts between *Dermatophagoides pteronyssinus* and *D. farinae*.¹ Limited cross-reactivity has been demonstrated in various studies between *Dermatophagoides*, *Euroglyphus*, *Blomia* and other storage mites, and with the scabies mite.^{2, 3} Tropomyosin, an actin binding protein, has been found to be a panallergen from a variety of species of mollusks, crustaceans, mites, and insects.^{40, 45} A recently characterized Der f allergen of 98 kD appears to be a major allergen. It shows homol-

ogy to paramyosin, a ubiquitous muscle protein, and another high-molecular-weight allergen showing homology to prawn chitinase.^{39, 69}

Cockroaches

The major cockroach allergens primarily originate in the gut epithelium, as is true for dust mites. Three allergens have been characterized: Per a 1, Bla g 1, and Bla g 2: the first two are cross-reactive, while the latter is species specific.⁷² The cross-reacting group 1 cockroach allergens, Per a 1 and Bla g 1, are gut-derived serine proteases.²⁵ Cockroach extract contains tropomyosin, found in mollusks, crustaceans, mites, and some insects.⁴⁰

Danders

The major domesticated cat allergen, Fel d 1, is a product of sebaceous and salivary glands and is shared by all cats, and similar cross-reacting proteins have been found in large (jungle) cats as well.¹⁴ The minor allergen, cat albumin, shares cross-reactivity with albumins of other animals, such as dog albumin. Patients with selective cat sensitivity are most likely to be reactive to Fel d 1, while a number of patients sensitive to cats and dogs will be sensitive to albumin.⁸

Hymenoptera and Diptera

Hymenoptera show variable cross-reactivity. Members of the subfamily Vespinae (hornets and yellow jackets) have the strongest cross-reactivity.³⁵ There also is a relationship between *Polistes* and vespid venoms but not to the same high degree as between yellow jackets and hornets.^{27, 56} Honeybee and vespid cross-reactivity is limited to minor allergens. Bumblebee venom has been assumed to be similar to honeybee venom; however, fresh data suggests this assumption is not entirely warranted. A recent study using RAST, RAST inhibition, and immunoblotting showed unique allergens not shared by honeybee venom, and also differences between the European bumblebee (*Bombus terrestris*) and American bumblebee (*Megabombus pennsylvanicus*) venoms.⁶² Fire ant cross-reactivity with the winged hymenoptera is variable, primarily with yellow jacket.²⁸

Cross-reactivity data for biting insects is minimal. A shrimp food allergen, tropomyosin, has been found in a variety of arthropods, including mites and fruit flies.^{7, 40} Peng and Simons have demonstrated cross-reactivity between mosquito species allergens.⁵¹

SUMMARY

A wide variety of plant aeroallergen sources are found throughout the floristic zones. Members of the grass family are extremely important in pollinosis. A wide variety of fescue subfamily grasses are found from the northern tier into the southern states. These northern pasture grasses are highly cross-reactive. Bermuda and Johnson grasses are increasingly important south of the 38° parallel, and bahia is a significant allergenic plant in the Gulf states. Southern grasses show significant differences, and need to be treated individually. Palms, sedges, and cattails are all minor factors in hayfever, and immunotherapy with these is not indicated, except for unusual cases.

Closely related cedars such as *Juniperus communis*, *J. ashei* or *J. occidentalis*, are found across the United States. Immunotherapy for these cypress family members can be accomplished by the use of a representative member. Maples and box elder are widely found throughout the United States, with the exception of the arid southwest. Oaks and elms are prevalent in the eastern and central states, with more limited distribution west of the continental divide. Other trees are varied enough to require observation in a given area to determine what is prevalent. There is sufficient diversity among tree pollen aeroallergens that with the exceptions noted in the text, most trees need to be addressed individually.

One or another of the major ragweeds (e.g., short, giant, western, and false) are found throughout the United States, and there is sufficient similarity between these that not all need to be treated simultaneously. Sages and mugwort likewise have a large distribution, being especially abundant in the western states, and a single representative species is adequate for therapy. Members of the chenopod and amaranth families likewise have wide ranges, and have mixed degrees of cross-reactivity.

The major dust mites, *Dermatophagoides pteronyssinus* and *D. farinae*, are ubiquitous, other than in the arid or semi-arid states. Standardized extracts are available for immunotherapy for these former two, but commercial extracts are not presently available for other house dust or storage mites. Cat dander immunotherapy should be performed with standardized extracts of cat hair (Fel d 1 only) or pelt (Fel d 1 plus cat albumin). A mix of German and American cockroach (or with Oriental as well) is most appropriate for immunotherapy.

References

1. Arlian LG: House-dust-mite allergens: A review. *Exp Appl Acarol* 10:167-186, 1991
2. Arlian LG, Rapp CM, Fernandez-Caldas E: Allergenicity of *Euroglyphus maynei* and its cross-reactivity with *Dermatophagoides* species. *J Allergy Clin Immunol* 91:1051-1058, 1993
3. Arlian LG, Vyszynski-Moher DL, Fernandez-Caldas E: Allergenicity of the mite, *Blomia tropicalis*. *J Allergy Clin Immunol* 91:1042-1050, 1993

4. Barletta B, Afferni C, Tinghino R, et al: Cross-reactivity between *Cupressus arizonica* and *Cupressus sempervirens* pollen extracts. *J Allergy Clin Immunol* 98:797-804, 1996
5. Bassett IJ, Crompton CW, Parmelee JA: An Atlas of Airborne Pollen Grains and Common Fungus Spores of Canada. Hull, Quebec, Canada, Supply and Services, 1978, pp 269-300
6. Bauer L, Ebner C, Hirschehr R, et al: IgE cross-reactivity between birch pollen, mugwort pollen and celery is due to at least three distinct cross-reacting allergens: Immunoblot investigation of the birch-mugwort-celery syndrome. *Clin Exp Allergy* 26:1161-1170, 1996
7. Bernhisel-Broadbent J: Allergenic cross-reactivity of foods and characterization of food allergens and extracts. *Ann Allergy Asthma Immunol* 75:295-303, 1995
8. Boutin Y, Hebert H, Vrancken ER, et al: Allergenicity and cross-reactivity of cat and dog allergenic extracts. *Clin Allergy* 18:287-293, 1988
9. Burge HA: Fungus allergens. *Clin Rev Allergy* 3:319-329, 1985
10. Clausen RR, Ekstrom NH: Perennials for American Gardens. New York, Random House, 1989, pp xi-xv
11. Colloff MJ, Ayres J, Carswell F, et al: The control of allergens of dust mites and domestic pets: A position paper. *Clin Exp Allergy* 22(suppl 2):1-28, 1992
12. Custovic A, Fletcher A, Pickering CA, et al: Domestic allergens in public places. III: House dust mite, cat, dog and cockroach allergens in British hospitals. *Clin Exp Allergy* 28:53-59, 1998
13. Custovic A, Simpson A, Pahdi H, et al: Distribution, aerodynamic characteristics, and removal of the major cat allergen Fel d 1 in British homes. *Thorax* 53:33-38, 1998
14. de Groot H, van Swieten P, Aalberse RC: Evidence for a Fel d 1-like molecule in the "big cats" (Felidae species). *J Allergy Clin Immunol* 86:107-116, 1990
15. deShazo RD, Butcher BT, Banks WA: Reactions to the stings of the imported fire ant. *N Engl J Med* 323:462-466, 1990
16. De Zubiria A, Horner WE, Lehrer SB: Evidence for cross-reactive allergens among basidiomycetes: immunoprint-inhibition studies. *J Allergy Clin Immunol* 86:26-33, 1990
17. Duff AL, Platts-Mills TAE: Allergens and asthma. *Pediatr Clin North Am* 39:1277-1291, 1992
18. Egmar AC, Almqvist C, Emenius G, et al: Deposition of cat (Fel d 1), dog (Can f 1), and horse allergen over time in public environments: A model of dispersion. *Allergy* 53:957, 1998
19. Ellingson AR, Ledoux RA, Vedanthan PK, et al: The prevalence of *Dermatophagoides* mite allergen in Colorado homes utilizing central evaporative coolers. *J Allergy Clin Immunol* 96:473-479, 1995
20. Freeman GL: Pine pollen allergy in northern Arizona. *Ann Allergy* 70:491-494, 1993
21. Ghosh B, Rafnar T, Perry MP, et al: Immunologic and molecular characterization of Amb p V allergens from *Ambrosia psilostachya* (western Ragweed) pollen. *J Immunol* 152:2882-2889, 1994
22. Gould FW: Common Texas Grasses: An Illustrated Guide. College Station, TX, Texas A&M University Press, 1978, p 185
23. Gravesen S, Frisvad JC, Samson RA: Microfungi. Munksgaard, Copenhagen, 1994, pp 15-19, 118-119
24. Hallas TE: The biology of mites. *Allergy* 46(suppl 11):6-9, 1991
25. Helm RM, Squillace DL, Jones RT, et al: Shared allergenic activity in Asian (*Blattella asahinai*), German (*Blattella germanica*), American (*Periplaneta americana*) and Oriental (*Blattella orientalis*) cockroach species. *Int Arch Allergy Appl Immunol* 92:154-161, 1990
26. Hirschehr R, Heppner C, Spitzauer S, et al: Identification of common allergenic structures in mugwort and ragweed pollen. *J Allergy Clin Immunol* 101:196-206, 1998
27. Hoffman DR: Allergens in hymenoptera venom. VI. Cross reactivity of human IgE antibodies to the three vespid venoms and between vespid and paper wasp venoms. *Ann Allergy* 46:304-309, 1981
28. Hoffman DR, Dove DE, Moffitt JE, et al: Allergens in Hymenoptera venom: XXI. Cross-reactivity and multiple reactivity between fire ant venom and bee and wasp venoms. *J Allergy Clin Immunol* 82:828-834, 1988

29. Huang X, Johansson SG, Zargari A, et al: Allergen cross-reactivity between *Pityrosporum orbiculare* and *Candida albicans*. *Allergy* 50:648–656, 1995
30. Ipsen H, Hansen OC: The NH₂-terminal amino acid sequence of the immunochemically partial identical major allergens of alder (*Alnus glutinosa*) *Aln g* I, birch (*Betula verrucosa*) *Bet v* I, hornbeam (*Carpinus betulus*) *Car b* I and oak (*Quercus alba*) *Que a* I pollens. *Mol Immunol* 28:1279–1288, 1991
31. Iverson M, Dahl R: Allergy to storage mites in asthmatic patients and its relation to damp housing conditions. *Allergy* 45:81–85, 1990
32. Joint Task Force on Practice Parameters: Practice parameters for allergen immunotherapy. *J Allergy Clin Immunol* 98:1001–1011, 1996
33. Katial RK, Lin FL, Stafford WW, et al: Mugwort and sage (*Artemisia*) pollen cross-reactivity: ELISA inhibition and immunoblot evaluation. *Ann Allergy Asthma Immunol* 79:340–346, 1997
34. Kemerman SM, McCullough J, Green J, et al: Evidence of cross-reactivity between olive, ash, privet, and Russian olive tree pollen allergens. *Ann Allergy* 69:493–496, 1992
35. King TP, Joslyn A, Kochoumian L: Antigenic cross-reactivity of venom proteins from hornets, wasps, and yellow jackets. *J Allergy Clin Immunol* 75:621–628, 1985
36. Laffer S, Valenta R, Vrtala S, et al: Complementary DNA cloning of the major allergen Phl p I from timothy grass (*Phleum pratense*); recombinant Phl p I inhibits IgE binding to group I allergens from eight different grass species. *J Allergy Clin Immunol* 94:689–698, 1994
37. Lang JD, Mulla MS: Distribution and abundance of house dust mites, *Dermatophagoides* spp., in different climatic zones of southern California. *Environ Entomol* 6:213–216, 1977
38. Leiferman KM, Gleich GJ, Jones RT: Cross-reactivity of IgE antibodies with pollen allergens. II. Analysis of various species of ragweed and other fall weed pollens. *J Allergy Clin Immunol* 58:140–148, 1976
39. Le Mao J, Mayer CE, Peltre G, et al: Mapping of *Dermatophagoides farinae* mite allergens by two-dimensional immunoblotting. *J Allergy Clin Immunol* 102:631–636, 1998
40. Leung PS, Chow WK, Duffey S, et al: IgE reactivity against a cross-reactive allergen in crustacea and mollusca: Evidence for tropomyosin as the common allergen. *J Allergy Clin Immunol* 98:954–961, 1996
41. Lewis WH, Vinay P, Zenger VE: Airborne and Allergenic Pollen of North America. Johns Hopkins University Press, Baltimore, 1983
42. Little EL: Audubon Society Field Guide to North American Trees: Eastern Region. New York, Alfred A. Knopf, 1987, pp 420–425
43. Luczynska CM, Li Y, Chapman MD, et al: Airborne concentrations and particle size distribution of allergen derived from domestic cats (*Felis domesticus*): Measurements using cascade impactor, liquid impinger, and a two-site monoclonal antibody assay for *Fel d* I. *Am Rev Respir Dis* 141:361–367, 1990
44. Martin BG, Mansfield LE, Nelson HS: Cross-allergenicity among the grasses. *Ann Allergy* 54:99–104, 1985
45. Martinez A, Martinez J, Palacios R, et al: Importance of tropomyosin in the allergy to household arthropods: Cross-reactivity with other invertebrate extracts. *Allergol Immunopathol* 25:118–126, 1997
46. Matthews PA, Baldo BA, Howden ME: Cytochrome c allergens isolated from the pollens of the dicotyledons English plantain (*Plantago lanceolata*) and Paterson's curse (*Echium plantagineum*). *Mol Immunol* 25:63–68, 1988
47. Milne L, Milne M: Bees, wasps, and kin. In Audubon Society Field Guide to North American Insects and Spiders. New York, Alfred A. Knopf, 1980, pp 801–864
48. Milne L, Milne M: Insects and Spiders. In Sutton A, Sutton M (eds): Eastern Forests. New York, Alfred A. Knopf, 1988, pp 516–518
49. Muller WD, Karamfilov T, Bufer A, et al: Group 5 allergens of timothy grass (Phl p 5) bear cross-reacting T cell epitopes with group 1 allergens of rye grass (Lol p 1). *Int Arch Allergy Immunol* 109:352–355, 1996
50. Niederberger V, Pauli G, Gronlund H, et al: Recombinant birch pollen allergens (rBet v 1 and rBet v 2) contain most of the IgE epitopes present in birch, alder, hornbeam,

- hazel, and oak pollen: A quantitative IgE inhibition study with sera from different populations. *J Allergy Clin Immunol* 102:579-591, 1998
51. Peng Z, Simons FE: Cross-reactivity of skin and serum specific IgE responses and allergen analysis for three mosquito species with worldwide distribution. *J Allergy Clin Immunol* 100:192-198, 1997
 52. Peng Z, Yang M, Simons FE: Immunologic mechanisms in mosquito allergy: Correlations of skin reactions with specific IgE and IgG antibodies and lymphocyte proliferative response to mosquito antigens. *Ann Allergy Asthma Immunol* 77:238, 1996
 53. Pham NH, Baldo BA, Bass DJ: Cypress pollen allergy. Identification of allergens and crossreactivity between divergent species. *Clin Exp Allergy* 24:558-565, 1994
 54. Phillips JW, Bucholtz GA, Fernandez-Caldas E, et al: Bahia grass pollen, a significant aeroallergen: evidence for the lack of clinical cross-reactivity with timothy grass pollen. *Ann Allergy* 63:503-507, 1989
 55. Obispo TM, Melero JA, Carpizo JA, et al: The main allergen of *Olea europaea* (Oleaceae) is also present in other species of the Oleaceae family. *Clin Exp Allergy* 23:311-316, 1993
 56. Reisman RE, Wypych JL, Mueller UR, et al: Comparison of the allergenicity and antigenicity of *Polistes* venom and other vespid venoms. *J Allergy Clin Immunol* 70:281-287, 1982
 57. Reunala T, Brummer-Korvenkontio H, Räsänen L, et al: Passive transfer of cutaneous mosquito-bite hypersensitivity by IgE anti-saliva antibodies. *J Allergy Clin Immunol* 94:902-906, 1994
 58. Rosenstreich DL, Eggleston P, Kattan M, et al: The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. *N Engl J Med* 336:1356-1363, 1997
 59. Schumacher MJ, Egen NB: Significance of Africanized bees for public health: A review. *Arch Intern Med* 155:2038-2043, 1995
 60. Solomon WR: Common pollen and fungus allergens. In Bierman CW, Pearlman DS (eds): *Allergic Diseases From Infancy to Adulthood*, ed. 2. Philadelphia, WB Saunders, 1988, pp 141-164
 61. Solomon WR: Pollens and fungi, in Aerobiology and inhalant allergens. In Middleton E Jr, Reed CE, Ellis EF (eds): *Allergy Principles and Practice*, ed 5. St Louis, Mosby-Year Book, 1998, pp 367-393
 62. Stapel SO, Waanders-Lijster de Raadt J, van Toorenbergen AW, et al: Allergy to bumblebee venom: II. IgE cross-reactivity between bumblebee and honeybee venom. *Allergy* 53:769-777, 1998
 63. Tsai L-C, Chao PL, Shen HD, et al: Isolation and characterization of a novel 98-kd *Dermatophagoides farinae* mite allergen. *J Allergy Clin Immunol* 102:295-303, 1998
 64. Valenta R, Breiteneder H, Pettenberger K, et al: Homology of the major birch-pollen allergen: *Bet v* I, with the major pollen allergens of alder, hazel, and hornbeam at the nucleic acid level as determined by cross-hybridization. *J Allergy Clin Immunol* 87:677-682, 1991
 65. van Ree R, Driessen MN, Van Leeuwen WA, et al: Variability of crossreactivity of IgE antibodies to group I and V allergens in eight grass pollen species. *Clin Exp Allergy* 22:611-617, 1992
 66. van Ree R, van Leeuwen WA, van den Berg M, et al: IgE and IgG cross-reactivity among *Lol p* I and *Lol p* II/III: Identification of the C-termini of *Lol p* I, II, and III as cross-reactive structures. *Allergy* 49:254-261, 1994
 67. Wahl R, Schmid-Grendelmeier P, Cromwell O, et al: In vitro investigation of cross-reactivity between birch and ash pollen allergen extracts. *J Allergy Clin Immunol* 98:99-106, 1996
 68. Weber RW: Cross-reactivity among pollens. *Ann Allergy* 46:208-215, 1981
 69. Weber RW, Nelson HS: Pollen allergens and their interrelationships. *Clin Rev Allergy* 3:291-318, 1985
 70. Whitson TD, Burrill LC, Dewey SA, et al: *Weeds of the West*. Jackson, WY, University of Wyoming, 1991, pp 274-279
 71. Williamson JF: *Sunset New Western Garden Book*, ed. 4. Menlo Park, CA, Lane Publishing, 1979, pp 8-29
 72. Wu CH, Wang NM, Lee MF, et al: Cloning of the American cockroach Cr-P11 allergens:

- evidence for the existence of cross-reactive allergens between species. *J Allergy Clin Immunol* 101:832-840, 1998
73. Yasueda H, Yui Y, Shimizu T, et al: Isolation and partial characterization of the major allergen from japanese cedar (*Cryptomeria japonica*) pollen. *J Allergy Clin Immunol* 71:77-86, 1983
74. Yoo T-J, Spitz E, McGerity JL: Conifer pollen allergy: Studies of immunogenicity and cross antigenicity of conifer pollens in rabbit and man. *Ann Allergy* 34:87-93, 1975

Address reprint requests to

Richard W. Weber, MD
Austin Allergy Associates
1600 West 38th Street #120
Austin, TX 78731